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**JOURNAL OF
THE MOUNT SINAI
HOSPITAL**

VOLUME XXVI

1959

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POLYCYTHEMIA

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Polycythemia refers to an increase above normal in the number of circulating erythrocytes and may be classified as follows:

I RELATIVE POLYCYTHEMIA

- A Secondary to fluid loss or fluid shift
- B Idiopathic (stress)

II ABSOLUTE POLYCYTHEMIA

- A Secondary
 - 1. a) Cardiac
 - b) Pulmonary
 - c) Respiratory center dysfunction
 - d) Abnormal hemoglobin pigments
 - e) High altitude
 - f) Capillary stasis and stagnation
 - g) Bone marrow capillary fibrosis
- 2. Humoral
- 3. Hormonal
- 4. Neurogenic
- 5. Cobalt
- B Primary
 - 1. Erythremia

RELATIVE POLYCYTHEMIA

Secondary

In *relative* polycythemia the total circulating red cell mass is normal or even decreased but there is a slight to marked reduction in the total plasma volume resulting in a relative increase of erythrocytes per unit volume of blood. This syndrome may be associated with an excessive loss of body fluid as in hyperemesis, protracted diarrhea or excessive sweating. In adrenal insufficiency, hemoconcentration, with a shift of fluid from the plasma into the tissues, may result in pseudo-polycythemia; and shock due to various causes, with loss of fluid into the extravascular spaces, may show a similar picture. The polycythemia associated with infections, particularly tuberculosis, is most likely due to Addison's disease, the result of adrenocortical necrosis. The plasma volume in such instances may be as

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The various studies reported in this paper were aided by the Albert A. List, Frederick Machlin and Anna Ruth Lowenberg Research Funds.

low as 15-20 ml./kg. body weight as compared with the normal of about 40 ml./kg. body weight. In all of these conditions, regardless of etiology, the total blood volume is decreased as a result of the plasma depletion. The cause of this type of polycythemia may be determined from a good history and physical examination. Only a blood volume determination, however, will indicate the true nature of the polycythemia since the red count, hemoglobin, and packed red cell volume do not differentiate between relative and absolute polycythemia. Therapy is obviously directed at correcting the etiologic factors causing the loss or shift of body fluid.

Idiopathic (Stress)

Relative polycythemia of undetermined origin has been reported as hypovolemic polycythemia (1), pseudopolycythemia (2), and stress erythrocytosis (3). Recently Lawrence and his associates (3) found, in almost 10 per cent of cases referred to them for treatment of polycythemia vera, a low plasma volume with no true increase in the total red cell volume. Clinically these patients with low plasma volumes had many similarities, i.e., they were predominantly male, appeared plethoric and about half were somewhat overweight and hypertensive. Symptoms were similar to those of polycythemia vera but there was no splenomegaly nor leukocytosis nor thrombocytosis; the arterial oxygen saturation was normal and there was no demonstrable evidence of cardiac or pulmonary pathology. Contrary to the findings in secondary erythrocytosis or polycythemia vera, the study of iron kinetics in such patients utilizing radioactive Fe^{59} has revealed a normal iron turnover in the marrow signifying normal erythropoiesis (4).

This pseudopolycythemia may occur de novo with no specific etiologic factors responsible. Lawrence has suggested that it might be a reaction to the stress of daily living hence the term "stress erythrocytosis" (3). An awareness of its existence is important; it is only by doing blood volume studies in all cases of unexplained polycythemia that these cases can be singled out. Therapy on the whole is unsatisfactory; reducing the red cell mass in these patients should be avoided.

ABSOLUTE POLYCYTHEMIA

Secondary

Anoxic

By far the most common cause of absolute secondary polycythemia is anoxemia (5). Erythrocytosis of a mild to severe degree may be seen in any cardiac or pulmonary condition which interferes with the proper oxygenation of the blood. Probably the most extreme degree of secondary anoxic polycythemia is seen in the cyanotic type of congenital heart disease. Of the pulmonary conditions, extensive fibrosis of the lungs, idiopathic or secondary, and emphysema, produce severe anoxemia due to impaired pulmonary diffusion of gases. It would appear that the degree of polycythemia is directly related to the severity of the anoxic

state. Although the red cell increases may approximate those found in polycythemia, the white cells and platelets are not significantly effected. Interestingly enough, the platelets in the congenital forms of heart disease may be markedly reduced (6); no satisfactory explanation has been found to account for this thrombocytopenia but it assumes considerable importance when cardiac surgery is contemplated in such cases, since severe uncontrollable bleeding due to the thrombopenia may be a serious problem.

The recognition and proper evaluation of this type of polycythemia is usually easy since the underlying pathology is generally apparent. If there is doubt, blood volume studies and a determination of the arterial oxygen saturation must be performed. The arterial oxygen saturation in these anoxic states is invariably low in contrast to the low normal or normal values in polycythemia vera (7-11). Bone marrow aspiration is of no diagnostic value in differentiating true from secondary polycythemia (12-14); although the megakaryocytic and leucoblastic activity are not increased in the secondary types, the normal fatty marrow may be replaced by active hematopoietic tissue as in polycythemia vera. Trephine biopsy on the other hand has been helpful in the diagnosis with the panmyelosis of polycythemia vera absent in anoxemic erythrocytosis (15, 16).

Treatment must be directed at correcting the underlying pathology and thus increasing the available oxygen supply to the tissues. In some of these cases there may be overcompensation of erythrocyte production with the red cell increase greater than necessary. This great mass of red cells may then only aggravate the condition and cause many of the associated symptoms. Venesections performed cautiously have, in such instances, given considerable relief. X-irradiation to the long bones and radioactive phosphorus has also been successfully employed in the management of some of these patients (17).

Polycythemia has been reported in patients with no evidence of cardiac or pulmonary pathology yet anoxia has been present due to unexplained alveolar hypoventilation. In some of these cases the polycythemia has been associated with marked obesity (18-21). It has been postulated that reduction in functional residual capacity occurs with extreme obesity. This may be due either to a mechanical effect or else to a reflex effect giving rise to a diminished tidal volume (18-20). An associated decreased sensitivity of the respiratory center may produce intermittent hypoventilation and hypoxia with compensatory polycythemia, increased pulmonary vascular resistance and hypertension, and even congestive heart failure (18, 19). This syndrome is reversible following weight reduction.

Impairment of the respiratory centrogenic drive without any known cause with anoxemia and compensatory erythrocytosis has been reported by Pare and Lowenstein (22). Their case, which unequivocally demonstrated for the first time respiratory center dysfunction, showed a markedly reduced alveolar minute ventilation at rest, a decrease on breathing 100 per cent carbon dioxide and a poor response to five per cent carbon dioxide. Although patients with emphysema might also show a similar response there was no evidence of idiopathic obstructive emphysema with a normal total capacity, a normal vital capacity, residual volume and ratio of residual volume to total pulmonary capacity. In addition,

maximum breathing capacity was normal and voluntary hyperventilation did saturate the arterial blood. Thus the basic defect in this patient was one of an increased respiratory rate with a normal minute ventilation accounting for a greater dead space volume of ventilation per minute. This alveolar hypoventilation then resulted in hypoxia and hypercapnea.

Alveolar hypoventilation has also been demonstrated in patients with residual respiratory paralysis complicating poliomyelitis (23). Intermittent mechanical assistance to respiration in these patients improved the hypoxia and resulted in lower red cell levels (24).

Anoxemia may be the result of low atmospheric oxygen tension, as seen in people living at high altitudes (25-28). The polycythemia that develops under these circumstances is due to increased erythroblastic activity in the marrow and may be marked, but again the white cells and platelets are normal and there is no hepatosplenomegaly (29, 30, 11). The red cells fall rapidly to normal after return to sea level and there is no residue of the previous polycythemia. A condition known as chronic mountain sickness may develop, with erythrocytosis becoming more marked due to extreme anoxemia (26, 27). Although the exact cause in many cases is unknown, this syndrome may well be due to pulmonary fibrosis or silicosis superimposed upon the preexisting low oxygen tension. There seems to be no doubt that hypoxia produces increased erythropoiesis (31) yet Reissman (32) has demonstrated bone marrow hyperplasia without the mediating anoxemia in parabiotic animals. This would imply and support the existence of a humoral factor, recently isolated, as controlling erythropoiesis (33-39).

Polycythemia due to anemia anoxia may occur as the result of a defect in the hemoglobin of the red cells which interferes with their ability to utilize available oxygen. Unless there is a congenital deficiency in an enzyme such as methemoglobin reductase (40) this is usually the result of chronic poisoning with carbon monoxide or aniline derivatives particularly acetanilide, nitrite, etc., which produce abnormal hemoglobin pigments such as carbon monoxide hemoglobin, methemoglobin and sulfhemoglobin (11, 41). The oxygen combining capacity of the blood is reduced, resulting in a condition simulating anemic anoxemia, with no reduction however in red cell mass. Erythrocytosis secondary to acquired methemoglobinemia or sulphhemoglobinemia will persist for the approximate duration of the life of the abnormal red cell after the noxious agent is removed.

Anoxic polycythemia as the result of extreme capillary dilatation with stagnation of red cells has been hypothesized (5); and relative bone marrow anoxemia as the result of thickened fibrotic sclerotic bone marrow capillaries has been suggested as the cause of polycythemia vera (42) (for further discussion of this, see section on polycythemia vera).

Humoral

The concept of the humoral regulation of erythropoiesis stems from the original observations of Carnot and Deflandre in 1906 (34) who produced rapid and marked erythropoiesis in normal rabbits by injecting them with plasma from

anemic animals. In addition to a marked increase in red cells, the bone marrow was found to show erythroid hyperplasia. Although conflicting opinions (43-45) concerning the existence of this humoral factor "hemopoietine" were reported and interest in it seemed to decline until recently, the intensive investigations of Erslev (35), Linman and Bethel (38, 39), Borsook et al (33), Jacobson (36, 37), and others (46-48), have tended to confirm the original hypothesis of Carnot and Deflandre. Fried, Plzak, Jacobson and Goldwasser (49) have been able to show the presence of this red cell stimulating substance more effectively by using hypophysectomized rats as more sensitive recipients. Although the exact site of the origin of erythropoietine still is obscure, as is the mechanism of its formation, recent evidence seems to focus on the kidney as the mediating organ (37). It appears that the rate of erythropoiesis may be controlled by circulating "erythropoietine" and its production in the kidneys determined by the oxygen supply-demand relationship of the body (37). The increased erythropoietine may be the direct result of anoxemia and be responsible for secondary erythrocytosis, but its relationship to polycythemia vera has not been elucidated as yet.

Hormonal

Endocrinal influence on erythropoiesis has been extensively investigated. The thyroid, adrenals and gonads appear to play little or no role in red cell production (5). On the other hand the relationship of the pituitary gland to erythropoiesis is well established (50-57); hypophysectomized animals almost always develop a 30 per cent reduction in red cells with a hypoplastic bone marrow and a decrease in erythrocyte precursors (5, 54, 55, 57). Van Dyke et al (56) found a marked reduction of the erythropoietic response to hypoxia in addition to the severe anemia. These data plus the fact that erythropoiesis is stimulated in normal animals by fresh anterior lobe of pituitary gland would seem to indicate the existence of a specific pituitary hormone that has a direct stimulating effect on bone marrow erythropoiesis. This hormone is distinct from ACTH (56) and is apparently unrelated to the humoral agent "erythropoietine".

Neurogenic

The relationship between red cell formation and an erythropoietic regulatory center in the brain has been suggested by the many clinical associations of brain tumor and polycythemia (58-62). Although blood volume studies were rarely, if ever, reported in such cases, hemoconcentration may have accounted for the apparent polycythemia in some instances. Experimental studies attempting to relate erythropoiesis to central nervous system function have been carried out. Such procedures as injuries to the midbrain (63), electric shock (64) and lumbar or cisternal puncture may produce a temporary polycythemia (65-67) but, as noted by Grant and Root (5), too many reflex responses occur to constitute evidence favoring any special neural center controlling red cell formation. Haynal and Graf (60) however, entertained little doubt that there was a relationship between polycythemia and a red cell regulatory center in the brain located

in the hypothalamic-hypophyseal area. Pituitary hyperfunction, demonstrated in four polycythemic patients by them, was treated by irradiation of the hypophysis (60). Completely negative results were obtained in two patients and at best equivocal responses in the other two. Many years prior to this, as a result of a report by Moehlig and Bates (61) suggesting a relationship between the pituitary and erythropoiesis, Bassen irradiated the pituitary in five cases of polycythemia vera with completely negative results (68). The question is far from being answered at this time but the possibility of a relationship between erythropoiesis and some neurogenic stimulus, cannot be completely dismissed.

Cobalt

The ability of cobalt to stimulate red cell production and produce polycythemia in man and animals has been established (69-73). It acts solely upon the erythropoietic tissue through an as yet obscure mechanism. The erythropoiesis which follows the administration of cobalt is accompanied by a reticuloocytosis and an absolute increase of the red cell mass consisting of red cells normal in all respects and with a normal survival time (70). Certain substances such as choline hydrochloride (74), methionine and cystine (72, 75) inhibit the action of cobalt and the prevention of cobalt-induced polycythemia has been accomplished in rats by the administration of calcium ethylene diamine tetra acetic acid (76). Although cobalt may act by inhibiting those enzymatic activities that deal with the transport of oxygen, there does not appear to be sufficient evidence for this. Recently Goldwasser et al (77) reported the increased formation of "erythropoietine" in cobalt induced polycythemia thus suggesting a similarity in the mechanism of cobalt polycythemia with anemic or anoxemic erythropoiesis.

Primary Polycythemia (Erythremia, Polycythemia Vera)

Polycythemia vera is a chronic progressive disorder of insidious onset characterized in its early phase by an absolute erythrocytosis and frequently associated with a leukocytosis, thromboocytosis and splenomegaly (11, 16, 78, 79, 80, 81). Subsequently there develops a gradual but invariable anemia which is usually accompanied by leukemoid or leukemic changes. The disease was originally described by Vaquez in 1892 (82) and delineated as a specific disease entity by Osler in 1903 (83) when he reported three additional cases. Shortly thereafter, Turk (84), Weber (85, 86), and Blumenthal (87), broadened our concept of the disease by directing attention to the increased myeloid activity accompanying the erythrocytosis which Vaquez and Osler had considered to be the sole hematological abnormality.

The occurrence of granulocytic leukocytosis and the presence of immature red and the white cells in the peripheral blood of patients with polycythemia vera was noted by Turk (84) and an overactivity of the leukopoietic as well as the erythropoietic tissue due to a primary hyperplasia of the marrow was suggested. The associated increased megakaryocytic activity in this disease was reported by Hutchinson and Miller in 1906 (88). Thus it became apparent that erythremia, a term suggested to distinguish the disease from secondary erythrocytosis, was

not merely a disease of the red cells but actually a hematopoietic disorder involving all the marrow constituents. It was not until 1919 however, 27 years after Vaquez' original description, that the development of anemia was reported for the first time by Freund (89) in a long standing case of polycythemia. Anemia was also noted in three of 15 cases of erythremia reported by Minot and Buchman in 1923 (90) who suggested that the greatly increased leucoblastic and megakaryocytic activity in the bone marrow could depress erythropoiesis and account for the development of anemia (90). That hematic cellular activity could eventually be crowded out by fibrosis and osteosclerosis of the marrow was described as a final development in a case of 31 years duration by Hirsch in 1935 (91). As a result of many careful studies it finally became apparent that the basic disturbance in this disease was a panmyelosis manifested chiefly at its onset by polycythemia. The hematological changes which occur during the course of the disease are determined by the tempo, intensity and direction of the stimulus to the various cellular constituents of the marrow. Recognition of the varied response of the hematic and non-hematic derivatives of the primitive reticulum to the abnormal proliferative stimulus is essential for a proper understanding of the diverse hematological pictures encountered during the course of polycythemia vera.

CLINICAL AND HEMATOLOGICAL MANIFESTATIONS

Polycythemia vera is a disease of the middle or later years of life with an average age of diagnosis of 48 years ranging from about 18 to 80 or more years (Fig. 1). It is rare, however, to see cases under 30 years of age. The male to female ratio is about 1.8:1; the disease occurs in all races, with perhaps some increased incidence in Jews, and is rarely found in Negroes and Orientals. Patients with polycythemia vera have been described as being of the thin "spare" type although the majority have been normal with only a small percentage overweight.

The overall course of the disease may be arbitrarily divided into the polycythemic and anemic phases.

Polycythemic Phase

The symptoms of the polycythemic stage are referable to the increased red cell mass, its concomitant increased viscosity, and to the thrombocytosis. Cardiovascular symptomatology may include angina, dyspnea on exertion, coronary disease, intermittent claudication, erythromelalgia, phlebitis, thrombosis and embolism. The blood pressure is often moderately elevated, as would be expected in the age group represented, but normal pressures are not unusual even with markedly elevated red cell levels. A form of polycythemia without splenomegaly and associated with hypertension has been reported by Gaisböck (92) as representing a separate clinical entity but the existence of such a specific condition is highly questionable; it is more reasonable to consider the hypertension as coincidental in those cases of erythremia without splenomegaly. Hemorrhage, particularly following minor surgery and ranging in severity from slight ecchy-

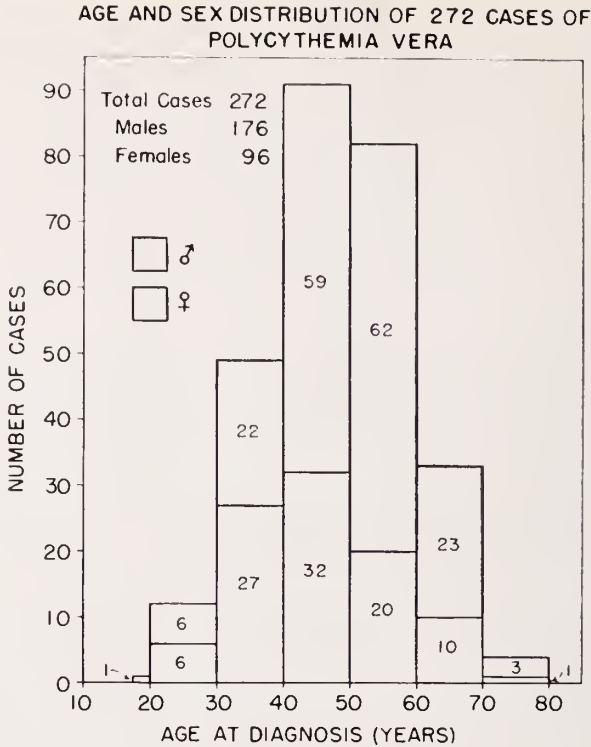


Fig. 1. Age and sex distribution in 272 cases of polycythemia vera. The average age at the time of diagnosis was 48.1 years with a male to female ratio of 1.8:1. (Reprinted with permission of the publisher from Wasserman, L. R., *Polycythemia Vera—Its Course and Treatment: Relation to Myeloid Metaplasia and Leukemia*. Bull. N. Y. Acad. Med., 3: 343, 1954).

moses to exsanguination frequently has been the first symptom to call attention to the diagnosis. Cerebral, gastrointestinal, urinary and nasal hemorrhages may occur at any time during the course of the disease.

The heart may appear moderately enlarged in some instances but this is related to the hypertension and the arteriosclerosis frequent in this age group rather than to the hypervolemia. Atheromatous changes are no more marked than would be expected and the coronary vessels may be relatively unaffected by sclerosis (93). Pierce and Gofman found the serum lipoproteins to be normal in erythremia (94). The lungs are normal but almost invariably show increased vascular markings on x-ray.

Headache, transient syncope attacks, dizziness, weakness, paresthesias and insomnia are common. Pruritis is a frequent and distressing symptom. Occasional cases present as brain tumors, paresis or epilepsy and psychotic manifestations may obscure the diagnosis (95, 96). Associated visual changes such as scotomata, blurring of vision, muscle paralysis and even blindness have been reported. These severe symptoms disappear rapidly following suitable therapy.

Gastrointestinal symptoms are varied and non-specific. Ulcers occur in 8.6

per cent of the patients (11). Pressure symptoms due to splenomegaly and hepatomegaly occasionally occur (97) and hemorrhage either from an ulcer or a ruptured varix is not unusual (11).

Vascular thromboses are directly related to the viscous circulating blood. Thrombosis of any vein or artery may occur and embolic phenomena are not infrequent. Splenic, portal or mesenteric vein occlusions may give rise to serious complications of erythremia (98). Segmental thrombi of the splenic vein may cause varices of the fundus of the stomach with intractable hemorrhage (99).

The increased blood volume and viscosity produces a ruddy cyanosis that is quite characteristic of erythremia. The viscosity of the blood is increased proportionately to the increase in the number of red cells (100). The circulation time varies almost directly with the viscosity yet the cardiac output and cardiac work have been found to be normal (101-103). Capillary blood flow is slowed as a result of the increased viscosity with many of the symptoms in this disease due to this sluggish capillary flow (11, 16, 104). The mucous membrane and skin reflect the plethora of erythremia and together with splenomegaly and erythrocytosis form the diagnostic triad recognized by Osler as characteristic of the disease (83).

Splenomegaly occurs in about 75 per cent of cases (11, 16, 78) and may vary in size extending from the costal margin into the pelvis. Although initially the spleen may be enlarged due to engorgement with blood because of polycythemia, subsequently, proliferation of the reticulum and its derivatives and extramedullary blood formation are of greater importance in determining the extent of the splenomegaly. The liver is similarly enlarged in about half the cases but is usually felt only a few centimeters below the costal margin.

Examination of the blood is essential in establishing a diagnosis of erythremia. During the polycythemic stage the morphologic changes in the peripheral blood reflect the panmyelosis in the marrow. Erythrocytosis, polychromatophilia and occasional nucleated red cells accompanied by granulocytic leukocytosis with a shift to the left and thrombocytosis are found in about two-thirds of the case (11).

Examination of the bone marrow in erythremia reveals a hyperplastic grossly red marrow with varying degrees of replacement of the yellow fatty marrow of the shafts of the long bones by active hematopoietic areas. However, the aspirated marrow in polycythemia vera is frequently hypocellular due to admixture with peripheral blood from ruptured distended capillaries and the qualitative and quantitative changes unfortunately are not usually apparent. Berlin et al (12) using P^{32} tagged red cells found that the marrow nucleated count must be at least five times the peripheral white count if the qualitative picture is to be significant. Assuming a satisfactory specimen the marrow shows a definite increase in megakaryocytes and early red cells with a reduction in the myeloid:erythroid ratio (Fig. 2).

The increase in red cell concentration is always due to an increase in the total circulating red cell mass. The total blood volume however may not be increased proportionately due to a reduction in the plasma volume (105, 106). In

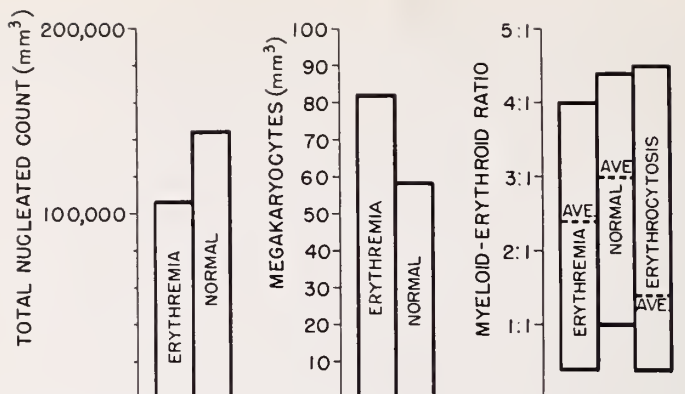


FIG. 2. Average bone marrow results in normal patients and 131 cases of polycythemia vera before treatment contrasted with erythrocytosis (secondary polycythemia). The questionable reduction in total nucleated count and the slight increased megakaryocyte concentration in the bone marrow of erythremia are accompanied by a decreased M:E ratio (aver. 2.5:1; range 0.5 to 4:1). Because of extreme overlapping in all groups however, marrow aspiration findings are rarely helpful as a diagnostic aid. (Reprinted with permission of the publisher from Wasserman, L. R., Polycythemia Vera—Its Course and Treatment: Relation to Myeloid Metaplasia and Leukemia. Bull. N. Y. Acad. Med., 3: 343, 1954).

the normal individual the red cell concentration and mass are remarkably constant. Variations in the erythrocyte concentration will bring into play compensatory homeostatic mechanisms in an attempt to restore the changes to normal, which may explain the somewhat reduced plasma volume in polycythemia vera. The normal red cell volume using isotope tagged cells as indicators ranges from 25 to 30 cc./kg. (average 26 cc./kg.) body weight (107). In polycythemia vera the total blood volume may range from 72 to over 100 cc. per kg. with the red cells constituting the greatest portion of this increase (105, 107).

The polycythemic phase of the disease may last for many years and during its course considerable variation may be observed in the white cells and platelets. This is apparently determined by fluctuations in marrow activity and differs from one patient to another. A wide variety of hematological pictures may develop so that in addition to the polycythemia there may be qualitative and quantitative white cell changes ranging from a leucocytosis with or without slight leukemoid characteristics, to white cell proliferation simulating in every respect myelocytic leukemia. At the same time the platelets may become decreased or increased. Any and all combinations of blood pictures may be seen and when the fact is recognized that exhaustion of one element can occur while another begins or continues to proliferate the wide variation of hematologic pictures that may develop becomes understandable (11, 78).

Anemic Phase

Almost without exception patients diagnosed as having primary polycythemia receive treatment to reduce the great numbers of red cells. This is usually accomplished fairly successfully. Regardless of therapy however, the disease reasserts itself for many years but ultimately the polycythemia diminishes. The

duration of time that elapses before this stage is reached varies considerably from patient to patient (5 to 25 years) (11, 78, 108). A period of normal red cell values may follow the polycythemic stage resulting in the so-called remissions that have been reported. This stage must be considered the beginning of the spent phase and may last a considerable length of time (11, 78).

Eventually, in all patients who survive this phase, an anemia ensues (11, 78, 89, 90, 109). From this point on the course is one of gradually increasing anemia with associated white cell, red cell and frequently platelet changes in the peripheral blood. Before the anemia develops however, the patients are quite comfortable when there is no polycythemia and they no longer have the symptoms which are directly due to the increased blood volume. On physical examination the plethora is reduced, but strangely enough the color is often higher than one would suspect from the much lowered red cell count. The spleen at this point frequently enlarges rapidly and is very firm to palpation. The liver is enlarged to a moderate degree in most of the patients. The white cells are usually increased with a granulocytic leukocytosis accompanied by a small percentage of immature forms. Thrombocytosis is frequent and bizarre and giant platelets may be noted.

As time passes the anemia becomes more severe and patients who formerly required therapy for reduction of the red cells may now be in need of blood transfusions. More immature white cells appear and, on occasion, immature white cell proliferation may become so accelerated that a blood picture indistinguishable from that of acute myeloblastic leukemia may be seen (11, 16). More often however, the picture remains more leukemoid than leukemic, the course of the disease may become protracted, and transfusions may be required at more and more frequent intervals with the development of a hemolytic component. The tempo is occasionally so slow that the patient may be quite well clinically for many years with only a slight anemia and minimal leukemoid changes.

During the early "spent" phase of polycythemia vera the platelets remain normal or even become increased to thrombocythemic levels, but as this final stage progresses, thrombocytopenia frequently ensues. Examination of the blood during this supposed normal period shows a relatively normal or slightly reduced red cell concentration with a leukocytosis and thrombocytosis. A leukoerythroblastic blood picture with a few myelocytes and normoblasts is seen on the smears (11, 18, 110). Characteristics of the increasing metaplastic blood formation are noted particularly in the red cells with polychromatophilia, marked aniso- and poikilo-cytosis, microcytosis, elliptical cells, "teardrop" cells and other bizarre red cell forms. Reticuloocytes may be increased. The marrow still may be hyperplastic but instead of showing a panmyelosis there is now minimal to marked reduction in the erythropoietic elements with an increase in the megakaryocytes and the non-hematic derivatives of the primitive mesenchymal cell as well as the fibrillar and cytoplasmic reticulum. Although the erythroid foci appear to be reduced due to encroachment by the other hyperplastic cellular elements, anemia is probably not explainable on this basis since total red cell erythropoiesis is still as great or greater than normal (110). Simultaneously with

the marrow changes, the spleen enlarges and becomes an active important site of extra-medullary blood formation. A splenic puncture done during this stage will show a picture similar to that seen in the marrow with blood cell hyperplasia and reticulum cell increase, the picture of myeloid metaplasia (11) (Fig. 3).

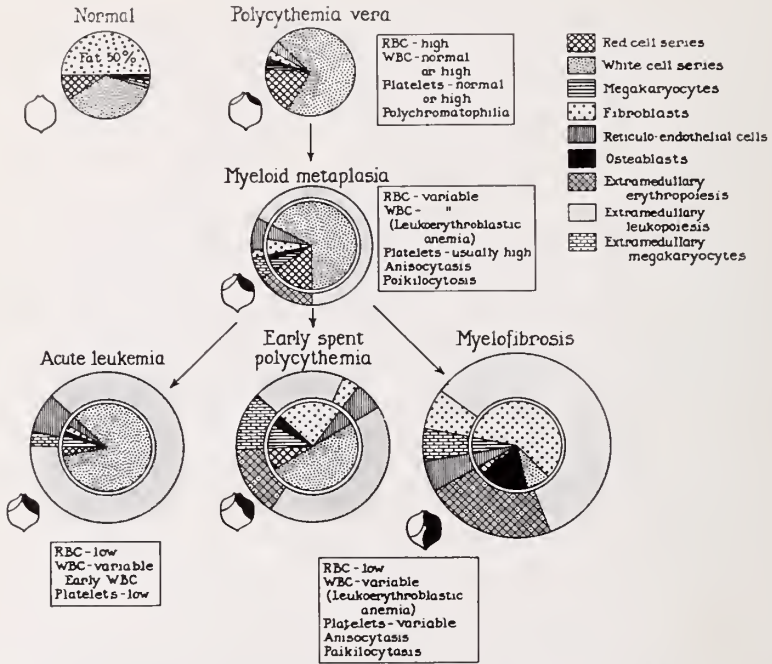


Fig. 3. Hypothetical concept of the course of polycythemia vera. The blood, bone marrow and extra-osseous potential marrow considered "the blood tissue" reflect simultaneous changes occurring during the course of polycythemia vera. In polycythemia vera the hyperplastic marrow expands to encompass the total marrow space at the expense of the fat cells. There is a pannmyelosis with stimulation of all hematic and non-hematic cellular derivatives of the reticulum cell. Blood examination reveals an erythrocytosis and usually a granulocytic leukocytosis, thrombocytosis and immature red and white cells. Splenomegaly and hepatomegaly is frequently present, initially due to the increase in blood volume but subsequently associated with reticulum cell hyperplasia and heteroplastic blood formation. With continued hyperactivity the dormant extra-osseous potential marrow becomes functionally active and the site of extramedullary hematopoiesis (stage of myeloid metaplasia) as the spleen and liver enlarge (outer circle designates extramedullary blood formation). The bone marrow shows diminution in erythropoiesis and proliferation of reticulum cells, fibroblasts, megakaryocytes and white cells. The peripheral blood mirrors the marrow changes and usually a mild to moderate anemia although normal values (compensated state) may prevail for many years. Thrombocytosis is common as is a leukoerythroblastic blood picture. With time, progressive changes in cellular composition of the marrow occur (stages of early spent polycythemia). Fibroblastic or osteoblastic proliferation enoaches on hematic cell activity with a reduction particularly in erythropoiesis. Megakaryocytes appear more plentiful due either to increased proliferative activity or a quantitative decrease in other hematic cells. The liver and spleen, the site of extra-medullary hematopoiesis, are not encased in bone, hence can expand markedly. There is anemia, leukocytosis and thrombocytopenia or thrombocytosis, leuko-erythroblastic anemia with morphologically bizarre red cells. Further fibroblastic or osteoblastic proliferation may obliterate the marrow cavity with all blood formation occurring in the extra-osseous marrow (stage of myelofibrosis). Note that non-hematic cell proliferation occurs in the liver and spleen also. The anemia becomes more severe with usually a leukopenia, thrombopenia and a more marked leuko-erythroblastic blood picture. Hepatosplenomegaly may be tremendous. This phase of myelofibrosis (myeloid metaplasia) may be a terminal picture in

The changes in the marrow and spleen proceed unchecked with increased proliferation of fibroblasts and osteoblasts and continuing encroachment upon the hematic cells. Although hematic cell activity is diminished to varying degrees nevertheless the marrow remains the site of extreme proliferative activity. It is only that a shift in the direction and intensity of the stimulus now is apparent with increasing activity directed toward the hematic cells other than the red cell precursors as well as toward the reticulum and its non-hematic mesenchymal derivatives, the fibroblasts and osteoblasts. Red cell activity is gradually relocated to extramedullary sites and anemia may become prominent. This is due to the abnormal forms produced which have been shown to have a shortened survival (11, 111, 112). However, if the rate of red cell formation is increased to a sufficient degree, anemia may be mild or even absent and a compensated myelofibrotic state lasting for months or years may follow. Eventually the marrow cavity becomes almost completely fibrotic or sclerotic with perhaps a few megakaryocytes, reticulum cells and white cells remaining. Marrow aspiration now produces a "dry tap" and the peripheral blood shows a pancytopenia. If however white cell hyperactivity predominates in the marrow or extramedullary sources, a terminal picture of myeloid leukemia follows. Megakaryocytic hyperplasia may also be seen producing the condition of megakaryocytic leukemia or myelosis; in others all elements, megakaryocytic, myelocytic, fibroblastic and osteoblastic, may all be stimulated to produce diverse clinical and pathological pictures (Fig. 3).

COMPLICATIONS

Vascular

The complications that occur during the course of polycythemia vera (Fig. 4) are in most instances related to the hypervolemia. The increased red cell mass, circulating in a relatively reduced plasma volume, results in a thick viscid fluid that courses slowly through dilated and distended capillaries; as a consequence, vascular thromboses are of frequent occurrence (11, 78, 113, 114). This tendency to thrombus formation is greatly enhanced by the fact that in the majority of patients excessive numbers of platelets are present (11, 78, 115-119). Large,

polycythemia vera. Other lines of proliferation may gain ascendancy e.g., the white cells, with development of an acute leukemia occasionally preceded by a stage similar to chronic myelocytic leukemia; megakaryocyte hyperactivity may result in so-called megakaryocytic myelosis, etc.

Acute leukemia, spent polycythemia and myelofibrosis are all depicted as stemming from a common stage of myeloid metaplasia. Variation in proliferative activity of any combination of cellular categories may produce complex clinical and pathological syndromes. Thus, well developed myelofibrosis may frequently show large numbers of myeloblasts and myelocytes in the blood and, similarly, a terminal acute blastic leukemia may show extensive fibroblastic proliferation. (The areas represented for any specific cellular series is only approximate and merely represents an attempt to demonstrate graphically a few of the multiple developmental potentialities in polycythemia vera). (Reprinted with permission of the publisher from Wasserman, L.R., *Polycythemia Vera—Its Course and Treatment: Relation to Myeloid Metaplasia and Leukemia*. Bull. N. Y. Acad. Med., 3: 343, 1954).

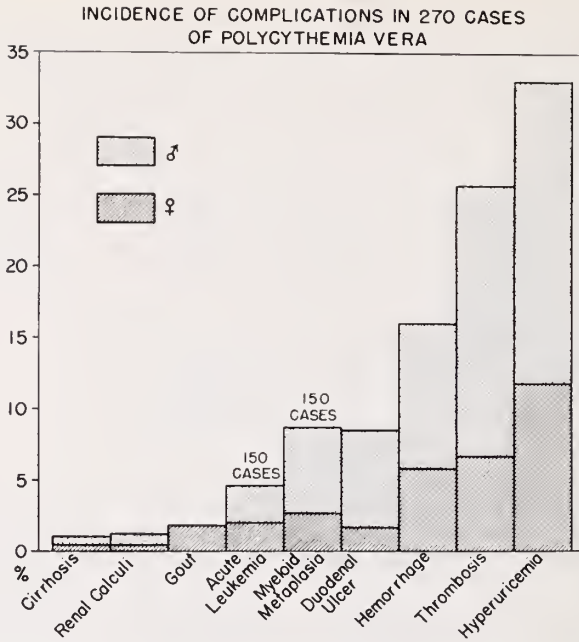


FIG. 4. Incidence of complications in 270 cases of polycythemia vera. The data of only 150 cases were utilized for determining the percent incidence of acute leukemia and myeloid metaplasia. These latter should not be classified as complications since they are stages in the course of polycythemia vera. (Reprinted with permission of the publisher from Wasserman, L.R., *Polycythemia Vera—Its Course and Treatment; Relation to Myeloid Metaplasia and Leukemia*. Bull. N. Y. Acad. Med., 3: 343, 1954).

small or intermediate veins, arteries or capillaries in any organ or tissue in the body may be effected, with resultant cardiac, neurological, cerebrovascular, gastrointestinal, renal, peripheral vascular (120) or any other system, disease.

Hemorrhage similarly results from long standing venous and capillary engorgement due to the hypervolemia. It may be slight or serious, and like thromboses, involve any tissue or organ in the body. Stroebel et al (121, 122) reported an incidence of hemorrhage and thrombosis in 31.1 per cent of their cases of erythremia and in an extensive series reported by Wasserman (11), vascular accidents occurred in 42 per cent of cases, with 26 per cent thrombosis and 16 per cent hemorrhage. Hemorrhages of a minor nature such as easy bruisability and bleeding from the nose or gums of a mild degree were not included in deriving the above statistics. The seriousness of these vascular complications is emphasized by the fact that in this group (11), 56 per cent of the patients succumbed as the result of hemorrhage or thrombosis. These vascular complications, frequent in untreated erythremia, are readily controllable by adequate therapeutic measures, such as reduction in hypervolemia and maintenance of the blood at normal or near normal levels. In a group of 128 cases treated with radioactive phosphorus and triethylene melamine (11), prior to therapy, there was an incidence of 24 per cent thromboses and 10 per cent hemorrhages; subsequent to myelosuppressive measures only 5.5 per cent and 2.2 per cent developed

thromboses and hemorrhages, respectively. Those patients developing thromboses, despite therapy, rarely demonstrated a satisfactory therapeutic response.

This hemorrhagic and thrombotic tendency must be considered when surgery is contemplated during the polycythemic phase of the disease. In a series reported by Wasserman and Kirschner (123) of 26 cases undergoing surgery, 50 per cent had severe thrombotic and hemorrhagic complications. Five (20 per cent) of the patients died; four as the result of bleeding and one of shock, two had pulmonary embolism but recovered. More striking however, were the results demonstrating the beneficial effects of long standing successful preoperative therapy on postoperative complications. Of 13 cases successfully controlled, postoperative complications occurred in only two as compared with the 11 instances of hemorrhage and thromboses and even death in those cases therapeutically uncontrolled. It is obvious that hemorrhage and thromboses constitute a threat to the lives of the patients with this disease at all times, but in those undergoing surgery, bleeding particularly, becomes a hazard so ominous that elective surgery should never be contemplated until such time as the blood volume has been returned to, and maintained at, normal levels for as long a time as possible. Even then bleeding may pose a serious problem as a result of the loss of capillary elasticity from long standing vasodilatation. If surgery is deemed imperative and urgent preoperative venesections should be performed in an attempt to minimize the risk.

The problem of hemorrhage in polycythemia vera (11) as well as in erythrocytosis secondary to congenital heart disease has been extensively investigated (6). As far as can be determined by present techniques no abnormalities in plasma factors are detectable (124, 125). The clotting defect is apparently a complex one involving the formation of a small well contracted fibrin clot, which is functionally inadequate to cope with the mass of red cells which remain untrapped by the fibrin meshes. This relative deficiency of fibrin cannot be corrected by injection of fibrinogen, antihemophilic globulin or any other plasma factor (124). Additional factors provoking hemorrhage in polycythemia are contributed by thrombocytopenia in congenital heart tissue (6) and, paradoxically, thrombocytopenia in erythremia as shown by Spaet (126); long standing capillary dilatation and loss of vessel wall elasticity contribute to this complex hemostatic defect (127-129).

Hepatic

Enlargement of the liver in polycythemia occurs in approximately 50 per cent of cases (11, 16, 78). The degree of enlargement in the early phase of the disease is usually slight or moderate and is due to the marked congestion secondary to the hypervolemia. Although hepatomegaly increases in general with the progress of the disease numerous exceptions to this occur with absence or minimal enlargement in some cases. The size of the spleen similarly shows great variability particularly following myelosuppressive therapy.

Sudden marked enlargement of the liver as reported by Sohval (98) indicates the occurrence of a serious complication, as seen in phenylhydrazine jaundice,

myeloid metaplasia, myocardial decompensation, cirrhosis of the liver or thromboses of the splenic, portal or hepatic veins (98). Cirrhosis is an unusual complication occurring in only two cases of a large series (11). The association of cirrhosis and polycythemia vera, (Mosse Syndrome (130)) is probably coincidental. Earlier reports have failed to emphasize the relationship of the cirrhosis to phenylhydrazine, hemolysis and jaundice seen with such treatment.

Polycythemia has also been observed to be associated with multiple myeloma (131), lymphatic leukemia (132), Hodgkin's disease (11), hypernephroma (133, 134), and other renal tumors (135), uterine fibroids (136-138), and brain tumors (58-62). The association of the former three diseases with polycythemia vera lends support to the unitarian concept of the reticuloses. A relationship may be presumed to exist between the polycythemia and some tumors since removal of the tumors resulted in disappearance of the polycythemia (58, 59, 135, 137, 138). In other cases, where polycythemia is of the true type, the relationship is probably only coincidental.

Ascites in polycythemia, although infrequent, is due to portal vein hypertension resulting from portal vein or splenic vein thrombosis or cirrhosis of the liver (98). Portal vein thrombosis occurring without an associated ascites is attributable to good collateral circulation or recanalization of the vessels. In one case advanced myeloid metaplasia of the liver found at post mortem examination was presumed to have caused ascites since no other ascertainable factor could be responsible (139).

Segmental thromboses of the splenic vein may give rise to varices of the lower esophagus or the fundus of the stomach (99). This has been noted in idiopathic myeloid metaplasia as well as in polycythemia both in the erythrocytic as well as in the spent phase. When bleeding from these dilated vessels becomes marked and difficult to control, surgery is indicated. Whereas splenectomy appears to be curable in the idiopathic variety, local repair of the varices is indicated in polycythemia (99).

Duodenal Ulcer

Peptic ulcer was noted in 8.6 per cent of the series reported by Wasserman (11), and a similar incidence by others (16, 78). This is about four times the expected frequency of ulcer in the general population. Even without a demonstrable ulcer the occurrence of gastric symptoms is high. Lawrence noted complaints of this type in 26 per cent of his series, and 48 per cent of these cases had ulcers (16). The most common complaints were flatulence, pyrosis, thick coated tongue and hyperacidity, often thought to be related to the high incidence of ulcer. The cause of the high incidence of gastric ulcer is obscure; thrombosis of the small mesenteric vessels as well as impaired circulation due to capillary dilatation and hyperacidity probably account for this increased incidence of ulcer. Whatever the etiology, these ulcers at operation and at autopsy appear in no way different from those seen in non-polycythemic individuals and they should be treated in the same fashion. Bleeding from the ulcer site is not uncommon and death from exanguination may occur. Surgical intervention should be avoided but may have to be considered despite the risk, if bleeding is uncontrollable.

Uricemia

The pannyelosis which gives rise to the erythrocytosis, thrombocytosis and leukocytosis results in an hyperuricemia in about a third of the cases (11, 122, 140-144). In a series of cases reported by Wasserman (11), 33 per cent (12 per cent females and 31 per cent males) had an elevation of the uric acid, results similar to the 27 per cent noted by Stroebel (122). Despite the uricemia however, only 1.9 per cent (five cases) had clinical gout and only 0.8 per cent (two cases) had renal calculi. The incidence of gout has been reported as higher in other series (141, 144), ranging from 4.7 to 10 per cent, but this may be due to the inclusion of cases of "spent" polycythemia where there seems to be an increased incidence of gout (145). The hyperuricemia results in an increased incidence of uric acid crystals in the urine with, however, only about 1 per cent of the cases developing renal calculi (11).

Although the hyperuricemia is due to the tremendous cellular catabolic activity with degradation of nucleoproteins to purines and uric acid, there is no apparent correlation with the red and white cell levels. Patients with the highest red and white cell counts frequently show normal uric acid values. Following myelosuppressive therapy, a definite reduction in the serum uric acid and urinary excretion of uric acid occurs as contrasted with the unchangeable pattern following venesection or the use of hemolytic agents. In a severe case of secondary polycythemia, Yü et al (146) using N^{15} labelled glycine found a direct relationship between uric acid excretion and the erythro-normo-blastic nucleoprotein synthesized and destroyed in the erythrocythemic reaction; similar results were obtained by Gutman et al in primary polycythemia (140).

It is difficult to explain the fact that uricemia is most marked in the "spent" anemic phase of the disease, particularly in those cases where most of the marrow is fibrotic and osteosclerotic. It would appear that the fibroblastic proliferation in the marrow and the turnover of cells in the extramedullary centers is in excess of the cellular activity that occurs early in the disease.

DIAGNOSIS

The diagnosis of polycythemia vera in the fully developed early phase of the disease is usually made with little difficulty (147, 148). The symptoms combined with the ruddy cyanosis and enlarged spleen suggest the correct diagnosis which is confirmed by hematological examination. Where the symptoms are not striking however, the spleen not palpable, and the erythrocytosis not marked, the diagnosis may become a problem. In such instances the differential diagnosis must include, in addition to polycythemia vera, all those conditions which give rise to an erythrocytosis. From the clinical standpoint, the polycythemia resulting from anoxic states, secondary to cardiac or pulmonary pathology, is the most frequently encountered. The degree of erythrocytosis in these conditions, as already noted, may be as severe as that seen in polycythemia vera. Blood volume studies serve no useful purpose in differentiating one type from the other since in both conditions the red cell mass is absolutely increased above the normal (105, 149). The plasma volume although usually normal may be depleted in both

types as the result of homeostatic mechanisms attempting to keep the total blood volume as near normal as possible. Blood volume is only helpful in excluding relative or stress polycythemia as a possible diagnosis (16). The overall blood picture in both the primary and secondary types under discussion may also be remarkably similar, although in polycythemia vera the white cells and platelets are usually elevated and immature white cell and red cell forms are present; however these changes may be absent early in the disease.

The bone marrow in erythremia as well as in anoxic erythrocytosis reveals a hyperplastic grossly red marrow with varying degrees of replacement of the yellow fatty marrow of the shafts of the long bones by active hematopoiesis. In secondary polycythemia the hyperplasia is primarily due to an increase in early red cell precursors whereas in polycythemia vera there is a panmyelosis. However from the diagnostic standpoint the aspirated marrow in polycythemia vera is frequently hypocellular due to an admixture with peripheral blood from ruptured distended capillaries and neither qualitative or quantitative changes are apparent (12-14). Block and Bethard (15) and Lawrence (16) and Lawrence et al (150) found marrow biopsies to be of diagnostic significance in distinguishing secondary erythrocytosis from polycythemia vera by the replacement of normal fat tissues with increased megakaryocytes and myeloid and erythroid hyperactivity. Others however have reported noting no essential differences between polycythemia vera or secondary polycythemia. It would appear that the results of bone marrow aspiration are of very little value as a differential diagnostic aid but that marrow biopsy may be useful (11, 15, 16).

A good history and physical examination are usually sufficient to establish the correct diagnosis where cardiac or pulmonary pathology are responsible for the anoxic polycythemia; determination of the arterial oxygen saturation will confirm the diagnosis. Hypertrophic pulmonary osteoarthropathy, fairly common in cardiac and pulmonary polycythemia, is very rare in polycythemia vera occurring in only one instance in a series of over 400 cases (139).

All patients with suspected polycythemia vera should have an x-ray examination of the chest and heart as well as an electrocardiogram to rule out any cardiac or pulmonary abnormality as the cause of the erythrocytosis, particularly when an arterial oxygen saturation test cannot be done.

The arterial oxygen saturation is probably the only test capable of differentiating between primary and secondary polycythemia. As mentioned previously there is some evidence for a slight oxygen unsaturation in polycythemia vera; the deviation from the normal is so slight, (8, 10, 11, 151, 152) however, that the results are nevertheless diagnostic. It follows that a low oxygen saturation excludes the diagnosis of polycythemia vera.

Occasional cases of mild erythrocytosis of a transient nature may be due to the presence of abnormal hemoglobin pigments that are non-functioning as far as oxygen carrying capacity is concerned. Methemoglobinemia, sulfhemoglobinemia and carbon monoxide hemoglobinemia, if of sufficient degree to produce a relative anoxemia, may result in an erythrocytosis. In these cases however, the marrow panmyelosis as found in erythremia with changes in the peripheral blood

are absent, and the arterial oxygen capacity is low. These abnormal pigments may be demonstrated by spectroscopy quite readily.

Relative erythrocytosis secondary to fluid loss or fluid shift rarely is mistaken for polycythemia vera. The increase in red cells is usually moderate with the packed red cell volume between 50 to 60 per cent and the sequence of clinical events is fairly obvious. In this type of "stress" erythrocytosis the blood volume examination is the sole means of determining the factitious erythrocytosis.

Polycythemia has been reported in association with hypernephromas (133), brain tumors (58-62), and uterine fibroids (136-138). Studies on these cases have not always been adequate and it is not clear whether the erythrocytosis is a relative or absolute one and whether anoxic or not anoxic. Cases of these types are not common but may offer serious diagnostic difficulties.

Problems in diagnosis not primarily of a hematological nature are usually encountered when patients have been asymptomatic and present themselves for the first time because of one of the complications of the disease. These are primarily vascular in nature and syndromes resembling diseases of the neurological, cardiovascular and gastrointestinal systems may be closely simulated. If severe bleeding occurs as the initial sign of the disease, the blood picture may be so altered that the true diagnosis may be delayed.

Cerebrovascular hemorrhage or thrombosis have been particularly noteworthy in creating serious diagnostic difficulties. The early signs and symptoms may suggest a brain tumor and craniotomy advised. Conversely, in a case reported by Oppenheimer (62), post mortem examination revealed a brain tumor, although the polycythemic patient had been suspected of having a cerebrovascular accident.

Complications associated with hyperuricemia, such as gout or uric acid calculi in the kidney, may be the first symptoms to attract attention, or duodenal ulcer with its concomitant symptoms may be the first sign of the disease. Since duodenal ulcers in non-polycythemics are frequently associated with erythrocytosis of a moderate degree, it can readily be understood how the diagnosis might be overlooked. Polycythemia vera of a severe degree has been noted after subtotal gastrectomy for bleeding peptic ulcer (139).

Liver complications may attract attention to the disease as in the case reported by Sohval (98). Such complications are usually vascular in nature with only rare parenchymal involvement of the liver except in the later stages of the disease when metaplastic myeloid foci may become prominent.

The myelofibrosis and osteosclerosis that develop in cases of polycythemia vera, seem in all respects identical with that in other non-polycythemia patients with the myeloproliferative syndrome. In polycythemia vera during the cellular proliferative phase, there is rarely bone pain, nor are x-ray changes noted. The fibrotic changes that ultimately develop may be minimal and restricted to the marrow cavity or they may invade the endosteum, the cortex and even the periosteum. At this time bone pain may occur but pathological fractures are rare. X-ray examination of the bones may be negative or reveal minimal changes even though the marrow biopsy shows extensive fibrosis or sclerosis.

In most cases there are mottled areas of rarefaction or irregular condensations in the cortical portions of the bones and splintering or elevation of the periosteum. Myelofibrosis and osteosclerosis may occur in a variety of other conditions and in carcinoma with bone metastases the x-ray findings may appear identical. Usually in these patients the spleen is not enlarged or the enlargement is minimal in contrast to the marked splenomegaly seen in the myeloproliferative syndrome. Leukoerythroblastic anemia may occur in either myelofibrosis or metastatic carcinomatosis although the degree of immaturity of the cells is greater in the former condition. It might be mentioned however, that on rare occasions, splenic enlargement may be absent in spent polycythemia with myelofibrosis as well as in the primary idiopathic type. The serum alkaline phosphatase determination may be helpful in such cases with normal values usually found in spent polycythemia in contrast to the elevated levels found in some cases of carcinoma with bone metastases. In instances where the disease is asymptomatic and no complications occur, the disease may only be discovered accidentally during the course of a routine examination. It is conceivable that some patients may reach the anemic phase of the disease without ever being recognized as polycythemia vera. Patients presenting themselves for the first time with idiopathic myeloid metaplasia of the spleen with or without myelofibrosis, may, in some instances, have had long periods of asymptomatic polycythemia. Actually anerythroid cases of myeloid metaplasia are only examples of the myeloproliferative syndrome in which the stimulus has not been directed to the erythroid series. Cases have been observed where the polycythemia has developed only after long periods of increased megakaryocytic, leucoblastic and fibroblastic activity (153, 154).

ETIOLOGY AND PATHOGENESIS

Polycythemia may occur because of increased production of red cells due to various causes, decreased erythrocyte destruction or a combination of both. The presence of early red cells and polychromatophilia in the peripheral blood together with an erythroblastic hyperplasia in the bone marrow is strong evidence favoring increased erythrogenesis as the cause of the erythrocytosis in polycythemia vera. More definitive evidence for increased red cell production has been obtained by the use of radioactive iron (4, 155) and isotopically labelled glycine (139, 146, 156, 157). The plasma serves as the transport pool for iron released from the cells, such iron being carried as a complex with the beta-1-globulin component of the protein (158-164). Iron is distributed to the bone marrow for red cell formation or to the various organs such as the liver and spleen for deposition as storage iron (155, 165-167). Changes in the rate of red cell formation or destruction should be reflected in the turnover of iron in the plasma pool and in the red cells (4, 155). These rates can be readily measured with intravenously injected radioactive Fe^{59} , which will mirror the changes in the stable iron metabolic cycle (4, 155). In the presence of normal iron stores and normal degradation of hemoglobin, as occurs in early polycythemia vera, the half-time of disappearance of intravenously injected radioactive iron, i.e., the time for half of the

injected radioactivity to leave the plasma, has been found to be a function of erythropoiesis (155). In normal individuals the half-time of clearance of this iron ranges from 70 to 120 minutes with an average of 90 minutes. Those diseases associated with an empty marrow as in aplastic anemia show a prolongation of the half-time to over 200 minutes, whereas increased erythropoietic activity in the marrow is always associated with an accelerated rate of iron clearance. In polycythemia vera the half-time of iron clearance ranges from 10 to 60 minutes signifying increased erythroblastic activity in the marrow (155).

Another factor to be considered in judging erythropoiesis is the utilization of this injected iron. Assuming a steady state, the uptake of iron by the erythropoietic tissue in polycythemia vera is usually maximal, over 90 per cent utilization in about ten days. From the values obtained for the total plasma iron and the maximum red cell incorporation of the radioiron, the plasma and red cell iron turnover rates can be determined (4). The normal plasma iron turnover is about 27 mg. per day or 0.35 mg./kg./day and for the red cell turnover 20 mg./day or 0.26 mg./kg./day. In untreated polycythemia vera the plasma iron turnover values range from 0.36 to 1.1 mg./day (4, 167). These increased turnover rates are indicative of marrow hyperactivity and have been found helpful in the diagnosis of those borderline cases of erythremia manifested by only moderate increases in the total red cell volume (4, 150).

Another theory postulated to explain the mechanism of erythrocytosis in polycythemia vera is decreased red cell destruction or, synonymously, an increased life span of the red cell. A method for measuring the survival of red blood cells utilizing N^{15} tagged glycine has been described by Shemin and Rittenberg (168) and London et al (157). In the normal, a value of 120 days was obtained confirming the results obtained using the differential agglutination technique of Ashby (169). In polycythemia vera an average life span similar to the normal was found by London (157) and Wasserman et al (139) agreeing favorably with the results obtained by other methods (142, 170). It appears, therefore, that the erythrocytosis of polycythemia vera is due not to the production of red cells of increased longevity but rather to a two to three fold increase in the production of normal red cells and hemoglobin by the hyperplastic bone marrow.

Since the values for hemoglobin renewal as determined by iron turnover studies in polycythemia vera as well as in erythrocytosis secondary to anoxemia of varied cause have been far in excess of the normal of about one per cent per day (171) a shortened life span of the red cell was postulated as the basis for the erythrocytosis. Berlin et al (156) using C^{13} labelled glycine to measure red cell survival in polycythemia vera, were able to demonstrate deviations in the initial part of the glycine curve. From this observation it was suggested that an admixture of at least two red cell populations was produced in polycythemia vera, one short-lived and one of normal life span. This could explain the increase in the hemoglobin renewal rate in erythrocytosis and erythremia obtained with radioiron. However, further studies by London (157) and Wasserman et al (139) have not been able to detect this short-lived component (156) and in a case of sec-

ondary polycythemia studied by Yü and associates (146) only one normal cell population was demonstrated.

Increased production of red cells of normal longevity would indicate an increase in the excretion of hemoglobin breakdown products in the stool. Although low values for stercobilin have been reported in polycythemia vera (172), other more recent data would appear to show a more favorable relationship in the pigment excretion (173). It seems reasonable to conclude that the normal values obtained with N^{15} labelled glycine and other methods for the red cell life span in polycythemia vera are correct and that the erythrocytosis is due to increased erythropoietic activity in the marrow.

Since the original description of polycythemia vera by Vaquez (82) and its clinical delineation by Osler (83) many hypotheses have been proposed for the etiology of the increased erythropoiesis. The early appreciation of the relation of the anoxemia of high altitude to erythrocytosis (28) and the polycythemia found in congenital heart disease and pulmonary conditions, directed attention to bone marrow anoxia as the cause of the erythrocytosis in erythremia. Since a state of relative anoxia had been presumed to exist in the bone marrow at all times, any decrease in the oxygen content of the marrow would result in an increased rate of erythrogenesis and polycythemia. Marrow anoxemia has been postulated to be due to one of the following causes.

1. Impaired pulmonary diffusion; increased tissue respiration; vasoconstriction of capillaries.
2. Abnormal hemoglobin pigments; poor dissociation of oxy-hemoglobin
3. Sclerosis and fibrosis of bone marrow capillaries.
4. Capillary dilatation with stagnation.
5. Competitive anoxemia due to myeloid hyperplasia.

The average arterial oxygen saturation of the blood, of primary interest in these cases of polycythemia vera, has been found to be at the lower limit of normal by numerous investigators (7, 8, 10, 151, 174). Careful studies done recently, in which an attempt was made to preclude the enhanced consumption of oxygen by polycythemic blood as demonstrated by deWardner and Young (8) and others (10) show a small albeit significant reduction from the normal oxygen saturation. In a continuation of a study reported previously by Wasserman et al (10) the oxygen saturation in over 50 additional patients with erythremia ranged from 91.0 to 98.3 per cent with a mean of 93.3 per cent. This slight arterial unsaturation can result only from venous admixture, or impaired pulmonary diffusion or ventilation of various causes. Neither venous admixture nor hypoventilation has been demonstrated to be a factor (see section on erythrocytosis). The increased volume and viscosity of the blood in the pulmonary capillaries may, by a mechanical effect or reflexly, cause a reduction in the functional residual capacity of the lungs with arterial oxygen unsaturation of a mild degree resulting. By a similar mechanism, gas diffusion may be impaired as noted by Harrop in severe polycythemia vera, with a minimal reduction in arterial oxygen content (151).

Increased tissue respiration leading to relative anoxia has been advocated by

some to account for the erythrocytosis (175); and localized vasoconstriction of the vessels of the marrow has been hypothesized as the cause of the increased red cell level (1, 176, 177). Others have advanced the ingenious hypothesis of an abnormal hemoglobin being present in polycythemia vera which has great avidity for oxygen which it releases slowly or not at all to the tissues. Recent studies (7) have demonstrated a normal oxygen dissociation curve for polycythemia vera blood, however. Reznikoff et al (42) postulated the presence of increased fibrosis and sclerosis of the bone marrow capillaries resulting in relative bone marrow anoxia because of inadequate oxygen diffusion, but this was probably coincidental in the group studied. Localized relative anoxemia of the erythrogenic centers due to greater affinity or utilization of oxygen by the larger volume of myeloid tissue (178) or by stagnation of blood in dilated marrow capillaries has also been advanced as causes for erythropoietic hyperplasia.

No evidence for support of the many theories resulting in bone marrow anoxia has been produced; rather the studies do not support the thesis of bone marrow anoxia as the primary stimulus for the erythrocytosis of erythremia. The question of the presence or absence of bone marrow anoxia in polycythemia vera was finally resolved by the definitive studies of the oxygen saturation of the bone marrow by Schwartz and Stats (179) and Berk et al (180). Utilizing the material obtained by marrow aspiration, these investigators found either normal or increased oxygen saturation values in erythremia. The fact that many patients with very high polycythemic levels have normal arterial oxygen saturation would indicate that the polycythemia per se is not the cause of the minimal unsaturation occasionally found. Breathing oxygen raises the arterial oxygen content to normal eliminating venous admixture as a cause; and the arterial oxygen dissociation curve is normal (7). The evidence thus suggests that the minimal arterial oxygen unsaturation found in polycythemia vera is of little or no significance in causing the erythrocytosis and that the impaired pulmonary diffusion found in polycythemia vera by Harrop (151) and others (7, 174) is an effect of, and not the cause of, the increased red cell mass. In erythrocytosis secondary to anoxemia or any other cause the pancytosis and hepato-splenomegaly of erythremia are absent.

Satisfactory evidence for the etiologic relationship of any humoral or hormonal factor to polycythemia vera has also been lacking. The early studies on "hemopoietine" could not be duplicated in polycythemia vera (5). Shortly after Castle's work on intrinsic factor and pernicious anemia, an excess of intrinsic factor was hypothesized as causing erythremia (41, 178); and a gastric humoral agent "Addisin" was also postulated (181). X-irradiation to the stomach, gastric lavage and even gastrectomy were thus recommended for therapy of polycythemia vera (182-186) but the results hardly justified the use of such measures.

Recently, interest has been revived in the presence of some circulating erythrocyte stimulating factor in polycythemia vera (33, 35-39). Further investigations are necessary however to establish a definite causal relationship to the polycythemia of erythremia. The possible relationship of polycythemia to an erythrocyte regulatory center in the brain has been discussed; Haynal and Graf (60)

report numerous lesions of the hypothalamus associated with polycythemia and occurring too frequently to be considered coincidental. Because of evidence of hyperfunction of the pituitary and hypothalamic region, four cases of polycythemia vera received x-irradiation to the hypophyseal area with equivocal responses; unsuccessful results were obtained in five patients with erythremia by Bassen (68).

It is of interest to speculate on the relationship of brain lesions to polycythemia and there is ample clinical and hematological evidence to indicate there may be such a relationship; but it must be emphasized that in *polycythemia vera*, the polycythemia is only one facet of a much more profound hematologic disorder in which the white cells and platelets are as much involved as are the red cells.

An appreciation of the developmental potentialities in cases of polycythemia vera and the close relationship to other myeloproliferative syndromes has emphasized the neoplastic nature of the underlying disease (Fig. 5).

Polycythemia vera represents a proliferative neoplastic disorder of the primitive mesenchymal tissue (187). As a result of a stimulus which may vary both quantitatively and qualitatively, this embryonal tissue is incited to proliferate rapidly. Initially the response is predominantly erythroid with the characteristic polycythemic peripheral blood picture. There is nevertheless at the same time also evidence of increased leucoblastic and megakaryocytic activity. This overall response with a pannyelosis was noted by Turk (84) and others (85-88, 90). Weber (85) doubted that the erythrocytic producing function of the bone marrow could ever be greatly increased without the myelocytes being involved in the activity. Wasserman (11) has depicted the marrow responding as an hematic unit with considerable variation in the proliferative activity of the different cell types. The erythropoiesis in polycythemia vera is actually only one facet of a complex disease process. It may be noted at this point that less erythropoietic tissue is necessary in the marrow to maintain a normal red cell concentration than myeloid tissue for a normal white cell level (188). Two factors account for this disproportion; the longer cell life of the red cell as well as the completely intravascular existence of the red cell as contrasted with the granulocytes.

The protean pathological findings that evolve from the very beginning depend on the continuing changing response of the derivatives of the primitive mesenchymal tissue. This may be due to changes in the initial stimulus or possibly to changes in the host response to a stimulus that remains constant. Although there is no set pattern, the early erythroid activity seen at the outset eventually begins to falter and the leucoblastic or megakaryocytic activity, or both, accelerate. This may eventually be followed by intense proliferation of the non-hematic derivatives of the reticulum, the fibroblasts and osteoblasts. In rare instances localized hematic tumors (78, 189) may even develop terminally. As a result of this disorderly progression there emerges a variety of hematological pictures similar in all respects to conditions designated as agnogenic myeloid metaplasia (190), myeloid leukemia, myelosclerosis, osteosclerosis, megakaryocytic leukemia and acute myeloblastic leukemia. On occasion white cell proliferation of leukemic proportions may develop while polycythemia to a marked degree is still present.

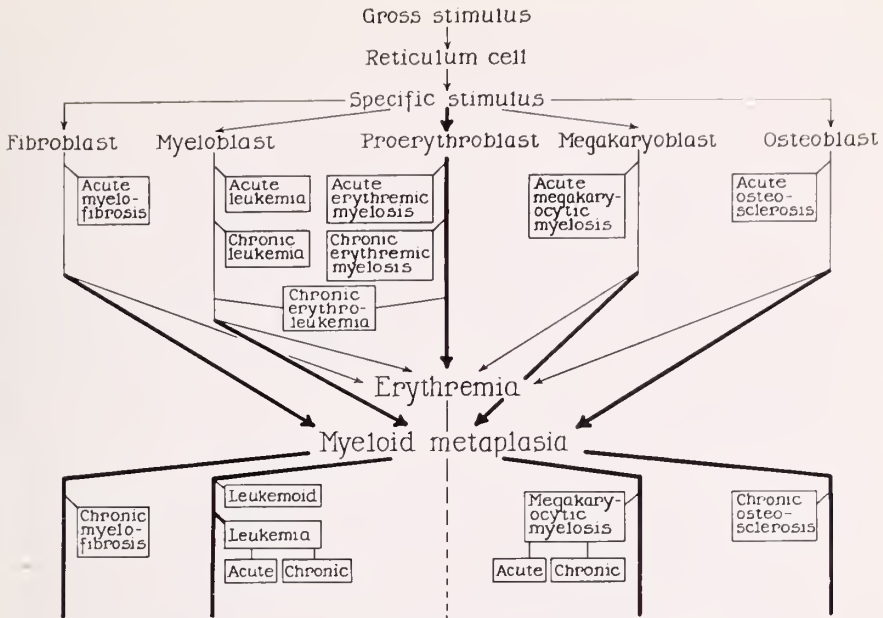


FIG. 5. Schematic concept of the interrelationship of polycythemia vera (erythremia) with myeloid metaplasia and other proliferative diseases of the reticulum. Stimulation of the primitive reticulum cell must be hypothesized to account for the proliferation of all hematic and non-hematic mesenchymal derivatives occurring in polycythemia vera. Qualitative and quantitative variations in the intensity of the stimuli will determine the hematologic and pathologic changes occurring during the course of erythremia, e.g., megakaryoblast stimulation to produce thrombocytosis or megakaryocytic myelosis and stimulation of the white cell precursor to produce a leukemoid or leukemic picture. Fibroblastic and osteoblastic hyperactivity may result in myelofibrosis or osteosclerosis ("spent polycythemia"). Erythremia and myeloid metaplasia are closely related, the latter probably always associated with erythremia of sufficient duration. With development of extramedullary hematopoiesis, erythrogenesis may diminish as denoted by the dotted line whereas other specific stimuli appear to grow more intense (heavy lines). Myeloid metaplasia may occur without antecedent erythremia, the erythrogenetic stimulus initially appearing normal or diminished, whereas the other stimuli are increased from the onset (note heavy lines bypassing erythremia). The hematologic and pathologic picture in myeloid metaplasia associated with polycythemia vera of long duration and that of the idiopathic variety are indistinguishable. (Modified from Rosenthal, M. C., Bull. New England Med. Center 12: 154, 1950). (Reprinted with permission of the publisher from Wasserman, L. R., Polycythemia Vera—Its Course and Treatment: Relation to Myeloid Metaplasia and Leukemia. Bull. N. Y. Acad. Med., 3: 343, 1954).

Any and all combinations of cellular activity may occur and when viewed simply in the light of varying reticulum cell responses the later developments that occur in polycythemia should be easily understood.

Blood cell formation in the embryo takes place in the bone marrow as well as in the extraosseous organs as the liver and spleen. Shortly before birth hematopoiesis becomes localized to the marrow cavity and a physiologic regression of the heteroplastic foci derived from the cytoplasmic reticulum occurs. These areas however still retain their functional capacity to produce differentiated hematic cells under the proper stimulus. The undifferentiated reticulum is common to both the adult bone marrow and the liver and spleen; stimulation of the reticu-

lum in the marrow should produce a similar response in the dormant extra-osseous reticulum cell and subsequently in its derivatives. The fundamental disturbance in erythremia thus is a reticulosis and the extra-medullary blood formation always present in polycythemia vera of long duration is of autochthonous origin and not compensatory due to the exhausted fibrotic bone marrow. Myeloid metaplasia has been noted in the presence of a full and active marrow; and when fibrosis has been present, it has also been noted to a marked degree in the extra-osseous organs, particularly the spleen, indicating an extra-medullary response identical to that in the marrow. Vaughan has noted that even in advanced myelofibrosis there still remains red marrow in excess of that found normally (110). The myeloproliferative syndrome includes a broad spectrum of conditions (145, 191-196) and from the standpoint of tempo, polycythemia vera may be visualized at one end and acute myeloblastic leukemia at the other (11, 78, 100, 124, 153, 190, 197-211).

The condition designated as agnogenic myeloid metaplasia was considered by Jackson et al (190) to be a disease entirely distinct from chronic myeloid leukemia. Heller et al (193) and others (11, 191, 124) on the other hand noted the many similarities and grouped these two conditions together. The cytochemical studies of Valentine et al (212) on leukocytic alkaline phosphatase confirmed the views of Jackson et al (190) by noting an increase in the alkaline phosphatase content of the cells in myeloid metaplasia in contrast to low to absent leukocyte enzyme levels in chronic myelocytic leukemia. From the clinical and hematological standpoint, however, the leukemic pictures that develop in polycythemia vera, may resemble in all respects the chronic, subacute or acute leukemia that is seen without a prior polycythemia.

The incidence of the later development of leukemia in polycythemia vera, varying from 12 to 80 per cent in different series, is misleading if calculated only on the basis of any one group of cases studied, since a high percentage of patients succumb to complications, particularly thromboses and hemorrhages, early in the disease. The incidence would be much higher and more accurate if based only on the percentage of those patients who had survived to the anemic phase. This could be even further corrected by taking out those cases who die of conditions unrelated to the polycythemia. Careful study reveals that the incidence increases with the duration of the disease thus indicating the almost inevitable progression to a leukemic state if the patient survives long enough. The development of leukemia in this disease is predestined from the very beginning. Although the course may be long, the original stimulus that created the disease is relentless and ultimately achieves its objective in all patients who survive long enough.

PATHOLOGY

The pathological findings of early polycythemia vera may bear little or no resemblance to those found in the "spent phase". During the early plethoric stage of the illness only a hyperplastic red marrow throughout all the bones may enable one to make a diagnosis. There is a total panmyelosis with obliteration of the normal yellow fatty marrow spaces. The spleen is enlarged, and may

CAUSES OF DEATH IN POLYCYTHEMIA VERA
(64 CASES)

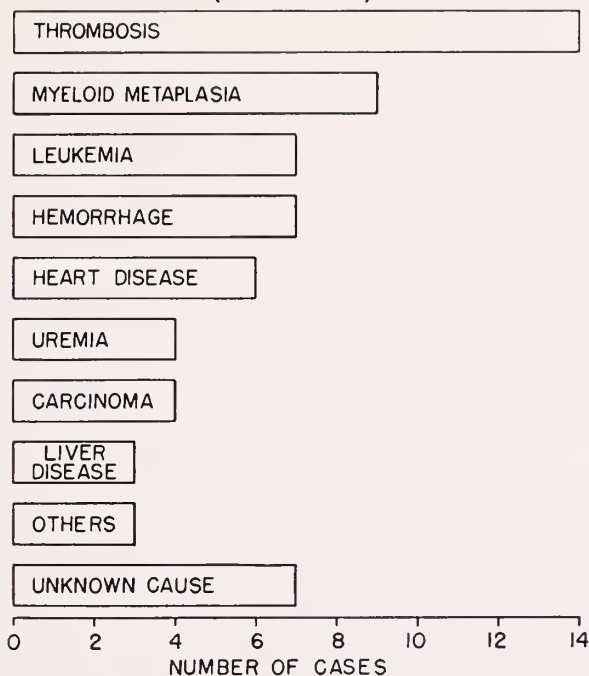


FIG. 6. Causes of death in 64 cases of polycythemia vera treated by all forms of therapy. "Leukemia" refers only to the acute type; myeloid metaplasia includes myelofibrosis and all associated pathological entities. Where hemorrhage, thrombosis, etc., occurred as a direct cause of death in advanced myeloid metaplasia, death was classified as being due to myeloid metaplasia only. (Reprinted with permission of the publisher from Wasserman, L. R., *Polycythemia Vera—Its Course and Treatment: Relation to Myeloid Metaplasia and Leukemia*. *Bull. N. Y. Acad. Med.*, 3: 343, 1954).

reveal only congestion, slight metaplastic blood formation and an increase in the pulp. The hypervolemia is reflected in all the organs which reveal marked vascular engorgement with tortuous and conspicuous vessels. Hemorrhages may be noted in the skin and mucous membranes or thromboses may be found in any organ; anemic infarcts in the spleen are not uncommon. Although thromboses are frequently noted, the blood vessels themselves show no more arteriosclerosis than would be expected in the age group involved (93).

The cause of death at this stage is primarily hemorrhage or thrombosis; at autopsy, coronary, cerebral or mesenteric or other major vessels may be involved (Fig. 6).

The pathological changes found later in the disease after anemia has ensued, are very much different. A variety of complex pathological pictures are found due basically to proliferation of the various derivatives of the reticulum cell. The spleen is usually very much enlarged, bluish red, smooth, shows signs of previous infarcts, and at times, almost fills the entire abdomen. It may be markedly fibrotic and on section reveals myeloid metaplasia, often so extensive

that it appears like active cellular bone marrow. In addition considerable fibroblastic and reticulum cell hyperplasia may be noted. The marrow at this stage no longer has a red appearance; rather it is pale, firm and dry due to fibrosis and/or osteosclerosis; megakaryocytes and early white cells may be scattered in the fibrous tissue. Very late in this disease, the cellularity may be completely replaced by fibroblastic and osteosclerotic tissue (11, 78, 91). The entire bone structure may be thickened by this process and on microscopic examination the endosteum, cortex and periosteum are involved. Where the hematological picture of acute myeloblastic leukemia is noted the autopsy findings reflect the leukemic changes as well as the proliferative aspect of the reticulum cell derivatives.

Myeloid metaplasia is extensive in the liver, at times giving rise to nodular formation simulating cirrhosis or even a hepatoma when growing rapidly. The liver, as the spleen, may reach enormous proportions weighing as much as 5000 grams. Heteroplastic blood formation may also be noted in the lymph nodes and kidney.

Ascites seen at autopsy in a small percentage of cases is generally due to hepatic or portal vein thrombosis. Although cirrhosis of the liver may be seen in rare instances, it may be coincidental or secondary to the use of hemolyzing agents. Figures 3 and 5 graphically depict the patho-physiologic changes occurring in polycythemia vera.

TREATMENT

Intelligent management of a case of polycythemia vera throughout its course can be accomplished only by a complete understanding of the pathophysiology of the disease in its various stages. The inevitable progression of polycythemia vera from the erythrocytic stage through the complex changing pattern of clinical and pathological alterations of the "spent phase" requires constant reappraisal of the prescribed therapy. Treatment to be adequate and satisfactory during the polycythemic stage must in some way control the marked hematic cell proliferation with its resultant complications, and provide symptomatic relief for as long a period of time as possible. Reduction of the red cell mass may be accomplished by (a) removal of the excessive quantity of blood by venesection, (b) production of intravascular hemolysis by the use of a hemolytic agent as acetylphenylhydrazine, (c) suppression of marrow hyperactivity by chemicals, x-irradiation or isotopes or (d) any combination of the above. The most successful form of therapy for erythremia however is the combination of venesections followed by the use of a myelosuppressive agent (Tables I and II).

Phlebotomy is the oldest, and still effective, method in the management of cases of polycythemia (108, 134, 213, 214). Repeated phlebotomies of 200 to 500 ml. can reduce the blood volume to normal within a short period of time and relieve the patient of many of the uncomfortable symptoms, the direct result of the greatly increased blood volume and viscosity. In the very mild cases this method of therapy may be all that is required and lengthy remissions may be produced. In the more severe cases, however, management with venesection

TABLE I

Preferred Forms of Therapy of Erythremia (In order of Preference)

I Polycythemic Phase

- a) Radioactive phosphorus (P^{32}):
treatment of choice; oral or intravenous
- b) Total body radiation:
used when P^{32} not available; may produce radiation sickness
- c) Venesection:
for initial rapid reduction of blood volume to normal; may be used subsequently when indicated for emergency or preparatory to further myelosuppressive therapy
- d) Triethylene melamine (TEM):
frequent gastrointestinal and hematologic toxicity; response unpredictable; short remissions

II "Spent Phase"

- a) no treatment if no anemia
- b) Transfusions:
for anemia
- c) ACTH or cortisone:
for anemic stage with hemolytic syndrome; for bone marrow failure; prior to splenectomy
- d) Splenectomy:
only when careful evaluation indicates probability of success; not to be lightly recommended.

TABLE II

Principles of Management of Polycythemic Phase of Polycythemia Vera

- I Reduction of blood volume by 300 to 500 ml. venesections every 1 to 2 days to normal levels.
- II Myelosuppressive therapy
 - a) Radioactive phosphorus or
 - b) Total body irradiation or
 - c) Triethylene melamine
- III Individualize therapy
 - a) Tolerance of patient to myelosuppressive agents must be titrated
 - b) Give no more than 3 to 7 mc. P^{32} every six months
 - c) TEM in small doses of 2.5 to 5 mg. per dose for total of 10 to 20 mg.
- IV Venesections used routinely only in resistant cases
 - a) myelosuppressive agent in addition for thrombocytosis
- V Periodic blood examination
- VI Elective surgery delayed until blood under control for at least 2 months. Emergency surgery only after rapid normalization of blood by venesection.

alone is usually difficult and unsatisfactory since the red cell regenerative rate is so rapid. Each 500 ml. phlebotomy results in the removal of 250 mg. of iron in addition to red cell stroma, plasma proteins, etc. Marrow activity is indeed stimulated by removal of blood to produce red cells, white cells and platelets at an even faster rate and ultimately a peculiar type of iron deficient anemia develops with a thrombocytosis and granulocytic leukocytosis. In cases treated solely in this fashion, hemoglobin values in the anemic range have been associated with polycythemic red cell counts ("chlorotic phase") (78). This iron deficient hypochromic microcytic polycythemia may be associated with all the

symptoms of severe hypoferremia as glossitis, dysphagia, anorexia, and asthenia. Also, since iron is an essential trace metal taking part in many metabolic activities, serious depletion may impair normal cellular function. Patients with erythremia treated by repeated venesection may become severely incapacitated due to the induced iron deficiency. In such instances the administration of iron in therapeutic doses may produce dramatic improvement in the physical state with the polycythemia subsequently controlled by myelosuppressive agents (11).

An effort to circumvent some of the disadvantages of venesections was attempted by replacing the total red cell and plasma volume removed with simultaneous plasma infusions (215). However, danger of transfusion serum hepatitis as a complication of this procedure discouraged further investigation. Utilization of the newer plastic containers for venesections will permit salvage of the homologous plasma and subsequent reinjection thus restoring the plasma proteins and volume to prephlebotomy levels.

Chronic blood loss in erythremia has been accomplished by deliberate infestation with *ancylostoma duodenale* (216, 217). This treatment does not appear to have any advantage over venesections.

Iron poor diets have been recommended as a supplementary form of treatment of erythremia together with venesection (218-220). This is a most uncomfortable procedure however, for a disease so chronic in its duration. A positive iron balance is maintained on an absorption of about 1 mg. of elemental iron per day to compensate for the same amount excreted. Only five to ten per cent of the iron in the normal daily diet, which contains about 20 mg. of available iron in conjugated form, is absorbed. It is thus obvious that severe limitation of food intake must occur to reduce the daily iron absorption to the 1mg. level. Elimination of such iron containing foods as muscle and glandular meats, eggs, bread, green leafy vegetables, cereals and fresh fruits from the diet is required. This enforced iron deprivation may be compared with the results of one venesection of 500 ml. wherein 250 mg. of iron are removed in a few moments.

Reduction of the red cells by intravascular destruction using a hemolytic agent has been successfully and rapidly accomplished by the potent hemolytic agents, acetylphenylhydrazine (Pyrodine[®]) and phenylhydrazine (221-223). Pyrodine[®] is usually given in a dosage of 0.1 gram three times a day until the red cells approach normal, after which the dosage may be reduced to maintenance levels which varies considerably in different individuals. The fall in red cells is accompanied by a reticulocytosis, bilirubinemia and all the other findings associated with hemolytic anemia. Like venesection however, this type of therapy has disadvantages (224-226). Patients on maintenance pyrodine therapy have a muddy complexion due to the low grade bilirubinemia. The marrow is greatly stimulated by the products of hemolysis with a marked leukocytosis and thrombocytosis; and since the response is very variable it becomes difficult to standardize the dosage. Severe hemolytic anemias necessitating transfusions have resulted in previously resistant cases and vice versa. The most serious disadvantage

however is the toxic effect this hemolytic agent with its bilirubinemia has on the liver. In the cases of polycythemia associated with cirrhosis of the liver (Mosse syndrome), phenylhydrazine had been used and it may well be that there is a causal relationship.

Reduction of the red cell mass by suppression of marrow activity may be accomplished by drugs or radiation (188). The fundamental disturbance in polycythemia vera is the marrow pannyelosis and paneytosis producing the symptoms and complications of the disease. Since hemorrhage and thrombosis will occur in about 50 per cent of untreated or inadequately treated erythremic patients, it is necessary to expedite the correction of the polycythemia by rapid reduction of the blood volume by venesections until normal or almost normal red cell levels are attained. A myelosuppressive agent should then be administered.

Drugs known for their inhibitory action on the bone marrow and thus used in the treatment of polycythemia vera have been benzol (227), lead (228), Fowler's solution (229), the alkylating agents (230-237), and the antifolts (238, 239). The results following Fowler's solution are unsatisfactory, and the necessity of pushing the drug to the limit of tolerance with its associated symptoms of arsenic intoxication make this drug undesirable for treatment of erythremia.

Other agents such as lead (228) and benzol (227) have been tried with either no or questionable benefit to the patient.

Nitrogen mustard (HN_2), methyl-bis-(chloroethyl) amine hydrochloride, cannot be recommended for the treatment of polycythemia vera because of the severe gastrointestinal reactions occurring in many cases, the frequent excessive marrow depression induced and the necessity of hospitalizing the patient; the responses obtained, although satisfactory in many, are short-lived.

Triethylene melamine (TEM) is a radio-mimetic agent similar in chemical structure to the active transformation form of nitrogen mustard, is effective when taken orally and is less toxic than HN_2 . Its cytotoxic action in inhibiting mitotic division makes it most effective in tissues with increased cellular proliferation. TEM shows reduced pharmacologic activity at an acid pH, combines readily with organic material but is relatively stable in an alkaline medium and is usually administered in a fasting state with alkali. This latter method of administration has been used extensively yet there has been no reduction in the gastrointestinal disturbances, nor in the variability of effects produced. Although the oral route of therapy presents readily apparent advantages to the patient, it may be precisely this mode of administration which accounts for the variability in response; thus the intravenous route has been used (11, 239). Suppression of hemopoiesis with reduction in the peripheral cellular elements occurs and remissions in erythremia have been produced with both oral and intravenous administration of TEM (231, 233, 236, 237).

The "simple" cases, i.e., those not associated with excessive myeloid hyperactivity accompanied by a high white count and leukemoid reaction, respond best to TEM therapy. Early cases appear to benefit more than patients with long standing disease. The effect of TEM is variable, patients responding to one

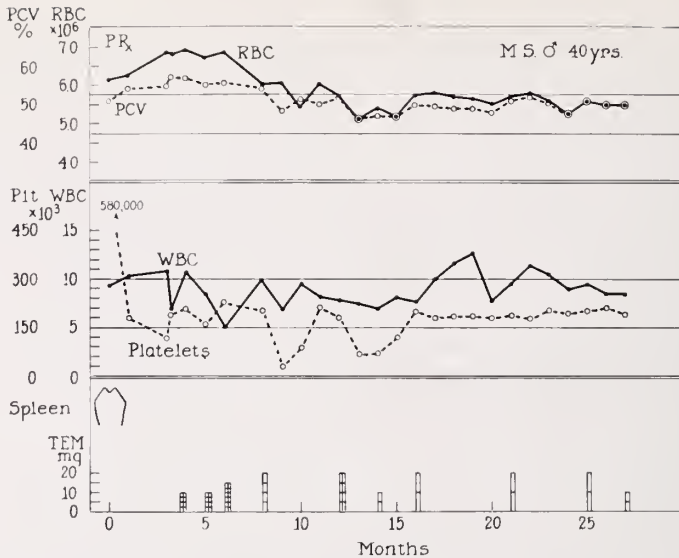


FIG. 7. Typical response of "simple" case of polycythemia vera to TEM; note "titration" of dose from 10 mg. in 8 divided doses to eventual use of 20 mg. in 2 doses.

dose once and not thereafter. Since small doses of triethylene melamine may be effective and cumulative, readministration of the drug in polycythemia vera should not occur for at least two months. The initial response usually occurs in two to four weeks with a maximum reduction in red cells attained in two to four months, with the longest remission about two years. One third of the patients treated with oral TEM develop severe nausea and vomiting which limit its use. The effective dose can only be arrived at through trial and error although a good starting course appears to be 10 mg. in two divided doses over a two or three day period. TEM may be used with satisfactory results if one is aware of its dangers and limitations and watches its results carefully. Figure 7 denotes the method of therapy with TEM.

Daraprim[®] (pyrimethane) is an anti-malarial with weak antifolic and antifolinic acid activity (238). Similar to aminopterin and methotrexate, it is capable of causing a megaloblastic transformation of the bone marrow with an anemia and leukopenia. Although daraprim has been reported to be effective in the treatment of erythremia (238), experience has not borne this out (236, 239). The action of the drug is slow and unpredictable and gastrointestinal disturbances occur in about 50 per cent of patients. Toxic signs such as marrow aplasia, petechiae, mouth ulcerations and gastrointestinal hemorrhage may complicate treatment with daraprim. Since it is rarely effective it should not be used.

Various forms of irradiation have been utilized to reduce bone marrow activity, e.g., local x-irradiation to spleen and long bones, total body irradiation (240, 241) and administration of radioactive isotopes in ionic or colloidal form of phosphorus, sodium, gold, zirconium columbium and yttrium (242-244). Despite the multiplicity of therapeutic measures available for myelosuppressive use only two can be recommended (a) radioactive phosphorus and (b) spray

irradiation, with the former preferred because of its ease of administration and absence of any symptoms associated with its use. Local x-ray to the long bones or whole body radiation (240, 241) has been used quite successfully for many years. It may require several weeks to obtain an effect with radiation therapy of any sort; hence reduction of the blood volume by prior venesection is advisable at the onset. Excellent remissions lasting from several months to a few years have been obtained with roentgen therapy. There are no serious disadvantages except for the inconvenience to the patient and the frequent occurrence of radiation sickness. Overdosage may occur despite careful observation and the red count will often continue to drop despite the fact that therapy had been discontinued. The megakaryocytes are most sensitive and thrombocytopenia may persist, even after the polycythemia recurs. Usually the hypoplasia of the marrow and the anemia that ensue are corrected rapidly and spontaneously.

Radiation therapy in the form of radioactive phosphorus is the most satisfactory treatment for the control of polycythemia. Since the original report by Lawrence in 1940 (245) numerous comprehensive publications concerning its use have appeared (246-265). P^{32} formerly produced in the cyclotron by bombardment of a red phosphorus target with deuterons is now made in the uranium pile by transformation of an atom of sulfur into one of P^{32} . The isotope thus produced is carrier free and has a high specific activity lending itself to successful therapeutic use. The half-life of P^{32} is 14.3 days and the element emits a fairly strong beta ray with a maximum energy of 1.7 MEV. The maximum tissue penetration is about 8 mm. with a mean tissue path of about 2 mm.

Radioactive phosphorus when absorbed into the body in polycythemia vera is initially concentrated by a factor of two to three in the nucleoprotein of the mitotically active cells particularly in the bone marrow, liver, spleen and tumors (266-268). The extent of this initial concentration is dependent upon the total exchangeable phosphorus in the tissue, the rate of utilization of the phosphorus and the rate of growth of new tissue (263). Eventually, depending on the turnover rate of the tissues, the phosphorus is deposited in the large phosphorus pool of the body, the calcium phosphate of bone. This deposition of the radioactive isotope in the bone spicules furnishes additional radiation to the marrow beyond that of the nucleoprotein. A normal blood picture is achieved by the myelosuppression induced by the beta rays of P^{32} on the mitotically active bone marrow cells. The hyperplastic marrow returns to normal and the marrow of the shafts of the long bones once again becomes normally fatty. With the proper dosage deleterious effects are avoided and the morbidity and mortality associated with untreated or poorly treated polycythemia vera is markedly reduced. Thrombosis and hemorrhage rarely complicate the well treated case of erythremia. Lawrence has noted that the patient with polycythemia vera when properly treated has a nearly normal life expectancy (150). Although, according to the ideal criteria established by Hahn and Shepard (244), the half-life of P^{32} may be too long and localization poor, nevertheless the successful experience of 20 years makes P^{32} the method of choice in the treatment of polycythemia vera at this time.

Following the intravenous injection of P^{32} about 5 to 25 per cent of the dose is excreted during the first few days and about one per cent per day is excreted thereafter (266). Almost twice that amount is excreted following the oral administration of the isotope, and since the absorption may be irregular intravenous treatment is preferred. Good results, however, have been obtained with oral radiophosphorus therapy (265) in which case larger amounts must be administered.

Lawrence (150) Wasserman (11) and others (122, 251, 263, 265) have demonstrated the excellent results obtained in relief of symptoms and disappearance of abnormal physical signs in large series of cases. Complete relief of the most disturbing symptoms occurred in over 75 per cent of the cases treated and the abnormal physical findings disappeared in most of the cases. Figure 8 illustrates the response of a case given P^{32} initially followed by phlebotomy. This patient had a history of polycythemia for two years during which time she was treated by venesections and x-irradiation to the long bones. Phlebotomies had frequently been followed by circulatory collapse and because of her apprehensiveness, no pre-treatment venesections were performed. Within one month after 5mc. P^{32} had been administered intravenously the packed cell volume had risen precipitously and marked acrocyanosis with burning and pain in the fingers occurred. Phlebotomy at this time relieved these most distressing symptoms which have not recurred. Maximal response occurred in five months with however a disturbing persistent leucopenia despite the initial high values for the white cells and platelets. The remission was short-lived lasting only a few months yet therapy was withheld because of the low white cell level. After 12 months because of recurrence of symptoms, particularly headaches and dizziness, an additional 5mc. dose was given. There was a prompt reduction in the red cells reaching a maximum in three months, again with a marked thrombopenia and leucopenia lasting a few months. This remission lasted over a year; a subsequent dose of 3mc. was tolerated well with only a slight depression of the leukocytes and thrombocytes although the hematologic remission was somewhat shorter.

Maintaining a patient in a hematologic remission will produce a reduction in morbidity and mortality. Patients are thus examined at four to eight week intervals and when the count begins to rise further therapy is administered. When TEM was introduced, some patients were utilized to evaluate the efficacy of this new drug. As noted in Figure 8 a course of 10 mg. in four daily divided doses of 2.5 mg. produced a temporary decline in the erythrocytosis for about five months, the maximum depression occurring a short time before this with again a leukopenia. Retreatment with the same dose was ineffective on this occasion the white cells remaining unchanged. Cautious increase to a dose of 5 mg. daily for two days produced a slight remission that lasted only one month. Because of intolerance to the drug the patient refused the larger dose and repetition of the course of TEM at more frequent intervals was necessary to bring the hemogram to normal values. The short-lived remissions, the variability in response, fear of over-treatment as well as under-treatment and the frequency of gastrointestinal disturbances with TEM limit its value as a therapeutic agent.

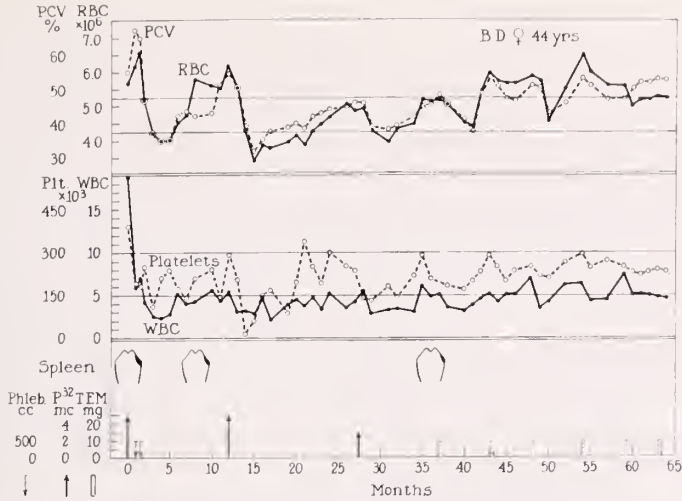


FIG. 8. Polycythemia vera treated with radioactive phosphorus followed by venesection. Subsequent therapy with TEM demonstrates the variability in response as well as short duration of effectiveness of the drug as compared with P³².

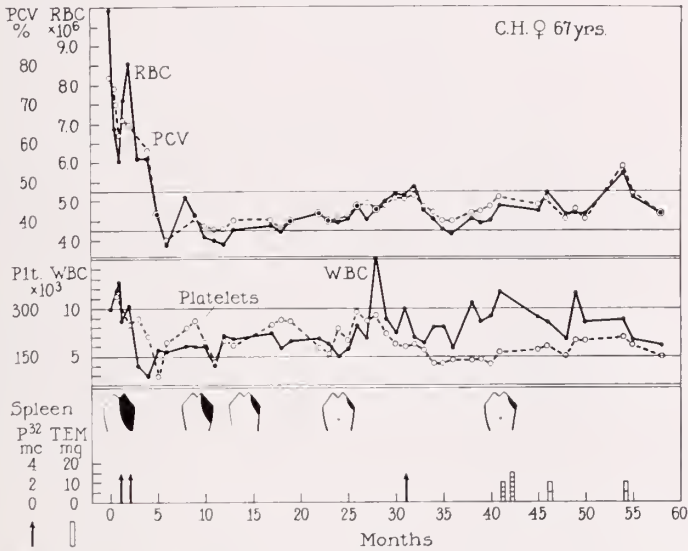


FIG. 9. Resistant case of polycythemia vera of 16 years duration. Note lack of effectiveness of P³² during erythrocytic phase; TEM produced severe thrombocytopenia leading to hemorrhage and death.

A case difficult to control with myelosuppressive therapy is illustrated in Figure 9. Following an 11 year course during which treatment with venesection, phenylhydrazine and x-ray to the long bones and spleen had been unsatisfactory, P³² was administered. Little if any response occurred in any of the cellular elements over a four year period and frequent venesections were performed to relieve the symptoms. Subsequently the hematocrit and platelets were

maintained at normal levels in the face of a rising white count. This undoubtedly was the onset of a decompensated hemopoietic state. Because of numerous symptomatic complaints TEM in monthly 10 to 20 mg. doses was given totalling 50 mg. in five months. The marked fall in red cells and platelets is apparent. At this time the leukoerythroblastic blood picture previously found became more pronounced and although marrow was difficult to obtain by aspiration, an increase in immature myeloid elements was found. Bone marrow biopsy showed a hypoplastic marrow with marked reticulum cell hyperplasia, increase in megakaryocytes and focal myelofibrosis. Severe bleeding manifestations necessitated frequent transfusions but despite blood and hormonal therapy the patient died of a cerebral hemorrhage. In retrospect it appears as if the TEM precipitated the rapid downhill course which, if delayed, might have culminated in a full blown acute leukemia. Post mortem examination showed extensive reticulum cell hyperplasia of the marrow, spleen, liver and lymph nodes with megakaryocytic infiltration in the organs and focal myelofibrosis, the picture of a leukemic megakaryocytic myelosis.

Reference to Figure 10 demonstrates the method of therapy employed in most cases of polycythemia vera. This type case of erythremia has proven to be an ideal case for treatment with a myelosuppressive agent (11, 239). The excellent response to small doses of P^{32} may be noted. Following an initial removal of 2000 ml. blood, 3 mc. P^{32} was injected. One month later with a rise in the red cells and hematocrit an additional 3mc. P^{32} was administered. A response then occurred promptly and over two years elapsed before retreatment with 3mc. P^{32} was necessary due to the recurrence of headaches and dizziness and elevation of the hematocrit. A hematologic remission was maintained for over 3 years and splenomegaly disappeared on minimal doses of P^{32} . Three millicuries are now used as the initial dose followed in one month by an additional 2 to 3mc. if necessary.

It appears fairly clear from statistical evidence that leukemia in one form or another is a naturally occurring late or terminal event in the course of polycythemia. The relationship of this development to radiation therapy has long been questioned, however. That it may occur in patients when no radiation therapy has been given has been well documented (78, 87, 153) but it still is not clear whether the development of the leukemic phase is accelerated by radiation therapy. Unfortunately, comparable statistics are not available for large series of cases treated with and without radiation therapy. The management of patients with this disease is usually difficult and almost invariably at some time during the course, radiation therapy in one form or another, is used. Although the survival time of patients treated with radioactive phosphorus is considerably prolonged, about 13 years as compared with six years in those cases not so treated, the occurrence of acute myeloblastic leukemia seems to be greater in P^{32} treated cases as evidenced by its development in 11 per cent of 64 cases studied by Wasserman (11).

A valid answer to the relationship of the time and occurrence of leukemic changes to radiation therapy seems unlikely until such time as a group of cases

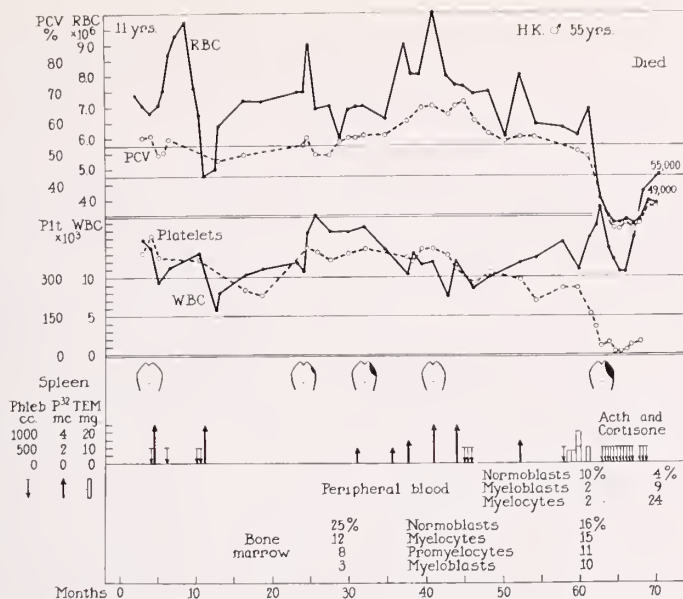


FIG. 10. Typical response to P³² and TEM of polycythemia vera. Note over 2 year effective response to P³² as compared with variable effect of TEM.

large enough to be of statistical value is treated with no radiation therapy of any kind throughout the entire course of the disease.

Management of polycythemia vera in the anemic phase is rarely considered in a discussion of therapy in this disease despite the fact that this phase may last for several years. In general, in the early "spent phase" no therapy of any type is required. Patients in this stage rarely have complaints and may remain normal hematologically and clinically for a considerable time, the period of so-called remission. This phase actually is the earliest sign of diminished erythropoietic activity in the marrow and is indicative of the progressive nature of the disease. Ultimately anemia becomes quite severe and transfusions become necessary. Hematinics such as iron and vitamins are of no value.

The spleen often enlarges considerably at this time and may produce a great deal of discomfort by mechanical pressure or by splenic infarction. X-ray therapy directed to the spleen has on occasion been employed successfully in reducing the splenic mass and normalizing the blood; its routine use is not to be recommended however because of the intractable severe thrombopenia that may ensue. The advisability of splenectomy is often considered at this time but the indications must be evaluated carefully (194, 269-271). This question has most often been discussed with relation to the enlarged spleen observed in myeloid metaplasia not necessarily preceded by polycythemia. Although at one time the consensus was opposed to splenectomy in this disease, modification of this view has occurred, since in some cases splenectomy has been beneficial. Cases selected for removal of the spleen should be restricted to those in whom there is evidence of a severe hemolytic component as well as a thrombopenia. The

development of extreme thrombocythemia with multiple thromboses is a frequent occurrence post splenectomy in those cases with preoperative normal or increased platelets. Prior to splenectomy an intensive trial course of steroid therapy should be given (271); a good response is fairly good presumptive evidence that splenectomy will be beneficial. Steroid therapy has been found to be effective, however, without the need to resort to splenectomy (271).

It should be emphasized that despite comparatively good results in a small percentage of selected patients splenectomy as a general rule is not to be recommended.

The frequent occurrence of thromboses in polycythemia vera naturally leads to a consideration of the therapeutic use of anticoagulants. In the limited experience with therapy of this type bleeding complications were encountered. The tendency to thrombosis in this disease certainly seems to be a natural indication for the use of anticoagulant drugs but the tendency to bleed is an equally strong contraindication. In addition about 30 per cent of erythremic patients have a slightly prolonged prothrombin time indicative of some liver dysfunction; hence, there may be a marked sensitivity to dicumarol and similar drugs (11, 16).

Management of patients has been so much improved by the use of radioactive phosphorus in recent years that the incidence of thrombosis has been considerably reduced (11, 16) and the long term use of anticoagulants as a prophylactic measure does not require serious consideration. When the indication exists for anticoagulants, cautious use may be instituted; heparin or dicumarol, with the former preferred, may be administered but only if protamine or vitamin K₁ oxide are available. In the postoperative management, particularly in those selected cases in the "spent" phase where splenectomy is performed, serious consideration should be given to the use of anticoagulant therapy. The thrombocythemia that almost invariably follows splenectomy in these patients may be extreme and the incidence of postoperative thromboses is so high that judicious use of anticoagulants is justified.

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MODERN CONCEPTS IN THE MEDICAL TREATMENT OF GLAUCOMA

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Glaucoma may be defined as an ocular syndrome whose outstanding characteristic is an abnormally elevated intraocular pressure. Other manifestations of the disease are diminution in visual acuity, characteristic field defects, and a cavernous type of optic atrophy. It has been suggested that the abnormally high ocular tension may not be the cause of the progressive visual dysfunction but only an associated manifestation of the disease. Support for this theory is derived from the fact that often there is no exact correlation between the degree of tension elevation and the severity of the other manifestations of the disease. Furthermore, in certain instances, loss of acuity, optic atrophy, and field defects may occur in the absence of abnormally high tension; a condition referred to as "low tension glaucoma". However, there is no doubt that in the majority of cases, high intraocular pressure is followed by progressive visual deterioration, and that the maintenance of ocular tension within normal limits generally slows or completely stops progression of visual dysfunction. The specific aim of therapy in glaucoma is, therefore, the stabilization of intraocular pressure within a range that has been clinically established as normal.

The pressure within the eye is the result of a complex homeostatic equilibrium between the production and outflow of aqueous humor, and local vascular hemodynamics; all enclosed by the semirigid sclera and cornea. Most recent studies indicate that the upper limit of normal ocular tension is 25 mm. of mercury as measured on the Schiøtz tonometer (1). However, since some eyes may suffer no injury from even higher tension and others occasionally show deterioration in acuity and fields even when the intraocular pressure is below this level, the measurement of tension in glaucoma must always be supplemented by examination of acuity, central fields, and the optic nerve head to estimate the adequacy of therapy and the completeness of glaucoma control. Once the diagnosis of primary glaucoma has been established, such periodic ocular surveys become a life-long necessity.

The physiologic mechanisms whereby intraocular pressure is normally maintained within a relatively narrow range is not clearly understood, and the precise derangement which causes its abnormal elevation is not known. Nevertheless, mounting experimental evidence and clinical experience indicate that the immediate cause of abnormally high intraocular pressure is interference with the free outflow of aqueous humor from the anterior chamber of the eye. Normally, this fluid leaves the eye through the trabeculae of the angle of the chamber which lead into Schlemm's canal, and thence through outflow channels into episcleral veins and the general venous circulation outside the globe. A method

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called tonography has recently been developed with which the rate of aqueous outflow of any eye may be determined clinically (2). Studies employing this technique have shown that in most cases of glaucoma, the outflow of the aqueous is retarded in the region of the angle of the anterior chamber. Gonioscopy is a method of ocular examination that employs a contact lens to permit careful examination of the angle of the anterior chamber under magnification (3). This technique has demonstrated that primary glaucoma in the adult may be divided into two groups. The first classification is referred to as narrow angle glaucoma and corresponds to the group previously called acute and chronic congestive glaucoma. In these eyes the angle of the anterior chamber is anatomically so acute that the base of the iris may readily be brought into contact with the trabeculae of the outer wall of the angle; thus closing in varying degree this portal of aqueous outflow. Such closure of the angle may be temporary, and between attacks egress of aqueous and, therefore, ocular tension may be quite normal. However, with repeated closure of the angle firm adhesions between the base of the iris and the trabeculae may form, and the diminishing patency of the trabeculae that results causes a chronic state of glaucoma that eventually may not be amenable to medical alleviation. The exact cause of the original elevation of the iris base onto the angle wall in these cases is not known, but the immediate opening of the angle in such instances is one of the most urgent therapeutic emergencies in ophthalmology, since the acutely elevated intraocular pressure that results may cause rapid visual deterioration unless immediately relieved.

The second category of primary glaucoma comprises those cases which have open angles. In these eyes gonioscopy generally reveals an angle width which is sufficiently ample so that adhesion of the iris base to the trabeculae would require an unlikely degree of forward movement of the iris diaphragm. Nevertheless, in these cases, too, tonography generally indicates an inhibition of aqueous outflow but the exact site and cause of this obstruction is as yet unknown. These eyes clinically correspond to those formerly classified as having chronic simple glaucoma. If the disease is not controlled by treatment, this reduction in outflow of aqueous may become more marked, with a corresponding gradual rise in ocular tension and increasing evidence of visual deterioration. The progress of glaucoma in these patients is generally slower than in the narrow angle group but the need for adequate therapy is none the less urgent to avoid an insidious but constant and irreversible loss of field and acuity.

To complete this simple modern classification of glaucoma, congenital glaucoma may be described as that occurring in infancy, and generally due to malformation of the angle or its obstruction by residual embryonal tissue. In such cases the elevated intraocular tension generally causes the relatively elastic infantile sclera and cornea to stretch and the result is an abnormally large eye referred to as buphthalmos. The treatment of such eyes is generally surgical.

Other cases of glaucoma are directly attributable to certain known pathological conditions in the eye. Where such causes for the abnormally high intraocular pressure are apparent the condition is called secondary glaucoma. The treatment

of such eyes basically is that of the primary disease, with the secondary application of standard antiglaucomatous procedures as indicated.

From the earliest days of modern ophthalmology, the mainstay of the medical treatment of glaucoma has been the topical administration of miotics. The rationale for this therapy was purely empirical until the development of gonioscopy revealed the anatomy and probable mechanical role of the angle in providing an outlet for aqueous humor. It can now be readily visualized how the production of miosis by pulling the iris base centrally toward the pupil tends to open the angle and facilitate the flow of aqueous through the trabeculae. Secondary hypotonic effects have been attributed to actions of miotics in contracting the ciliary muscle and so pulling on the scleral spur to open Schlemm's canal; in opening venous channels in the choroid; and in dilating vessels and crypts in the iris to facilitate aqueous absorption through that tissue.

The principal miotic drugs used in the eye are parasymphathomimetic in action and may be classified into acetylcholine-like and anticholinesterase groups (4). The acetylcholine-like drugs have a direct muscarinic effect on the structures enervated by post-ganglionic parasympathetic nerves. In this group may be included pilocarpine, methacholine or Mecholyl[®], and carbaicol, though the latter may also have some anticholinesterase activity.

Pilocarpine is by far the most commonly employed topical medication in the treatment of glaucoma. Its value lies in the fact that while it produces choline-like effects directly on the effector cells, it is not actually a choline derivative and hence is not inactivated by the cholinesterase of the surrounding media. In proper dosage it produces a prolonged effect, usually lasting about six hours. The frequency with which pilocarpine should be administered, and its effectiveness, must be determined individually for each patient. An obstacle to its use sometimes encountered is a local sensitivity of the conjunctivae or lids to the drug. A change in the salt of the drug and careful buffering of its hydrogen-ion concentration have been found to overcome this difficulty in most instances.

Mecholyl[®] or methacholine chloride, like acetylcholine itself is not very satisfactory since it is very unstable and its effect is brief. However, in 20 per cent solution together with the anticholinesterase prostigmine, it has a useful function where pilocarpine may prove ineffective. Carbaicol, also known as doryl or earcholin, is a satisfactory agent where pilocarpine cannot be used either because of sensitivity of the patient, or the development of tolerance. It is generally administered in $\frac{3}{4}$ or $1\frac{1}{2}$ per cent solution in 1:3000 benzalkonium chloride which facilitates its absorption through the cornea.

The anticholinesterase drugs are effective miotics because they destroy the natural cholinesterase present at parasympathetic nerve endings. In so doing, they permit the acetylcholine normally present at these sites to act powerfully and for long periods before being destroyed by reformed cholinesterase. The most commonly employed anticholinesterase drugs are eserine or physostigmine, neostigmine or prostigmine, and diisopropylfluorophosphate or Floropryl[®].

Eserine[®] was the first miotic employed locally in the eye to reduce the tension of glaucoma and it is still widely used for that purpose. However, it produces

such intense miosis and ciliary spasm that it may be painful, and it occasionally causes inflammatory reactions such as a transient iritis. It is therefore generally used only briefly where a rapid reduction in ocular tension is desired, or in very dilute solutions as an adjuvant to pilocarpine therapy. Sensitivity reactions are common and its prolonged use is generally not advisable.

Neostigmine or prostigmine is similar to eserine in action but somewhat less intense in degree. It is useful as a synergist with choline-like drugs, particularly mecholyl whose action it prolongs and supplements. Diisopropylfluorophosphate or Flopropyl® produces intense ciliary spasm and miosis that may last for days. Its severe parasympathomimetic effects result from its complete and irreversible inactivation of cholinesterase. The intense spasm of accommodation it causes may result in blurred vision for prolonged periods so that its use is generally restricted to aphakic eyes. Retinal detachment has been attributed to the severe ciliary spasm it induces, and its intense vasodilating effect on intraocular structures may occasionally aggravate an acute congestive glaucoma. Consequently, it is used only in a dilute concentration of 0.1 per cent; generally for short periods, and with caution.

Sympathomimetic drugs have been employed locally in the eye to reduce tension for many years. However, their effects are extremely variable, and generally undependable. Tonographic studies have shown that they do have an inhibiting effect on the formation of aqueous humor (5), and a recent revival of interest in such therapy has occurred. The topical administration of 1 per cent to 4 per cent epinephrine bitartrate has been advocated for this purpose, as has 0.5 per cent isoproterenol or isuprel. A secondary effect of these drugs that may be beneficial is that of vasoconstriction. However, they exert a mydriatic effect which may interfere with aqueous drainage and they are generally administered, therefore, in conjunction with a miotic drug such as pilocarpine.

Probably the most promising recent advance in the treatment of glaucoma has been the development of the carbonic anhydrase inhibitors. One of the most perplexing problems in ophthalmology has been the method of formation of the aqueous humor. Based on an accumulation of experimental evidence Friedenwald (6) suggested that the fundamental process involved an electrolytic exchange in the ciliary epithelium. Subsequent investigations, particularly by Kinsey (7) supported this theory and showed that in this process high concentrations of bicarbonate ion occurred in the aqueous. This seemed to result from the activity of the enzyme carbonic anhydrase known to be present in the ciliary processes. The formation of bicarbonate ion thus seemed to play some important role in the production of the aqueous humor.

With the discovery of carbonic anhydrase inhibitors it became evident to many investigators that a means was provided to reduce the activity of carbonic anhydrase and so possibly to interfere with the process of aqueous formation. The systemic administration of carbonic anhydrase inhibitors has proven this hypothesis to be correct and numerous tonographic and fluorometric studies have attested to the reduction in aqueous formation that results.

The first and most commonly employed drug of this group is acetazolamide

or Diamox® (8, 9). It is effective only by systemic administration either orally or intravenously. The dose required to lower the tension in glaucoma varies with the individual and must be empirically determined. It is most effective when administered in conjunction with local miotic therapy and it may be potentiated by the simultaneous administration of potassium bicarbonate (10). The efficacy of Diamox® therapy must be carefully followed since tolerance may rapidly develop. In narrow angle glaucoma its prolonged use is generally inadvisable since its hypotensive effect may mask progressive mechanical closure of the angle and render later surgical correction more difficult.

More recently another drug of this group has been introduced, called ethoxzalamide or Cardrase® (11). It is similarly administered but seems to be effective in approximately half the dose of Diamox®. Consequently the incidence of such common side effects as parasthesias, anorexia, and nausea may be reduced when the newer drug is employed.

Although our growing knowledge of intraocular physiology has led to a better understanding of some problems in glaucoma, and newer drugs have led to more effective medical therapy, the adequacy of any therapeutic regime still requires constant appraisal through periodic re-examinations. Tests of tension, acuity, fields, and fundi are necessary to evaluate the degree of control, and if any evidence of visual dysfunction develops, a change in treatment becomes necessary. When the medical armamentarium has been fully tried and proven ineffective, surgery must be resorted to without delay since visual deterioration is inevitable and irreversible if the glaucomatous process is uncontrolled. The surgery of glaucoma is not the subject of this discussion but it should be noted that following operation control of glaucoma may still require supplementary medical treatment, and constant surveillance of the patient is still a life-long necessity.

No review of therapy in glaucoma is complete without some consideration of the glaucoma patient as a whole. Glaucoma is generally considered to be one of those diseases in which psychic disturbance may play an important role. It is a common clinical experience that the condition may be aggravated by psychological factors. Accordingly, patients with glaucoma require the careful psychosomatic approach employed in the treatment of such diseases as vascular hypertension or peptic ulcer; and the general hygienic care necessary for all chronically ill patients. In the treatment of the glaucomatous eye, the care of the patient and his relationship to his environment must not be overlooked.

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SEPARATION FROM A LOVE OBJECT AS AN ETIOLOGICAL FACTOR IN FUNCTIONAL UTERINE BLEEDING*

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On a recent visit to Israel I passed near the very locale where, according to the Bible, the first recorded cure of functional uterine bleeding took place. This was near the Sea of Galilee and is described thus in the Gospel of St. Mark (Chapter V, 25-29):

“And a certain woman, which had an issue of blood twelve years,

“And had suffered many things of many physicians, and had spent all that she had, and was nothing bettered, but rather grew worse,

“When she had heard of Jesus, came in the press behind, and touched his garment:

“For she said, If I may touch but his clothes, I shall be whole.

“And straightway the fountain of her blood was dried up; and she felt in her body that she was healed of that plague.”

This historic quotation is an apt introduction to my paper. The woman's simple words, “If I may touch but his clothes, I shall be whole,” state the essence of a modern psychosomatic concept. After twelve years of bleeding, touching another Person accomplished what, at that time, could only be considered a miracle.

What is there in touching that is so powerful? When two people touch each other they establish that they are together, that they are not separated. This can easily be seen if you watch two people meet after they have been separated for a long time. After they have looked at and embraced each other, one will touch and feel the body of the other to obtain this feeling of togetherness. To understand what happened when the woman touched Jesus we must go as far back in the life of the individual as history takes us at the Sea of Galilee.

Life begins as a physical separation of two bodies which were joined together. In the course of growing up we experience many separations, some of a purely psychological nature. Careful observations in recent years have shown us that during the first years of life the child-parent relationship has a profound impact upon the later life of a person. These observations throw light upon the process by which the growing infant gradually becomes aware that he is a separately functioning organism, no longer part of his mother, but apart from her. To mature into a healthy individual, the various separations should take place neither too early nor too late. Too often the child experiences a traumatic separation because of the death of a parent, hospitalization of child or mother, or, at times, the withdrawal of affection, as when the mother becomes severely de-

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* Read in part before the Fourth Annual Meeting of the Academy of Psychosomatic Medicine, Chicago, Illinois, October 18, 1957.

pressed and neglects the child. Such traumatic experiences in infancy and childhood have a lasting effect. They may cause emotional or physical disturbances, or both, in later life.

The first case, in the literature, of functional uterine bleeding in which psychological causes were suspected takes us back more than fifty years. It was at the turn of the century, when a young girl, following an exciting sexual experience, bled continuously for five years. She was successfully treated by suggestive therapy. During the following six years she experienced the death of her fiancée and the death of her brother, three years apart. She responded to the first with a renewed bout of bleeding, to the second with a severe depression. I think this case gives us an introductory clue to the psychological mechanisms in certain cases of functional uterine bleeding.

While all of us are familiar with a depression following the death of a loved one, uterine bleeding as a reaction to the loss of a person seems strange and unfamiliar to most of us. Yet, *it is my observation and it is the thesis of this paper that in certain women sensitive to it,—perhaps on account of early life experiences—the loss of a person close to them, either through death or by separation, may precipitate uterine bleeding.*

Death, however, is only one of the ways in which we lose a person. Someone close may take a trip or move to another part of the country; a mother loses her child through marriage, a wife might lose her husband through divorce. Each of these is an instance of separation.

I certainly do not intend to say that every uterine bleeding where no gross lesion is found is what I have called "separation bleeding." As a matter of fact, there are a variety of emotional stress situations which have been found to be associated with uterine bleeding,—for example severe shock or fright. I distinguish "separation bleeding" from bleeding due to other emotional causes because it seems more specific, we have some understanding of its psychodynamics, and this understanding shows us a way to a rational therapeutic approach.

We have good reason to assume that at least some instances of uterine bleeding resulting from an emotional stress situation do not fall into the category of psychogenically influenced hormonal uterine bleeding. One reason is that uterine bleeding may follow emotional shock within such a short span of time (sometimes only a half hour to an hour later) that it cannot be explained on the basis of withdrawal bleeding.

Stieve (1) collected a convincing number of clinical cases, with supporting anatomical evidence, showing that no ripe follicles were present in the ovaries of his patients and that the bleeding issued from an atrophic endometrium. He called such uterine bleeding "Schreckblutungen" (fright-bleeding). Stieve has a predecessor in Tilt (2), an English gynecologist, who in the year 1851 had the following to say: "Menstruation and ovulation are parallel facts, originating in the same organ, and hereafter it may be shown that they stand related as cause and effect; but this is not yet proved, and we defy the staunchest supporters of the ovular theory to explain . . . why in Mrs. M. who had begun to menstruate 12 hours before her execution "no appearance of recent rupture of a vessicle, or

of the discharge of an ovum, could be found in either ovary' (on the post mortem examination)." Stieve's anatomical material, like Tilt's case, consisted of executed prisoners.

Based on these observations we may state that emotional stimuli may bring about functional uterine bleeding either via the hypothalamic-pituitary-adrenal-ovarian pathway, i.e., via the hormones, or, such stimuli—if intense enough—may find their target organ, the endometrial vessels, directly via the autonomic nervous system. We do well to think of a combination of both bringing about such bleeding, for instance the liberation of corticosteroids or other hormones due to stress.*

Whatever the pathways by which psychological impulses find their expression, the psychological settings in which they occur needs to be examined more closely. Loss of a person or separation from a person, actual, anticipated or imagined, constitutes one of the most important *psychological* factors bringing about or precipitating uterine bleeding. It is well to remember at this point that "loss of a person" means, at times, loss of the love or affection of a person. Whether or not such psychological factors are the *causative* agents, they represent the *setting* in which the uterine bleeding takes place.

In a recent study by Schmale, Jr. (3), on the relationship of separation and depression to disease, the author examined an unselected group of 42 hospitalized medical patients with the aim of determining separation or object loss preceding the hospitalization. Seventy-four per cent of the patients developed the onset of their disease within one week after such change in object relationship.

In my own study of 28 women with functional uterine bleeding (observed on the Gynecological Ward at The Mount Sinai Hospital) I found that in about 73% of the cases such separation or loss preceded the onset of bleeding.

It is in the nature of the subtle and intricate relationship between two people that there is a reaction not only to the actual loss of a love object but, at times, to the loss of the love of the person. Thus, among the instances observed, one finds alienation of affection at one end of the range and a death at the other end.

Below is a table showing the various situations found in studying 54 cases in the literature plus 28 cases I observed. Some of the instances occurred more than once.

Disappointment in men	Dispossessed
Alienation from husband	Leaving native city (and mother)
Husband unfaithful	Fear of impending death
Son left for service	Fear of bombing
Son married	Following misarrriage
Son withdrew affection after his marriage	Following Caesarian section
Deserted by lover	Following breast disease
Deserted by husband	Hopelessness about life's problems
Husband asking for divorce	Death of fiance

* A paper presenting a hypothesis regarding the mechanism by which emotions influence the reproductive organs and/or functions via hypothalamic-pituitary pathways is in the process of being published (*Fertility and Sterility*, Jan.-Feb. 1959).

Death of husband	Death of mother-in-law and separated from husband
Death of sister	
Death of son	Son tried to choke patient to death
Death of father	Obsessive thoughts of killing own child
Death of boy to whom patient was attached	
Death of mother	Attempt to kill baby

Following the death of a person, grief is normal. We mourn the death of a beloved person and consider the process of mourning healthy because it permits us, eventually, to accept the loss. When the mourning does not resolve but becomes deeper, then grief can become depression, and mourning—melancholia. There are instances when the loss of a person cannot be acknowledged. Not only the loss is denied but the accompanying psychological reaction too. In such instances we suspect a hidden depression.

Take the case of a woman who was informed, during World War II, that her son was missing in action. Like so many other women, she hoped he would turn up as a prisoner of war. When in due time she received a letter stating that her son must finally be considered dead, she could not accept this but wrote a number of letters to Washington. To each of these she received a tactful answer. After her twelfth letter she received no further answers and it was then that she started bleeding. This patient had denied the death of her son and had tried to keep him alive through the correspondence. When she no longer received any answers and would have been forced to acknowledge his death, another mechanism set in taking the place of the previous one which was denial. This new mechanism is the very one which concerns us here. It permits us to consider functional uterine bleeding, *in such instances*, a psychosomatic condition. Acknowledgement of her son's death would have led this woman to grieve and mourn and weep but there was a shift in her reaction, a shift from the psychologic to the somatic. In this instance this woman's bleeding takes the place of mourning and still permits her a denial.* However this time she does not deny the death, she denies her reaction to the death. The uterus becomes the executive organ: The uterus expresses the grief by bleeding just as in the usual psychological reaction the eye expresses grief by weeping. The bleeding represents the somatic equivalent of the psychologic reaction,—grieving. You may recall the saying that in a woman who wants a baby, menstruation is "the weeping of the disappointed womb." In association to this, I have called "separation bleeding," "the weeping of the mourning womb."

The uterus is not the only organ that can be used as a somatic equivalent to express grief or the mood of depression. There have been observations which indicate that other organs may take over the function of grieving. Kepecs and his co-workers (6) found that "weeping" eczema stopped when the patient was able to cry in the course of therapy. In a study of five women with atopic dermatitis Kepecs found that "actual weeping, and more important, inhibited weeping,

* Why some women employ the mechanism of denial when they experience death or separation has to do with the psychological aspects of depression. I have dealt with this, in detail, in previous publications (4, 5) and shall not go into these here.

...is a prominent symptom in ... these patients. ... All five women wept considerably and spontaneously under hypnosis. ...” Kepecs made an observation which parallels my own, namely, that “*the most characteristic situations giving rise to weeping were those in which a strong desire to be reunited with a mother figure was expressed.*” One woman under hypnosis did not just cry, but bawled in a loud, childish manner saying, “I never cry. I feel sorry for myself. I want to cry, but I can’t.” “I would like to be in mother’s arms, I want to feel wanted.” When she is able to go home, she lies in her mother’s arms. There “she relaxes and feels like crying.”

These authors concluded that “weeping expressed a desire to overcome separation from a loved object, basically the mother,” that the weeping was suppressed, and that the skin condition was an expression of the suppressed weeping.

To return again to my observations: Take the numerous instances in which a woman is separated from a love object. Her husband leaves her, or she leaves him. Her son or daughter marries; or she moves away from her mother, perhaps following her husband to a distant place. The woman who has moved away from her mother cannot admit to herself that she feels *as if* her mother has died, but her reaction is as severe. A psychological mechanism sets in by which she denies any reaction whatsoever,—instead she bleeds.

I saw a 36 year old woman who was admitted to the hospital with a history of abnormal vaginal bleeding of 11 years duration. Hystero-gram and dilatation and curettement were negative. She started bleeding on the very night her husband brought her to New York from Georgia where she had been living with her mother. Mother and daughter (an only child) were devoted to each other and the patient felt she couldn’t live without her mother. While in New York she sometimes dreamt that she was back with her mother. Even as she was relating to me how she awoke and, looking around, found herself alone, she began weeping. She admits that she does not want to be sad, but sometimes, when she wants to be with her mother, she feels very blue. We can see, here, the patient’s need for denial and how she immediately starts weeping when this mechanism is no longer effective.

In connection with this patient’s need for closeness with her mother, a need many of the women observed had in common, I return to my earlier remarks on the importance of a feeling of togetherness as contrasted to separation. This fear of separation and wish to be reunited with mother is dramatically illustrated in the case of a private patient at The Mount Sinai Hospital admitted for uterine bleeding. Her mother had moved in with her and slept in the same room with the patient. One week-end I informed her that she would have to continue her treatment by moving out of the hospital and coming to my office. She promptly started bleeding that same night. She was depressed and vomited. This was how she expressed her need for physical contact: She said she was very glad that she had remained in the hospital because neither I nor any other analyst could have come “to hold my hand,” if such a bleeding had occurred while she was alone in the hotel where she lived.

Many of these women are infantile and react to a separation from mother

with uterine bleeding in much the same way that a baby starts crying when left by mother. We may assume that at a certain stage of his development the infant experienced being left by mother *as if* the mother had died. I want to emphasize that this is by no means an anecdotal comment but constitutes an important aspect of the psychic difficulty we assume to be present in such patients.

My search for some factors responsible for such reactions as uterine bleeding following separation was facilitated by the opportunity to have two patients in analysis who had uterine bleeding as one of their symptoms.* One of them had been in a nursing home for the first half year of her life and thus separated from her parents. The other patient's father committed suicide, in her presence, when she was a child. I mentioned earlier the patient who developed functional bleeding after moving to New York with her husband. Her father had left the home when she was a baby.

My observation of these patients indicates that the loss of, or separation from, a parental figure in early life could be responsible for their later reactions. This seems to be confirmed by the work of others. If we assume that separation bleeding is a reaction in adult life comparable to the grief reaction to the loss of a person in childhood, therapeutic measures should be in line with un-doing the separation. This could be done (a) by uniting those who have been separated, or (b) replacing the lost object (perhaps through a pet), or (c) in a physician patient relationship of a supportive nature which, without "holding hands," gives the patient the desired contact with a parent substitute.

SUMMARY

Functional uterine bleeding may be caused or precipitated by emotional stress situations. In this paper particular attention is directed towards one such stress situation: Loss of or separation from a love object. These women are apt to deny the loss or their reaction of grief and depression to the loss.

Because of the frequency with which I could observe this kind of bleeding and the psychological specificity which I postulated, I call this bleeding "separation bleeding." Such "separation bleeding" is the somatic equivalent to the psychological reaction of grief and depression. Thus "separation bleeding" may be thought of as "the weeping of the mourning womb."

The therapeutic approach based on acceptance of this idea is in the direction of uniting the patient with the lost love object or finding an adequate substitute.

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A METHOD OF ANALYZING ELECTROCARDIAC ENTITIES IN SPACE

V. A THREE-DIMENSIONAL STATISTICAL TECHNIQUE: ITS APPLICATION TO THE VENTRICULAR GRADIENT

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We have described a method of determining the spherical coordinates of spatial forces (1-4). If a large series of normal gradients is so determined, a standard will be available against which the gradients of other individuals may be evaluated. We shall deal now with a method by which such comparison can be made and shall accordingly define the following problem: given a group of spatial forces, the gradients of normal subjects, determine the probability that the gradient of an unknown individual belongs to that group, i.e., is normal. As this is a routine procedure when the standard deviation (S.D.) is known, the problem may be presented in another form: determine the standard deviation of the ventricular gradient in a group of normal subjects.

We are concerned, note, with the standard deviation of the gradient, and not with those of its coordinates. As the distinction is fundamental to our problem, it shall be illustrated by an example. In a recent study of 49 normal subjects (4), the mean spherical coordinates of the gradient were found to be 54 microvolt-seconds, 23° , and 38° (magnitude, azimuth, and elevation). The S.D. of magnitude was calculated, and the histogram of Fig. 1a drawn. We could have then determined the S.D.'s of azimuth and elevation, respectively. Instead, these two coordinates were replaced by the single term, axis, and the S.D. of the axis determined on a sphere. In Fig. 2, reproduced from this study, the star is at the mean axis, and the circles centered on it have radii of 1, 2, and 3 S.D.'s, respectively. The distribution of axis in S.D. units is shown in Fig. 1b. We were confronted then with two values, the S.D. of the axis, representing two coordinates, and that of the third coordinate, magnitude. In our problem, however, we are concerned with the gradient itself rather than its coordinates. In brief, we seek the single value that may be properly termed the standard deviation of the gradient.

METHOD

Let us consider a group of 2-dimensional forces. These radiate from a null-point as in Fig. 3a. The mean force has been determined and is drawn as a heavy line. It is a simple matter to determine the S.D. of magnitude and that

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This paper is abstracted in the proceedings of the 31st scientific sessions of the American Heart Association, *Circulation*, Oct., 1958.

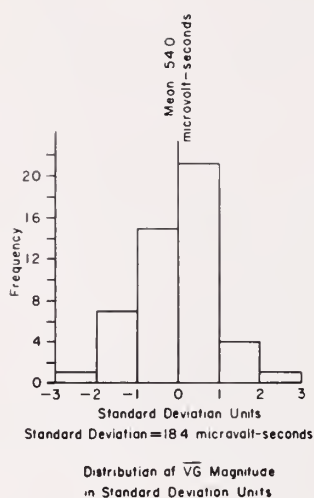


FIG. 1a.

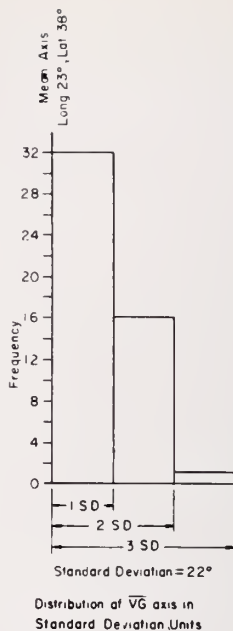


FIG. 1b.

FIG. 1a. Distribution of magnitude of ventricular gradient in standard deviation units.
 FIG. 1b. Distribution of axis of ventricular gradient in standard deviation units.



FIG. 2. Ventricular gradients of 49 normal subjects as determined from the twelve-lead electrocardiogram. The star is at the mean axis. The circles centered on it have radii of 1, 2, and 3 standard deviations. The standard deviation equals 22° . The area of each spot is proportionate to the magnitude of the vector it represents. The posterior hemisphere is shaded.



FIG. 3a.

FIG. 3a. A group of two-dimensional forces. The mean is shown as a heavy line. When forces are represented by vectors, we can determine the standard deviation of their coordinates, i.e., of magnitude and of axis.

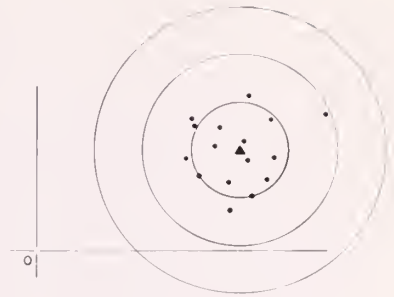


FIG. 3b.

FIG. 3b. The forces are represented by their vector termini. The triangle is at the mean terminus. We may now measure the distance between each point and the triangle, i.e., the deviates, apply the formula for standard deviation, and obtain the S.D. of the forces. It is expressed as a distance, or radius, and circles of 1, 2, and 3 S.D.'s may be centered on the triangle.

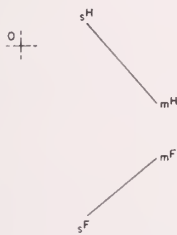
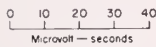


FIG. 4a.

FIG. 4a. Determination of the deviation of a subject's gradient, S, from the mean gradient, M. S is represented by its projections s^F and s^H , and M by m^F and m^H . The projections of the deviate are then $m^F s^F$ and $m^H s^H$. Its spherical coordinates may be determined by construction (not shown).

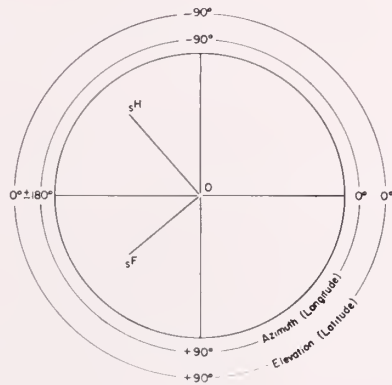


FIG. 4b.

FIG. 4b. Determination of the deviate on a chart. Here the null-point represents the terminus of the mean gradient. The cartesian coordinates of the deviate of S from M are obtained by subtracting those of the latter from those of the former. As the X, Y, Z components of the mean are 39, -33, and -17 microvolt-seconds, respectively, and those of subject S are 19, -50 and 6, the components of the deviate are -20, -17 and 23. These are laid off on the axes of the chart and the projections of the deviate, Os^F and Os^H , derived. Its spherical coordinates relative to the mean gradient terminus are then determined by revolution (not shown).

of axis and obtain two values. Let us represent these forces by their termini, as in Fig. 3b. Here the triangle represents the mean force. We may now measure the distance between each point and the triangle, i.e., the deviates, apply the formula for standard deviation, and obtain a single value. The S.D. is then expressed as a distance, or radius, and circles of 1, 2, and 3 S.D.'s may be centered on the triangle.

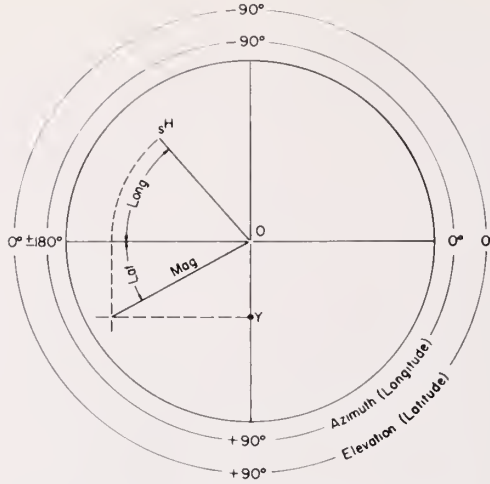


FIG. 5. In determining spherical coordinates it is unnecessary to derive the frontal projection. We may start with the horizontal projection and the vertical component, Y . The horizontal projection is revolved to the line of abscissa, and at the point of intersection a perpendicular is drawn to the altitude of Y .

Let us imagine a group of 3-dimensional forces, for example, the gradients of our 49 normal subjects. Their termini form a cluster of points in space. The terminus of the mean gradient lies at the center of this cluster and may be considered as the null-point from which the gradient termini are measured. Concentric spheres with radii of 1, 2 and 3 S.D.'s are centered on this terminus. The standard deviation of the gradient, the answer to our problem, then equals the radius of the smallest sphere expressed in microvolt-seconds.

To determine this, we need no longer picture the cluster of points. We work with projections. The two projections of the mean gradient in our series are shown in Fig. 4a. m^F is the frontal projection, and m^H , the horizontal projection. The gradient of one subject, S , is represented by its projections, s^F and s^H . The projections of the deviate are then $m^F s^F$ and $m^H s^H$, and we may consider that they have been obtained by vectorial subtraction. Scalar subtraction may be more expedient or elegant as it facilitates the use of a convenient chart (1, 2, 3). Thus, if the X , Y , Z components of the mean gradient are 39, -33 , and -17 , respectively, and those of subject S are 49, -50 , and 6, the components of the deviate are -20 , -17 , and 23. These are laid off on the axes of the chart, and the projections of the deviate derived, as in Fig. 4b. Here the null-point represents the terminus of the mean gradient, and the projections of the deviate are Os^F and Os^H . The magnitude of the deviate is then determined on the chart by revolution (1, 2, 3). This is repeated for each subject, and the standard deviation of the series calculated.

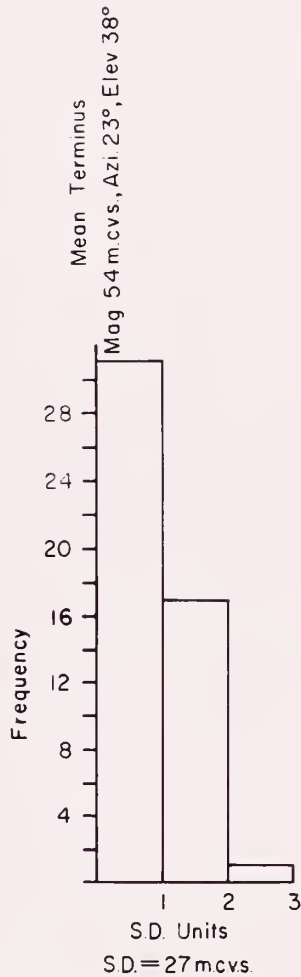
In determining spherical coordinates, it is unnecessary to derive the frontal projection. In the construction (1, 2, 3) an arc is enscribed from the horizontal projection to the ground-line, and at the point of intersection a perpendicular

is drawn to the altitude of the frontal projection. As this equals component Y , the construction may be performed as in Fig. 5.

RESULTS

The mean deviation of the ventricular gradient is 25 microvolt-seconds, and the standard deviation, 27 microvolt-seconds. The range is 6 to 68 microvolt-seconds. The distribution in standard deviation units is shown in Fig. 6. Thirty-one gradients lie within a sphere whose radius is 1 S.D., 48 within one of 2 S.D.'s, and 49 within one of 3 S.D.'s.

As the spherical coordinates of each terminus relative to the mean terminus



Distribution of V.G.
in S.D. Units

FIG. 6. Distribution of 49 gradients in S.D. units relative to a mean gradient terminus whose spherical coordinates are 54 m.c.v.s., 23°, 38° (magnitude, azimuth, elevation). S.D. equals 27 m.c.v.s.

have been determined on the chart of Fig. 4b, it is possible to depict the cluster of termini in space by means of a sphere. If the terminus of the mean gradient is considered to lie at the center of this sphere, each deviate may be represented by a spot on its surface. This was not performed in this series.

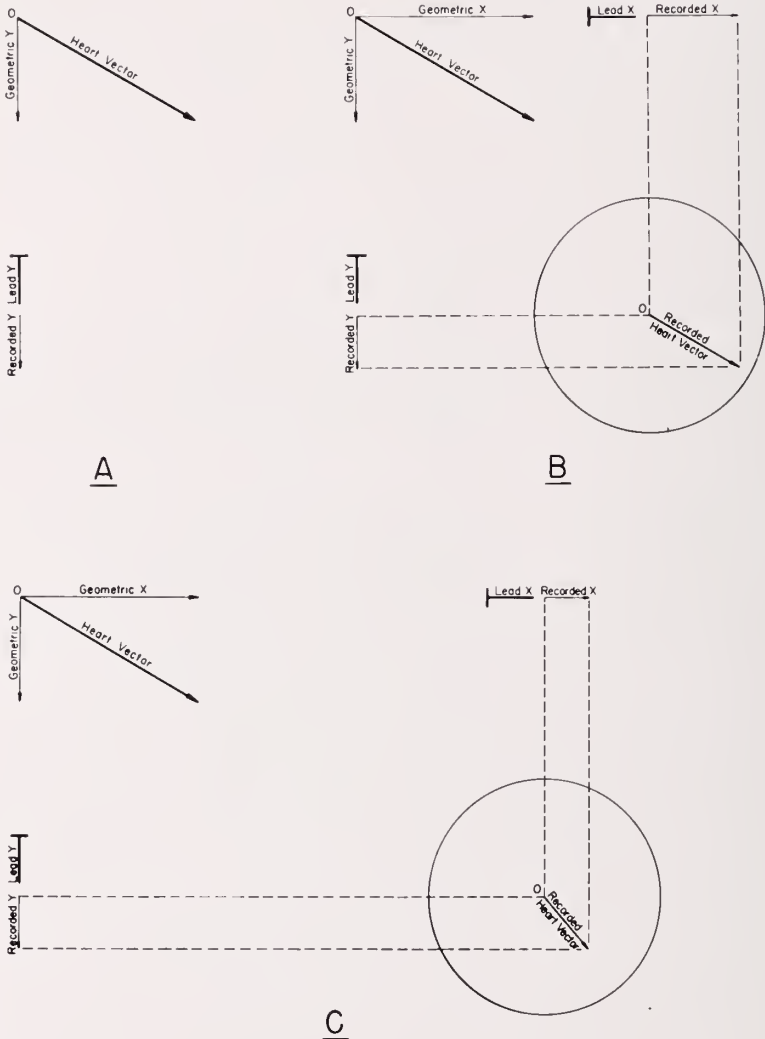


FIG. 7a. Lead vector concept. The myocardium generates a force, the *heart vector*. Its geometric component on the Y axis may be called *geometric Y*. An electrode positioned on this axis records a component termed *recorded Y*. If this is half of geometric Y, lead Y, in recording geometric Y, has multiplied it by a factor of 0.5. This is the *lead vector* of lead Y. In brief: (geometric Y) (lead vector of lead Y) = recorded Y.

FIG. 7b. If lead X is constituted by placing an electrode on the X axis and if its lead vector also equals 0.5, *recorded X* equals half of *geometric X*. The resultant of recorded X and recorded Y, or the *recorded heart vector*, then exhibits the same orientation as the heart vector and half its magnitude. It is a miniature of the heart vector.

FIG. 7c. If the lead vectors are not equal, e.g., if that of lead Y is 0.5 and that of lead X is 0.25, then the recorded heart vector differs from the heart vector in both orientation and magnitude. It is a distortion.

DISCUSSION

Although we have dealt with methods of geometric precision, their complete application, and, indeed, that of all quantitative techniques in electrocardiography, is subject to a limitation which is best demonstrated in the light of the lead vector concept (5).

Assume that the myocardium of an individual generates a force called the *heart vector* (5), as in Fig. 7a. We may refer to its geometric component on the Y axis as *geometric Y*. A surface electrode positioned on the Y axis records a voltage which may be called *recorded Y*. As geometric Y and recorded Y have been drawn to the same scale, and as the latter has half the magnitude of the former, it is apparent that lead Y, in recording geometric Y, has multiplied it by a factor of 0.5. This is the *lead vector* (5) of lead Y. We may then say that:

$$(\text{geometric Y})(\text{lead vector of lead Y}) = \text{recorded Y}$$

If lead X is now constituted by placing an electrode on the X axis and if its lead vector equals that of lead Y, i.e., 0.5, *recorded X* equals half of *geometric X*, as in Fig. 7b. The resultant of recorded X and recorded Y, or the *recorded heart vector*, then displays the same axis as the heart vector, but half its magnitude. It is a miniature. If the lead vectors of X and Y are not equal, however, the recorded heart vector differs from the heart vector in axis as well as in magnitude. We record not a miniature but a distortion, as in Fig. 7c, in which the lead vectors of X and Y are 0.25 and 0.5, respectively. To avoid this, systems of electrode placement that display equal lead vectors have been proposed (6, 7, 8). At best these record miniatures. As the magnitude of a force generated by an individual is multiplied in the record by a factor unique to him, it follows that, unless this factor is known in each case, statistical techniques applied to magnitude have limited significance. The most that can be hoped for with systems employing equal lead vectors is accuracy of axis, and these may be statistically analyzed with validity (4). To achieve maximum efficiency in the method described in this paper, however, it is not only necessary that lead vectors be equal, but also that they have the same magnitude in all subjects. Forces would then be recorded to the same scale in all cases. To equate recorded heart vectors with heart vectors, all lead vectors must equal 1.0.

SUMMARY

1. A three-dimensional statistical technique is described and applied to the ventricular gradients of 49 normal subjects. The gradients are represented by their vector termini, which form a cluster of points in space. The mean gradient terminus lies at the center of this cluster, hence at the center of concentric spheres whose radii are expressed in standard deviation units. It is taken as the null-point from which the individual termini are measured. The deviate of each gradient is therefore the distance in space between its terminus and the mean terminus and is expressed in microvolt-seconds.

2. From a mean gradient whose spherical coordinates are 54 m.c.v.s., 23°, and 38° (magnitude, azimuth, elevation), the mean deviation is 25 m.c.v.s., and the standard deviation, 27 m.c.v.s. The range is 6 to 68 m.c.v.s. Thirty-one

gradients lie within a sphere whose radius is 1 S.D., 48 within one of 2 S.D.'s and 49 within one of 3 S.D.'s.

3. The conditions under which this method would operate at maximum efficiency are discussed in terms of the lead vector concept.

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OPHTHALMODYNAMOMETRY

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Ophthalmodynamometry (ODM) is a method of indirect measurement of the ophthalmic artery pressure. The purpose of this paper is to evaluate ODM as a tool in clinical neurology.

Pulsations of the retinal veins were first described early in the 19th century (1). In later years it was noted that the retinal veins pulsate in the normal subject whereas the retinal arteries do not. It was also noted that the digital pressure to the globe caused conspicuous pulsations of the retinal arteries. However, there was no quantitative method for compression of the globe until 1917 when Balliart (2) first described an instrument for measuring the tension when pressure was applied to the external eye. Thus by compression of the globe with this instrument it could be ascertained at what tension the retinal artery begins to pulsate.

METHOD

The Balliart ODMeter is a method of quantitating the pressure applied to the globe. The flat part of the ODMeter is placed directly to the lateral aspect of the sclera with or without local anaesthesia. If the tension applied to the globe is sufficient to raise the intraocular pressure above the diastolic pressure, the retinal arteries will empty during diastole. At this point ophthalmoscopy reveals that the arteries will begin to pulsate. When the intraocular pressure is raised above the systolic blood pressure the arteries collapse and the pulsations stop.

With the patient lying flat the examiner simultaneously views the fundus directly with an ophthalmoscope and applies pressure to the eye with the ODMeter. Pressure is slowly exerted. When the arteries begin to pulsate a reading is taken. This measurement, the first recording on the ODMeter, corresponds to diastolic arterial pressure. As further tension is exerted the arterial pulsation increases to a maximum and then begins to decrease. When the pulsations stop, a reading again is taken. This second reading corresponds to the systolic pressure. The procedure is then terminated. At the moment the pulsations disappear (systolic pressure) the patient frequently reports a transient blindness. This transient blindness may be used as an end point for the systolic reading. It appears to be as accurate as the routine method for measuring the systolic reading. The intraocular pressure is normally about 20 mm. of Hg., where the diastolic retinal artery pressure is said to be about 75 per cent of the systemic diastolic pressure or approximately 60 mm. of Hg. in patients with normal blood pressure (3). The retinal vein pressure is usually a few mm. of Hg. higher than the intraocular tension and is therefore much higher than the systemic venous pressure.

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The readings of the ODMeter, which are merely absolute values of a springed instrument, are reported as systolic/diastolic. This is similar to routine blood pressure readings. The variations in the normal population are large. In the present series of 40 patients the variations ranged from a reading of 70/10 in both eyes of a young woman, to values of 160/110 in both eyes of a 50 year old woman. The wide range of readings is due to the many variables which control them, such as systemic blood pressure, systemic pulse pressure, intraocular tension, elasticity of the sclera and retina, and finally the elasticity of the retinal arterial wall. Generally, young people have lower readings than older individuals. The examination is simple, takes approximately three to five minutes with a cooperative patient, and is not associated with discomfort or morbidity. The examination is impossible to perform with accuracy in uncooperative patients, or in those who have defects in ocular media such as severe cataracts, as the fundus must be clearly seen. In approximately 20 per cent of patients it is necessary to apply a local anaesthetic to the eyes for an adequate examination. It is not necessary to dilate the pupils prior to the ODMetry.

For the purpose of this test the absolute pressure value of the ODMeter reading is of no significance. The only important element in this examination is the comparison between the right and left eyes of one patient, or in comparing values in one eye before and after surgical manipulation of the ipsilateral carotid artery. As the ophthalmic artery is a direct branch of the internal carotid, an occlusion of the carotid artery tends to lower arterial tension in the ipsilateral eye. The examiner should be aware of any unilateral ocular disease such as glaucoma, iritis, or other diseases of the eye before concluding that his examination showed a significant difference between the two eyes. Difference in the pressure of the two carotids as seen in congenital heart disease is a possible cause of variation between the two eyes.

Recorded studies (4) note that contraindications to the use of ODMetry include the presence of glaucoma, retinal artery thrombosis, chorioiditis, high myopia or any condition that predisposes to retinal detachment. There has been no mention in the available literature of a case of retinal detachment or any other complication due to this examination.

RESULTS

We have studied forty patients who have had ODMetry performed. These cases included patients with papilledema, aneurysms, optic neuritis, brain tumors and vascular disease. None of these patients had striking elevations or reduction of ODMeter pressure in both eyes as compared with the findings in normal subjects. A review of the forty patients shows that the systolic reading can be correlated with the clinical picture, whereas the diastolic pressures were not accurately correlated with clinical findings (Figs. 1 & 2).

Thirty-three of these forty patients had no significant difference between the two eyes. Moreover these patients had no clinical or angiographic evidence of occlusive disease of the carotid artery.

There were seven cases of spontaneous narrowing or occlusion of the carotid artery, as demonstrated by angiography, with neurological symptoms. Of these

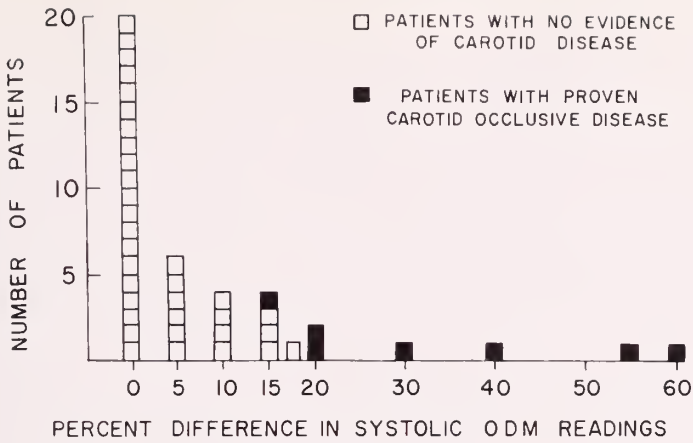


FIG. 1

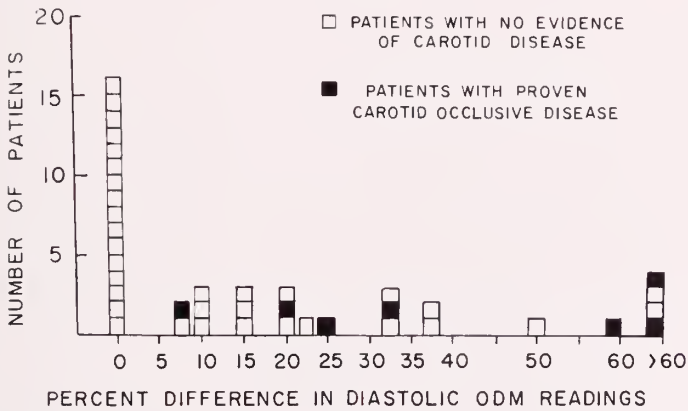


FIG. 2

seven cases, six showed lower readings in the ipsilateral eye with systolic reading difference of 20 per cent or more.

The seven patients with proven spontaneous occlusion or stenosis of the carotid artery had the following readings:

Case	ODM Readings		Side of abnormal carotid	S ¹ —Higher systolic reading; S ² —lower systolic reading	Systolic per cent difference
	OD	OS		$\frac{S^1 - S^2}{S^1}$	
1	130/50	60/0	Left	70/130	54
2	50/30	130/70	Right	80/130	62
3	70/10	120/50	Right	50/120	42
4	120/75	150/100	Right	30/150	20
5	100/50	85/40	Left	15/100	15
6	100/40	125/40	Right	25/125	20
7	140/60	100/40	Left	40/140	29

Case #3 had an *endarterectomy* for a partial occlusion of the right internal carotid artery. His ODM readings before and after operation were the following:

	OD	OS	Systolic per cent difference
Preoperative	70/10	120/50	50/120 = 42%
Postoperative	130/60	130/40	0/130 = 0%

There was no essential change in his clinical picture. Angiography was not done postoperatively.

Case #5 was the only instance in which the systolic per cent difference was less than 20 per cent in a case of proven carotid stenosis.

One patient who was not included in the above series was studied before and after a carotid ligation for a huge infraclinoid aneurysm of the left internal carotid artery. Her pre and postoperative ODM reading were the following:

	OD	OS	Systolic per cent difference
Preoperative	120/80	120/50	0/120 = 0%
Postoperative	140/10	70/40	70/140 = 50%

One patient was studied after a Selvertone clamp had been applied because of an aneurysm of the carotid artery. The ODM readings were within the normal range. Angiography subsequently proved that the internal carotid artery was patent throughout its entirety (directly through the clamp). Evidently the clamp was not tightened sufficiently to cause obliteration of the flow.

DISCUSSION

In the early days of ODMetry the ophthalmologists were mainly interested in the absolute values of the examination and correlating them with the vascular supply of the eyes, and with diseases of the eyes (1). There was no emphasis on, and only rare mention of, the comparative arterial tension between the two eyes. Elaborate schemes were hypothesized relating the brachial artery pressure and the readings of the ODMeter (1). There was also an attempt by Berens (5) and others to correlate increase in the cerebro-spinal fluid pressure with the ODMeter readings. A high retinal artery pressure with a normal brachial artery pressure was at one time said to be caused by high cerebro-spinal fluid tension. None of the above theories has been verified. It is of interest to note that Fremont-Smith (6) states that intraocular pressure does not rise concomitantly with an increase in the cerebro-spinal fluid pressure. In general, there had been little interest in ODMetry in the past fifteen years, until the development of interest in the diseases of the carotid artery (7, 8).

Normal subjects show little difference between the right and left eye. In large groups of normal people the variation between the two eyes is usually below 15 per cent difference, in either the diastolic or systolic readings. When one is concerned with carotid artery disease the systolic reading appears to be more im-

portant than the diastolic. Bakay and Sweet (9) measured the systolic and diastolic pressure in the distal portion of diseased or surgically occluded carotid arteries in acute surgical situations and also in follow-up studies. They found that diastolic pressures in the distal carotid artery often near normal after carotid ligation or occlusion, whereas the systolic pressure usually was well below the systemic systolic blood pressure. This corroborates the impression that the systolic pressure is more significant than the diastolic pressure for ODM studies. Recent investigations (4, 10, 11) tend to support the following conclusions:

1. A difference in ODM recording of over 20 per cent in the systolic reading is abnormal, and indicates some defect in the arterial blood supply of the eye with the lower reading.
2. Approximately 80 per cent of people with carotid occlusive disease will show significantly lower ODM readings in the ipsilateral eye.
3. Surgical occlusions of the common or internal carotid artery will cause a significant drop in ODM readings in the ipsilateral eye.
4. Surgical endarterectomies can reverse abnormal readings. The ODM findings are usually corroborated by angiograms in these cases. However, too few cases of this type have been reported to be certain that the ODM readings will always disclose the success or failure of endarterectomy.
5. Cases have been reported in which tumors invaded the carotid artery in the neck or in the middle fossa, and in whom the ODMetry showed a significant difference, with a low reading on the side of the tumor.
6. False positive cases, using the criteria of systolic reading per cent difference of over 20 per cent as positive, are rare.

Experience at The Mount Sinai Hospital is similar to that recently reported elsewhere. We have found no false positives. Approximately 80 per cent of patients with carotid occlusive disease had abnormal ODM studies.

The incidence of disease of the carotid artery both in the neck and in the thoracic region appears to be higher than suspected ten years ago. In a study of 432 consecutive autopsied cases Fisher (7) found that 6.5 per cent had occlusion of at least one carotid artery and that another 3 per cent of cases had severe narrowing of the carotid artery, giving an incidence of nearly 10 per cent in a random sampling of autopsy cases.

Because of the possibilities of surgical or medical therapy in this disease the importance of distinguishing patients with carotid artery disease from those with intracranial vascular disease or neoplasm, is great. At the present time we have many methods of diagnosing carotid artery occlusive disease. A summary of these methods is as follows:

1. The clinical history. The syndrome of ipsilateral blindness and contralateral hemiplegia speaks for carotid occlusion (8). The classical syndrome is infrequent and only 10-20 per cent of the patients show it. Most clinicians find it impossible to make the diagnosis by history alone. Any patient with unilateral disease of the cerebrum should be considered as possibly having carotid occlusive disease.

2. Palpation of the carotid arteries in the neck. This has been found to be grossly inaccurate and unreliable.
3. Palpation of the carotid arteries in the pharynx. This has been claimed to be an accurate method of diagnosis by Dunning (12). Others have found this to be a difficult examination, and unreliable.
4. Occlusion of the carotid artery by the examiner. Patients with this disease frequently show symptoms of cerebral dysfunction when the normal carotid is compressed and no effect when the diseased carotid is manually occluded. Although some observers claim this maneuver might be dangerous, experience at The Mount Sinai Hospital in the past two years has shown that it is a reliable, helpful and safe adjunct to the neurological examination.
5. Auscultation of the neck. Occasionally a localized bruit may be heard at the site of stenosis of the artery.
6. Manual occlusion of the carotid artery during the EEG examination. The conclusions of this test are not yet clear, although it may be an important refinement in method number four above.
7. Angiography.
8. Exploration of the neck.
9. ODMetry, as described above.

Of the nine methods cited, ODMetry is one of the simplest, safest and most reliable in the diagnosis of carotid artery disease. It is the one technique that is suitable for routine use and at the same time is capable of making a reliable diagnosis in approximately 80 per cent of cases. This test is particularly reliable and significant because the false positive test is rare.

CONCLUSION

ODMetry is an indirect method of measuring retinal artery pressure. It is helpful in diagnosis of carotid artery disease and in evaluation of the various surgical procedures now being done on the carotid artery. It should be part of the routine neurological examination in all patients with unilateral cerebral disease.

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Radiological Notes

BERNARD S. WOLF, M.D.

CASE NO. 61

A 17 year old girl was admitted with the chief complaint of recurring epigastric pain for 7 months. The pain was associated with substernal burning, gaseous eructations and occasionally a sensation of food sticking at the level of the xiphoid. These symptoms started during a febrile episode attributed to a virus infection. With antibiotic therapy at that time, the temperature fell to normal within a few days. The patient, however, began to lose weight and vomited on occasion. In a period of 6 months, she lost 12 pounds. The epigastric pain occurred usually about 1 hour after meals and was relieved by belching. Other findings during this period were an occasional rise in the temperature to above 100°F., a reduction of the hemoglobin to 70% and an increased sedimentation rate. For several nights prior to admission, she had been awakened with night sweats.



Case 61, Fig. 1A. Barium meal examination shows remarkable limitation in distensibility of the antrum with an effaced amorphous mucosal pattern. The duodenal bulb shows no gross deformity but its contours are irregular or scalloped and the fold pattern of the bulb was quite indistinct and hazy. At the junction of the 1st and 2nd portions of the duodenum, there is an abrupt transition to the normal fold pattern of the descending duodenum.

On admission, temperature was elevated for 2 days up to 101°F. The white blood count was 10,000 with 77% polymorphonuclear leukocytes, 50% of which were nonsegmented. Hemoglobin was 11.6 grams. There was no evidence of

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Case 61, Fig. 1B. Film from the small bowel series shows a persistent linear streak of barium (upper arrow) in the spastic antrum. This suggests a linear ulcer. The fold pattern of the contracted duodenal bulb is obviously irregular and thickened. The terminal ileum (lower arrow) shows ragged contours and effaced coarse mucosal pattern. The space between the terminal ileum and adjacent loops is increased.

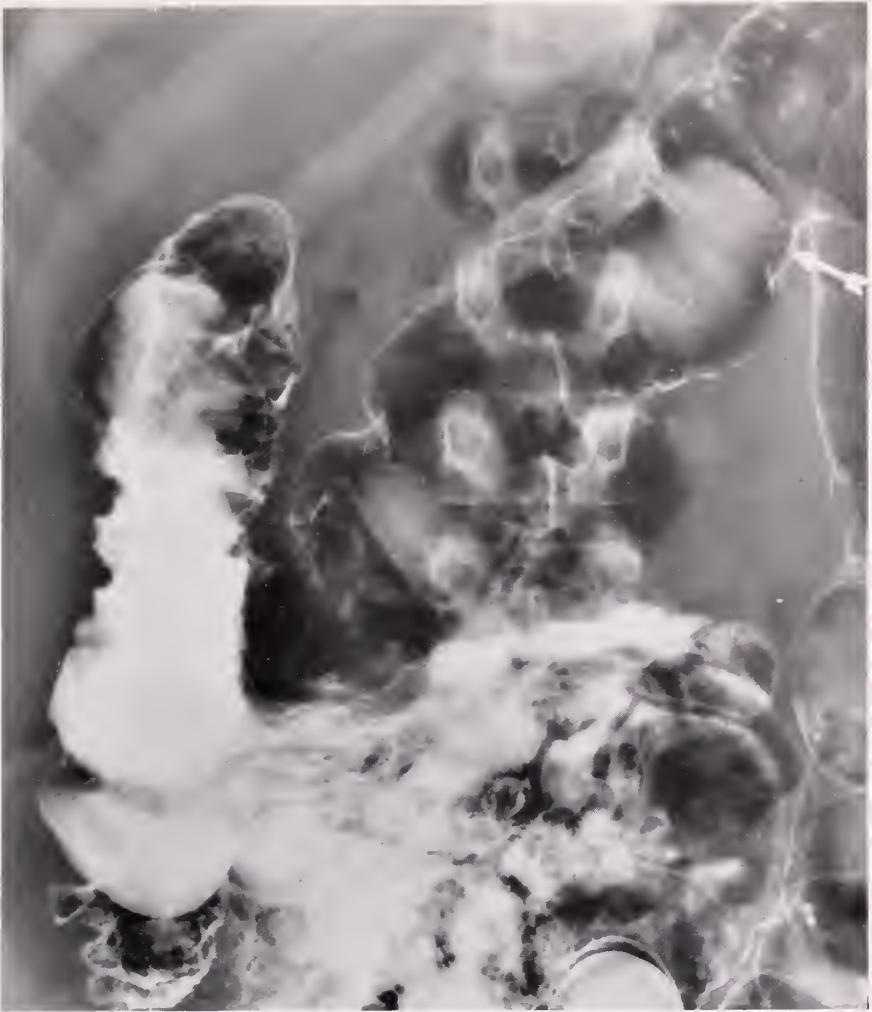
jaundice and liver function tests appeared to be normal. Physical examination was not contributory except for questionable tenderness in the right upper quadrant. Barium meal examination and serial examination of the small bowel were performed. The antral portion of the stomach was distinctly limited in distensibility and the mucosal pattern in the antrum effaced (Fig. 1A). In the antrum, there was on several films a somewhat elongated persistent patch of barium suggestive of superficial ulceration. The duodenal bulb showed no characteristic deformity but the mucosal pattern within it was quite hazy and indistinct and the margins of the filled bulb showed an irregular contour. No discrete ulcer crater was demonstrated within the duodenum. The remainder of the duodenum and the jejunum did not appear remarkable. The terminal ileum (Fig. 1B) over a distance of about 6 or 7 inches showed marked irregularity in its contour with



Case 61, Fig. 2A. Double contrast portion of the barium enema examination (patient prone) confirms the changes in the terminal ileum. In addition, there is limited and irregular distensibility of a portion of the ascending colon and of the proximal transverse colon. In this latter area, there appear to be several pseudopolypoid intraluminal projections (arrow). A short "skip" area of involvement is also present in the distal transverse colon (arrow).

multiple spiculations and effacement of the mucosal pattern. The adjacent loops of ileum were separated from the terminal ileum by an unusually large space. The findings in the terminal ileum were characteristic of granulomatous ileitis. Barium enema examination (Fig. 2A and 2B) confirmed the changes in the ileum. In addition, however, there was limited and irregular distensibility of the ascending colon and of the proximal transverse colon. At this latter site there appeared to be several pseudopolypoid, intraluminal projections. The mid-transverse colon appeared to be normal but in the distal transverse colon, there was a short segment about $1\frac{1}{2}$ inches in length which also showed distinct and constant limited distensibility and irregularity of its contours. The remainder of the colon did not appear to be remarkable.

The roentgen findings in the terminal ileum of this patient were characteristic of terminal granulomatous ileitis. The changes in the colon are segmental in character with skip areas suggesting that the involvement of the colon may be



Case 61, Fig. 2B. Same examination (patient supine). The irregularity of the ascending colon is more evident with barium filling. The organic nature of the lesion in the distal transverse colon is confirmed by its persistence (arrow).

of a similar nature. From a roentgen point of view, differentiation between segmental *ulcerative colitis* and segmental *granulomatous colitis* cannot be made with certainty. It is also assumed, without definite proof, that the changes in the antrum and the duodenal bulb may also be granulomatous in nature. It is of interest in this patient that the symptoms due to the gastro-duodenal lesion were predominant although on close questioning the patient did admit to the passage of a considerable amount of flatus and a possible increase in the number of bowel movements during periods of abdominal distress. From a limited experience with similar lesions of the stomach, it would appear that symptomatic medical therapy may be successful in controlling the patient's gastric symptoms

and has in at least one previous case been associated with improvement of the roentgen findings as well. In the case quoted, the improvement in the gastro-duodenal findings was in contrast to the persistence of the roentgen findings in the terminal ileum.

Final Diagnosis: GRANULOMATOUS TERMINAL ILEITIS; SEGMENTAL GRANULOMATOUS COLITIS. GASTRITIS AND DUODENITIS, GRANULOMATOUS?

CASE NO. 62

A 6 day old male infant was admitted with a history of vomiting of 2 days duration. Delivery had occurred without incident. Vomiting of feedings mixed with bile started 4 or 5 days after birth and continued despite changes in the infant's formula. About 2 days after the vomiting started, it was noted that 2 stools contained bright red blood.

Examination of the infant showed an easily palpable mass in the right upper quadrant which appeared to be about 2 inches in length and an inch in width. It was smooth and soft but did not impress the examiner as being cystic.



Case 62, Fig. 1. A simple film of the abdomen shows moderate distension of numerous loops of small bowel. At the level of the crest of the right ilium, there is a wide loop of bowel with a long fluid level. Into the superior aspect of this loop, there is a hemispherical soft tissue protrusion (arrow). Close observation shows 2 linear crescentic air collections in the right upper quadrant (upper arrow) which appear to outline a portion of a large ovoid homogeneous soft tissue mass occupying the right side of the abdomen.



Case 62, Fig. 2. Barium enema examination confirmed the presence of a large sharply demarcated, smooth filling defect (arrow) presumably in the region of the cecum. Obstruction was incomplete and barium entered somewhat dilated loops of distal ileum.

Roentgen examination of the abdomen (Fig. 1) showed distension of multiple loops of small bowel which, however, was not extreme. The most interesting findings, however, were on the right side of the abdomen. With the child erect, there was a wide loop of bowel with a fluid level in the right lower quadrant. Into the superior portion of this loop of bowel, there protruded a hemispherical soft tissue mass. Moreover, in the right upper quadrant adjacent to the lateral abdominal wall, there were two crescentic linear air densities which appeared to outline the superior and lateral portion of a large, ovoid, homogeneous soft tissue tumor.

Barium enema examination (Fig. 2) confirmed the presence of a large ovoid, smooth, sharply demarcated filling defect occupying the lumen of the bowel on the right side of the abdomen. There was no evidence of intussusception. Obstruction at the site of the filling defect was incomplete. Barium also entered terminal loops of ileum which were moderately dilated.

The nature of the filling defect could not be definitely determined from the roentgen examination but it was assumed to be benign and developmental in origin, possibly a noncommunicating intestinal duplication. At exploratory laparotomy, a large cyst was discovered in the region of the ileocecal valve and an ileocolic resection was performed. The cystic mass was demonstrated to occupy the lumen of the cecum, was quite tense and measured almost 2 inches in its greatest diameter. The mucosa over it was completely flattened and markedly reddened with focal hemorrhages. The ileocecal valve was markedly elongated.

The appendix was normal. The actual origin of the cystic structure appeared to be the terminal ileum. There was no communication with the intestinal lumen. The cyst was lined by mucus producing epithelium.

Post-operatively, the child did extremely well and was discharged in 12 days.

Final Diagnosis: LARGE ILEOCECAL DUPLICATION IN A NEWBORN WITH BLEEDING.

CASE NO. 63

This was the first admission of a 37 year old white female with the chief complaint of a "polyp" in her left ear. A year and a half prior to admission, the patient noted a stuffy feeling in her left ear and muffled hearing on that side. After about 6 months, she consulted a physician who recommended local medication. Six months prior to admission, the patient fainted and, on awakening, noted a ringing noise and a persistent audible pulsation in her left ear. A month prior to admission, a "polyp" appeared in the external meatus. This was biopsied and although at first reported as a "cavernomatous hemangioma", review of the slide indicated the presence of a glomus jugulare tumor. A short time prior to admission, the patient began to complain of a fullness and pain in the left temporozygomatic area.

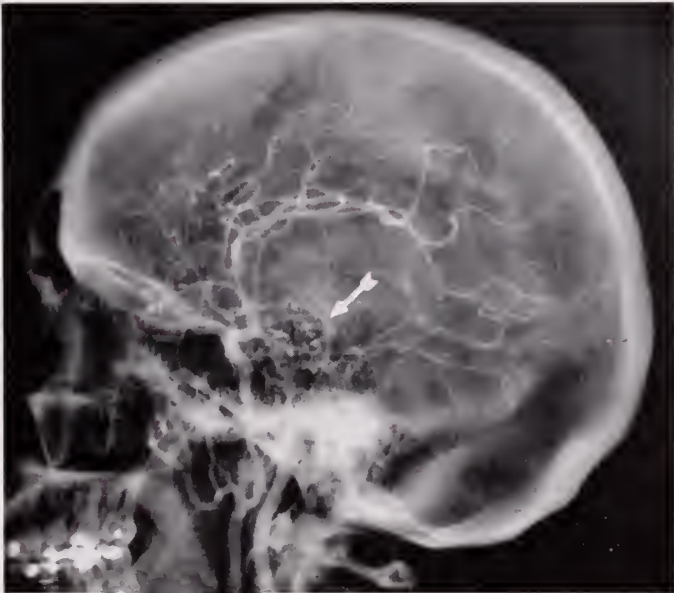
Examination on admission showed purulent secretions in the left external auditory meatus. The edge of the canal was lacerated from a previous biopsy. When the secretions were wiped away, a bluish wrinkled mass was seen antero-superiorly at the junction of the annulus and the canal. A perforation of the drum



Case 63. Fig. 1A. Fronto-occipital (Towne's) view of the skull shows a huge bony defect (arrow) involving the entire base of the left petrous pyramid from jugular foramen through the middle ear to the external auditory meatus. The defect extends forward to the greater wing of the sphenoid and medially to the parasellar region.



Case 63, Fig. 1B. Lateral view of the skull shows mottled destruction of the squama of the temporal bone (arrow). The posterior clinoids are shortened.



Case 63, Fig. 2A. Lateral view of the skull during left percutaneous carotid angiography shows extreme elevation of the middle cerebral group of vessels, elevation of the carotid siphon and flattening of the posterior cerebral artery. A large tumor stain consisting of a network of abnormal vessels occupies the region of the middle fossa (arrow).

was present and, through it, a similar mass could be seen filling the floor of the middle ear. The discharge was pulsating. There was tenderness to pressure over the temporal bone anteriorly and above the ear. A left facial weakness was present as well as a diminished gag reflex and spontaneous past pointing to the left with the right arm. There was distinct weakness of the right hand clasp. Audiometric examination showed normal bone conduction on both sides but a marked conductive deafness on the left.

X-ray examination of the skull showed a huge destructive lesion involving the tip and inferior portion of the petrous pyramid on the left side, the floor of the middle fossa and the squama of the temporal bone (Figs. 1A, 1B). The greater wing of the sphenoid was decalcified and the posterior clinoids were shortened. The pineal was displaced slightly towards the right.

Left percutaneous carotid angiography (Figs. 2A, 2B) confirmed the presence of a huge mass occupying the middle fossa with marked upward and medial displacement of the middle cerebral vessels. Within the tumor, there was an extensive network of irregular vessels. The posterior cerebral artery and the posterior communicating artery were thinned and elongated.



Case 63, Fig. 2B. Antero-posterior view of the skull during carotid angiography shows extreme medial displacement of the middle cerebral artery with a huge tumor stain lateral to it which extends into the petrous pyramid and through the base of the skull. The anterior cerebral artery is poorly filled.

The case presented above unfortunately is fairly typical of the clinical story in a glomus jugulare tumor. The diagnosis is difficult until the mass presents in the external auditory meatus. The case is somewhat unusual because of the extreme amount of bone destruction and the huge intracranial component with relatively minimal neurological findings. It was considered that the tumor was inoperable and the patient was started on radiotherapy.

Final Diagnosis: GLOMUS JUGULARE TUMOR WITH HUGE INTRACRANIAL EXTENSION DEMONSTRATED BY CAROTID ANGIOGRAPHY.

CASE NO. 64

This was the third admission of a 38 year old white female with the chief complaint of bloody diarrhea. The first admission was 5 years previously because of recurrent bloody diarrhea over a period of several months. A week prior to her first admission, she had developed a nodular eruption on both arms and legs which had the appearance of an erythema nodosum. There had also been a loss of 10 pounds in weight. Physical examination at the time of this patient's first admission was essentially negative except for the erythema nodosum. Hemoglobin was 11.3 grams, red blood count 3.9 million, white blood count 10,000 with 94% polymorphonuclear leucocytes. Agglutinations for typhoid and paratyphoid were negative, no ova or parasites were found in the stools and stool



Case 64, Fig. 1. Spot view of the sigmoid during the course of barium enema examination shows limited distensibility of the sigmoid with irregularity of its contours and thickening of the fold pattern. Straightening or flattening of the superior contour extends into the proximal descending colon.



Case 64, Fig. 2. Similar view of the sigmoid 2 years later shows essentially the same findings except that the mucosal folds are thicker and in places appear to be nodular. These nodular defects have the appearance of so-called pseudopolyps. The extent of the disease appears to be unchanged.

culture showed only *B. coli*. On sigmoidoscopy at that time, the mucosa of the rectal ampulla appeared entirely normal but the mucosa of the rectosigmoid was rather markedly congested and friable and bled easily. The impression of the sigmoidoscopist at that time was of "ulcerative (segmental) colitis". On a conservative regime, the patient improved rapidly. The temperature rapidly fell from 101.4°F. to normal and she was discharged after 3 weeks. During the subsequent year, the patient had 2 episodes of mild diarrhea each lasting about a month which did not require hospitalization. Three years prior to the current admission, however, the patient again had to be hospitalized because of recurrent diarrhea, abdominal cramps, recurrence of the erythema nodosum over the legs and arms and arthralgias. Sigmoidoscopy on this admission again showed a normal appearing rectal mucosa but the mucosa of the rectosigmoid was granular and friable without evidence of active ulceration. In the year prior to the current admission, there had been recurrent diarrhea, fever, anorexia and abdominal cramps and these had been particularly marked during the previous 6 months in which she had lost 21 pounds in weight. She complained of 6 to 9 bowel movements a day but there was very little red blood in the stool. On admission, the temperature of the patient was 101°F., hemoglobin was 10.3 grams, white blood count 8,400 with 65% polys. With the administration of sulfathala-

dine, the temperature fell to below 100°F. in about 3 or 4 days and the patient appeared to be improved.

On each of the 3 admissions of this patient, barium enema was performed. While the colon as a whole appeared to be somewhat irritable, definite evidence of intrinsic inflammatory changes appeared to be confined to the rectosigmoid and the sigmoid. On the first admission (Fig. 1), this segment of the bowel did not distend normally, showing considerable thickening of the fold pattern and in places flattening and straightening of the contour of the bowel. Similar changes (Fig. 2), perhaps with increased nodular thickening of the mucosal folds, were evident on re-examination 2 years later. On the current examination (Fig. 3), the same segment was involved but to a considerably greater degree and, in addition, there was a Y-shaped fistulous tract extending into the mesentery of the sigmoid. A short second tract was seen on the opposite contour of the involved area. There had been little, if any, longitudinal spread of the diseased process during the entire interval.

Barium meal examination with serial small bowel examination was performed



Case 64, Fig. 3. Barium enema examination 5 years after the original observation shows an obvious increase in the severity of the inflammatory process in the sigmoid but the length of the involved segment appears to be unchanged. A long Y-shaped sinus tract is seen extending superiorly (arrow) and a shorter tract extends inferiorly.

in this patient on two of her admissions including the most recent admission and no abnormality was noted.

The case presented is an example of colitis of limited extent which has increased in severity locally but has not spread during a period of 6 years. There is considerable interest at the present time in such instances of so-called "segmental" colitis. In some of these patients (Case 61, for example), there is in addition a granulomatous ileitis which immediately creates a suspicion that the colitis is of a similar nature. In other instances, however, no disease of the small bowel exists and the question whether the colitis is of granulomatous or non-specific ulcerative nature cannot be decided on clinical or roentgen grounds. In some cases proved by resection to be granulomatous in nature, large pseudopolypoid defects have been noted with marked thickening of the wall, linear ulceration and fistula or sinus tract formation. Sinus tracts such as those demonstrated in this patient in the sigmoid are quite rare in nonspecific ulcerative colitis and it therefore seems likely that the disease in this patient is granulomatous. It is likely that differentiation between these two types of limited or seg-



Case 65, Fig. 1A. Barium enema examination showed no abnormality in the colon. The terminal ileum appears unusually distensible with almost a haustral pattern on its medial border. The lateral border (arrows) of the terminal ileum on close examination is flattened and shows very fine spiculation.

mental colitis will be of clinical significance because of the fact that preliminary evidence suggests that the prognosis is different, with medical or surgical therapy.

Final Diagnosis: SEGMENTAL COLITIS, GRANULOMATOUS (?).

CASE NO. 65

This was the first admission of a 25 year old white female with the chief complaints of diarrhea, abdominal cramps and fever. These symptoms developed rather abruptly 7 months prior to admission with fever and leucocytosis. At that time, all of the symptoms apparently subsided on symptomatic therapy within a period of a week. Six months later, however, a similar episode occurred and work-up at that time consisting of sigmoidoscopy, barium enema examination, gastro-intestinal and small bowel series and examinations of stools for occult blood, ova and parasites and stool culture were negative. The patient again improved rapidly on symptomatic treatment. One week prior to admission, the symptoms recurred for the third time and were associated with marked anorexia and occasional vomiting. During the 6 months prior to admission, the patient had lost about 12 pounds in weight.

Physical examination on admission was noncontributory. Hemoglobin was



Case 65, Fig. 1B. After evacuation of the enema, the terminal ileum shows irregular contractility. Fine spiculation of its lateral border is more evident. The mucosal pattern on the ileal side of the ileocecal valve (arrow) is coarse and irregular.

11.6 grams, white blood count 5,800 with 31% segmented polys and 44% non-segmented polys. Sedimentation rate was consistently elevated. The stool showed occult blood on several occasions but was negative for ova and parasites. Serologic tests for amebiasis and enteric organisms were negative.

Review of films taken during the course of barium enema examination 7 months prior to admission to the hospital (Figs. 1A and 1B) show, in retrospect, minimal findings—which must be considered to be the earliest changes on roentgen examination in granulomatous ileitis. The terminal ileum shows no limitation in distensibility but on the contrary appears to be somewhat more distensible than would be anticipated. Moreover, along the lateral contour of the terminal ileum there is a distinct flattening of the border with slight spiculation. After evacuation of the enema, the terminal ileum shows irregular contractility and the spiculation of the border is more apparent. Moreover, the mucosal pattern in the region of the ileocecal valve appears thickened and irregular. A second barium enema examination (Fig. 2A and 2B), 6 months later, showed obvious limitation in distensibility of the terminal ileum over a distance of about 3 inches with marked irregularity of the mucosal pattern and fine and coarse serration of the contours of this segment. These findings were confirmed by re-examination



Case 65, Fig. 2A. Barium enema examination 6 months later shows marked spasticity of the terminal ileum with a grossly abnormal mucosal pattern.



Case 65, Fig. 2B. After evacuation, the abnormal mucosal pattern, the spiculation and the irregular contractility of the terminal ileum are more prominent.

after admission and, in view of the clinical picture, must be considered to be due to terminal granulomatous ileitis.

The patient again responded promptly to symptomatic and antibiotic therapy and was discharged for further observation.

Final Diagnosis: TERMINAL GRANULOMATOUS ILEITIS, EARLIEST ROENTGEN FINDINGS.

CASE NO. 66

A 40 year old white male was admitted for the third time. He had been treated for a malignant melanoma of the right temporal area which had been discovered about a year and a half prior to admission. At that time, the lesion was widely excised and a skin graft applied. Nine months later, however, further excision had to be performed because of the appearance of nodules above and below the area of the graft. On the current admission, there was evidence of widespread metastatic disease but of particular interest was the roentgen examination of the chest (Fig. 1), which showed innumerable small nodular densities throughout both lungs. These were confirmed at necropsy.

This case is presented because of the resemblance of the chest film to a large number of benign conditions characterized by "miliary" infiltrations. The diagnosis of metastatic carcinoma is rarely considered in such instances.

Final Diagnosis: MILIARY DISSEMINATION OF MELANOCARCINOMA TO THE LUNGS.



Case 66, Fig. 1. See text.

CASE NO. 67

This was the second admission of a 60 year old white male who 6 years previously had been operated on for "intracystic papillary carcinoma of the thyroid". A second operation was performed 3 months after the first and, subsequent to this, he received radiotherapy to the neck. Three years prior to admission, he noted a swelling of the right side of the neck and was admitted to the hospital for a neck dissection. A large mass adherent to the larynx was resected but complete removal was impossible because of invasion of the trachea. Silver clips were placed around the periphery of the residual tumor and radiotherapy applied post-operatively. In the year and a half before admission, he had lost 40 pounds in weight because of anorexia and 3 months before admission developed a hacking cough and dull pain in the lower thorax bilaterally and on elevating the right arm.

Roentgen examination of the chest (Fig. 1), showed a large number of nodular densities throughout both lungs most of which are about 1 cm. in diameter but several larger lesions up to 2 or 3 cm. were also noted. Below the glenoid fossa



Case 67, Fig. 1. Examination of the chest shows a very large number of nodular densities throughout both lungs. Most of these are about 1 cm. in diameter but several, particularly in the mid-portion of the right lung, are 2 or 3 cm. in diameter. Below the right glenoid fossa (arrow), there is an ovoid lucent zone with sclerotic margins. Metallic clips in the neck were placed around the residual tumor adherent to the trachea.

of the right scapula, along the axillary margin of the bone, there was an ovoid lucent zone with a somewhat sclerotic periphery. Radioiodine uptake studies demonstrated uptake in the neck, in the chest and over the right scapula.

The case is presented to emphasize the fact that metastases to the lungs from a papillary carcinoma of the thyroid are often characteristically very numerous, small and nodular. They usually grow slowly and may persist for several years. The expanding character of the metastasis in the scapula is also frequently seen in metastases from the thyroid which grow slowly, particularly the so-called benign metastasizing thyroid adenoma.

A therapeutic dose of 100 millicuries of iodine 131 was administered to this patient without incident and he was discharged for further follow-up.

Final Diagnosis: PAPILLARY CARCINOMA OF THE THYROID OF LONG STANDING; TYPICAL PULMONARY AND BONY METASTASES.

CASE NO. 68

This was the first admission of a 50 year old white female with the chief complaint of epigastric pain of 3 days duration. On each of these 3 days, she had passed a tarry stool and vomited non-bloody material. For several years, she had also complained of so-called hunger pain relieved by food. Seven years prior to admission, a cholecystectomy had been performed without incident.

Examination on admission was non-contributory except for the sensation of a mass in the epigastrium and moderate anemia.

Barium meal examination (Fig. 1), showed marked delay to the exit of barium from the stomach which was quite distended. A very bizarre appearance was seen in the region of the pylorus and the duodenal bulb. These landmarks could not be identified. Instead, there was evidence of a large globular, sharply demar-



Case 68, Fig. 1. On barium meal examination, there was marked delay in gastric emptying. The normal landmarks—*antrum, pylorus and duodenal bulb*—cannot be identified. Instead, a large ovoid filling defect occupies and markedly distends the region of the duodenal bulb. A thin crescentic barium line outlines a portion of the periphery of the tumor (arrow) and parallel elongated folds (arrow) cap it distally. These folds suggest the so-called "coiled spring" appearance seen in intussusception. The defect extends into the region of the antrum and the folds extending to the greater curvature appear to be pulled toward it.



Case 68, Fig. 2. Re-examination 3 days later shows the normal landmarks to be restored. The sharply demarcated filling defect is now seen in the middle of the body of the stomach (arrow).

cated filling defect which appeared to occupy the anticipated position of the duodenal bulb with an associated defect or deformity of the antrum. The duodenal folds beyond the filling defect appeared to be stretched around it.

The appearance demonstrated in Fig. 1 is characteristic of a tumor arising in the stomach and prolapsing into the duodenal bulb and pulling a portion of the gastric wall with it. The smooth surface and sharp demarcation of the filling defect are characteristic of an intramural neoplasm, usually a leiomyoma. The diagnosis was therefore made of a gastroduodenal intussusception due to a gastric myoma. This was confirmed by a repetition of the barium meal examination 3 days later at which time the patient's symptoms had subsided considerably. On this examination (Fig. 2), barium left the stomach promptly. The pylorus and the duodenal bulb could be easily outlined and within the body of the stomach there was a large ovoid filling defect which corresponded to the defect seen on the previous examination in the duodenum.

At laparotomy, a local resection of an intramural gastric myoma was performed. The post-operative course of the patient was uneventful.

Final Diagnosis: GASTRODUODENAL INTUSSUSCEPTION DUE TO A MYOMA.

Clinico-Pathological Conference

RENAL FAILURE 20 YEARS AFTER NEPHRECTOMY

Edited by

FENTON SCHAFFNER, M.D.

A 70 year old white male retired post office worker was admitted to The Mount Sinai Hospital on 1/20/58 because of inability to urinate for two days.

He had gradually increasing urinary frequency during the previous 18 months until he was voiding every one to two hours during the day and two to three times at night. He also had increasing burning on urination and terminal dribbling. For the week prior to admission, he had difficulty in voiding and had to be catheterized on the day before the day of admission. He also stated that he had some tightening in his chest on exertion and some back pain on and off since 1953.

Past history included diphtheria and scarlet fever as a young child, tonsillectomy in 1894, malaria in 1909 (the last attack occurred in 1916), sprue (in the Army in the Philippines) during 1910, removal of left turbinate bone in 1913, right nephrectomy followed by incision and drainage of postoperative abscess in 1937, during 1939-1940, he had right-sided abdominal pain because of which he was hospitalized but no diagnosis was made, right ureterectomy for stones and infection in 1941, hemorrhoidectomy followed by hemorrhage in 1943, herniorrhaphy in 1945, angina in 1948, glaucoma and osteoarthritis of the back in 1950, coronary thrombosis and hypertension in 1951, bleeding peptic ulcer during 1953-54, and peptic ulcer, bleeding hemorrhoids and hypertension in 1957.

Between hospital admissions the patient was followed in the Out-Patient Clinic during 1956-58. X-rays revealed a hiatal hernia, a deformed duodenal bulb, a normal colon, osteoarthritis of the spine, a normal cystogram, no visualization on an intravenous pyelogram, vascular calcifications on both sides of the pelvis, and an irregular oval calcific density below the left sacroiliac joint. Clinic laboratory tests showed 1+ albumin in the urine with a specific gravity of 1.017, 1-3 WBC/HPE, and 0-3 finely granular casts, a normal hemogram, BUN 28 mg. % (in 1956), calcium 9.5 mg. %, phosphorus 2.6 mg. %, uric acid 6.2 mg. %, and normal liver function.

Physical examination revealed the patient to be a well developed, well nourished man in obvious distress. Temperature was 99.2°F., pulse 88 and regular, respirations 24, and blood pressure 190/110. Intraocular pressure was increased on the right. The teeth were in poor repair. The heart was enlarged to the left but no murmurs were heard. Breath sounds were decreased throughout the

lungs but no adventitial sounds were heard. A right flank scar was noted and tenderness was elicited in the left flank. No organs or masses were felt. Slight edema of the ankles was present. A left varicocele was felt and the prostate was 3+ enlarged, firm and smooth.

Urinalysis showed the specific gravity of 1.010, 1+ albumin, no sugar, 28-38 WBC/HPF, with 5-10 clumps, casts and bacteria. Hemoglobin was 11.2 G., WBC 6,600 with 59% neutrophils and 7% band forms. BUN was 82 mg.%, blood sugar 76 mg.%, uric acid 5.9 mg.%, acid and alkaline phosphatase 3.2 and 6.0 KA units respectively. Serologic test for syphilis was negative. Chest x-ray was negative and minutes after dye was injected, the renal collecting system was faintly and incompletely delineated on the left. Cystogram showed prostatic enlargement.

Two days after admission, the patient was cystoscoped and some hemorrhagic areas were seen on the anterior wall of the bladder. A suprapubic cystostomy and bilateral vasectomy were performed with biopsy of the hemorrhagic area in the bladder. The biopsy was reported as only inflammation. The patient was well for one week except that his temperature reached 100°F. almost every day.

One week after cystoscopy, he had a chill and fever to 104.2°F. and left kidney tenderness. No malarial organisms were found and blood cultures were negative. No urinalysis was reported but urine culture grew pneumococci and enterococci. Sedimentation rate was 112 mm./hr. WBC was 11,600 and hemoglobin 9.8 G. He was given various antibiotics and the fever subsided, but he developed upper abdominal and anterior chest pain with vomiting. Pulse was 78 and blood pressure 120/80. Electrocardiogram showed an old infarction with recent nonspecific changes.

One week later, BUN was 76 mg.% and the cystostomy tube was changed under general anesthesia. The patient continued to vomit and then twitch. Urinary output remained over 1,000 cc. per day but the patient became weaker. Blood pressure dropped to 102/78 and râles were heard all over the chest. Chlorides were 85 meq./L., sodium 109 meq./L., potassium 4.9 meq./L., BUN 86 mg.%, and CO₂ 15.1 meq./L. He lapsed into coma and expired after 25 days in the hospital.

*Dr. Louis Soffer**: We have a man of 70 who had had a right nephrectomy about 20 years ago. Twenty years later, before he developed the symptoms suggestive of prostatism, he began to show evidence of progressive renal failure, characterized by a mild elevation of the blood urea nitrogen and failure of the left kidney to visualize. He subsequently developed symptoms of prostatism and hypertrophy of the prostate with further destruction of whatever parenchyma of the kidney he had remaining on the left side.

When he came into the hospital, he had uremia, lapsed into coma and died. Before he ceased, we find that the serum sodium level and the chloride level were markedly reduced. He had a mild acidosis. Can we put all this together?

The first impression one might have would be that this man, aged 70 had

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prostatism with hypertrophy of the prostate, on which was superimposed an infection of the left kidney, destruction of renal parenchyma, and uremia. The arguments against this thesis are obvious in the sense that evidence of renal failure occurred before he developed evidence of prostatism. The hypertrophy of the prostate and the ascending urinary tract infection were added to the underlying and more significant renal disease.

Our problem is to uncover the nature of the underlying renal disease. I am an old-fashioned clinician and I think in terms of trying to explain the entire clinical picture, if we can, on one basis. Twenty years ago he had a right nephrectomy and I wonder if the nephrectomy had anything to do with the subsequent development of renal failure.

What could have been the reason for the nephrectomy? In the first place, this could not have been a chronic diffuse glomerulonephritis. There would be no conceivable situation in which the physician could possibly mistake a chronic diffuse nephritis for a surgical kidney. I therefore do not think he had chronic nephritis.

He could conceivably have had a tumor on the right side but, if he had, his left renal lesion must be completely unrelated. I would like to think, however, of one clinical entity. Consequently, I do not think he had a tumor.

It is very possible and perhaps even likely that he had recurrent renal calculi on the right side and that, as a result of such recurrent renal calculi he developed destruction of the right renal parenchyma, hydronephrosis, and therefore the right nephrectomy. If so, it is possible that the reason he had trouble with his left kidney was the development of recurrent left renal calculi. The same process now involves the left side as had occurred with the right. This is a very reasonable hypothesis, it seems to me.

However, I am troubled by two features. In the first place, this was a man with many medical experiences and at no time is there any mention in the history to the effect that he ever had kidney stones. Is it conceivable that a man could have had a nephrectomy on the right side due to stones and recurrent renal calculi on the left side without his knowledge of this fact? I am hard-pressed to believe this.

In the second place, as far as I can tell from the intravenous pyelograms on the two occasions in which they were done in 1956 and again in 1958, there is no mention of left renal calculi. Therefore, unless I were to assume that he had uric acid stones which are not roentgenologically visible, I would have expected, since ours is a good hospital and the intern staff competent, that this possibility would have been looked for and, if found, mentioned. However, there is no mention of it. Therefore, I am inclined to think that he did not have uric acid stones and the x-rays do not show any left renal calculi.

Although this seems like a very good possibility, I am hard-driven to accept it in view of the absence of any history and in view of the fact that on x-ray he shows no stones at present nor has he in the past, as far as we can tell. What can it be that would involve the removal of the kidney on the right side and be associated with the destruction of the kidney on the left side over a period

of two decades? It is possible that he had a cyst of the right kidney and that he bled into the cyst. A large mass was felt and he was therefore operated upon. If he had a solitary cyst in the right kidney, that still would not explain the fact that he had left renal failure subsequently. However, it is possible that he may have had multiple cysts of the right kidney which the surgeon had not expected. One of the possibilities which we have to entertain, therefore, is the possibility that this is really a case of polycystic kidneys, that a right nephrectomy was performed because he bled into one of the cysts and, since the surgeon had not expected polycystic kidneys, encountered difficulties which required a nephrectomy. If this thesis is correct, then the left kidney too was the site of multiple cysts and the patient subsequently developed renal failure on this basis. This is a very good possibility.

There is one serious drawback to this thesis and that is the fact that the patient was 70 years old. Polycystic kidneys most frequently occur in a younger age group and they get into difficulties in the fourth, fifth and sixth decades. Half of the patients have hypertension. They may or may not have a palpable mass on one side or the other and they frequently show hematuria.

To me, the patient's advanced age is the major obstacle to the diagnosis of polycystic kidney. If we assume, and I am making this assumption that the right-sided nephrectomy was related to the subsequent development of renal damage on the left side, then I am forced to only two conclusions. One is that this man has pyelonephritis. In a male, this is almost always due to renal calculi and here we have no evidence of recurrent renal calculi or calculi at any time.

Secondly, that he had polycystic kidneys. I would gladly embrace the second possibility. I am bothered by his age of 70 but, nevertheless, of these two possibilities, I think that polycystic kidney is the better one.

We come to another point in the story that is important, a serum sodium of 109 meq./L. and chlorides of 85 meq./L. before he died. In renal failure, significant hyponatremia occurs but the present clue seems inordinately low and suggestive of adrenal failure. But there is nothing in the clinical picture reminiscent of Addison's disease. Despite the marked reduction of the serum sodium level, the serum potassium value is normal. We must assume, therefore, that the hyponatremia is specifically related to the kidney damage.

In the 1940's, Thorn described a syndrome which he referred to as a salt losing nephritis. This generally occurred in young people with pyelonephritis or chronic diffuse glomerulonephritis. Within the past few years, this syndrome has also been described in patients who have ingested large amounts of alkali. This is why I bring this up.

This patient has a history suggestive of an ulcer. There is no evidence that he consumed large amounts of alkali, but it is possible. Such patients may develop tubular damage as a result of tubular calcinosis.

I would suggest the following. This man of 70 probably had polycystic kidneys. He may very well have had recurrent renal calculi with pyelonephritis but I cannot accept this diagnosis on the basis of the available clinical data. I think he probably has, in addition, an ascending urinary tract infection secondary to

the hypertrophy of the prostate but this is only an added insult to the already existing underlying renal injury. I think it possible that he has ingested considerable amounts of alkali with resultant calcinosis of the tubules and a salt losing syndrome, and finally coronary artery disease. He succumbed to the uremia.

I want to call on Doctor Swick to review the x-rays and then we will discuss this problem.

*Dr. Moses Swick**: This case presents rather interesting facets. This patient was admitted in a state of uremia with a history of prostatism and a surgically acquired solitary kidney. Back pressure from long-standing urinary retention incidental to prostatic hypertrophy affecting the kidney appeared to be the most likely diagnosis to entertain. Repeated catheterizations, each time about 600 cc. of urine being obtained, were required. One assumed the likelihood that the uremia was on the basis of prostatic hypertrophy with urinary retention and also arteriolar disease in a hypertensive, affecting the kidney, probably in association with infection and ascending pyelonephritis, although the patient had no elevated temperature on admission.

I do not know what was wrong with the right kidney. But it should be stressed that subsequent to the nephrectomy a surgeon removed a calculus and the stump of the ureter on that side which was associated with an abscess of that stump. Therefore, one must assume that twenty years ago one was dealing with calculus disease of the right kidney. Clinically, it is known that polycystic kidney disease may be complicated by other entities such as calculosis, tuberculosis, tumor and infection. Let us for a moment consider the probability of polycystic kidney disease in this case. Less than ten per cent of polycystic kidney disease is unilateral. More important is the report by Campbell on 42 autopsies in children in whom, at least microscopically, he found 20 cases of unilateral kidney disease although he states that the potentialities of what appears to be a normal kidney on the contralateral side could very well go on to develop polycystic disease in later life. An interesting feature of this case is the intravenous pyelogram done in 1956 in this hospital. This depicted a functioning left kidney with a relatively normal pattern at a time when his blood urea was 28 mg. %. At most, one can state that the kidney outline appeared to be hypertrophied. Certainly, there was no calculus disease and nothing to suggest a polycystic kidney in the left remaining organ. That was one consideration that troubled us when this patient was last admitted to the hospital in urinary retention. One possibility entertained was that, with a past history of a calculus on the one side, we could perhaps be dealing with a left upper urinary tract obstructive uropathy on the basis of a uric acid stone. However, the patient's urinary output in 24 hours was anywhere from 2,000 to 3,000 cc. Consequently, it was reasoned that it was very unlikely that the patient had a completely obstructive uropathy of the remaining kidney. It was also considered somewhat dangerous to perform retrograde pyelography in a seriously ill patient in uremia and one remaining kidney.

Clinically, the patient had been given several trials at spontaneous urination.

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It was felt that loss of kidney reserve would be progressive due to the back pressure effect and infection. The hope, therefore, was that a cystostomy, a relatively simple procedure, would perhaps improve the patient's renal status. Unfortunately, the postoperative course was one of regression and death. One would ordinarily expect that cystostomy would improve the renal function where there is reversibility in cases of prostatic hypertrophy with back pressure. But this did not occur in this instance.

Dr. Soffer: Doctor Wolf, is there anything on the x-rays of 1956 that ought to be of interest?

Dr. Bernard Wolf:* The kidney was large, its lower pole extending to the crest of the ilium. The pyelogram showed no hydronephrosis and no malconfiguration.

Dr. Soffer: Thank you very much. Dr. Levitt, how do you feel about the level of the blood electrolytes in this patient?

Dr. Martin F. Levitt†: Pyelonephritic and sometimes polycystic kidneys from which obstructions are removed are frequently the subject of a profuse salt and water diuresis. Electrolyte levels as in this patient occur in renal failure although occasionally they may be due to a frank salt losing nephritis. They much more frequently result from a fall in filtration rate and inability to excrete water without sodium, that is, the inability to make a dilute urine. In addition, the patients often will be given water without sodium. Severe hyponatremia is a rare but important phenomenon, usually characteristic of acute renal failure, and results from absence of awareness that such patients cannot be given water with impunity. Only a small percentage of patients will develop it as a consequence of the actual loss of salt.

Dr. Hans Popper‡: I want to congratulate Dr. Soffer on such a fine analysis. The clinician should not know the diagnosis when he discusses a case at a clinical-pathological conference and should come to the correct diagnosis as he did.

In another institution 21 years ago, calcified areas in the right lumbar region, which were considered calcified glands, were observed on a flat plate. In May of 1937, it was assumed to be a tumor of one of the calices. For this reason and also because intermittent pain was present with hematuria but apparently no urgency, frequency or burning, the operation was performed with a preoperative diagnosis of a possible carcinoma of the kidney.

First, let us turn to what we could observe here when the patient came to autopsy. The skeletal muscles indicated what must have been a prolonged hypertension, leading to spasm as well as thickening of the arterioles in the musculature.

The heart was enlarged. It weighed 380 grams and was covered by a pericardial fibrinous exudate typically seen in uremia. In the cardiac chambers, we saw hypertrophy and dilatation of the left chamber, molding of the papillary muscle and trabeculi carni. In the myocardium, widespread subendocardial

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fibrosis extended far into the medial portion of the left ventricle. The heart muscle fibers were encased in a connective tissue sheath which must have interfered with contractibility as well as with nutrition. It must have caused some element of myocardial failure. The lumen of the right coronary artery was considerably narrowed and probably also thrombosed, primarily because the entire wall was altered. It may have been preceded by hemorrhage six or seven years before death when the myocardial infarction took place.

There was no pulmonary arteriosclerosis but pneumonic foci of various sizes were seen. These foci were different stages of classical, rather recent bronchopneumonia.

The spleen was small, weighing only 120 grams. There was rather significant arteriosclerosis with severe thickening of vessel walls. In the red pulp, some reticuloendothelial hyperplasia was presented but no evidence of pigment was found which we would have expected with malarial history.

In the bone marrow, the most impressive finding was marked thickening of the walls of middle-sized or small arteries, mainly due to intimal thickening of arteriosclerosis (Fig. 1).

The liver was distinctly yellow and fatty. Small cysts were seen. A fat stain showed rather extensive fatty metamorphosis extending up to the portal tracts which revealed a moderate degree of inflammatory reaction in the presence of a probably systemic inflammatory or toxic process. Arteriosclerosis was seen also in the liver, supporting the general concept that this gentleman had severe arteriosclerotic changes throughout the body. There was centrolobular necrosis with destruction of fatty liver cells and some pooling of blood suggesting the presence of shock. This we expected to be present from the blood pressure readings which have been given. However, looking at the liver, we found symmetrica

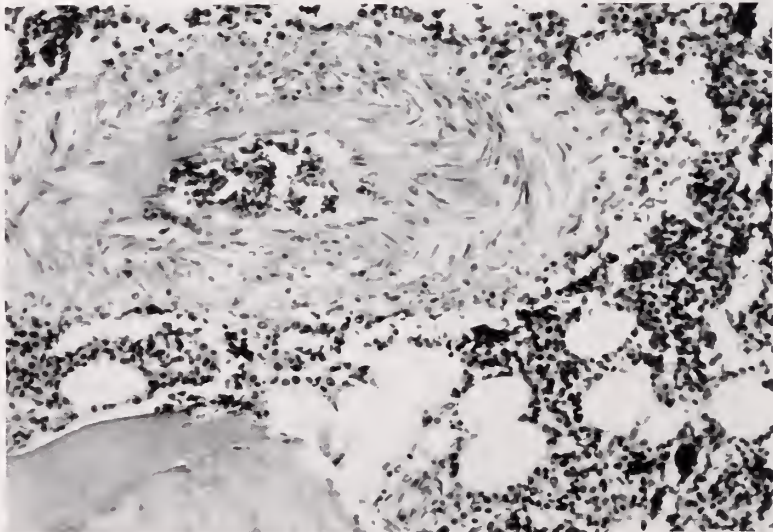


FIG. 1. Normal bone marrow showing thick-walled arterioles. (H & E, $\times 120$).

enlargement of the portal tracts with extensive proliferation or excess of small bile ducts or ductules surrounded by widened connective tissue. These bile duct proliferations with their surrounding fibrosis seemed to connect with the biliary tree since they contained bile (Fig. 2). These lesions are small hamartomas or disorganization of the original structural development in the embryonic or post-embryonic stage. They have been described as Meyenberg complexes. Probably sometime during the development, excess bile ductular structure was formed. While they should have normally regressed, they persisted in large numbers. They have little clinical significance although the claim has been made that portal hypertension may be associated with such little nodules. In this case, they assumed some importance because they became dilated and filled with fluid, as they occasionally do. In this liver, multiple cysts of this type were present. This could not have been called a polycystic liver but multiple cysts were present. They were lined with irregular epithelium, proliferating in nature and projecting in form. In some cysts, hemorrhage occurred. The fibrosis and hemorrhage in the cysts will be of interest to us in reference to other organs to be discussed.

If polycystic changes have been found in the liver, they should be looked for in the pancreas. We saw cystic dilatation in that organ but this did not look like the thin-walled cysts of polycystic disease of the pancreas. An advanced degree of perilobular and intralobular fibrosis was found in the pancreas. We also noted excess proliferation of ductular structures in the pancreas, surrounding normal islands. In the pancreas, this ductular proliferation was far more common than in the liver and resulted also from some disturbance of normal development (Fig. 3). In addition, ducts were greatly dilated and filled with fat, protein and pus. They probably were ductules with abnormal dilatation,

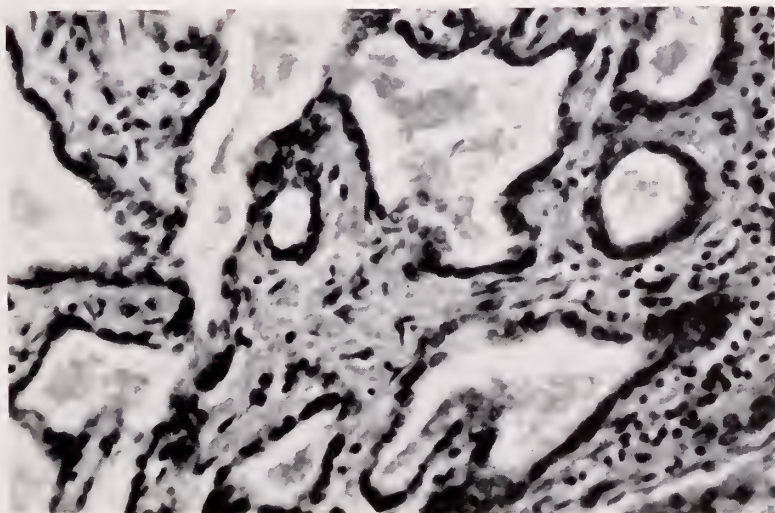


FIG. 2. Bile in proliferated bile duct showing connection with biliary cyst. (H & E, \times 240).

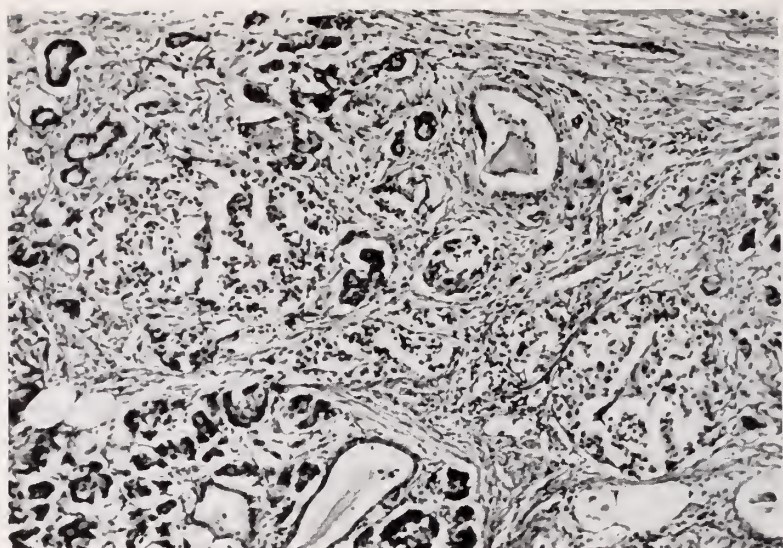


FIG. 3. Excessive ductal proliferation in pancreas with surrounding fibrosis. (H & E \times 63).

stagnation, inspissation and pus accumulation. This process involved even the smallest ductules and probably resulted from a destructive type of pancreatitis with interstitial filtration. In the lengthy history of this gentleman, 42 years before his death when he was a soldier in the Philippines, he had sprue. I wonder if he really did have sprue or whether it was pancreatitis as a result of cystic dilatation of ducts which may have produced the lesion that subsequently subsided.

In Doctor Soffer's discussion, I was impressed with his correlation of the peptic ulcer providing the reason for hyponatremia due to alkali therapy. We demonstrated the duodenal ulcer just beyond the pylorus in the first portion of the duodenum. This could have developed one year or five years before death but acute digestion was still present and it was progressing through the muscle. The small intestine and the colon failed to reveal any changes. Even if the gentleman had sprue 42 years ago, it had enough time to cure itself.

Now we come to the urinary problem. The urinary bladder showed subacute cystitis. It was dilated, somewhat hyperemic and had a cystostomy wound. The prostate was large and nodular; a benign hyperplasia. This was not prostatitis, but some estrogenic effect was present in this elderly gentleman as discerned from the squamous cell metaplasia of the prostatic lining glands. This incidental finding was associated with what we would expect, namely, atrophy of the testes.

The adrenals showed hyperplasia, a stress phenomenon, confirming Doctor Soffer's idea that Addison's disease was not present.

The remaining left kidney was large, weighed almost 400 grams, and contained a large number of cysts (Fig. 4). Grossly, no evidence of infection could



FIG. 4. Gross picture of cut surface of left kidney showing multiple cysts and normal renal pelvis.

be demonstrated. On cut section, the multiple cysts were seen to be filled with clear fluid. In the renal pelvis, no evidence of infection was found, a witness to the excellent urological care. As Doctor Soffer pointed out, the polycystic kidney usually becomes clinically manifest in the 40's, and the two reasons are infection or hypertension. Here, despite the story of obstructive uropathy, we saw no pyelonephritis. Histologically, the cysts were present in large numbers. They were lined by undifferentiated epithelium. This is a generalized structure in a certain period of development in the pancreas, in the liver and in the kidney. The excess of ductular structures, which normally regress, persisted and led to cyst formation in all the organs. It was clinically of major importance in the kidney. Some of the cysts contained inspissated material and some even calcified material which fell out on sectioning. Much of the inspissated material was in the lumen of the cysts and some in the many projections.

Very rarely were any foci of infection found in the kidney (Fig. 5). However, the cysts compressed renal parenchyma between them and excessive fibrosis could be demonstrated (Fig. 6). In these fibrotic areas, vascular changes were evident (Fig. 7). The parenchyma between these cysts on gross inspection appeared firm and the architecture was not completely altered. There was arteriosclerosis in the larger arteries. Most of the glomeruli were in fairly good condition but severe elastica changes in the middle-sized arteries and arteriosclerosis of the small vessels were noted in some areas. These were the only places associated with glomerular changes. Fat stain revealed the fatty imbibition of the small arterioles and the fibrosing glomeruli. Obliteration of tubules with atrophy was seen in the surrounding excess fibrosis. This has been called atrophic glomer-

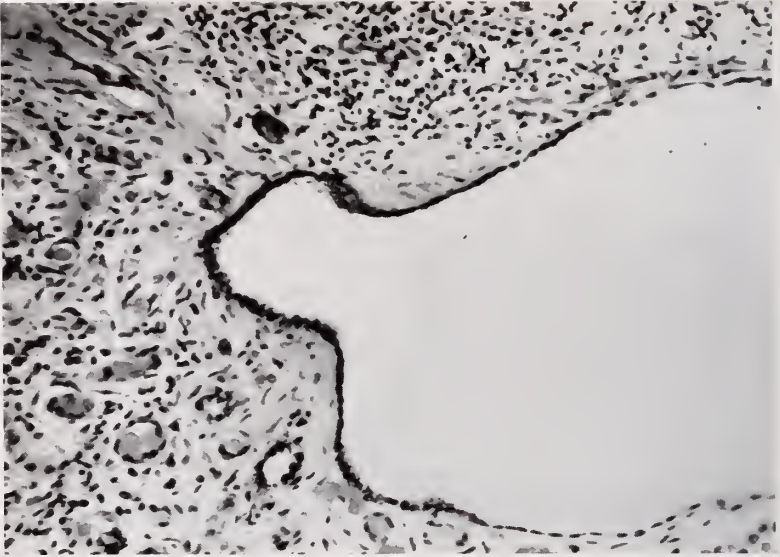


FIG. 5. Minimal infiltration with inflammatory cells around cyst in kidney. (H & E, $\times 120$).

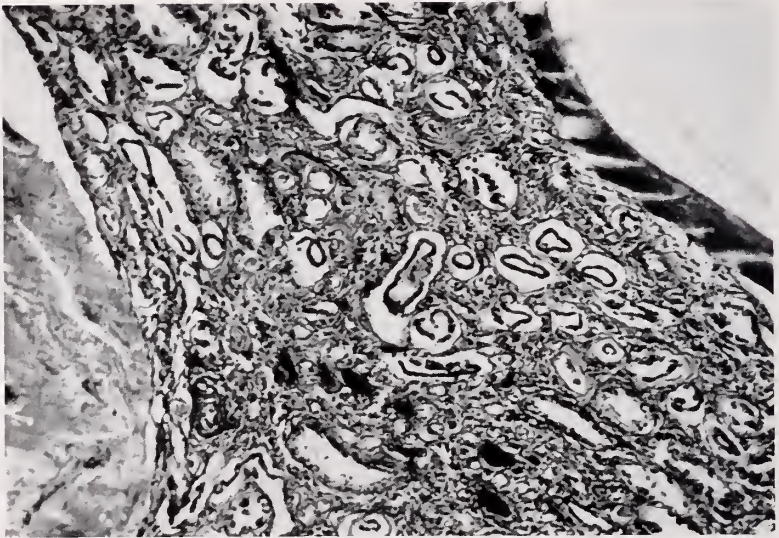


FIG. 6. Compression and fibrosis of renal parenchyma between cysts which are lined by flattened epithelium. (Mallory aniline blue, $\times 120$).

ulonephritis but there was no nephritis. It was the result of the impairment of the glomerular and tubular blood flow, with atrophy and fibrosis. Inflammatory changes were virtually absent except some interstitial fibrosis. We were fortunate enough to get the 21 year old specimen from the other hospital. There was some fibrosis and arteriosclerosis present at that time but there were also quite a

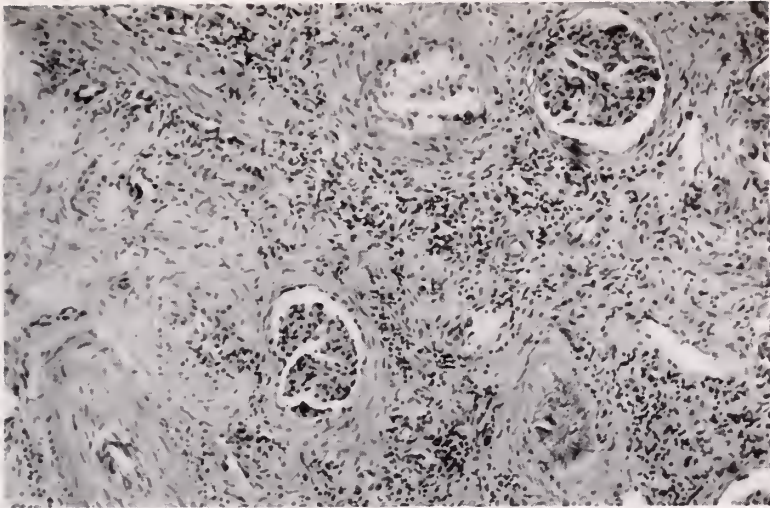


FIG. 7. Thickening of renal arterioles indicating nephrosclerosis. (H & E, $\times 63$).

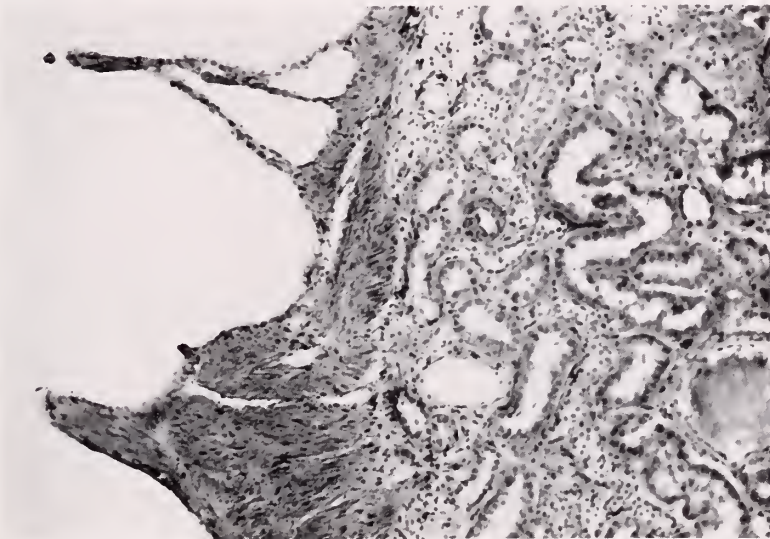


FIG. 8. Section of right kidney removed 20 years earlier, showing cysts similar to those in left kidney. (H & E, $\times 63$).

large number of large cysts (Fig. 8). From the slides and description we had, we could confirm the presence of polycystic disease but not as far advanced.

Why did they remove the kidney? In one of the cysts, calcification and probably hemorrhage developed. I think that blood in a cyst at that time, just as Doctor Soffer said, gave the clinical symptoms. There was a perfectly normal pelvis and perfectly normal ureteral stump with no stone from the description and none in the specimen. A stone formed later but this is rather peculiar.

Trying to correlate clinical and pathologic findings, we had a patient with

polycystic disease. In the liver we found some cysts with calcification and Meyenberg complexes. In the pancreatic ductules we saw proliferation, dilatation, inspissation, hesitatingly called healed chronic pancreatitis, maybe connected with the fatty liver he had at the time of death and with the sprue he had 48 years before death. Twenty-one years before death, a right nephrectomy was performed and a polycystic kidney removed. Four years later there were stones, developing after the operation, removed from the ureteral stump. One of the reasons for the development of hypertension in the polycystic kidneys is that the arteries become stretched by the developing cysts. A Goldblatt phenomenon is set up and hypertension develops. I am well aware that in a patient who is 60 years old, hypertension can develop without a polycystic kidney. At any rate, hypertension and arteriosclerosis having been present, he developed a coronary thrombosis with subsequent myofibrosis seven years before death. He had a bleeding ulcer. He developed a nodular prostatic hyperplasia with urinary retention. The combination of polycystic kidney with arteriosclerosis probably with some contribution from the obstructive uropathy, produced azotemia, reflected in the pericarditis, acidosis, anemia, hyponatremia, and finally death.

Dr. Swick: In summary, I believe that this patient, 20 years ago, had had a stone in the right kidney which had produced hematuria, and that the renal stone had dropped down into the ureter. A nephrectomy was done, a ligature applied to the ureter about the stone, leaving the stone in the stump of the ureter. That, as we know from experience, not infrequently follows with abscess formation above the stump. Furthermore, polycystic kidney disease may show no manifestations for a long period of time. I believe that, although there were some cysts in the right kidney that had been removed, that primarily was not an important disease entity 20 years ago. It is also evident that the mortality rate in truly polycystic kidney disease is high, and that a nephrectomy on one side is followed by death in at least half of the cases. Finally, this patient went on from 1937 to 1958 with polycystic kidney disease which I do not feel was the primary cause of his demise.

Final anatomical diagnosis: Polycystic disease involving kidneys, pancreas and liver; benign prostatic hypertrophy; uremia (clinical) with pericarditis; generalized arteriosclerosis; duodenal ulcer.

ACUTE GASTROINTESTINAL ULCERATION: A COMPLICATION
OF CARDIAC SURGERY—A REVIEW WITH A REPORT
OF FIVE CASES*

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Numerous stressful situations have been found to evoke an ulcerative response in the gastrointestinal tract. Burns, trauma, central nervous system disease and fractures, have been implicated (1-8). Major surgical procedures have been particularly well documented as ulcerogenic stimuli, even though the surgery may be quite unrelated to the gastrointestinal tract (9, 10).

The growth of cardiac surgery within the past ten years has brought to surgery many patients with formerly untreatable congenital and acquired heart disease. The procedures undertaken in these patients is usually associated with great stress. It would appear that the acute stress of surgery, superimposed on a patient who is frequently chronically ill, would present a maximum ulcerogenic stimulus. This report confirms this situation, and emphasizes a serious and potentially lethal extra-cardiac complication of heart surgery.

CASE REPORTS

Case 1

R. F., a thirteen year old boy, was admitted to The Mount Sinai Hospital because a heart murmur was present since birth. Physical examination revealed a harsh systolic murmur over the base of the heart, and associated cardiomegaly. Cardiac catheterization revealed evidence of a large left-to-right shunt, and associated pulmonary hypertension. There was no history of gastrointestinal disease.

At surgery, a huge patent ductus arteriosus was discovered and successfully closed. A congenital aortic stenosis of very mild degree was also found, but this was not treated.

For the first four days, the patient had an uneventful postoperative course. Normal gastrointestinal peristalsis appeared on the third postoperative day, and the patient was placed on a soft diet which he took well.

Five days after surgery, the patient developed massive hematemesis and melena estimated at two thousand cubic centimeters. This was not accompanied by abdominal pain or other prodromal symptoms. He was treated with immediate blood transfusion totalling twenty five hundred cubic centimeters.

Over the next nine hours, the patient's condition remained stable. The only

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* Supported in part by Grant HTS-5206, The National Heart Institute, U.S.P.H.S.

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evidence of gastrointestinal bleeding was a minute amount of guaiac positive material from the naso-gastric tube. Nine hours after the first bleeding episode, the patient had another bout of hematemesis and a frankly bloody stool. Two thousand cubic centimeters of blood were required to maintain a stable blood pressure. Less than one half hour after this second bleeding episode, the patient developed sudden epigastric pain and boardlike rigidity throughout the anterior abdominal wall. In less than one minute the patient developed cyanosis and apnoea, and expired.

A limited post mortem examination showed the peritoneal cavity to be completely filled with blood and bubbles of gas. The area of closure of the patent ductus was intact. Examination of the individual organs was not obtained.

It was felt that the patient had sustained an acute gastrointestinal ulceration, with free perforation into the peritoneal cavity as the terminal event.

Case II

M. I., a fourteen year old boy, was admitted to The Mount Sinai Hospital for surgical correction of an interatrial septal defect.

The defect was of the septum secundum type and was closed uneventfully, utilizing cardiopulmonary bypass with the De Wall bubble-oxygenator. Total perfusion time was twenty two minutes.

In the early postoperative period the patient developed renal shutdown, with marked oliguria and a progressive rise of blood urea nitrogen which reached a maximum of 88 milligrams per cent on the seventh postoperative day. However, ten days after surgery his renal status improved. He had an effective diuresis, and his blood urea nitrogen returned to normal levels.

Twenty one days after surgery, when the patient's cardiovascular and renal status appeared normal, he began to pass tarry stools. His hemoglobin level fell from eleven to nine grams within twenty four hours. The patient's stools remained guaiac-positive for the next seven days, during which time his hemoglobin level was maintained at eleven grams by blood transfusions totalling twenty five hundred cubic centimeters. Following this, the blood disappeared from his stools and he required no further transfusions.

Prior to discharge from the hospital, barium studies of the gastrointestinal tract showed scarring and deformity of the duodenum, suggestive of a healing peptic ulcer. At no time did the patient have any abdominal pain.

Case III

L. R., an eleven year old boy, was admitted to The Mount Sinai Hospital for surgical correction of congenital aortic stenosis. An aortic commissurotomy was performed under direct vision utilizing extracorporeal circulation and potassium-induced cardiac arrest. Total perfusion time was fourteen minutes.

Two days after surgery the patient began to pass tarry stools. Guaiac-positive coffee ground material was aspirated from a naso-gastric tube. After two days, this gastrointestinal bleeding stopped. He required a total of one thousand cubic centimeters of blood to maintain a hemoglobin level of twelve grams.

When seen in follow-up clinic six months after surgery, the patient was doing well and had no evidence of residual gastrointestinal disease.

Case IV

R. M., a seventeen year old girl, was admitted to The Mount Sinai Hospital for surgical correction of an atrial septal defect.

A septum secundum type of defect was closed utilizing extracorporeal circulation. Total perfusion time was eighteen minutes.

On her fourth postoperative day, her stools became guaiac positive and remained so for three days. She had no evidence of blood in the stomach. Her hemoglobin did not fall, and she required no blood replacement.

Case V

P. B., a thirty seven year old male, was admitted to The Mount Sinai Hospital because of repeated bouts of syncope, and episodes of cyanosis of the upper half of his body while in the recumbent position. A diagnosis of right atrial tumor was confirmed on angiocardiography.

At operation, myxoma was removed from the right atrium. The operation utilized the De Wall bubble-oxygenator. Cardiopulmonary bypass lasted fourteen minutes.

Seven days postoperatively, he developed evidence of occult gastrointestinal bleeding which persisted for five days. His hemoglobin fell from eleven to eight and one half grams. He required a total of two thousand cubic centimeters of blood over a five day period to restore his hemoglobin to normal levels, and to maintain it there. When evidence of bleeding first appeared, his diet was supplemented by frequent bland feedings, antacids, and antispasmodics.

The patient had had no previous evidence of gastrointestinal disease. Abdominal pain was absent throughout the bleeding episode. A gastrointestinal x-ray study was normal.

DISCUSSION

Historical Background

There is a long history of awareness of a relationship between stress and acute gastrointestinal ulceration.

Curling collected eleven cases of duodenal ulceration following burns, four of which he treated personally in the wards of St. George's Hospital in London (1). The first report of ulceration following surgery was given by Billroth who cited a case of fatal gastrointestinal hemorrhage following surgery to decompress a large retrosternal goiter (11).

Numerous reviews began to appear following these original reports, each indicating the seriousness of gastrointestinal bleeding following operations other than those on the bowel.

Incidence

Recently published investigations indicate that acute gastrointestinal ulceration is a fairly frequent complication of acute illness. Mears found in one thousand

consecutive autopsies that gastric or duodenal ulceration or erosion appeared in 3.2 per cent after excluding from the series all cases where peptic ulcer disease was the primary cause of death (12). McDonnell and McCloskey reported acute peptic ulcers in 3.2 per cent in two hundred and forty three patients who had died within two months of surgical procedures in general (10).

The incidence of acute ulceration has varied rather widely with the nature of the acute illness. Thus, Harkens reported that 3.8 per cent of those dying of burns had ulcerations of the stomach or duodenum, while 2.2 per cent of those dying of fractures had such ulcerations (2). Davis et al., reported that in seven thousand neurosurgical procedures, merely 0.7 per cent showed melena in the postoperative period (13). Even as a complication of internal medical diseases, such as coronary occlusion and hypertensive heart disease, melena occurs with the same frequency.

In our own experience, four of the last twelve cases successfully undergoing open heart surgery have had some evidence of gastrointestinal bleeding in the early postoperative period.

Etiology

More than thirty theories have been advanced to explain the relationship between acute illness and ulcer diathesis.

Early theories suggested a neurogenic mechanism involving the hypothalamus and the vagus nerves. In 1932 Cushing pointed out that irritation of the hypothalamus was liable to cause gastrointestinal hemorrhage (14).

Circulatory disturbances have been implicated in the pathogenesis. Penner and Bernheim in studying the systemic effects of shock, showed that a large number of patients dying in shock had extensive gastrointestinal ulcerations (15). Numerous investigators have produced diffuse gastrointestinal erosions in experimental animals subjected to shock induced by hemorrhage or muscle trauma. Curare has been implicated in upper gastrointestinal hemorrhage and hemoconcentration has been shown to definitely abet the ulcer diathesis (16, 17). Baronofsky and Wangenstein have also shown that portal hypertension predisposes to erosion or ulcer (18). Hulten advanced an interesting theory based on the physical changes in blood following shock. He claimed that the raised viscosity of the blood due to hemoconcentration and agglutination of red cells combined with anoxic changes in liver cells to develop a state of acute portal hypertension (19). This results in stasis in the entire area of portal drainage, with a tendency to epithelial damage and superficial ulcerations throughout the gastrointestinal tract.

In assessment of the "shock" theory of etiology, it is worth mentioning that in none of our reported cases has prolonged shock been a feature of the operative or postoperative period.

The theory which is currently receiving the greatest interest is a hormonal one. Selye, in his classic experimental work, has shown that all forms of stress, trauma, operation, infection or thermal changes, evoke in the body a massive hormonal response characterized by an outpouring of adrenocorticotrophic

hormone with subsequent increase in the secretion of cortisone (20). There is good evidence that adrenocorticotrophic hormone, or cortisone increases the secretion of both hydrochloric acid and pepsin in gastric juice, with a parallel rise in the urinary pepsinogen (21, 22).

Although we have no determinations in our own patients to show the quantitative changes in adrenal cortical secretions in the postoperative period, it may be postulated that the stress of surgery evokes an increased secretion of such hormones. The increased hydrochloric acid and pepsin secretions resultant from this may play an essential role in ulcerogenesis.

Clinical Features

Several clinical features emerge from this study. Firstly, the acute ulceration may be totally unrelated to previous ulcer disease. In none of our cases was there previous gastrointestinal symptoms of any sort. Secondly, there is a wide age distribution. In our series, the youngest patient was eleven years old and the oldest thirty seven. It is noteworthy that the majority of our patients were very young.

The dominant clinical manifestation is bleeding. This bleeding may be in the form of occult blood in the stool, melena, or frank hematemesis. Perforation was a feature in only one case, and in this patient it represented the terminal event. In all cases, except Case III, the evidence of gastrointestinal bleeding did not appear before the fourth postoperative day. In none did it persist for longer than seven days. It is noteworthy that in none of the cases was abdominal pain or tenderness a feature. In all patients, appetite was good once the initial postoperative ileus had passed. Radiographic studies of the gastrointestinal tract revealed evidence of an ulcerative process in only one patient (Case II). Erosions of the intestinal tract are notoriously hard to define radiologically.

All patients reported here have been seen in follow-up clinic in periods of from one to seven months following operation. In none, has bleeding or other gastrointestinal symptoms reappeared.

Management

Arising without prodromata, acute gastrointestinal ulceration must be recognized as a cause of unexplained shock or anemia in the postoperative period following cardiac surgery. All attempts should be made preoperatively to discover those patients with an ulcer history and, where possible, to give them added protection. In all patients undergoing heart surgery, frequent examinations of the abdomen, and of the stool for occult blood should become a routine postoperative management. Where there is any evidence of gastrointestinal bleeding, this should be treated vigorously with a regime of frequent feedings, antacids and antispasmodics. When anemia develops, it should be corrected promptly with adequate blood replacement.

The authors now are of the opinion that in those cases where massive hemorrhage or perforation supervene, a direct surgical attack should be made, notwithstanding the rather precarious state these patients may be in from their earlier surgery.

SUMMARY

1. Five cases of gastrointestinal bleeding following cardiac surgery are presented.
2. The historical background, incidence and theories of etiology of acute gastrointestinal ulceration following surgery or trauma are discussed.
3. Clinical features of the disease are discussed, emphasizing the absence of prodromata and the prominence of bleeding as the presenting symptom.
4. A plan of management is offered involving early detection and a vigorous medical regime.
5. Early surgery for severe bleeding or perforation is advocated.

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THE PRESENT STATUS OF CONTRACEPTION

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The great interest of this department in contraception is attested to by the fact that a contraceptive clinic was initiated synchronously with the opening of the obstetric division. Two features of the clinic were unique. First, the contraceptive clinic was made an integrated part of the usual six weeks postpartum clinic. Each patient who so desired was given birth control advice and care at the same time that she was receiving her obstetrical check up. This eliminated an extra visit and granted clinic patients the same superior care in this area which ordinarily is only given to private patients. The second unique feature was that The Mount Sinai Hospital six weeks postpartum-contraceptive clinic was established as a research clinic to compare the efficacy of various established contraceptive techniques and to seek new methods. It is not the purpose of this paper to review the work of the clinic; this has been done in another publication (1). The purpose of this discussion is to list the various contraceptive methods now available and in the light of our clinical experience, and the experience reflected in current literature to evaluate them.

Any comparative study of the effectiveness of different contraceptive methods is liable to many sources of error because of differences between samples in respect to their socio-economic level, motivation, religion, home conditions and degree of acceptance of the particular method under analysis. It is clear that no single method of birth control is at present the most successful for all couples, nor is one method at all times the best for the same couple.

Pearl, in 1932 introduced the standard method generally employed for expressing contraceptive effectiveness (2). It computes the "pregnancy rate per one hundred years of coital exposure" according to the formula:

$$\text{Rate} = \frac{\text{Total Number of Pregnancies} \times 1200}{\text{Total months of exposure}}.$$

The factor "1200" represents the number of months in one hundred years. This formula permits the pooling of the experience of many different couples who used the same technique. In arriving at the total months of exposure a correction is made by deducting those months from the total, during which conception was impossible because of existing pregnancy or geographic separation of the marital partners. All pregnancy rates quoted for different methods of contraception are computed by the above formula. A pregnancy rate of 60 to 80 usually is accepted as the rate for couples using no contraception.

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For purposes of discussion, we have divided available methods of contraception into three broad categories, (a) not medically approved, (b) medically approved, (c) experimental.

NOT MEDICALLY APPROVED METHODS OF CONTRACEPTION

Coitus interruptus, or withdrawal before emission, the most primitive method of birth control, is still extensively practiced because of its simplicity and ready availability. It is unsafe, giving no assurance of protection because of uncontrollable, premature emission and the fact that active spermatozoa are frequently present in the pre-ejaculation penile mucus. Furthermore, many couples find this method sexually unsatisfactory because of the woman's inability to achieve orgasm after exit of the penis. In some unions coitus interruptus has an injurious effect upon the psycho-sexual lives of the marital partners. The pregnancy rate for withdrawal reported from New York by Stix and Notestein was 12 (3), and by Stix from Cincinnati it was 38 (4).

Post-coital douche, even minutes after intercourse, gives poor protection against impregnation because of the rapid travel of spermatozoa. This preventive is used extensively in Europe and to a more limited degree in this country. The rate of travel of spermatozoa on a glass slide is approximately $\frac{1}{4}$ inch in two minutes. Disregarding the possibility of even more rapid travel in the vagina due to its more favorable environment, it is readily seen that spermatozoa may travel well beyond the reach of a post-coital douche, having attained the sanctuary of the cervical canal before the flood commences. The pregnancy rate imputed to the douche is 21 (5).

Intrauterine rings and stems. Intrauterine devices are mentioned only to be thoroughly condemned because of their ineffectiveness, their potential source for infection and irritation, as well as their carcinogenetic potentialities. The rings are flexible, usually made from silver or gold wire or twisted worm-gut shaped into a coil about $1\frac{1}{2}$ inches in diameter. They are inserted into the uterus while compressed and expand in the cavity of the uterine body. Intrauterine contraceptive rings are sometimes passed spontaneously as foreign bodies, many have to be removed because of bleeding, and gestations have occurred and progressed to term with the ring still in place.

Intrauterine stems are Y shaped, made of gold plated wire or hard rubber. The base of the Y disc is flush with the external os and the two arms which are held together by a dressing forceps during the process of introduction, when released spread apart within the uterine cavity above the internal os and anchor the device. It is believed that both intrauterine rings and cervical stem pessaries function by causing very early abortion soon after the egg implants. A pregnancy rate is not available for these methods since they have been rarely prescribed in recent years.

MEDICALLY APPROVED METHODS OF CONTRACEPTION

The condom or sheath is one of the most popular methods of contraception. Its disadvantages include; (a) dulling of sensation, (b) the penis remaining in the

vagina after ejaculation makes possible leakage of semen around the condom as erection subsides, (c) starting intercourse without the condom with expectation of withdrawal before ejaculation, then putting on the condom and reinserting it is unsafe because of possible leakage of semen during the first stage, and (d) husband's inhibition to use a condom because of his psychic connection of it with pre-marital experiences.

The advantages of the condom are its general availability and simplicity of use. Skillfully used, it furnishes security against impregnation and until experimental studies perfect "the ideal method" contraceptors will undoubtedly continue to use the condom. For many couples the immediate evidence of protection that the condom gives makes the method particularly desirable. Its use is often advised for intercourse with the uninitiated virginal woman and the multipara with a relaxed vagina. The vulva or condom itself should be well lubricated with a contraceptive jelly or cream before insertion. Withdrawal at the conclusion of intercourse, before complete shrinkage of the erection, while holding the base of the condom will increase its effectiveness. Condoms are routinely tested by The Federal Food and Drug Administration. Samples of condoms are bought on the open market and tested for imperfections by means of measured amounts of water. Since American condoms are plain ended, it is advisable at the time of adjusting the condom to allow a small pocket to form between the glans and the end of the sheath for collection of the seminal ejaculation. Recent publications by Tietze and Gamble give a pregnancy rate for condoms from 6 to 16 (6).

Diaphragm. Given a highly motivated, intelligent woman with a good sub-pubic angle, and vaginal tissues not excessively relaxed by childbirth (to assure a snug fit of the diaphragm) who has received not only the proper size diaphragm but careful instruction in its use, and who always inserts it prior to vaginal penetration and before sex-play, the diaphragm with jelly or cream probably bestows optimum contraceptive protection. However, one must understand that all these conditions for perfect use are seldom met and even when met they may not be consistently present. For example, a particularly tiring day may make the ritual of diaphragm insertion too tedious. At these times one of the simpler methods such as jellies or creams or vaginal tablets will certainly afford more protection than a diaphragm resting in its container in the vanity drawer. It is for this reason that we often prescribe one of the simpler methods instead of the diaphragm.

At The Mount Sinai Hospital contraceptive clinic, we instruct the patient to insert the diaphragm with the dome facing up toward the cervix, the concavity toward the outside. As the diaphragm is compressed with the fingers or stretched on an introducer, about an inch of contraceptive jelly or cream is placed in the depression that forms in the diaphragm. The spermatoxic material is then spread over the surface and around the edges. After insertion of the diaphragm the patient tucks the rim under the pubic bone and if possible checks its position by palpating the cervix through the rubber dome to assure herself that the external os is covered. The diaphragm should be left in place for at least eight hours following intercourse. The question of douching after eight hours is de-

TABLE 1

	Jan. 1953 to Jan. 1957	Jan. 1953 to Jan. 1957	Jan. 1953 to Jan. 1957	Jan. 1956 to Jan. 1957
Methods used	Diaphragm with jelly or cream	Diaphragm with gel (Preceptin)	Gel alone (Preceptin)	Cream alone (Delfen)
Total women	271	269	458	137
Total months of use	2843	2971	3728	633
Planned pregnancies	17	21	37	1
Pregnancies*; incor- rect use, irregular use, etc.....	13 (4.8%)	14 (5.2%)	15 (3.3%)	3 (2.1%)
Pregnancies; (con- stant use).....	10 (3.7%)	8 (3.0%)	10 (2.2%)	1 (0.7%)
Pregnancy rate; Pregnancies \times 1200 Months of exposure	9.7	8.9	8.0	7.6
Pregnancy rate; con- stant use.....	4.3	3.3	3.3	2.0

batable. Although it is unnecessary for contraceptive safety, experience shows that many women feel cleaner douching at this time. A strong antiseptic is unnecessary, two tablespoons of white vinegar to a quart of warm water forms an excellent douche mixture. Most commercial douche powders are wholly acceptable, they are carefully buffered and have a pleasant deodorant effect. The pregnancy rate at The Mount Sinai Hospital contraceptive clinic was nine for the diaphragm with jelly or cream, and rates as low as five have been reported for private patient groups (5).

Cream or Jelly. Investigations at The Mount Sinai Hospital contraceptive clinic confirm the effectiveness of precoital vaginal cream or jelly. A pregnancy rate of 8 occurred for Preceptin® and Delfen®. Instructions are simple, the insertion of an applicator filled with cream or jelly prior to intercourse. The applicator being a plastic injector which is screwed on to the tube, filled, unscrewed and its five cc. contents injected into the upper vagina.

Given routinely at the time of the six weeks postpartum obstetric checkup in the clinic, the simpler methods of conception control have been most valuable, for not only were they more readily and widely accepted, but they could also be more easily explained and used by (a) women with language difficulties, (b) women whose limited intelligence could not grasp instructions readily, (c) patients reporting unplanned pregnancies with the more complicated methods refusing to accept their prescription again, (d) women who refused complicated methods, and (e) women with poor motivation toward conception control. Table I presents data concerning methods prescribed for 1135 women attending the six weeks postpartum contraceptive clinic and also gives the pregnancy rates for each. The months of use by women claiming constant use for a method ranged from 2 to 22 months. Finklestein, Guttmacher and Goldberg, in their study,

calculated the pregnancy rate by eliminating those pregnancies "apparently due to lapses in use or unwillingness to follow directions" (7). We have made a similar correction to establish the pregnancy rate for each method in the table. Since the cream alone method has been available for such a short period it would be incorrect to draw exact comparisons in regard to it.

Suppositories. One of simplest methods of contraception is the intravaginal suppository. It is easy to use and offers no disposal problem at the conclusion of intercourse. Contraceptive suppositories usually made with a cocoa-butter or from a glycerol-gelatin base, melts at body temperature in seven to twelve minutes. The fact that the suppositories melt at temperatures above 98 degrees and therefore must be stored in the ice box in some climates and the additional fact that they may dissolve imperfectly retard their usefulness. Pregnancy rates for suppositories range from 22 to 27 as reported by Tietze and Gamble (8), and Eastman and Seibles (9).

Cervical cap. A cervical cap is difficult to fit properly and furthermore, the patient must be capable of removing and reapplying it herself. This is almost impossible in the nullipara; its application and removal is easiest for the multipara with some vaginal relaxation and cervical decensus. The cervical cap must fit so securely that impingement of the penis will not displace it. The dome shaped cap is made either of plastic or rubber and filled with a contraceptive jelly before its application. It may remain in place for days. Its effectiveness is high, Tietze et al., reported a pregnancy rate of eight (10).

While limitations of the method must be realized, the woman with a healthy cervix which has the proper anatomical relationship to a vagina suitable for the method, and who has sufficient intelligence and motivation to use a cervical cap correctly possesses a very reliable method of contraception. Unfortunately, too few women have all the qualifications.

Rhythm. Rhythm is based on the premise that the time of ovulation is both constant and predictable. However, because of the irregularity of ovulation and the unreliability of tests to pin point its exact time of occurrence this method has many failures. Furthermore, necessity to suppress the coital impulse during the fertile phase of the menstrual cycle limiting intercourse to a segment of the cycle is an additional argument against its prescription. Ovulation probably takes place 14 (plus or minus 2) days before the first day of the next menstrual flow. The egg is only fertilizable for 12 hours and within the human female spermatozoa retain their ability to initiate conception for about 48 hours. Therefore if a woman always had the same length cycle, for example 28 days, and she always ovulated with two days before and two days after the 14th day of her cycle, rhythm would work perfectly if continence were practiced from days 10 to 17. However, because of vagaries of woman-kind and her reproductive physiology, changes in length of cycles and days of ovulation occasionally occur in the most regular female. When the rhythm method was taught to a group of women highly selected because of their menstrual regularity, despite its theoretical safety, it carried a pregnancy rate of 14 (11). Methods of diagnosing the precise time of ovulation by intravaginal test-tape observations and the recording of the basal body temperature have not proved of practical value. If there

were an infallible, simple, effortless method to pinpoint the hour of ovulation and one could make sure that the patient in question never ovulated more than once a month, the rhythm technique would immediately become the world's ideal contraceptive.

EXPERIMENTAL METHODS OF CONTRACEPTION

Non-foaming vaginal tablets. Studies have been carried out with non-foaming Delfen Vaginal Tablet® in the contraceptive clinic at The Mount Sinai Hospital. After extensive laboratory tests, clinical tests were carried out with the Delfen Tablet.® Post-coital tests were done on 25 patients who had placed the tablet insert into the vagina prior to intercourse. Vaginal and cervical secretions were examined microscopically two to ten hours later. No live sperm were found in the vaginal specimens and no sperm could be found in secretions obtained from the cervical canal. Determinations also were made on the insert's intravaginal spermicidal activity. An insert was placed in the vagina of patients thought to be ovulating and samples of the secretions from the cervical os and the posterior fornix were later aspirated and immediately mixed with fresh semen of good motility. Live sperm could not be demonstrated in any semen specimen to which had been added vaginal and cervical secretions aspirated 15, 30 and 60 minutes after insertion of the tablet. Patients using the Delfen Tablet® for contraception are instructed to place the insert into the vagina a few minutes prior to intercourse. A pregnancy rate of 9.8 for Delfen Tablets® represents a preliminary figure from a pilot study. The work is being continued at The Mount Sinai Hospital and more recent figures may show a slight increase in the pregnancy rate. Work has been extended to several university and family planning clinics throughout the country.

Foaming vaginal tablets. Foaming vaginal tablets contain chemicals lethal to spermatozoa. The tablets effervesce when moistened and release carbon dioxide which forms a foam to disperse the spermicide. Such tablets are being tested in several clinics. In a study with one brand, Finklestein reported a pregnancy rate of 39 (12). Other reports of foam tablets are not yet available.

Oral Medication. Several steroid compounds with progestational activity have been tested during the past two years for their ability to inhibit ovulation. Among many experimental oral compounds the following three have been widely used, (a) 17-ethiny-lestranolone, Enovid® (Searle), (b) 17-ethinyl 19-nortestosterone, Norlutin® (Parke-Davis), and (c) 17-ethyl-nortestosterone, Nilevar® (Searle). These highly potent steroids are taken by mouth once daily for 20 days starting on the fifth day of the cycle. Seventy-two hours after they are discontinued withdrawal bleeding occurs. Paniaqua reporting on 2337 cycles in 418 women from Puerto Rico, stated that in the cycles in which the regime of treatment was followed precisely there was not a single pregnancy (13). However there were 20 unplanned pregnancies. Ten patients had discontinued the drug because of side reactions and ten patients had used it irregularly. The uncorrected pregnancy rate was 10.3. Eighteen per cent of the subjects withdrew from the study because of side effects from the drugs which were mainly gastrointestinal. Tyler reporting from Los Angeles on the same oral steroids, gives

a much less optimistic report (14). In 3000 women with months of use there were 22 pregnancies; a rate of nine. The pregnancies were definite method failures. He believes that these steroids fail to inhibit ovulation in certain instances. Tyler noted side-effects in a substantial proportion: (a) stimulation of the endometrium to produce a pseudo-decidua, (b) a questionable biopsy after medication, resembling malignancy, (c) 17 per cent gastrointestinal difficulties, (d) 30 per cent irregular bleeding, (e) constant weight gain one to two pounds per month, (f) decrease in libido, and (g) edema. He also noted that in some cases in whom the medication was stopped on the 25th day, ovulation occurred with menstruation two weeks later.

It is our opinion that the oral tablet has not yet been proved medically safe or highly effective. One of us previously pointed out that the steroid drugs are aimed at the wrong target organ. To attempt to inhibit the pituitary which has so many functions besides stimulating the ovary is fraught with danger. An oral medication affecting the Fallopian tube, uterus or ovary directly is far better. Currently we are just beginning human experiments with an oral compound which affects tubal eggs in the rats perhaps by inhibiting some tubal enzyme.

Experimental work on the ideal contraceptive is being carried on in many laboratories and clinics throughout the world in addition to our own. It is safe to prophesy that about the time the first earth man reaches the moon he will be able to carry with him the ideal pregnancy preventive.

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MACROGLOBULINEMIA: STUDIES OF SERUM AND SYNOVIAL FLUID FROM A PATIENT WITH MULTIPLE INFECTIONS

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Macroglobulinemia has become recognized as a clinical entity since Waldenström's original description in 1944 (1). Manifestations of this syndrome include those of malaise, mucous membrane bleeding, hepatosplenomegaly, chronic anemia and hyperglobulinemia (2, 3, 4). The very viscous serum of these patients contains excess protein of 19 s or greater on ultracentrifugation. This protein is thought to be produced by the many "lymphocytoid" cells present in the marrow and lymph nodes (1, 5). Both an ill-defined bleeding tendency and the recurrent infection seen in such patients have been ascribed to the presence of this protein (6, 7).

We have recently studied a patient with the characteristic findings of macroglobulinemia. The clinical course was complicated by severe mucous membrane bleeding and by repeated infections. While such diseases as lymphosarcoma (4), chronic myelogenous leukemia (8) and carcinoma of the biliary tract (8) have been described with macroglobulinemia, no associated disease could be identified in this patient.

Electrophoretic studies demonstrated a deficiency of normal gamma globulin and the presence of an excess of macroglobulins. The patient's serum was studied in tests for the rheumatoid agglutination factor to determine the effects of the large globulin in such test systems. In addition to other body fluids previously reported, synovial fluid was subjected to detailed examination.

CASE REPORT

A 71 year old housewife was first admitted to The Mount Sinai Hospital (Unit No. 59837) on January 19, 1956 because of pallor and weakness of ten years' duration.

One year prior to admission, splenomegaly was noted by her private physician. The hemoglobin was discovered to be 9 Gm. per cent, the white count 2,300 cells

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The authors would like to acknowledge the extensive aid given them by several investigators. Dr. E. C. Franklin of The Rockefeller Institute for Medical Research performed the ultracentrifugation studies. Dr. D. Hamerman of The Albert Einstein College of Medicine studied the synovial fluid hexosamines, while Dr. P. Aisen of that institution did the Tiselius electrophoresis. The sheep cell studies were performed by Dr. M. Ziff of the N. Y. U. College of Medicine. We also thank the following members of this hospital: Dr. J. M. Singer for the latex tests, Dr. S. Horowich for starch gel electrophoresis and Dr. S. Lee for valuable advice and criticism.

per cu. ml. and the platelet count 20,000 per cu. ml. Bone marrow examination showed 35 per cent normoblasts, a normal myeloid series, adequate megakaryocytes and no abnormal cells. The sedimentation rate was 98 mm. per hr. (Westergren). At that time there was no overt evidence of blood loss nor were hemorrhagic phenomena noted. Treatment consisted of blood transfusions. Because abnormal findings persisted, the patient was admitted to this hospital for a complete evaluation.

A past history of pain and swelling affecting both knee joints of fifteen years' duration was elicited. No other joints were involved. An episode of bronchopneumonia occurred eight months prior to admission. The remainder of the past history and the family history were non-contributory.

Physical examination revealed the patient to be a pale, elderly, white female appearing chronically ill. A smooth liver edge was palpable 5 cm. beneath the costal margin. The spleen was felt 10 cm. beneath the left costal margin. There was bilateral bony deformity of both knee joints. No other abnormal physical findings were encountered.

The hemoglobin was 7 Gm. per cent, the red blood count 2,400,000 cells per cu. mm., the hematocrit 22 per cent, the white count 2,600 cells per cu. mm., and the platelet count 12,000 per cu. mm.. Urinalysis revealed 2 to 3 plus proteinuria but no Bence-Jones protein was found. The following blood chemistries were within normal limits: urea nitrogen, uric acid, glucose, alkaline phosphatase, cephalin flocculation, calcium and phosphorus. Total protein was 9.0 Gm. per cent, with 2.3 Gm. per cent albumin and 6.7 Gm. per cent globulin. A bromsulphalein test indicated 4 per cent retention of the dye within 45 minutes. The sedimentation rate was 110 mm. per hr. (Westergren). Coagulation studies were within normal limits. The Coomb's test, both direct and indirect, was negative and no cryoglobulins were present in serum. Bone marrow examination from three separate sites showed hypercellularity with an increase of the erythroid series. Infiltrates of mature and immature lymphocytes totaling 41 per cent of the cells counted were present. One to three per cent of the cells seen were plasma cells. Serum electrophoresis on paper demonstrated a homogenous band between beta and gamma globulins characteristic of "M" protein. This protein proved to be precipitable by zinc sulfate. Serum globulin fractionation showed 28 mgm. per cent mucoprotein (normal 40-70 mgm. per cent), 6.9 units of acid precipitable globulin (normal 4-8 units), and 25.0 units of zinc sulfate turbidity (normal 4-8 units). Biopsy of lymph nodes from three separate sites showed extensive replacement by fatty tissue. Gingival mucosal biopsy revealed no evidence of amyloid material. A chest x-ray and upper gastrointestinal series were unremarkable. Skeletal survey revealed marked generalized demineralization of bone with collapse of several thoracic vertebrae. Marked osteoarthritic changes of both knees were present.

The clinical course was complicated only by a low-grade fever of undetermined origin. The patient was treated with blood replacement. No definite diagnosis was established, the provisional diagnoses on discharge being "atypical multiple myeloma" or "an unusual case of lymphoma with dysproteinemia."

The patient was readmitted to The Mount Sinai Hospital on January 9, 1958 because of rectal bleeding. Continued weakness and pallor were the only symptoms during the year interval. One week before admission two episodes of epistaxis occurred requiring full nasal packing for control. Persistent bright red rectal bleeding occurred on the night of admission in the absence of any other bleeding manifestations.

Additional physical findings on this admission included the presence of clotted blood in the nares and bright red blood in the rectum.

The initial hemoglobin was 7.4 Gm. per cent, the hematocrit 23 per cent, and the red cell count 2,670,000 cells per cu. mm.. The white cell count was 5,300 per cu. mm. with a normal differential distribution, and the platelet count was 128,000 per cu. mm.. Marked rouleaux formation was noted on the smear. The erythrocyte sedimentation rate was 120 mm. per hr. (Westergren). Urinalysis revealed an acid pH, a maximum concentration to 1.018, persistent 2 to 3 plus proteinuria, but no formed elements. No Bence-Jones protein was found. Total serum protein was 9.5 Gms. per cent, with albumin 1.9 Gms. per cent and globulin 7.6 Gms. per cent. Routine blood chemistries were again within normal limits. Total cholesterol was 78 mgm. per cent, cholesterol esters 53 mgm. per cent, phospholipid 124 mgm. per cent and total lipids 225 mgm. per cent. Owren prothrombin time was 62 per cent, serum prothrombin conversion activity 46 per cent, and labile factor 41 per cent. The bleeding time was 6½ minutes while a three tube clotting time equalled 9, 16, and 21 minutes. The clot retraction was ++ in two hours, with no fibrinolysis observed after one hour. Quick prothrombin time was 15 seconds (control 31 seconds) and serum prothrombin less than 5 per cent. No white cell or platelet agglutinins were observed in the serum. The marrow was normocellular and revealed an increased number of lymphocytes, some of which were atypical in appearance. Serum globulin fractionation now yielded 62 mgm. per cent mucoproteins, 2.5 units of acid precipitable globulin, and 20 units of zinc sulfate turbidity. The Sia test for euglobulin was negative and cryoglobulins again were not demonstrated. The C-reactive protein was absent and the Mazzini, Kahn and Wasserman reactions were negative. Serum electrophoresis on paper once again demonstrated an abnormal protein moving between gamma and beta globulins. Now a marked depression of the normal gamma component was also found. Moving boundary electrophoresis in the Tiselius apparatus indicated a large homogenous spike of abnormal mobility immediately after the beta lipoprotein abnormality (in the descending limb) with virtual absence of normal gamma globulin material (Fig. 1). Starch gel electrophoresis showed no migration of abnormal protein into the starch gel (Fig. 2), while protein of similar paper electrophoretic migration seemed to remain on the filter paper used to introduce the serum. Ultracentrifugation of the patient's serum demonstrated approximately 50 per cent protein having a sedimentation constant of about 19s, while smaller amounts of 25s and 32s protein were also identified (Fig. 3). Patterns approximating those of serum were given by paper electrophoresis of synovial fluid, cerebrospinal fluid, and urine (Fig. 4). Ultracentrifugation studies of the urine showed the presence of considerable

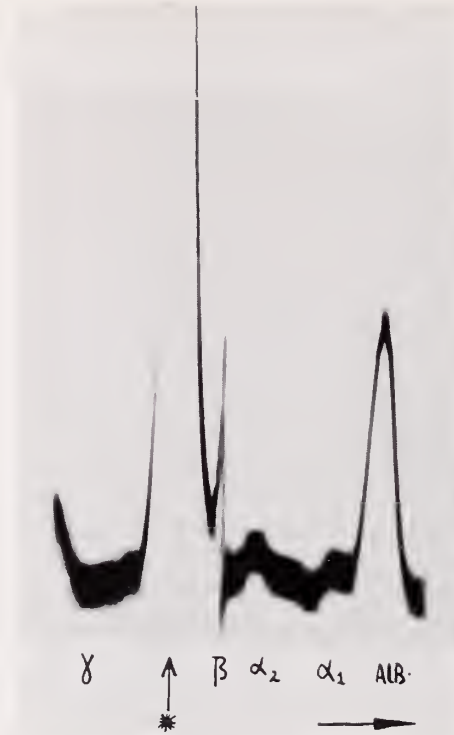


FIG. 1. Moving boundary electrophoresis of serum from a patient with macroglobulinemia. A large, abnormal spike is noted on this descending limb, immediately after the beta globulins. Note the paucity of normal gamma components. (Barbital buffer, pH 8.6)

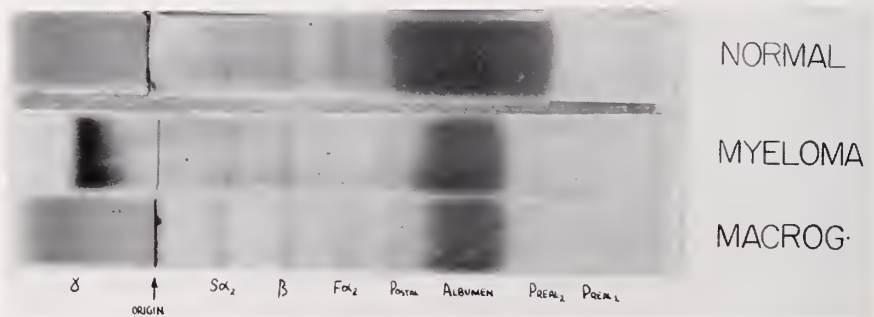


FIG. 2. Starch gel electrophoresis patterns of sera from normal, multiple myeloma, and macroglobulinemia patients. The alpha globulins are split into "S" or slow, and "F" or fast components, while two "prealbumin" and one "postalbumin" fraction is identified. Of salient interest is the demonstration that whereas the sharp, abnormal gamma protein of myeloma is clearly demonstrated, macroglobulins are *not* seen in starch gel.

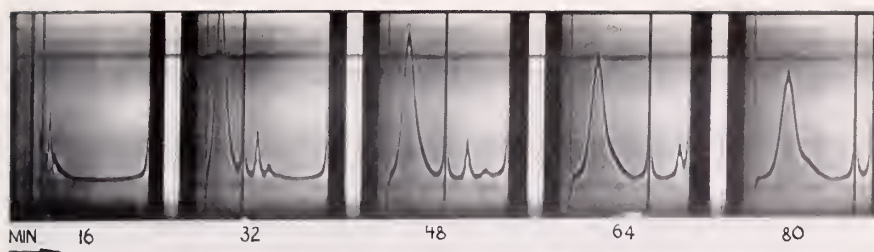


FIG. 3. Ultracentrifugation of 1:4 dilution of patient's serum. The tall component at the left of the patterns is presumably the 19s material, while smaller aggregates of 26s and 33s migrate before it. Time in minutes.

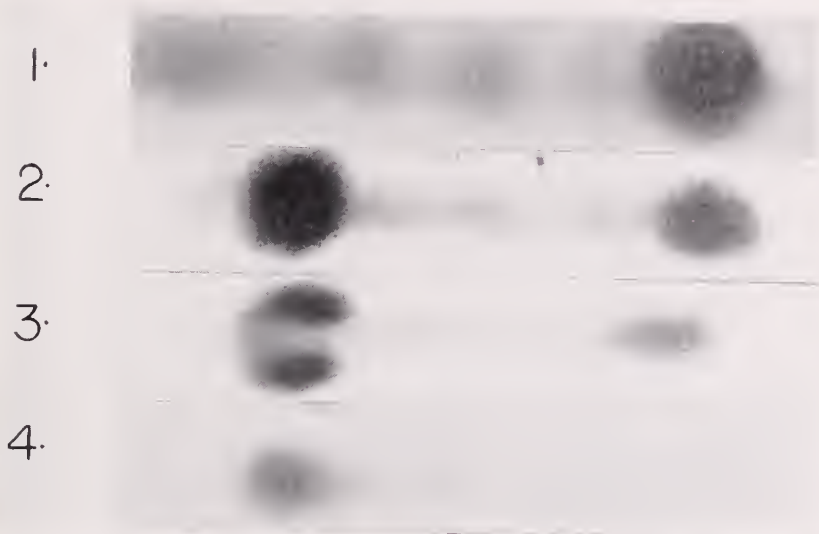


FIG. 4. 1. Normal serum paper electrophoresis. 2. Serum, 3. Synovial Fluid, 4. Urine paper electrophoresis from a patient with macroglobulinemia. The abnormal protein is demonstrable in all patterns. Cobalt salt precipitation of the hyaluronate-protein complex of synovial fluid yielded a pattern similar to #4.

amounts of protein having sedimentation constant of 19s. Four months after admission and following repeated infections, an increase of the normal gamma globulin band was demonstrable on paper electrophoresis. Tests performed in relation to the rheumatoid agglutination reaction are summarized in Table I. Synovial fluid exhibiting high viscosity, good mucin clot and less than 60 cells per cu. ml. was studied for polysaccharide and protein content. The results are summarized in Table II. Anion exchange column chromatographic separation of serum proteins indicated a large quantity of the abnormal protein to be extractable at pH 5 and separate from a small quantity of normal gamma globulin at pH 7.

After admission, the patient was given blood transfusions sufficient to replace gross blood loss. The rectal bleeding gradually subsided. Sigmoidoscopy was

TABLE I
Behavior of macroglobulinemic serum in rheumatoid agglutination reactions

Test Serum	Source of Normal Gamma Globulin	Indicator System	Result
B.B. whole serum	Commercial F11 added in vitro	Latex particles*	Pos. 1:320
B.B. whole serum	B.B. "euglobulin" fraction	Latex particles*	Neg.
B.B. whole serum	Pooled, commercial gamma globulin given I.M.	Latex particles*	Pos. 1:1280
B.B. whole serum	B.B. "euglobulin" fraction after I.M. gamma globulin	Latex particles*	Pos.
B.B. whole serum	Rabbit anti-sheep erythrocytes	Sheep erythrocytes†	Neg.
B.B. euglobulin	Rabbit anti-sheep erythrocytes	Sheep erythrocytes†	Neg.
B.B. euglobulin plus known pos. agglutination serum	Rabbit anti-sheep erythrocytes	Sheep erythrocytes†	No inhibition

* Method of Singer and Plotz (30).

† Method of Ziff *et al.* (19).

TABLE II
*Synovial fluid analyses in a patient with macroglobulinemia**

Determination	Patient (age 71)	Control (age 77)
Total synovial fluid hexosamine.....	2.08 mg./gm.	1.60 mg./gm.
Non-hyaluronate hexosamine.....	1.53 mg./gm.	0.39 mg./gm.
Hyaluronate hexosamine (glacial acetic acid ppt.).....	0.55 mg./gm.†	1.22 mg./gm.
Hyaluronate-protein hexosamine (cobalt salt pp.).....	1.59 mg./gm.‡	1.23 mg./gm.

* Method of Hamerman (33).

† Electrophoresis: traces of serum albumin.

‡ Electrophoresis: abnormal protein with migration of patient's macroglobulin as well as albumin.

negative and a barium enema revealed only the presence of several sigmoid diverticuli. Seven days after admission the patient began to suffer from shaking chills and intermittently high fevers at which time a beta-hemolytic streptococcus was cultured from the blood. Frank jaundice without demonstrable liver damage occurred during this sepsis and cleared after therapy. Four days thereafter, a pyarthrosis developed in the right knee joint from which a poorly viscous yet purulent fluid was aspirated. This contained over 25,000 cells per cu. ml. but proved sterile on culture. The blood stream infection was effectively treated with penicillin and streptomycin. Ten cc. of gamma globulin were administered

during this and subsequent septic episodes. Another massive rectal hemorrhage occurred thirty-two days after admission. This episode was managed by the transfusion of thirty-four units of whole banked blood, three units of fresh blood and corrective amounts of calcium lactate. Electrocardiograms taken shortly after this hemorrhage showed deep T wave inversions in lead I, a V1 and V4-V6 consistent with patchy myocardial necrosis. These changes reverted to normal during the next four weeks. Five weeks after admission, the patient developed a cough productive of purulent sputum, a septic fever, and aVL. A chest x-ray revealed an infiltrate in the right lower lobe. This episode of bronchopneumonia responded adequately to antibiotic and gamma globulin therapy. Oral moniliasis occurred seven weeks after admission and was successfully treated with Mycostatin® mouth wash. During the third month of the hospital stay the patient's hemoglobin dropped from 12.5 Gm. to 8.5 Gm. per 100 cc. without blood loss. Thus far, a total of 63 units of blood had been administered to replace the blood loss per rectum. A weakly positive Coomb's reaction was demonstrated using the direct technique. Chromium⁵¹ tagged red blood cell survival time was shown to be moderately diminished during this period of time. Four months after admission the patient developed another episode of sepsis, this time due to aerobacter aerogenes. This again was successfully controlled with antibiotics and gamma globulin. The patient's subsequent course was complicated by two further infections: a staphylococcal paronychia and a severe staphylococcal aureus and enterococcal submaxillary adenitis with abscess formation. These also responded to antibiotic therapy. Electrophoretic patterns after these episodes finally showed a definite increase of the normal gamma component. The antistreptolysin-O titer after streptococcal sepsis never rose above 125 units. Tests for delayed hypersensitivity to tuberculin and fungal antigens were negative. The patient is now wasted in appearance and markedly anemic with a hemoglobin of 7 gm. per cent. The spleen is enlarged to 16 cm. beneath the left costal margin, and the marrow now reveals some plasma cells (4-6 per cent).

DISCUSSION

The above patient manifested most of the clinical features of macroglobulinemia described by other observers (2). Marrow examination showed an increase in lymphocytic cells and only after repeated infections did plasma cells become more numerous, a finding that has been noted by Schlaub (9). Hepatomegaly was prominent but was not as marked as the splenomegaly which became the major physical finding. Mucous membrane bleeding, a symptom frequently listed as chief complaint by such patients, was manifested by repeated epistaxis and rectal bleeding (1, 4). The presence of low grade hemolysis was demonstrated by chromium⁵¹ labelled red cell survival studies. The half life of labelled cells was 17 to 19 days, the normal being 28 to 36 days. Repeated examinations failed to confirm the previously described hypofibrinogenemia associated with this syndrome (1, 5). The other clotting factors were irregularly impaired.

While normal serum contains several components of high molecular weight having sedimentation constants of about 19s, the amount of such heavy com-

ponents in patients with macroglobulinemia is much higher (10). Values of over 5 per cent of this serum protein have been described in patients with cirrhosis, lupus erythematosus and carcinoma. When more than 10 per cent is identified, the moving boundary electrophoresis show that most of the normal 19s globulins migrate in the gamma-1 and some in the alpha-2 globulin range. Identified in the normal heavy globulin fraction have been the isoagglutinins, cold agglutinins, and some antibodies to pneumococcal polysaccharide (10).

The amount of associated carbohydrate is greater for the normal and abnormal macroglobulins than for the 7s gamma globulin or myeloma protein of similar electrophoretic movement (8). This may be demonstrated by periodic acid Schiff staining or by direct carbohydrate analysis (10). Amino acid analysis of macroglobulins seems to parallel the observations made upon myeloma protein. Although individual macroglobulins may vary in a particular amino acid constituent, they are generally similar in amino acid composition to normal gamma globulin (13). Some macroglobulins may be cryoglobins as well (14).

The electrophoretic property of abnormal macroglobulins may vary from positions among the slower gamma globulins to positions where the typical "M" spike between the beta-2 and gamma-1 is simulated (2, 4, 8). Positions even closer to albumin have been described. In the patient studied, a large homogeneous band was seen to migrate in the "M" region. Thus moving boundary or paper electrophoresis can only suggest the presence of an abnormal protein. The use of starch gel electrophoresis has been suggested for the study of macroglobulins. Silberman (15) has observed that normal 7s gamma globulins, and even myeloma proteins, will migrate into starch gel from filter paper. Macroglobulins, however, display no such movement. If the filter paper that is used to introduce macroglobulinemic serum into starch gel blocks for electrophoresis is removed and stained for protein, the heavy globulin seems to remain on paper. This phenomenon was observed with our patient's serum. No visible band was seen in the gamma region of starch gel electrophoresis. The filter paper was shown to have remaining protein that migrated to the typical position of the patient's macroglobulin.

Ultracentrifugation of the patient's serum showed not only a major component with a sedimentation constant of about 19, but larger aggregates of approximately 25s and 33s material. The addition of sulfhydryl containing compounds, such as mercaptoethanol, will cause such heavy globulins to sediment with the remainder of normal 7s globulins (7). This may indicate that these large molecules are polymers of a smaller monomer bound by sulfur-sulfur linkages.

Quantitative precipitin techniques and agar diffusion methods have shown the partial antigenic identity of 7s and 19s gamma globulins (10, 16, 17). Franklin and Kunkel (10) have shown that antisera to whole gamma globulin, when absorbed with 7s gamma globulin antigen, still contained antibody to the 19s fraction. Mandema et al., (18) have shown similar behavior in the Oudin system with macroglobulinemic serum, while Korngold has established reactions of partial identity to be present in Ouchterlony plates (19). The latter technique may be used as a semi-quantitative screening method for the presence of macroglobulinemia.

The Sia test has been recommended as another readily available screening test for macroglobulinemia (8). When serum is diluted at least twenty volumes with distilled water, a precipitate forms. This fraction is mainly "euglobulin" and not infrequently the abnormal protein will precipitate as well. Yet with sera containing macroglobulins moving in the beta region, or having "M" mobility, this test is often negative. This was the case in our patient. The possibility of increased carbohydrate content being responsible for water solubility is a real one: in the proteins of myeloma carbohydrate content varies directly with electrophoretic movement (8).

The repeated infections sustained by this patient may have been related to the virtual absence of normal 7s gamma globulin at stages of her disease. These infections are frequently due to pyogenic organisms. Recurrent pneumococcal pneumonia has been demonstrated in multiple myeloma and has been attributed to decreased elaboration of type-specific antibodies (22). Similar infections with an analogous lack of antibody response have been reported with macroglobulinemia (7). The patient manifested the following septic complications: beta-hemolytic streptococcus septicemia, aerobacter aerogenes sepsis, septic pyarthrosis, bronchopneumonia, staphylococcal submaxillary adenitis, staphylococcal paronychia and oral moniliasis. Clinical improvement in each instance was obtained with antibiotics and gamma globulin as has been the case in the hypogammaglobulinemias.

Good (21), as well as Janeway and Gitlin (20), have reviewed the primary and secondary hypogammaglobulinemias. The latter have been associated with such diseases as malignant lymphoma, chronic lymphatic leukemia, thymic tumors, multiple myeloma and macroglobulinemia (22, 7). The inability to synthesize immune globulins need not be a complete one. Isohemagglutinins may be present, as they were in the above case (22). A decreased or delayed, rather than a persistently absent, gamma globulin response may exist (23). The most sensitive tests for presence of gamma globulin are those involving agar diffusion techniques (24). Hypogammaglobulinemic sera give values of 0 to 300 mgm. per cent as opposed to normal values of 600 to 1200 mgm. per cent (20). The more available techniques such as zinc sulphate precipitation or Howe fractionation will give roughly similar results. If abnormal proteins, such as those of myeloma or macroglobulins are present, deficiencies of normal gamma globulin may be obscured (25). Both zinc sulfate and routine salt fractionation precipitated the macroglobulin along with the mass of normal globulins. However, anion exchange column chromatography of the patient's serum, done at a time when paper electrophoresis showed little normal gamma globulin, yielded little protein extractable in the normal gamma range. During the initial infections, the patient had a virtual absence of protein with normal gamma globulin mobility by paper, moving boundary electrophoresis, or ion exchange column chromatography. Later, this became somewhat increased, demonstrating a quantitative rather than absolute failure to produce normal gamma globulin. Exogenously administered gamma globulin, while affecting rheumatoid agglutination reactions, will have little demonstrable effect on serum electrophoretic patterns and can be excluded as a cause for this rise (20).

The relationship of the patient's serum to the test systems used in the demonstration of the rheumatoid agglutination factor was also of interest. Essentially each test involves a reaction between the agglutinating rheumatoid factor and a normal gamma globulin that has previously coated an indicator system such as latex particles or sensitized sheep cells (26). It has been demonstrated that the isolated rheumatoid factor is a macroglobulin (19s) loosely complexed with 7s gamma globulins to produce large complexes having sedimentation constants of 22s (27). Patients with hypogammaglobulinemia do not show agglutinating activity even in the presence of clinically defined rheumatoid arthritis, nor do their sera contain the inhibitor of known rheumatoid agglutination activity which is demonstrable in normal sera (28). The test for absence of inhibitor in the euglobulin fraction of serum (obtained by dialysis against 1/150 phosphate/citrate buffer at pH 5) is considered by Ziff et al. to be the most clinically accurate test for rheumatoid arthritis (29). The behavior of our patient's serum was determined in two rheumatoid agglutination tests. The latex fixation test (30), (using pooled gamma globulin *in vitro*) was positive at 1:320, but when the patient's own gamma globulin was employed as a coating for the latex particles (31), no agglutination was observed. When exogenous gamma globulin was administered (basically as a therapeutic measure) agglutination was augmented to 1:1280 with positive tests by the "Owren gamma globulin technique." The patient's whole serum was negative in the sensitized sheep cell reaction, negative by the euglobulin technique, and no inhibitory activity was noted. Since the patient's 19s protein did not behave as a euglobulin, this dissociation between the positive latex and negative sheep cell tests is expected. The behavior described is in accord with the hypothesis that not only the rheumatoid factors, but other abnormal serum proteins will cause non-specific conglutination reactions if suitably provided with an indicator particle coated with 7s "reactant" globulins. This correlates with the frequently positive latex tests of patients with lupus erythematosus, syphilis, cirrhosis, sarcoidosis, macroglobulinemia and myeloma (32).

We were provided with a unique opportunity to study the synovial fluid of this patient. Synovial fluid is a viscous fluid containing a polysaccharide-protein complex which may be precipitated by polyvalent cobalt salts and cationic detergents (33). The polysaccharide is hyaluronate, while the protein fractions have been shown to be similar to plasma proteins by Schmid and McNair (34). The linkage of protein to hyaluronate is crucial. Papain degradation of the protein moiety will alter such characteristics as non-Newtonian viscosity (35). In normal fluid, 85 per cent of the discernible hexosamine is that of hyaluronate.

The right knee joint of the patient was aspirated several times. Initially the fluid was clear, viscous, formed a firm mucin clot and was compatible with the findings in osteoarthritis. At the time of a pyarthrosis, the viscosity was diminished, a scattered mucin clot was obtained, and over 25,000 polymorphonuclear leukocytes per cu. mm. were present. After this acute episode, the fluid again had the normal characteristics of a non-inflammatory arthritis. At this time, paper electrophoresis of the synovial fluid was performed. A distinct band, reproducing

the mobility of macroglobulin in serum, was discovered. When synovial fluid hexosamine determinations were performed, quantities of hyaluronate hexosamine compatible with the patient's age were found. Non-hyaluronate hexosamine was remarkably increased, compatible with Waldenström's observation of increased hexosamine content of the large molecule. Polyvalent cobalt complex precipitation of the hyaluronate protein mixture again yielded electrophoretic patterns with the expected band. Hexosamine values of this complex were high. Glacial acetic acid precipitates showed only an albumin band on electrophoresis. These studies are compatible with the theory that hyaluronate fortuitously forms complexes with any plasma protein available, in this case, the macroglobulin.

Urinary electrophoresis indicated the presence of an abnormal protein of the same mobility as the serum macroglobulin. The sedimentation constant of the abnormal urinary protein was also 19s. This has not been observed in another such case by Franklin (36). No significant hematuria or free urinary hemoglobin were present at the time of this determination. The presence of the rheumatoid factor in synovial fluid would indicate that 19s globulins may be found in joint spaces (29).

SUMMARY

A case of macroglobulinemia in a 71 year old woman is presented. Prominent features were severe mucous membrane bleeding and multiple infections. No other associated disease process could be identified.

A homogenous band between gamma-1 and beta-2 was demonstrated on paper electrophoresis. Starch gel electrophoresis indicated no migration of the abnormal protein. Ultracentrifugation studies identified large amounts of a serum protein having sedimentation constants of 19s and greater.

Repeated infections characterizing the clinical course were initially related to a quantitatively diminished normal serum gamma globulin concentration.

The patient's serum gave positive reactions in several tests for rheumatoid agglutination activity in the absence of clinical rheumatoid arthritis.

Synovial fluid studies indicated the presence of an abnormal protein containing large quantities of hexosamine. This protein was precipitable with hyaluronate by means of polyvalent cobalt complexes.

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HYPOGAMMAGLOBULINEMIA AND HYPERGAMMAGLOBULINEMIA

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Disturbances in gamma globulin have gained prominence in the literature in the last six years, at first because of their association with recurrent bacterial infection (1-6), later because of reports of various immunological experiments (3, 7-16) and most recently because of their association with "collagen diseases" (17) and allergic disorders.

PHYSIOLOGY

The gamma globulins were defined by Tiselius as the slowest moving plasma proteins on electrophoresis. They are proteins with various functions whose molecular weights range from 150,000 to 300,000. Proteins with similar functions may move at different speeds under identical conditions. Differences in biochemical and physical properties of the gamma globulin have been demonstrated immunochemically (7). They have been separated into two components according to their sedimentation rates (18). By the use of ultracentrifugal separation and the other methods described, several major components can be identified. Most antibodies against bacteria, viruses, and toxins are contained in the gamma globulin fraction; the isohemagglutinins and cold agglutinins are in a faster moving gamma globulin with a higher sedimentation constant (19, 20) often considered a beta-2 globulin (21) and some of the reagin type antibodies are contained in the beta fraction (22).

If gamma globulin is formed in fetal life, evidence suggests that it is formed later than the other plasma proteins (23). At birth the level may exceed the mother's (24-27); it is probably derived from maternal serum and transferred across the trophoblast (28). This is illustrated by an infant born with a high serum gamma globulin level and normal serum albumin to a mother who had cirrhosis with high gamma globulin but low albumin (29).

The possibility that the placenta may also synthesize gamma globulin has been studied by fluorescent antibody technique (30). In a mother with acquired agammaglobulinemia the newborn had agammaglobulinemia from the time of birth until he began to synthesize his own gamma globulin. In this mother despite antigenic stimulation no antibody could be demonstrated during the first trimester of pregnancy; it was demonstrable during the third trimester without a detectable rise in the gamma globulin level. This antibody was thought to be produced by the placenta (which contained plasma cells), since none was detectable in the baby's circulation. On the other hand, Dancis et al., (31) performed *in vitro* studies of placentas from the first and last trimesters of pregnancy and noted synthesis of alpha and beta globulins, but not of gamma

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globulins. In the normal full-term newborn gamma globulin values fall to one-third of their birth value by one month of age and further gradual decline occurs up to about three months. Synthesis begins between the sixth and twelfth weeks of life but a physiological hypogammaglobulinemia exists between the second and fourth months of life. Normal adult levels are approached by two years of age but frequently not attained until the sixth year.

Most plasma proteins are synthesized in the liver (32) but gamma globulins are synthesized in the reticulo-endothelial system and bone marrow (3, 10, 12, 14, 28, 33, 34). A high degree of correlation between gamma globulin levels and the number of plasma cells in the bone marrow has been demonstrated (33) and the localization of gamma globulin in plasma cells and in the germinal centers of lymph nodes has been carried out by fluorescent antibody techniques (10, 12, 14). Only the small lymphocytes in the germinal centers of the lymph nodes form gamma globulin, and the cells have to be in aggregate formation to be productive. Ortega and Mellors suggest that the cellular arrangement resembles that of a gland and that gamma globulin is released by holocrine and apoerine secretion (12). Mature and immature plasma cells also form gamma globulin as do macrophages but circulating lymphocytes and larger lymphocytes do not (8). In all instances the fluorescent antibody technique localized the gamma globulin formation in the cytoplasm and no nuclear participation was demonstrated.

The finding of low gamma globulin levels and reduced lymph tissue in germ-free rats and chicks suggests that bacteria stimulate gamma globulin formation (35, 36). Viral and bacterial infections show similar changes in the percentage distribution of serum proteins, principally a decrease in albumin and an increase in gamma globulin (37).

The mechanism and site of degradation are unknown. The half-life differs with the method of study. With radioactive iodine, tagged gamma globulin has been reported to have a half-life of 17 to 22 days (8) and 9 to 20 days (9), with N^{15} of 19 days (8) with S^{35} of 20 to 35 days (8) and 25 to 125 days (9). Wiener (38) by studying Rh antibody levels has found the half life to be 30 to 35 days. Each antibody is degraded at a different rate, the half life varying between 21.7 and 45 days (9b, 11). From studies of patients with agammaglobulinemia who have been given gamma globulin, the half life has been reported to be 36 days (9), 32.6 days (11), and 30 days (3). Using immunochemical methods it has been found by Gitlin to be between 30 and 60 days (7). The variable results are attributed in part to differences in methods, to possible detrimental effects of radioactivity on gamma globulin, to difficulties associated with iodination (7) and to the variety of proteins administered (9). Gitlin notes that a little over half the injected gamma globulin disappears from the serum into interstitial fluid shortly after injection (7, 8) and Martin (11) found that injected gamma globulin is distributed in a fluid volume of approximately 12 per cent of the body weight. Studies of antibody level of administered gamma globulin have shown a 1 to 40 dilution after injection into agammaglobulinemic patients. The gamma globulins are in a constant state of flux but there is no knowledge as to the regulation of their level.

The level may be decreased for various reasons:

- (a). Malnutrition, rarely encountered clinically but used as an experimental tool.
- (b). Injury to the synthesizing tissue by radiation, nitrogen mustard, metastatic disease, or steroids.
- (c). Deficiency of synthesis for reasons that are not understood as in congenital and acquired agammaglobulinemia.
- (d). Increased destruction or loss as seen in severe hemorrhage, burn, infection, chronic diarrhea, hyperthyroidism and nephrosis (39).

The level may be increased with repeated antigenic stimulation, chronic inflammatory disease, collagen disease, liver disease, immunological disorders, sarcoidosis, amyloidosis and beryllium poisoning as well as in lymphomas and multiple myeloma (8, 40-44). There may also be increased levels of abnormal globulins and larger globulins with molecular weights up to 1,000,000 which move with the gamma globulins electrophoretically, are normally not found in significant quantities, and whose function is little understood (40, 44, 45).

THE DETERMINATION OF SERUM GAMMA GLOBULIN

Various methods exist for the estimation of the serum gamma globulin level:

- (a). Moving boundary electrophoresis and paper chromatography.
- (b). Precipitation by various salts or metals.
- (c). Ethanol fractionation (Cohn's method, 46).
- (d). Immunochemical (Gitlin, 7, 8).

All of the above methods have some inadequacies. The precipitation methods lead to large errors if the gamma globulin level is low—and a low level may not be detectable by electrophoresis. The precipitation methods entail losses, if the gamma globulin is to be separated, which have been minimized in Cohn's procedure. The immunochemical method detects very low amounts but heterogeneous immunochemical composition may lead to error which, if levels are indeed low may be relatively large (8). Protein that will be part of the gamma globulin fraction by the immunochemical or fractionation procedures would nevertheless not be classified as such if it moves more rapidly by electrophoresis.

HYPOGAMMAGLOBULINEMIA

Congenital agammaglobulinemia was first described by Bruton who noted increased incidence of infection and lack of antibodies (1, 2). His patient was a male, and subsequent reports of congenital cases have described only males (3-6, 13). The disease represents an inborn error of metabolism, inherited as a sex-linked recessive (8, 13). The two brothers reported below illustrate this syndrome.

CASE REPORTS

Case 1

Rb. A. (#72893) a 6 year old white boy was first admitted to The Mount Sinai Hospital in October of 1956 with a history of persistent cough following an episode of pneumonia in

1955, night sweats and low-grade fever. He had chronic dermatitis since the age of three months, at which time he developed atopic eczema. The skin disease subsequently had been associated with frequent abscesses and had been treated with cortisone as well as antibiotics. He was subject to frequent upper respiratory infections, and one year prior to admission he developed pneumonia for which he was treated intermittently for three to four months with sulfonamides, erythromycin and tetracycline. The patient continued to cough, have night sweats and run a low-grade fever. Four months prior to admission he began to expectorate more than 100 cc. of greenish sputum daily and one month prior to admission, there was an episode of hemoptysis. The parents noted beginning clubbing of the fingers. There was no history of pertussis, foreign body ingestion or exposure to tuberculosis. The patient had two attacks of "asthma" which were treated with epinephrine injections at the age of six months. In June 1956, he had a negative PPD, and sputum concentration for tubercle bacilli was negative. He has always had very poor oral hygiene.

The developmental history was normal. He had had routine diphtheria, pertussis and tetanus immunizations and two Salk polio vaccine injections, the last one two months prior to admission.

The father reacts with urticaria to penicillin and tetanus antitoxin. The paternal aunt, and the maternal uncle and grandmother all have allergic histories. The mother has one sister living and well. Three brothers died in infancy; one of pneumonia, one of measles and one following mastoidectomy (Fig. 1).

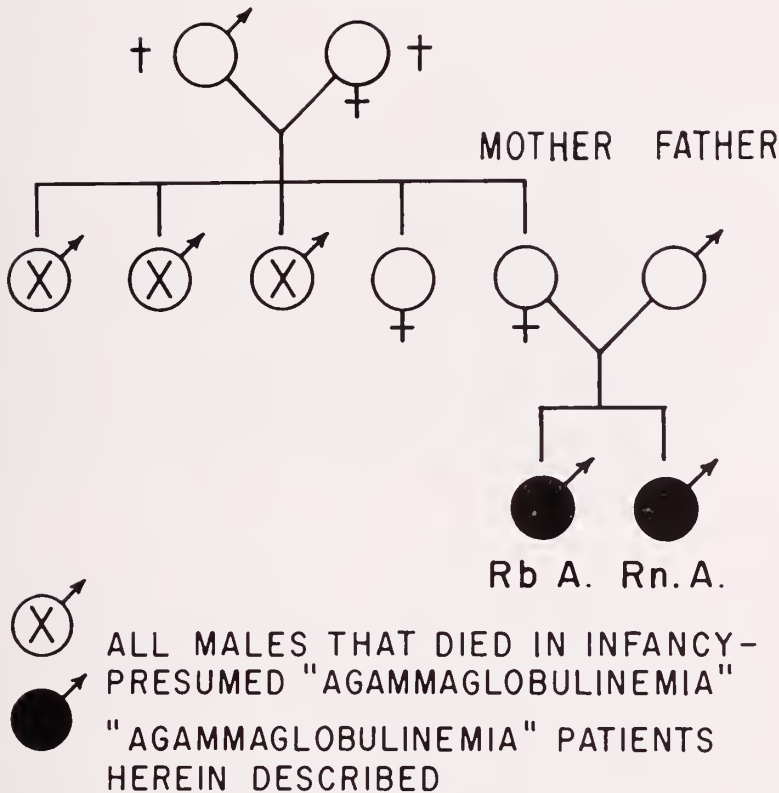


FIG. 1. The family members were studied electrophoretically. The parents and the maternal aunt as well as all of the father's relatives that could be studied had a normal protein pattern. No family member excreted uroporphyrin in the urine and no one, including the patients, excreted porphobilinogen in the urine.

Physical examination revealed a chronically ill and pale appearing white male with cough, early clubbing of the fingers but no cyanosis. Temperature was 101.4°F., pulse rate 120 per minute, respiratory rate 20 per minute. The skin showed numerous scars from healed abscesses. There were scaly, as well as lichenified lesions on the scalp, hands and feet and around the ears. A few pustules were seen in the same areas. The pharynx was injected and there was minimal erythema of the left ear drum; only one small anterior cervical lymph node was felt. The mouth showed very poor oral hygiene, multiple cavities with abscess formation at the roots of many teeth. The right hemidiaphragm moved less than the left; there was bronchial breathing and dullness to percussion at the right base. Rhonchi were scattered throughout all lung-fields with occasional wheezing but no rales were heard. The heart was not enlarged and there was a normal sinus rhythm. The spleen was three centimeters below the left costal margin. The patient was normal in height and weight.

Serial urinalyses were normal. Hemoglobin 11.4 grams per cent, white blood count 18,400 per cubic millimeter with 50 per cent segmented neutrophils, 32 per cent band forms, 12 per cent lymphocytes and 6 per cent monocytes. The sedimentation rate was 12 millimeters per hour. Subsequent blood counts during his hospital stay showed the hemoglobin to range between 10.9 grams per cent and 12.8 grams per cent, with a normal white blood cell count and differential. Mean corpuscular hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin concentration were all within normal limits, as was the platelet count. First and second strength PPD were negative and the Schick test was positive. Nose and throat culture revealed hemophilus para-influenza and staphylococcus aureus, the latter sensitive to erythromycin. Sputum examination showed aerobacter arogenes. Several blood cultures were negative. X-ray examination of the chest showed infiltration in both bases extending up to the eighth rib on the right and tenth rib on the left. In the right anterior oblique view a collapsed segment of left lower lobe was noted. The heart and mediastinum were normal. Sinus films showed cloudy ethmoids and antra. Bronchoscopy revealed purulent material to be coming primarily from the right lower lobe bronchus; its culture showed enterococci and gram negative chromogens. Bronchogram revealed fusiform cylindrical bronchiectasis involving all basilar segments of the right and left lower lobes but sparing the superior segments of both lower lobes. A similar process was seen to involve the superior and inferior segments of the lingular portion of the left upper lobe. Stool trypsin was present in a dilution of 1:1000 and sweat test showed normal sodium and chloride content.

The patient was treated by postural drainage, nebulization with isuprel and oral erythromycin and chloramphenicol therapy. Temperature became normal after two days but the cough persisted. Dermatological consultation occurred in the diagnosis of chronic dermatitis, probably of an atopic nature and skin biopsy confirmed this. The skin lesions were treated at first with hydrocortisone ointment and later with Tarbonis® ointment. Within one week of therapy most skin lesions had healed with some erythematous scaling lesions remaining on the extensor surfaces of the hands and on the ear lobes. Serum electrophoresis showed absence of gamma globulins.

Special Studies

1. Schick test: The Schick test was positive in spite of routine diphtheria immunization.

2. Isohemagglutinins: There were no anti B hemagglutinins although the patient was of blood type A.

3. Protein fractionation according to Cohn's method was performed by Russ (47).

Total Protein	6.3 gm. %
Fraction IV, V, VI	5.3 gm. %
Fraction II	0.1 gm. %
Fraction I, III	0.9 gm. %

Fractions IV, V, and VI represent mostly albumin. Fraction II contains 90 to 95 per cent of the gamma globulin, and in addition 1 to 4 per cent albumin and 4 to 6 per cent beta-2

globulin. Fraction I and III contain the alpha and beta globulins and 2 to 10 per cent gamma globulin. A low gamma globulin level was thus detected.

4. Serum globulin analysis according to method of Greenspan (48). Results:

	Normal	Rb. A.
Mucoprotein.....	75 mg. %	122 mg. %
Acid precipitable globulin turbidity.....	4-8 units	13.7 units
Zinc sulfate turbidity.....	4-8 units	0.5 units

This analysis showed high alpha and beta globulins, suggestive of chronic infection; the gamma globulins were virtually absent but nevertheless detected by this method.

5. Bone marrow aspiration revealed an absence of plasma cells. The marrow was hypercellular with an increase in eosinophilic forms, and increased erythroid activity leading to a markedly altered myeloid-erythroid ratio.

6. Smallpox vaccination: An accelerated take occurred within 3 to 4 days without complication, five years after the primary.

One month after admission, the patient developed bilateral otitis media with bulging of Schrapnell's membrane on the left side and fever of 102°F.. He did not have a leukocytosis but there were 56 per cent polymorphonuclear leukocytes on smear. Three days later there were no polymorphonuclear leukocytes, but 75 per cent lymphocytes and 25 per cent monocytes. Antibiotic therapy was changed to novobiocin and temperature returned to normal within 36 hours. The eardrum continued to bulge and after a further period of observation of one week a myringotomy was performed. Culture of the drainage revealed no growth. The incision healed slowly and the patient was discharged to be followed in clinic.

At the time of discharge from the hospital he was given 0.1 gram/Kg. of gamma globulin and instructed to take tetracycline prophylactically. In addition he was to use isuprel nebulization, frequent postural drainage and pHisohex[®] and Tarbonis[®] ointment on his skin lesions.

For the past year he has received 0.1 gram/Kg. of gamma globulin at six-week intervals and no serious illness has occurred. The amount of sputum produced has gradually decreased so that he now expectorates between 25 and 30 ml./day. X-rays have shown clearing of all infiltrates except for an area at the right base adjacent to the cardiac border. Sputum cultures grew *Aerobacter aerogenes* and *Hemophilus influenzae* resistant to antibiotics; after six months cultures became positive for *staphylococcus aureus* and the antibiotic was changed to novobiocin. The skin lesions have not recurred and the ear has remained well. The spleen is no longer palpable. Hemoglobin has risen to 12.6 grams per cent and white blood cell counts and differentials have remained within normal limits.

Gamma globulin could not be demonstrated by electrophoresis as early as two weeks after its administration.

Case 2

Rn. A. (#74094) is the 2½ year old brother of the above patient. He was admitted to The Mount Sinai Hospital for study of repeated superficial skin infections and arthralgia of the knees. He first developed a skin infection following vaccination at the age of one year. It is not known whether the vaccination took, but a large abscess subsequently developed. At one and a half years of age the patient developed multiple superficial skin abscesses particularly on the face, neck and extremities. These were treated with soaks and erythromycin, but nevertheless persisted for six months. About five months prior to admission he developed arthralgia of both knees, with pain on walking; this was not treated. The parents noted progressive swelling and warmth of the joints but no redness. The pain was described as most severe in the mornings and abating during the course of the day. No other joint complaints were elicited. Two weeks prior to admission the child developed a cough, expectoration of some white-yellowish phlegm and a running nose. He had no fever, and was not treated.

Growth and development and past history were unremarkable. He had received routine immunizations for diphtheria, pertussis and tetanus as well as two Salk polio vaccinations.

Physical examination revealed a thin, pale, chronically ill-appearing white boy. Blood pressure 105/70, pulse rate 140 per minute, respiratory rate 20 per minute, temperature 99°F., weight 26½ pounds. The skin presented many pitted scarred areas on the extremities, chin and neck. Examination of the eyes, ears, and pharynx was unremarkable. The neck showed multiple small anterior and posterior cervical lymph nodes. There were also lymph nodes in the epitrochlear, axillary and inguinal regions. The heart and lungs were normal clinically. The liver was four centimeters below the right costal margin and the spleen was not felt. Neurological examination was within normal limits. The thigh and calf muscles showed wasting with enlargement of both knees, the right more than the left. The knees were warm but no fluid was noticeable and a patellar click could not be elicited. Extension was limited by five degrees on the right and five to ten degrees on the left. There was questionable enlargement of the wrists.

Hemoglobin was 13.9 grams per cent with 16,000/cu. mm. white blood cells, 49 per cent segmented neutrophils, 8 per cent band-forms, 29 per cent lymphocytes, 5 per cent eosinophils, 5 per cent basophils, and 4 per cent atypical lymphocytes. The sedimentation rate was 12 mm. per hour. Urine was normal. Nose and throat cultures revealed hemophilus parainfluenza and streptococcus viridans. The blood cultures showed no growth. The first and second strengths PPD were negative. The total protein was 6.7 grams per cent, 4.7 grams per cent albumin, 2.0 grams globulin. X-rays of the chest showed a poorly defined hazy infiltration adjacent to the region of the left ventricular apex and examination of the bones showed soft tissue swelling about both wrists and both knees with bulging of the capsules of these four joints.

Because of agammaglobulinemia in the patient's older brother, this diagnosis was immediately entertained. It was held that rheumatoid arthritis was responsible for the child's arthralgia and limitation of motion in the knees and the orthopedic consultant concurred in that diagnosis. A consulting physiatrist found that the right knee extension was limited at 135 degrees and left knee extension at 160 degrees and it was his opinion that active stretching exercises after warm tub baths would increase his range of motion. Electrophoretic analysis of his serum failed to show gamma globulin.

Special Studies

1. Schick test: The Schick test was positive in spite of routine diphtheria immunization.
2. Isohemagglutinins: The patient was of blood type AB; the test was not applicable.
3. Protein fractionation performed by Russ (47):

Total Protein	6.4 gm. %
Fraction IV, V, VI	5.1 gm. %
Fraction II	0.1 gm. %
Fraction I, III	1.2 gm. %

A low gamma globulin level was thus detected.

4. Serum globulin analysis according to method of Greenspan (48). Results:

Mucoprotein	102 mg. %
Acid precipitable globulin turbidity	10.2 units
Zinc sulfate turbidity	0.5 units

This analysis showed high alpha and beta globulins, suggestive of chronic infection; the gamma globulins were virtually absent but nevertheless a low level was detected by this method.

5. Bone marrow aspiration revealed an absence of plasma cells. The marrow was hypercellular with an increase in eosinophilic forms, and increased erythroid activity leading to a markedly altered myeloid-erythroid ratio.

6. Smallpox vaccination: An accelerated take occurred within 3 to 4 days without complication, $1\frac{1}{2}$ years after the original vaccination.

Shortly after admission, the patient developed rhonchi in the left chest posteriorly. Bronchopneumonia was diagnosed and treated with aqueous procaine penicillin injections and oral tetracycline therapy with prompt improvement. Three weeks after admission the patient developed fever of 103°F . with chills and tachypnea. Physical examination at that time showed minimal pharyngeal injection and questionable dullness and coarsening of breath sounds at the right base posteriorly. His treatment was changed to erythromycin and chloramphenicol by mouth without diminution of fever which continued at 102° to 103°F .. Two days later the patient began to vomit his medications which were then given intravenously and intramuscularly. Vomiting decreased, but diarrhea began and after 36 hours the patient had a generalized clonic convulsion, lasting about 20 seconds, followed by several similar seizures. He was treated with intramuscular barbiturates without response so that the convulsions were stopped with chloroform inhalation. At the time the patient's urine was brownish-red in color with specific gravity of 1.022, 2 to 3 plus albumin and positive tests for hemoglobin and uroporphyrin. Thereupon all medication was stopped, with rapid improvement, cessation of diarrhea, the passing of normal urine and return of temperature to normal values.

At the time of the fever, nasopharyngeal, throat, blood cultures and stool examinations revealed no pathogens. Two cerebrospinal fluid examinations showed normal pressure, cell count, sugar and protein. Blood counts had shown a gradual drop in hemoglobin to 8.7 grams per cent and diminution in polymorphonuclear leukocytes. Just prior to the febrile episode there were 4,500 WBC/cu. mm., only 2 per cent segmented neutrophils, 3 per cent band forms, 76 per cent lymphocytes, 7 per cent eosinophils, 4 per cent monocytes, 8 per cent atypical lymphocytes. The fall in hemoglobin was attributed to the large amount of blood required for the various tests then being performed. It was suggested that the tetracycline drug might be responsible for the neutropenia or that the neutropenia might be a feature accompanying the agammaglobulinemia.

Bone marrow examination showed normal cellularity, increased erythroid activity with an altered myeloid erythroid ratio. On a large bone marrow survey increased eosinophiles but only one plasma cell was noted. The hemoglobin gradually rose to 10 grams per cent by the time of discharge. The differential blood count still showed a relative lymphocytosis. Only during the febrile episode itself was there a mild shift to the left with 32 per cent segmented neutrophil cells and 11 per cent eosinophils with a total white blood count of 7,200 cells per cubic millimeter.

Following the episode of convulsion, the urine was repeatedly tested for porphyrin; but no porphyrin excretion was noted. But after the patient received second sedation for an electroencephalogram a trace of uroporphyrin was detected in the urine. The electroencephalogram was normal. Blood chemistries (sodium, potassium, carbon dioxide, chloride, calcium, blood sugar, urea nitrogen) all were normal during the period of fever, vomiting and diarrhea.

The patient then continued afebrile until the time of discharge. He was given 0.1 grams/Kg. of gamma globulin at the time of discharge and instructed to receive prophylactic tetracycline therapy. He was to continue physiotherapy for his knee. For the past year he has received injections of gamma globulin at six-week intervals. He has had two episodes of mild upper respiratory infection without fever. Rn. A. has regained full use of his knees after a period of weekly physiotherapy. Antibiotic therapy was changed to erythromycin after three months because he developed diarrhea on the tetracycline preparation. Six weeks later systemic antibiotics were discontinued entirely but an eye infection prompted the use of local Polysporin® ointment. Hemoglobin rose to 12 grams per cent with a normal differential and white blood cell count. The patient has been gaining weight and is developing normally.

As early as two weeks after its injection into this patient, gamma globulin could not be demonstrated by electrophoresis.

DISCUSSION

The term "Agammaglobulinemia" was introduced by Bruton (2) but Pearce (49) proposed "Congenital Idiopathic Hypogammaglobulinemia". The latter name is more accurate but it is difficult to use in a discussion.

The sex-linked recessive characteristic of the congenital disorder is well demonstrated by the family tree of the two patients presented above (Figure 1).

In one instance of agammaglobulinemia, the patient's mother also had low serum gamma globulin (49); in another instance, both the mother and a sibling had hypergammaglobulinemia (50). Agammaglobulinemic patients with hypergammaglobulinemia in both parents have been cited (51, 52). Zelman and Lewin (51) have suggested the possibility that a single recessive gene may give rise to hypergammaglobulinemia and the double gene to hypogammaglobulinemia. The occurrence of acquired agammaglobulinemia in two adult brothers has also been reported (53).

Hypogammaglobulinemia may occur as an acquired disease, in either sex and at any age (9, 50-66); a case of a girl has been reported with the onset of her disease at eight months of age (49). Adults have had the disease in association with, or perhaps as a result of, lymphomas, leukemia (53, 54), sarcoidosis (55), and other diseases of the reticuloendothelial system (51, 52, 55-60). One patient had a large thymus at 63 years of age (9) and several had splenomegaly with hypersplenism, neutropenia and acquired hemolytic anemia (49, 52, 56, 59). Improvement after splenectomy has been reported (58). In one instance, the patient's lymph nodes and spleen were so large that the diagnosis of giant follicular lymphoblastoma was at first suspected (53). The association of sprue is frequently mentioned (50, 51, 58, 61-63).

The syndromes of congenital and acquired agammaglobulinemia have been uncovered by the availability of antibiotics for the treatment of recurrent bacterial infections, such as meningitis or pneumonia (67). Complications especially bronchiectasis, arthritis and hearing difficulties are common (3, 68-70).

Physiologic hypogammaglobulinemia may contribute to sudden death in infancy and Schick has proposed the use of gamma globulin against infections during this period (71, 72). The protective properties of gamma globulin particularly against infections with gram negative organisms have been emphasized (73).

Infants with edema, hypoproteinemia and hypogammaglobulinemia have been reported (74-79). In some instances the syndrome persisted up to fifteen months of age and anemia, hypoferrinemia and hypocupremia were also demonstrated. These infants had a normal amount of plasma cells, responded to antigenic stimulation with antibody rise and made spontaneous recoveries. Relatively inadequate protein synthesis with rapid degradation have been held responsible for the hypoproteinemia (77).

Once the diagnosis of agammaglobulinemia has been indicated by electrophoresis other corroborative studies can be performed:

A. *Schick test*: The Schick test is positive in spite of routine diphtheria immunization. This was true in the two cases presented.

B. *Isohemagglutinins*: The isohemagglutinins are a part of the beta-2 globulin

fraction now considered a faster moving gamma globulin (19-21); they are lacking in patients with agammaglobulinemia and fail to develop even after injection of mis-matched blood. Case 1 was of blood type A, but had no detectable anti-B hemagglutinins. The second patient was of blood type AB, and the test was not applicable.

Both of the above tests are simple screening tests for the diagnosis of agammaglobulinemia in suspected patients.

C. *Protein fractionation according to Cohn's method*: This is a more sensitive method; both patients had 100 mg. per cent gamma globulin and hence strictly speaking should be considered hypogammaglobulinemic.

D. *Serum globulin analysis* (Greenspan 48) measures the mucoprotein (representing 25 per cent of the alpha-1 globulins), the acid precipitable globulin turbidity (representing mostly alpha-2 and beta globulins), and the zinc sulfate turbidity (representing 90% of the gamma globulin). The globulin profile obtained is of value in diagnosing "dysproteinemic" diseases.

This analysis in our patients showed high alpha and beta globulins, suggestive of chronic infection; the gamma globulins were virtually absent but nevertheless detectable by this method.

E. *Bone marrow aspiration* revealed an absence of plasma cells in conformity with the studies previously described which relate the plasma cell to gamma globulin synthesis.

F. *Lymph tissue*: Patients lack palpable lymph nodes; the absence of adenoid tissue may be used as an x-ray screening test for congenital agammaglobulinemia (80-82). Lymph node biopsies have shown no discrete germinal centers and antigenic stimulation has not given rise to antibody synthesis (14). In acquired agammaglobulinemia, however, lymph node enlargement is seen in many patients (51, 53, 57, 63).

G. *Antibody response*: Studies reported include the lack of antibody development in agammaglobulinemic patients, after vaccination with tetanus, typhoid vaccine, pneumococcal polysaccharides, spotted fever and Q fever vaccines and the Salk polio vaccine (3, 9, 13). Positive Dick tests have been found after scarlet fever.

H. *Virus infection*: Patients seem to behave differently towards virus than towards bacterial infections. Patients who have had rubeola, rubella and varicella have been repeatedly re-exposed without acquiring a second infection. Similarly patients have had a normal course on exposure to certain adenovirus infections, the common cold, and poliomyelitis (3). One patient is reported to have developed paralytic poliomyelitis (with isolation of type I poliovirus from the stool) while on gamma globulin prophylaxis for hypogammaglobulinemia (49). Recurrent parotitis has been reported (1) but mumps virus may not always be responsible. Two patients have been reported with infectious hepatitis, whose disease progressed to a fatal outcome (3).

No antibody is demonstrable after poliomyelitis or influenza immunization, no complement-fixing antibody after an attack of mumps and no neutralizing antibody after herpes simplex infection (3, 4, 9, 13). Patients who have had a

normal primary response to vaccination have subsequently shown immune or accelerated reactions when revaccinated (3, 9, 83). Other patients have developed generalized vaccinia or vaccinia gangrenosa (84-88). Kozinn reports a fatal vaccination reaction in a three month old infant with agammaglobulinemia whose mother also had a low serum gamma globulin level. In this patient hemagglutination inhibition and neutralizing antibody could nevertheless be demonstrated. The lymph nodes draining the vaccination lesions failed to enlarge and treatment with gamma globulin and hyperimmune serum was unsuccessful (84). More recently antivaccinial gamma globulin has been successfully used (89). It should also be recalled that at three months of age the passively acquired antibody is at a low level. Both our patients were revaccinated. An accelerated take occurred within three to four days without complication, five years after the primary in case 1 and 1½ years after the original vaccination in case 2.

Whether the low levels of gamma globulin that are present in the agammaglobulinemic patient are sufficient to protect against virus infection but not against bacterial infection remains to be shown. The possibilities exist that a cellular antibody may be involved or that virus latency in some cells protects them against reinfection.

I. *Delayed sensitivity*: Bacterial and fungal hypersensitivity and positive purified protein derivative tests in patients with agammaglobulinemia are known (13, 16, 56, 64, 90). The transference of a positive purified protein derivative test and hence delayed sensitivity to a patient with agammaglobulinemia by the intravenous and subcutaneous injection of white blood cells from a sensitized donor has been reported; the reaction has persisted for two years, longer than can be attributed to the survival of the leukocytes (3, 9, 13, 16). Agammaglobulinemic patients can be sensitized to 2-4 dinitrofluorobenzene, a hapten, and to diphtheria toxoid by intradermal injection and this sensitivity can be transmitted to others by injection of viable leukocytes but not of serum. The mechanism for the development of delayed allergy is therefore intact in these patients (3, 13).

Good has shown that patients with congenital agammaglobulinemia support skin transplants from totally incompatible donors, whereas patients with acquired agammaglobulinemia reject homografts (3, 15). Antibody is produced in patients with acquired agammaglobulinemia by implanted lymph nodes, working for approximately 150 days, with ultimate rejection of the node. Delayed cutaneous hypersensitivity to the donor leukocytes also appeared (10).

J. *Other studies*: Complement and properdin levels have been found to be normal; the former may even be elevated, possibly indicating that it is not being utilized (8). Pituitary-adrenal function has been studied and found to be normal, and liver biopsy and function tests have been normal.

Hematological Findings

Patients suffer from a variety of hematological disturbances. The lack of plasma cells and lymphoid tissue has been mentioned. Neutropenia has been reported frequently, often of a cyclic nature (3, 39, 91, 92). Case 1 had no poly-

morphonuclear leukocytes at the time of his attack of otitis and Case 2 had marked neutropenia with his febrile illness. Transient or persistent lymphopenia has been reported, as well as eosinopenia, and a regenerative anemia (50, 53, 56, 58, 76, 86, 91, 92). Acquired hemolytic anemia with negative Coombs test has been seen (11, 44).

Primitive hemoglobin, normally found in the early months of fetal life has been found in association with severe hypoproteinemia and agammaglobulinemia (93).

"Collagen Disease" and Allergic Disorders

The association of agammaglobulinemia and "collagen disease" has been noted by several observers. Good and Janeway stress the frequency of rheumatoid arthritis, one-third of the former's patients having involvement of the large joints, especially the knees (16, 17, 39). Septic arthritis or its residual has to be ruled out. Scleroderma, dermatomyositis and lupus erythematosus have been reported (17). In the latter condition the possibility that the low gamma globulin is secondary to renal involvement has to be kept in mind. There is no recorded instance of glomerulonephritis, rheumatic fever or post-infectious encephalomyelitis (8).

Eczema has been recorded by Van Creveld (83) as has skin sensitivity to poison ivy (13). And more recently reports have appeared of acquired hypogammaglobulinemia associated with bronchial asthma (Freedman, S. O., Brown, E. B., and Myers, P. A.: Hypogammaglobulinemia and Bronchial Asthma. *Am. J. Med.*, 25: 961, 1958 and Pointer, T. S., and Karst, D. R.: Studies on Acquired Hypogammaglobulinemia. *New Eng. J. Med.*, 260: 15, 1959).

TREATMENT

The recommended treatment for patients with agammaglobulinemia is the injection of gamma globulin 0.1 gram/Kg. of body weight, intramuscularly every three to six weeks. The frequency of injection depends on the patient's need; cases have been reported who required injections every 20 days; the two patients reported here have not needed injections more than once every six weeks.

HYPERGAMMAGLOBULINEMIA

The syndrome of recurrent infections with hepato-splenomegaly, lymphadenopathy and hypergammaglobulinemia was first reported by Janeway et al. (94, 95). The usual sites of infection were the skin and respiratory tract and the patients frequently had pulmonary infiltrates, eosinophilia and neutropenia (91, 94, 96). Pathological studies revealed increased numbers of plasma cells in bone marrow, spleen and lymph nodes. All of the features of this syndrome are demonstrated by the following case.

CASE REPORT

E. P. (#81315) is a 12 year old white Jewish female who was admitted to The Mount Sinai Hospital for the first time because of recurrent infections. At two weeks of age, the patient developed a rash over her entire body. At four months of age, she had an episode characterized by fever, purulent ear drainage and, on her back, a crop of vesicles not sur-

rounded by erythema. From then to the present time, she has had recurrent temperature elevations, "fever blisters" on her tongue and lip, and ear drainage every three to four weeks. She was first seen at another hospital where sulfanilamide treatment was begun, but immediately discontinued because of granulocytopenia. It was not known if this had existed prior to the start of treatment. She was then treated with penicillin and discharged after six weeks. However, one month later, she again had fever with purulent discharge from both ears and she was seen at a second hospital where she had several further admissions with the same complaint. Granulocytopenia was repeatedly noted. Vincent's angina infection of the mouth was also diagnosed. She then had three admissions to a third hospital and five further admissions to the first hospital with the same complaints. She was treated with penicillin, but responded slowly. At one time, she was given blood transfusions, but nothing further is known about this episode. At two years and three months of age, she had a prolonged admission to the first hospital where bone marrow studies and cervical lymph node biopsy were done, but the results of these studies are not known. She then had continued episodes every three weeks of fever, purulent discharge from both ears, considerable lymph node enlargement, stomatitis and skin rashes. She was admitted to another hospital at the age of three and one-half years. She had purulent ear drainage and a purpuric petechial rash over the feet and legs. The only other physical findings of note were enlarged anterior cervical lymph nodes and shotty posterior cervical lymph nodes. The laboratory studies during that admission revealed anemia, an elevated sedimentation rate, and staphylococcus aureus hemolyticus was cultured from the right ear. The total proteins were 8.6 grams per cent, with 4.8 grams per cent of albumin and 3.8 grams per cent of globulin. X-rays of the mastoid areas were negative. X-rays of the long bones showed moderately severe osteoporosis. Her course showed continuous, though slow, improvement and it was noted that she had eosinophilia which gradually decreased as the number of her polymorphonuclear cells increased. Bone marrow study showed a relatively slight increase in nuclear red blood cells and lymphocytes. Tonsillectomy and adenoidectomy were done; the patient had a stormy post-operative course with high fever, associated with neutropenia and she had to receive 500 ml. of blood. Thereafter, she made steady improvement and was discharged. Another bone marrow study again showed an increase in eosinophilic cells, monocytes and lymphocytes.

Shortly after her discharge, she was readmitted to still another hospital with pneumonia. Thereafter, her course was as previously described with frequent admissions to a variety of hospitals. At the age of six years, a splenectomy was performed. The splenectomy was not followed by any marked improvement, except a slight decrease in the frequency of "fever blisters". She then received a course of steroid therapy which was continued for three years and then followed by a week's treatment with ACTH. There were no significant variations in her periodic relapses with fever and draining ears, except that her mother thought that there was a decrease in frequency and number of fever blisters.

Five weeks before admission, another bout of pneumonia occurred with cough, fever and right-sided flank pain. She was treated with antibiotics and after discharge had recurrent right ear drainage and fever. Two weeks before admission, the patient had a recurrence of the right-sided pain with fever and she was referred to The Mount Sinai Hospital.

A close review of the family history gave no evidence of Hodgkin's disease, diabetes or chronic illness. One of the patient's sisters died at the age of six months following illness characterized by vomiting and diarrhea. Another sister died at the age of two years of tuberculosis. Twin brothers died, one of diarrhea at the age of six months, and one following a severe bout of measles at the age of three years. A maternal aunt has gallbladder disease; the other aunt is healthy. The patient has two sisters by another father, one of whom has rose fever and atopic eczema. Three nephews and nieces, children of the patient's oldest sister are well.

The physical examination on admission showed blood pressure 98/60, respirations 12 per minute, pulse rate 100 per minute and regular, temperature 98°F.. The patient is a well developed thin female, pale and listless, and in no acute distress. There were no rashes or petechiae. The ears revealed bilateral cicatrization of the tympanic membranes with a

large circular perforation on the right. The mouth showed gingival inflammation, poor dentition and very large lingual tonsils. Examination of the lungs revealed percussion dullness in the right lower lobe area posteriorly, but nothing abnormal was detected on auscultation. Cardiac examination was normal. Abdominal examination was unremarkable except for a splenectomy scar in the left upper quadrant. Neuro-muscular examination was normal except for bilaterally defective hearing by air conduction.

Initial blood count showed a hemoglobin of 8.2 grams per cent, a white blood count of 12,650 cells per cubic millimeter with 32 per cent segmented forms, 15 per cent bands, 35 per cent lymphocytes, 9 per cent monocytes, 2 per cent eosinophils and 7 per cent atypical lymphocytes. Blood counts performed about three times weekly and sometimes daily showed her total white count thereafter to remain within normal limits. At intervals of 17 to 21 days, her polymorphonuclear leukocytes fell to between one and three cells per cent. At this time, there was often eosinophilia, once up to 14 per cent. The other cells were mostly lymphocytes with 10 to 15 per cent monocytes and occasionally some basophils, atypical lymphocytes and immature cells. Her red blood cell count was 3.72 million per cubic millimeter and the platelet count was 290,000 per cubic millimeter and normal on several repeat examinations. Red blood cell mean corpuscular volume was 90 cubic microns, mean corpuscular hemoglobin was 27 micromicrograms, and the mean corpuscular hemoglobin concentration was 30 per cent. Reticulocyte count was 1.2 per cent; serum iron was 42 gamma per cent. Iron binding capacity was 224 grams per cent. By the time of discharge her hemoglobin had risen to 11.1 grams per cent.

Bone marrow examinations were performed on three occasions with the following results: The marrow was hypercellular and showed adequate megakaryocytes. Myeloid elements were decreased, lymphocytes and eosinophils were increased and there was a marked increase in plasma cells. Immature myelocytic forms were seen but mature neutrophilic cells were rare or absent.

Four examinations of the total protein and albumin-globulin fractions were performed during her hospital stay as indicated in the following chart:

Total protein	Albumin	Globulin
9.1	2.2	6.9
7.4	3.6	3.8
8.3	4.0	4.3
7.0	3.9	3.1

Serum electrophoresis revealed diminished albumin, increased globulin and extremely elevated gamma globulin. The paper electrophoresis pattern showed a wide spread of the gamma globulin in contrast to the "spike" characteristically shown with myeloma and Waldenstrom's macroglobulinemia. Serum globulin fractionation showed an increase in zinc sulphate turbidity indicative of gamma globulin elevation, with normal mucoprotein and acid precipitable globulin turbidity. The patient's mother and two sisters had normal serum protein on electrophoresis; her father had a slight decrease in the gamma globulin level.

The calcium was 11.6 mgm. per cent; the phosphorous 3.1 mgm. per cent; uric acid 3.9 mg. per cent. The total bilirubin was 0.29 mgm. per cent and one minute bilirubin was 0.05 mgm. per cent. The thymol turbidity was repeated four times with the following results: 5.0 units, 2.9 units, 2.5 units, and 2.5 units. Cephalin flocculation was also repeated several times showing 3+ at first, then 2+, then negative on two occasions, and later 1+. The blood cholesterol was 214 mgm. per cent on one occasion and 252 mgm. per cent on another occasion with esters 194 mgm. per cent. Alkaline phosphatase was 8.6 KAU. Bromsulphalein test showed 3 per cent dye retention. The serum amylase was 65 units. The prothrombin time was normal on two occasions. A 24 hour urine specimen contained 30 mgm. of stereobilin per 24 hours, also within normal limits. Urinalysis was normal on several occasions.

Stool examination for occult blood was negative. Two blood smears for lupus erythe-

matous cells were negative; however, one of these examinations was at a time of neutropenia.

The nose and throat culture revealed pneumococcus, staphylococcus albus, neisseria catarrhalis and streptococcus viridans and the ear culture revealed a staphylococcus albus. Repeat examination during her hospital stay revealed staphylococcus aureus type A in both the nasopharynx and the ear drainage. Blood cultures were negative.

A purified protein derivative test was positive; gastric washings and guinea pig inoculations were negative. Serological test for syphilis was negative. The Schick test was negative; cold agglutination titer were 1:8, Streptococcus mg. agglutination: negative. Anti-streptolysin-O titer was 250 units. No complement fixing antibody test against adenovirus could be performed because the blood was anticomplementary. Direct and indirect Coombs tests were negative.

X ray examinations of the chest showed poorly defined haziness over the lower part of the right lung. X ray examination of the skeleton showed a moderate, but definite degree of demineralization of all bones. Mastoid examination showed no apparent abnormality of the left side, but there was slight overall haziness on the right side. X-rays of the mandible were negative.

The patient's course was characterized by recurrent ear infections at approximately three weekly intervals associated with ear drainage, gingivitis, swelling of the right side of the jaw and neutropenia. A dental consultant felt that she had a peridental infection above the first molar on the right, and that further orthodontic care was indicated. An otolaryngological consultant noted the findings reported above and audiology showed marked conduction deafness on the right side with only minimal impairment on the left. It was decided to follow the patient in the Out-Patient Department with repeated blood counts and attempt to control the infection with a variety of antibiotics.

DISCUSSION

The outstanding features of the syndrome described by Janeway et al., (94, 95) are:

1. Repeated infection.
2. Hypergammaglobulinemia.
3. Splenomegaly.
4. Neutropenia.

In their patients immunochemical analysis of the gamma globulin was normal (94) but electrophoretic study showed the level to be between 1.5 and 6.0 grams per cent, whereas the normal level ranges from 0.6 to 0.9 grams per cent. The patients had antibodies against the infecting organisms and bacterial antigen stimulation resulted in normal antibody response.

Causes for gamma globulin elevation have been mentioned in the first part of this paper. Contradictory evidence is at hand especially in the case of infection (96). High serum gamma globulin has been reported in fatal congenital agranulocytosis (97) as early as three and a half months of age (98). It may or may not be seen in patients with cystic fibrosis of the pancreas or bronchiectasis (94, 99). It may be low (100) or high (101) in acute leukemia and normal in chronic neutropenia (102, 103). It has been attributed to hypersensitivity (96, 99, 104, 105), but hyperimmunization does not produce it (106).

Other explanations for the high gamma globulin level are: The possibility of a dysgammaglobulinemia with abnormal or incomplete antibodies (107) or excessive antibody formation in response to one antigen preventing adequate

antibody synthesis or antibody rise in response to other antigens. Landing (108) raises the possibility of dysgammaglobulinemia in a syndrome in many respects similar to the above. It includes lymphadenitis, aphthous stomatitis, enteritis, osteomyelitis and pneumonia and elevated serum globulin. Organ study showed infiltration by lipid histiocytes containing yellow-brown pigment. Good reports an increased incidence of hypergammaglobulinemia with inflammatory liver disease in preadolescent and adolescent females (3).

Leonhardt (109) describes a family of fourteen siblings of whom four had a mild serum gamma globulin elevation; four of the others had a marked serum gamma globulin elevation; three of the latter had lupus erythematosus. The familial incidence raises the possibility of a genetic trait being responsible for hypergammaglobulinemia much as it has been implicated in agammaglobulinemia.

The accompaniment of hypogammaglobulinemia with collagen disease has been stressed. The accompaniment of collagen disease with hypergammaglobulinemia is known. An enzyme deficiency in protein synthesis probably on a genetic basis may be the fundamental disturbance causing the syndromes, and there may thus be a relationship between them.

Neutropenia may be responsible for the increased incidence of infection. The spleen does not seem to be the primary regulator of the neutrophil level for splenectomy has not altered that level even when a leukocyte agglutinin was demonstrated (103). Most patients have slight symptomatic improvement after splenectomy. Splenomegaly itself may be secondary to repeated infection, but in two siblings it was noted before infections increased in incidence (94).

Cyclic neutropenia has recently been reviewed (110); it is characterized by the regular disappearance of neutrophils from the circulation approximately every three weeks. The neutropenic stage is associated with fever, malaise and ulcers in the oral mucosa. There may be intermittent arthralgia, abdominal pain, pharyngitis, lymphadenitis and other infections in some patients.

Between attacks the neutrophils may attain normal levels. The total white blood count remains fairly constant so that there is a relative monocytosis.

Bone marrow studies have usually revealed hypoplasia with "maturation arrest" of the cells of the granulocytic series but immature cells disappear prior to the neutropenia and reappear before neutrophils return to the circulation.

Causes have been sought in the menstrual cycle; neither sex nor adrenal hormones could be implicated. Antibodies, C-reactive protein and delayed sensitivity were studied and found normal. The neutrophils migrate normally and have normal phagocytic activity and leukocyte agglutinins or serum factors toxic to neutrophils have not been found. Cyclic neutropenia therefore differs from chronic immunoneutropenia in which condition the clinical picture is similar but leukocyte agglutinins have been demonstrated in vivo and in vitro (103). Familial incidence has been reported (111).

Treatment by splenectomy or with adrenal hormones has resulted in symptomatic relief in a few patients but without a change in the blood picture. Good (110) reports a decrease in both the gamma globulin level and in the number of

plasma cells in the bone marrow in a patient on steroid therapy, without change in the neutrophil cycle.

The period of maximum symptomatology in our patient regularly preceded the maximum neutropenia by one or two days; this might be explained by "utilization" of the neutrophils.

Many attempts have been made to establish causal relationships between the clinical features listed above. Some explanatory theories have been presented. Cyclic neutropenia has been reported in association with agammaglobulinemia as well as with hypergammaglobulinemia. The entire syndrome may be a manifestation of a more fundamental disturbance.

SUMMARY

The physiology of the gamma globulins has been reviewed. Two brothers with hypogammaglobulinemia and a twelve year old girl with hypergammaglobulinemia and cyclic neutropenia are reported. Studies and theories pertinent to these conditions among many cases reported in the literature have been presented. The first syndrome is now well defined. It is not known whether hypergammaglobulinemia is a primary or secondary phenomenon, nor whether it can be related to the neutropenia.

The possibility has been raised that hypogammaglobulinemia and hypergammaglobulinemia are related and caused by an enzyme defect in protein synthesis.

ACKNOWLEDGMENT

The author wishes to express his gratitude to Dr. Stanley Lee for his helpful advice during the preparation of this review and to E. M. Russ for performing the protein fractionation.

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PSYCHIATRIC FINDINGS IN ADMISSIONS TO A MEDICAL SERVICE IN A GENERAL HOSPITAL*

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INTRODUCTION

The following report presents the findings of a preliminary psychiatric exploration, extended in time and based upon a large sample, that was made of medical ward admissions to The Mount Sinai Hospital of New York. The study was designed to answer the following questions:

1. What is the incidence of emotional illness among our medical ward patients? What types of psychiatric conditions are present?

2. Does any relationship exist between the medical and psychiatric conditions found? Is psychiatric illness found more often with certain medical diseases than with others?

3. Do the psychiatric conditions found show any relationship to age, sex, religion, or race?

4. Does a medical illness requiring hospitalization have any effect on the psychic equilibrium of the patients? Does this effect differ with the degree of emotional stability present?

PREVIOUS STUDIES

Zwerling et al. (1) studied 200 surgical admissions to a general hospital through psychiatric interviews, psychological testing and social histories. A diagnosable mental disorder was found in 86 per cent of the patients seen. In 48.5 per cent of the cases there was a significant relationship between the patient's surgical status and emotional disorder. This relationship consisted of a psychogenic simulation of surgical illness, behavior patterns producing surgical illness, psychological factors contributing to tissue changes and psychological factors aggravating surgical illness.

Berger (2) surveyed 1000 consecutive new patients in the office practice of internal medicine. He found that "72 per cent were . . . suffering entirely from functional diseases . . . the remaining 28 per cent possessed a large functional component in their otherwise organic illnesses." Mittlemann et al.,(3) studied 450

* This investigation was supported by a grant from The New York Foundation.

Presented at the Annual Meeting of the American Psychiatric Association, San Francisco, California, May 1958.

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male medical and surgical admissions in the 18 to 45 year age group by means of psychiatric interview and found that 30 per cent had some form of personality disturbance.

The marked difference in the findings of these surveys alone indicates a need for further study. The sample upon which the present study is based differs from these prior studies in that it includes medical ward admissions only, of all adult ages and both sexes.

PROCEDURE

Selection of Subjects

The medical service of The Mount Sinai Hospital has two male and two female wards with a liaison psychiatrist assigned to each. On a specified day, every week, each psychiatrist interviewed all patients admitted to his ward during the previous 24 hour period. These admissions, varying from none to six per ward, comprised the sample of this study. The collection of data extended over nearly one full year so that seasonal variations in numbers and types of admissions were controlled. When a liaison psychiatrist was on vacation, a fifth psychiatrist (S. F.) gathered the data. During the data collecting period, a total of 281 patients were examined. Of these, 28 could not be interviewed, either due to the serious nature of their illness or because of a language barrier. The sample of this study, therefore, comprises 253 medical ward admissions.

It should be borne in mind that the findings with the sample used in this study cannot be extended to the general population. First, all subjects were ill enough to require hospitalization, setting the sample aside from the rest of the population. Further, the unitary nature of any organism indicates that a medical disease requiring hospitalization may possibly have been induced or made more severe by stress based on psychic factors. On the other hand, a precariously maintained psychic balance may be upset by organic processes, leading to a more blatant picture of psychiatric disease than could otherwise be seen.

Another deviation from the general population was that 54.7 per cent of the patients in our sample were Jewish and cultural-religious differences may be related to differences in child-rearing ways and subsequent differences in types of psychiatric illness. An additional deviation of this sample from the general population was that the subjects were all urban ward patients.

Collection of Data

Each patient was interviewed by one of the five liaison psychiatrists for a maximum of one hour and each interview included a brief mental status examination, and a psychiatric, social, and psychosexual history. While patients may have been seen for further interviews since the interviewer was also the ward liaison psychiatrist, this study is based essentially upon the initial interview. Each examiner included a diagnostic evaluation and a characterological sketch of the patient in his report. The following additional data were obtained from the medical chart: age, sex, race, marital status, religion, and final medical diagnosis.

RESULTS

Frequency of Psychiatric Illness

The diagnostic system employed in this study varied slightly from that published in 1952 by the American Psychiatric Association in that we replaced the APA headings of "Personality Disorder" by "Character Disorder" with appropriate subheadings, and "Brain Syndrome" by "Organic Brain Disease" and "Senility".

Although any diagnostic system must necessarily have recourse to discrete diagnostic categories which cannot do full justice to the complex, adaptive and variable structure of the human psyche, it was always possible to make a diagnosis within this framework. On occasion, when it was necessary to make more than one diagnosis, the patient was classified so as to reflect the more profound psychiatric picture for the purpose of this study.

Case I

A 65 year old woman showed a life long pattern of moderately heavy drinking, marked dependency, labile social relations, and minimum overt anxiety or depression; indicating an infantile character disorder. However, during the interview, she manifested numerous signs of a senile psychosis and she was so classified for this study.

The type and frequency of psychiatric illness found are summarized in Table I. The outstanding finding is that some diagnosable psychiatric condition was found in 169 (66.8%) of the 253 patients studied. The benign psychiatric disorders were the most frequently found psychiatric illness. There were 35 cases (13.7%) of Character Disorders and 91 cases (36.0%) of Psychoneuroses of all types. Functional psychoses were found in 19 cases (7.5%). Of these, Schizophrenias, either overt, latent or in remission, totalled 14 cases (5.5%). Senility, with or without psychosis, was found in 13 patients (5.1%).

Medical Disease and Psychiatric Illness

Of the study sample of 253 patients, final medical diagnoses were obtainable for 208. The remaining 45 cases were either still hospitalized or, if discharged or deceased, had as yet no final diagnoses charted. A difficulty in comparing medical disease and psychiatric illness was that the 208 patients had over sixty different medical diseases listed as the primary diagnosis. Only one, arteriosclerotic heart disease, appeared as many as twenty times, and only one other, diabetes mellitus, as often as fifteen times. For this reason, individual medical disease entities could not be well correlated with the frequency of psychiatric illness. Instead, the data were synthesized under three major headings and then correlated with the frequency of psychiatric illness (Table II).

1. Those diseases for which at least a partial psychogenic etiology has been claimed, and variously called psychosomatic diseases, organ neuroses, or psychopathophysiological disorders. These included 51 cases of whom 82.3 per cent were found to have a concurrent psychiatric disease.

2. Those patients presenting an initial diagnostic problem and a later conclu-

TABLE 1
Summary of diagnoses

Classification	Number and Per Cent of Patients
A. Character disorder	
Mixed type	11 (4.4%)
Infantile	18 (7.1%)
Other	6 (2.3%)
All character disorder	35 (13.7%)
B. Psychoneurosis	
Mixed type	16 (6.3%)
Hysteria (conversion and phobic)	13 (5.1%)
Obsessive-compulsive	4 (1.6%)
Neurotic depression	41 (16.2%)
Anxiety reaction	15 (6.0%)
Other	2 (0.8%)
All psychoneuroses	91 (36.0%)
C. Functional psychosis	
Schizophrenia	14 (5.5%)
Psychotic depression	2 (0.8%)
Involuntional psychosis	2 (0.8%)
Other	1 (0.4%)
All functional psychoses	19 (7.5%)
D. Senility	
Without psychosis	9 (3.5%)
Senile psychosis	4 (1.6%)
All senility	13 (5.1%)
E. Organic brain disease	
Without psychosis	7 (2.7%)
With psychosis	1 (0.4%)
All organic brain disease	8 (3.1%)
F. Mental defective	1 (0.4%)
G. Psychiatric disease, undiagnosed	2 (0.8%)
Total with psychiatric disease	169 (66.8%)
Total without psychiatric disease	84 (33.2%)

sion that the symptoms were functional. These included 19 cases, of whom 89.3 per cent had a concurrent psychiatric illness.

3. Those comprising all other medical diseases. These included 138 cases of whom 60.9 per cent were found to have a concurrent psychiatric illness.

This last percentage is significantly less than that found among patients with "psychosomatic" disease. It is also significantly less than the proportion of psychiatric illness found in the group with functional diagnostic problems. The extremely high incidence of psychiatric illness among those patients who were

TABLE II
Medical and psychiatric disease

Category	With Medical Diagnosis	With Psychiatric Diagnosis
I. "Psychosomatic" group		
Diabetes mellitus	18	15
Peptic ulcer	11	8
Hypertensive CVD	8	6
Ulcerative colitis	4	4
Skin & respiratory allergies	5	4
Others	5	5
Total "psychosomatic" group	51	42 (82.3%)
II. Functional "diagnostic problem" group		
Gastrointestinal	10	9
Cardiovascular	5	5
Musculo-skeletal	3	2
Respiratory	1	1
Total functional group	19	17 (89.5%)
III. Other medical diseases	138	84 (60.9%)

diagnostic problems agrees with the findings reported by Kaufman and Bernstein (4) who studied 1000 unselected cases from a consultation service for diagnostic problems. They found that 81.4 per cent suffered from a psychiatric illness. The present findings with patients showing functional disturbances strongly implies that psychogenic factors are closely related to the presented pattern of symptoms.

Relationship of Psychiatric Illness to Age, Sex, Religion, and Race

While our group of 253 subjects showed considerable diversity as to age and religion; contained both Negro and white patients, and were about equally divided as to sex, it was not so constituted as to justify generalizations for these variables. However, for our group alone, certain characteristics were noted and these are presented below.

Age Differences

The age of 246 of our subjects was known. Distributing the group by decades, the median age is approximately 55 while the range is from 14 to 89 years. The sample covers eight decades with the mid-point being the age of 50. One hundred and four subjects were 50 years old or younger while 142 were from 51 through 89.

The frequency and type of psychiatric disease for all subjects by decades are summarized in Figure 1 and Table III. If the four older decades are compared with the four younger decades, we note the following:

1. As expected, senility, with or without psychosis, is entirely limited to subjects over 60 years of age.

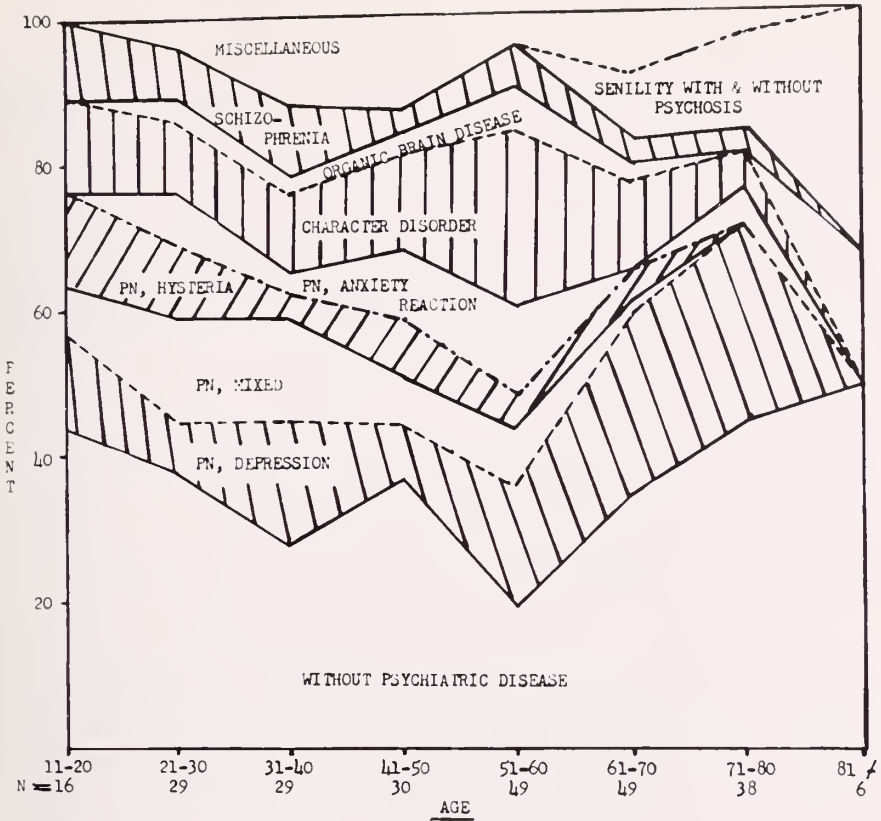


FIG. 1

TABLE III

Relative incidence of psychiatric disease for both sexes, older versus younger sample halves

Diagnosis	Frequency in Pts. 50 Yrs. & Younger N = 104	Frequency in Pts. 51 Yrs. & Older N = 142	Diff. in Per Cent	Sigma of Difference	C. R.	Level of Significance
Psychoneurosis mixed type....	10.6%	3.5%	7.1	3.4	2.09	.05
Psychoneurotic depression....	10.6%	21.1%	10.5	4.6	2.28	.05

2. Psychoneurosis, mixed type, is significantly more frequent in the four younger decades.

3. Psychoneurotic depression is significantly more frequent in the older half of the group. It is, in fact, the disorder most frequently found among patients over 50 years of age, occurring in 21.1 per cent of all subjects. This may be a response to illness at this age, with the illness secondarily representing the irrevocable loss of another body function. In the male group alone, it occurs six times more frequently in the over 50 age group as in the under 50 group (critical ratio (C.R.)

TABLE IV
Relative incidence of certain psychiatric entities, Jews versus non-Jews

Diagnosis	Frequency Among Jews N = 126	Frequency Among Non- Jews N = 98	Diff. in Per Cent	Sigma of Difference	C.R.	Level of Significance
Neurotic depression	23.8%	8.1%	15.7	4.8	3.3	.01
Hysterias	2.4%	9.2%	6.8	3.2	2.1	.05

equals 3.12). It is also noteworthy that there was no significant age difference in the incidence of neurotic depressions among female patients. This indicates that the age difference found for the total sample is due to the marked increase with age found among the males.

Among our female patients, two differences in frequency of psychiatric diseases were found when older and younger decades were compared.

1. Significantly more younger than older women were found to have a psychoneurosis with hysterical features (C.R. equals 2.30).

2. Significantly more younger than older women were found to have a mixed psychoneurosis (C.R. equals 1.99).

Sex Differences

When males were compared with females, one significant difference was found; namely, that females were diagnosed as psychoneurotic depression more frequently than were males (C.R. equals 2.01). The authors also expected to find a greater frequency of hysteria among the female patients but, although a higher proportion was found, the difference was not statistically significant.

Religious Differences

The religious affiliation was known for 231 of the 253 subjects; 126 (54.7%) were Jewish, 58 (25.0%) were Catholic, 40 (17.2%) were Protestant, and 7 (3.1%) were of other religions. Our comparison was made between the 126 Jews and the 98 Christians, i.e., Catholics and Protestants combined. It should be borne in mind that our findings can apply only to this study group as no attempt was made to stratify our sample as to religious affiliation.

Significant differences were found in two of the diagnostic categories (Table IV). The Jews in our group were found to have neurotic depressions more frequently than did the non-Jews. On the other hand, hysteria was found more frequently among the non-Jews.

As a large proportion of the Roman Catholics were also Puerto Rican while many of the Protestants were also Negro, these factors were studied separately to evaluate possible bias in our figures. The frequency of hysteria for Catholics was nine per cent; for Puerto Rican Catholics it was six per cent. For all Protestants it was ten per cent, and for Negro Protestants, eleven per cent. This indicates that the religious differences found were not biased by the factors of race or national origin.

Race Differences

When races were compared, no significant difference was found in the patterns of psychiatric illness.

A Preliminary Study of the Effect of Medical Illness on Psychic Equilibrium

When our study had been about two-thirds completed, the interviewing procedure was amended in an attempt to compare the patients' psychological status before and after the beginning of illness. Each patient was asked to report any changes that he noted in his feelings since the illness started and whether the illness led to any difficulties in terms of family, job, etc.. Affective changes and patterns of defensive functioning in the face of the medical illness were also noted.

In addition to the qualitative description, an attempt was made to rate quantitatively the impact of the medical illness. A nine-point scale was devised, assigning a score of one when physical illness was followed by an acute psychotic break, a score of three to the appearance of moderate symptoms, and a score of five when no change occurred in the psychiatric status. Scores of seven and nine are the reverse of three and one, respectively. Scores of two, four, six, and eight were similarly assigned in the sliding scale.

While this phase of the study is based on only 84 patients and only the diagnostic categories of "Psychoneurosis" (39 cases) and "Without Psychiatric Disease" (34 cases) were large enough to compare statistically, the results were sufficiently interesting to include in this report.

The psychoneurotic group has somewhat impaired ego defensive functioning, as seen by the fact that symptom formation had already taken place prior to the physical illness. With the impingement of further stress on the organism, due to medical disease, we should expect to find some increase in neurotic symptoms. The subjects without psychiatric disease have better integrated egos and should be able to withstand the added stress of disease to a greater degree than the neurotic subjects. On this basis, we expected—and found—that a greater proportion of psychoneurotic patients than patients without psychiatric disease reacted to their medical illness with at least a moderate increase (score of "3" or less) in their neurotic symptoms or in their feelings of psychic discomfort. The respective percentages were 64 and 26 and the difference was statistically significant (C.R. equals 3.45).

Only three neurotic patients, and no patients without psychiatric disease, reacted with a moderate, or greater, improvement in their feelings of well-being or in symptoms, and this difference was not statistically significant.

The outstanding qualitative finding was the wide variety of psychiatric reactions following physical illness. Although 29 out of the 84 patients showed little or no change in their psychic status and were assigned a score of "5", the remainder reacted with depression, anxiety, elation, and even remission of their psychiatric symptoms.

Case II

A 61 year old married Negro post office employee, neat, dignified and soft spoken, had been depressed for two years. He dated his depression to a growing feeling that he would never get adequate living quarters or neighborhood for his family and that his adolescent daughters would therefore become delinquent. The recent out-of-wedlock pregnancy of a 16 year old daughter increased his previously mild depression. His medical illness (ASHD with myocardial infarction) led to a further intensification of his depression. Crying, he told the interviewer that his age and his new illness made it appear that the family "would never get away."

Case III

A 44 year old woman had a long standing psychoneurosis marked by anxiety, compulsive housecleaning and occasional depression. In 1952, she developed Hodgkin's Disease, took to her bed, developed demanding attitudes towards her family, and lost her symptoms. She told the interviewer with obvious relish that doctors, welfare people, landlords, etc., all tried to take advantage of her but she knew just how to tell them off and battle with them until they withdrew, defeated. Her present admission was for a complication of her Hodgkin's Disease and it had no effect on her psychiatric status.

At times, the impingement of physical illness on the psychic apparatus makes the use of certain ego defenses more obvious. It is our impression that such mobilized defenses were more readily observable in those patients who otherwise showed little change in their psychic equilibrium. This is possibly due to the fact that the newly mobilized defenses were "successful" and could be maintained during the course of the illness. Besides the ubiquitous regressions, instances of repression, isolation, denial, introjection, and projection were observed.

Case IV

A 50 year old man with myocardial infarction showed no interest in his diagnosis and asked no questions about his condition. During visiting hours, he made no reference to his own status but asked many questions about his children.

Case V

A well educated middle aged man with myocardial infarction showed no change in his emotional status. However, he was very curious about his disease, its etiology and statistics connected with it. When a laboratory procedure was carried out by the medical staff, he attempted to become an intellectual participant, as if he were a new intern on the ward.

Case VI

A 43 year old man was admitted for the third time for relatively mild congestive heart failure associated with his inactive rheumatic cardiac disease. Quite familiar with the hospital, he greeted the interviewer in a jovial manner and was a spontaneous interviewee. He confided that he had been alarmed and depressed during his first admission for CHF two years ago, but that his present cheerful mood was part of his usual optimistic personality. He attributed this to his "realization" that he had nothing to worry about. "After all, it's not my problem; it's the doctors' problem. So I let *them* worry about it!"

DISCUSSION

The most important implication of this study is related to the fact that two-thirds of a group of ward medical patients suffer from some psychiatric illness.

In addition, these patients are hospitalized for the medical illness and, most often, they either ignore the psychiatric problem or regard it as an unwanted corollary phenomenon unrelated to the medical illness. It is therefore important that the ward medical staff does not adopt a similar attitude. When we consider that the majority of patients react to their medical illness with either a change in their psychiatric symptoms or heightened defensive measures, the need for psychiatric awareness on the part of the medical staff becomes even more important.

Enhanced medical staff awareness can assist recovery of a patient in a number of ways. First, the more obviously disturbed patients can benefit from psychiatric consultation and recommendations. A second and more important contribution can be made by the internists themselves. Brief psychiatric consultations alone can have no profound effect because recommendations still are carried out by the medical staff and because reality will always bring the patient back to the facts that the basis for hospitalization is a medical illness and that his most intensive contact must, of necessity, be with the medical attending and house staff. This intensive patient-physician relationship leads to transference phenomena and makes it possible for the internist to alleviate some psychiatric symptoms without engaging the patient in psychotherapy. For example, one striking finding was that over one-fifth of the older patients have neurotic depressions, either stimulated or exacerbated by their medical illness. If the medical staff is prepared to respond to such reactions, measures such as early activity and responsibility can be taken to counteract the patient's feeling of loss of body function and self-esteem. Anxious patients can be helped by a few minutes of reassurance by the house staff. Even those patients who show only heightened ego defensive measures can be assisted. If efforts are made to recognize such defenses, not to interfere with them, but to support them, the patient can be aided in his efforts towards both physical and psychical recovery. The patient who denies the implications of his illness in order to avoid a depressive reaction can be helped through stressing functions that the patient will still possess. A patient who avoids anxiety through intellectualization can even be helped by a brief discussion of his laboratory tests.

The broader implication of these findings must relate to medical education. Although it is easy to pay lip service to the concept of organismic unity, undergraduate and specialty education still tends to isolate the different medical fields from each other with the result that unrelated phenomena come to be regarded as unwelcome intrusions rather than as additional manifestations of the whole patient. As long as the psychiatric patient is thought of only as an individual in psychotherapy or in a mental hospital, medical evaluation and treatment will remain incomplete.

SUMMARY

1. A psychiatric survey of 253 ward medical patients of The Mount Sinai Hospital of New York revealed some diagnosable psychiatric disorder in 66.8 per cent of the cases. Patients with "psychosomatic diseases" or functional disorders had an even higher incidence of psychiatric illness.

2. Age, sex, and religious differences in patterns of psychiatric disease were found.

3. Patients react to physical illness in a variety of ways with the pre-illness psychic structure and stability playing an important role.

4. The implications of these findings for medical management are discussed.

5. The significance of these findings in relation to basic undergraduate and graduate medical training is stressed.

ACKNOWLEDGMENT

The authors express their appreciation to Dr. Alexander B. Gutman and the Department of Medicine for their cooperation in this study.

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DEMONSTRATION OF CARCINOMA CELLS IN THE BLOOD STREAM

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INTRODUCTION

The lymphatic mode of spread of malignant epithelial tumors has been known and extensively studied for many decades. The impact of these studies was responsible for the introduction of radical surgery in cancer and to a large extent, still dominates the present day concepts of cancer therapy. Thiersch (10) in 1865 was one of the first to recognize malignant epithelial cells in venous blood and expressed the opinion that some of these cells could retain their malignant potential during their brief passage in the blood stream. Since his time, until the last decade, only one systematic study of hematogenous spread of carcinoma was carried out. Dunlop and Pool (1) in 1934 were able to demonstrate atypical cells in the peripheral blood of 17 of 40 patients with advanced carcinoma.

The renewal of interest in the hematogenous spread of tumors coincides with the opinion of many surgeons that radical surgery for cancer has almost reached its limits. It appears unlikely that further extension or improvement of existing surgical procedures for cancer will modify considerably the cure rate for carcinoma. The attention of many investigators is shifting, therefore, toward the hematogenous spread of carcinoma, the rules governing it and the possibilities of minimizing or preventing it.

Numerous studies on the subject have been carried out since 1950, the most extensive ones by Engell (2), Cope and collaborators (6, 7) and Moore (4). It was the aim of the present study to reproduce the results obtained by others and to evaluate the methods as to their practical applications.

TECHNIQUES

Carcinoma cells are present in the blood stream in concentrations much lower than other cellular elements. These cells can be demonstrated by using five to ten cubic centimeters of whole blood and separating them from as many normal blood elements as possible. Once the separation is accomplished, the specimen is spread on glass slides for staining. The process of separation has to be carried out without damaging or altering the tumor cells in order to permit a reliable cyto-diagnosis.

The separation of epithelial cells from erythrocytes, can be accomplished by two techniques:

1. Hemolysis Method: The erythrocytes can be hemolysed by a variety of agents and separated by centrifugation from the rest of the cellular elements. Acetic acid and hydrochloric acid have been used for this purpose, but the slides ob-

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Supported in part by the Department of Surgery Research Fund.

tained are generally of poor quality. Saponin, used by Engell (2) gives generally better results, but the hemolysis is often incomplete.

2. *Fibrinogen Method:* Bovine fibrinogen added in adequate amounts to the blood produces rouleau formation and rapid sedimentation of erythrocytes. The plasma containing all other cellular elements can be decanted after 20 to 40 minutes when red cell sedimentation is almost complete. This method appeared to us superior to other techniques applied.

Separation of tumor cells from leucocytes and other cells of the hematopoietic system is much more difficult due to the overlap in size, specific gravity and other characteristics. Selective centrifugation over a layer of albumin of 1.065 specific gravity has been suggested and used by Roberts (6). In our hands, this method yielded poor results. Carcinoma cells added to the blood were consistently found to precipitate with the white elements when treated by this method. The use of millipore filters of five millimicron pore size seems to us more promising in spite of a certain overlap in sizes. Our personal experience with this technique has been insufficient to permit any conclusions.

DIAGNOSTIC CRITERIA

The diagnosis of individual tumor cells is essentially based on cytologic criteria of malignancy as generally described (11). The size and shape of cells, increase in amount and abnormal pattern of nuclear chromatin, number and shape of nucleoli and changes in nucleocytoplasmic ratio are the most important diagnostic features. Unequivocal diagnosis is only permissible when several malignant features are present. Similarity of the cells demonstrated to those seen in the contact smears prepared from the tumor can be considered as supportive evidence to their origin.

METHOD OF INVESTIGATION

The technique used in this study was similar to those used by Roberts (6) and Moore (4). To ten cubic centimeters of blood withdrawn from an antecubital vein 0.5 cubic centimeters of heparin and three cubic centimeters of fibrinogen solution was added. The fibrinogen solution used was Armour's Fraction I adjusted to a pH of 7.4 and containing about 14 milligrams of fibrinogen per cubic centimeter. As soon as the sedimentation of red cells was completed (usually 10 to 40 minutes) the supernatant fluid was carefully removed and centrifuged for ten minutes at 1000 revolutions per minute. As much as possible of the sediment was spread on four slides and stained by the Papanicolaou technique.

In the first few cases the selective centrifugation over albumin as described by Roberts (6) was used. This step was omitted in the latter cases in view of the poor results obtained in the experiments with suspensions of carcinoma cells.

In cases where veins draining the tumor were studied, blood was withdrawn directly from the vein immediately after removal of the surgical specimen and treated in the same manner.

All slides were carefully examined microscopically under low power, and cells unusual in shape, size or amount of chromatin were studied under high power.

The group studied consisted of 38 cases. Fifty specimens of peripheral blood and six specimens from veins draining the tumor were examined.

The patients in this investigation were all referred to the Surgical Service for operation. None had clinically obvious metastasis and all, but three, proved to have resectable lesions at time of surgery. This group represent fairly early lesions and is comparable to the groups classified in other reports as curable patients.

RESULTS

Carcinoma cells were found in six of 50 specimens examined (Table I), giving a total incidence of 12 per cent. This incidence is comparable to findings of Roberts (6) and Engell (2) on curable patients, but much inferior to the figures of Moore (4), though Moore included in his group a large number of advanced inoperable cases. The incidence of positive findings seems somewhat higher in breast carcinoma than in lesions of the gastrointestinal tract (Table I). In 14 cases, peripheral blood specimens were studied within the first twenty-four hours after surgery. No significant increase in carcinoma cells could be demonstrated (Table II). In nine cases of breast carcinoma studied before surgery and on the first and third postoperative days, (Table III) the findings remained essentially the same.

In all cases of carcinoma cells encountered in the peripheral blood, the number of cells permitting positive diagnosis was very small and no clumps of cells were noted.

In six cases, blood from veins draining the tumor was examined (Table IV). Carcinoma cells were found in two of four cases of colon carcinoma and one of

TABLE I
Occurrence of carcinoma cells in peripheral blood

Site of Tumor	Number of Specimens	Number Positive	% Positive
Colon	17	1	6
Breast	21	3	14
Stomach	6	1	16
Lung	4	0	0
Ovary	1	0	0
Pancreas	1	1	100
Total	50	6	12

TABLE II
Incidence of cancer cells before and after surgery

	Number of Cases	Number Positive	% Positive
Preoperative	36	4	11
Postoperative	14	2	15

TABLE III

Occurrence of cancer cells before and after surgery in 9 cases of carcinoma of the breast

	Preoperative	Postoperative	
		1st Day	3rd Day
A. H.	Positive	Negative	—
C. M.	Negative	Negative	Positive
G. L.	Negative	Negative	—
H. S.	Negative	Negative	Negative
J. H.	Negative	Negative	—
N. F.	Negative	Positive	Negative
C. F.	Negative	Negative	—
P. M.	Negative	Negative	—
W. M.	Negative	Negative	—
Total cases	9	9	3
Number of positives	1	1	1
Incidence of positives	11%	11%	33 $\frac{1}{3}$ %

TABLE IV

Cancer cells in veins draining the tumor (after surgical manipulation)

	Site of Tumor	Presence of Tumor Cells
A. F.	Stomach	Negative
E. M.	Colon	Positive
T. P.	Colon	Positive
B. V.	Colon	Negative
D. T.	Colon	Negative
F. M.	Stomach	Positive
Number of cases	6	
Number of positive cases	3	
Incidence of positive cases	50%	

two cases of gastric carcinoma. Contrary to the findings in peripheral blood, larger number of cells including clumps, were noted.

COMMENTS

Carcinoma Cells in the Peripheral Circulation

The studies of peripheral blood in patients with curable carcinoma revealed a low incidence of positive findings varying between 10 and 15 per cent. In this group no significant increase was noted after surgical manipulations. The demonstration of tumor cells in the peripheral blood remains a technically difficult problem. The slides prepared contain very few tumor cells scattered among a large number of blood elements.

The significance of the tumor cells encountered and their role in the causation of metastasis is not known at present. While they are more frequently encoun-

tered in advanced lesions, this could be interpreted as the result, rather than the cause, of the widespread dissemination. Only further experimental studies can enlighten us whether the single cancer cells observed are living cells, capable of multiplication under certain circumstances, rather than dead cells shed by the tumor.

Carcinoma Cells in Veins Draining the Tumor

Carcinoma cells are found in the veins directly draining the tumor much more frequently than in peripheral blood. The reported incidence varies from 30 to 75 per cent. Numerous cells and clumps were noted in many cases. Engell (2) found tumor cells before any surgical manipulation and reported no significant increase at the end of the surgical procedure. Roberts (6) found a significant increase in 5 out of 6 cases studied. No attempt to evaluate this factor was made in our study. These studies furnish ample evidence that large numbers of carcinoma cells are being discharged into the veins draining the tumor before any operative trauma. It appears plausible, therefore, that the cells discharged during surgery constitute but a minimal fraction of those spread during the months preceding surgery. Without minimizing the value of precautions taken during surgery, no significant reduction in occurrence of metastasis can be expected from these measures alone.

The blood from veins draining the tumor can be obtained, in most cases, only at the time of surgery and this constitutes a serious limitation of the method.

CONCLUSIONS

The occurrence of tumor cells in the peripheral blood of patients with curable carcinoma is infrequent and their significance unknown at present. Tumor cells are encountered frequently, and in relatively large numbers, in veins draining the lesion. Their study is limited, however, to the specimens available at the time of surgery.

Whether this method will prove of value in establishing the prognosis of cure in patients with early carcinoma cannot be stated on the basis of our investigations. The possibility of using this method for evaluation of the therapeutic effects of anti-carcinogenic compounds requires further study and improvement of techniques.

ACKNOWLEDGMENT

The author wishes to acknowledge the valuable assistance and guidance of Dr. Herbert E. Nieburgs, Research Associate, Department of Pathology, The Mount Sinai Hospital, New York 29, N. Y.

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MYASTHENIA GRAVIS WITH SARCOIDOSIS

A CASE REPORT

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The occurrence of myasthenia gravis in a patient with sarcoidosis has not been previously reported. The absence of a specific etiology requires the fulfillment of certain criteria for the diagnosis of each disease, which in themselves, have not been universally agreed upon. The following report describes a patient with typical myasthenia gravis and sarcoidosis involving the liver and voluntary muscles, with erythema nodosum and a positive Nickerson-Kveim test. In this patient, there was apparently a complete remission of the myasthenia gravis after treatment with Prednisone®. Since muscle weakness per se is a manifestation of sarcoidosis (1-10), clearcut evidence for myasthenia gravis is mandatory.

CASE REPORT

A. C. (MSH No. 61460), a forty-six year old Puerto Rican housewife, was first seen in The Mount Sinai Hospital Out-patient Department in November 1955, because of weakness, weight loss, and diplopia of one year's duration.

The past history revealed a luetic infection in 1935 which was treated with bismuth. She had an uncomplicated myomeotomy and appendectomy in 1941.

The patient enjoyed good health until November 1954 when she experienced the gradual onset of generalized weakness, left frontal headaches, blurred vision and diplopia. In January 1955, she noted the onset of migratory polyarthralgias without acute arthritis, vague abdominal pains and occasional nausea. During the year prior to her first clinic visit, she had lost 25 to 30 pounds. Physical examination revealed mild generalized weakness, and diplopia on left lateral gaze. Laboratory studies done prior to her first hospital admission revealed a peripheral eosinophilia of 42 per cent and an eosinophilia of the bone marrow. Stools were negative for ova, cysts and parasites and rectal biopsy did not reveal *Schistosoma* ova.

She was first admitted to The Mount Sinai Hospital medical service on February 20, 1956, to investigate the weakness and diplopia. The only significant physical findings at that time were bilateral pterygia and strabismus on left lateral gaze. The white cell count was 6,700 per cu. mm. with 20 per cent eosinophilia. Other studies including urinalysis, urea nitrogen, blood sugar, total protein, albumin, globulin, chest film, stools for ova and parasites, serologic tests for syphilis, filariasis, echinococcus and trichinosis were negative as were a lumbar puncture and skin and muscle biopsy done at that time. Electroencephalogram revealed an irritative focus in the left anterior temporal area. The patient was

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discharged on March 7, 1956 with a diagnosis of eosinophilia of unknown etiology.

The second admission to The Mount Sinai Hospital was for removal of a pterygium of the right eye.

The third admission was to the Neurological Service of The Mount Sinai Hospital in August 1956 because of diplopia. Examination revealed slight weakness of the upper extremities bilaterally, nystagmus on lateral gaze, and monocular diplopia in the left eye on left lateral gaze. An alternating lateral strabismus was elicited on cover test. An ophthalmological consultant's opinion was that the monocular diplopia was anatomically and physiologically inexplicable and the patient was interpreting blurred images as doubled vision. The patient was discharged without the diagnosis of a neurological disease having been made, although the EEG remained unchanged.

The patient continued to have episodes of vertigo, tinnitus, weakness, and migratory polyarthralgias. Three months prior to her fourth admission she noted an increasing amount of generalized peripheral weakness, as well as some difficulty in swallowing. Three weeks prior to this admission she developed a fever to 102° F. and acute pain and swelling of the small joints of both hands. An additional fifteen pound weight loss for six months was noted. Her dysphagia for liquids and solids progressed and on November 14, 1957, the patient was admitted to The Mount Sinai Hospital for the fourth time.

Physical examination on admission revealed a temperature of 101.4° F., pulse 108, respirations 24, blood pressure 102/58. She was a tall well developed but poorly nourished Puerto Rican female who appeared lethargic and chronically ill. There was strabismus on left lateral gaze and binocular diplopia. The thyroid was normal. There was no lymphadenopathy. The chest had a normal A-P diameter and the lungs were clear to percussion and auscultation. The heart was normal in size and a grade 2 apical systolic murmur was present. The liver was palpated 2 cm. below the right costal margin, firm and non-tender. The spleen was not felt. In the extremities, moderate generalized peripheral weakness was noted. There was no evidence of joint deformities or effusions. There were several raised tender erythematous nodules over the pretibial area having the appearance of erythema nodosum. The neurological examination showed the cranial nerves to be intact. There were no sensory or reflex changes.

Laboratory data included a urinalysis showing a few red blood cells and 10 white blood cells per high power field, no proteinuria. Hemoglobin was 10.4 Gm. per cent. The white blood cell count was 8100 per cu. mm. with an eosinophilia varying from 6 to 11 per cent. The Wassermann and Kahn now were positive. The Treponema Immobilization Test was non-reactive. The serum globulin was 4.9 Gm. per cent and 5.6 Gm. per cent and the albumin was 2.7 and 3.1 Gm. per cent. The urea nitrogen, blood sugar, calcium, phosphorus, serum electrolytes, bilirubin, cholesterol, alkaline phosphatase, thymol turbidity, cephalin flocculation and prothrombin time were within normal limits. The tests for the L.E. phenomenon were negative. Antistreptolysin titer was 125. The amoeba complement fixation test was negative. Tuberculin skin test with first strength

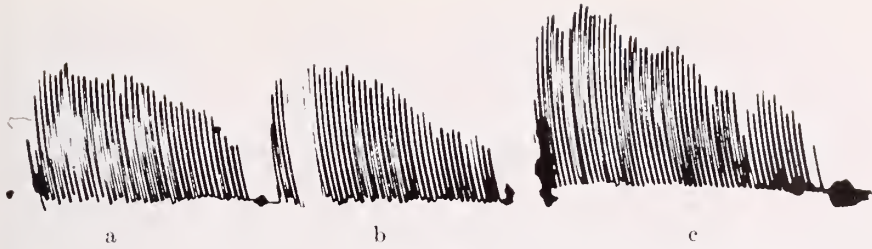


FIG. 1. Positive Tensilon test demonstrating: a. baseline, b. 0.5cc. normal saline intravenous control with no response, c. 0.5cc. Tensilon (edrophonium chloride) intravenous with myasthenic response.

purified protein derivative (1:10,000) was positive. The Frei test was negative. Lumbar puncture was again within normal limits.

The clinical course was characterized by moderate generalized weakness, dysphagia and diplopia. Low grade fever to 101°F. persisted. The lesions of erythema nodosum faded within several days.

A Tensilon test (11) using 2 mg. of edrophonium chloride intravenously produced a marked increase in strength, and a disappearance of the diplopia and dysphagia; a typical response as seen in patients with myasthenia gravis. This was preceded by a saline control which produced no response. As shown in figure 1, the myasthenic response was verified by ergographic recording (12). The patient was treated with Mestinon® (pyridostigmine bromide) 225 mg. daily (75 mg. every eight hours) with an excellent clinical response (13). On this dosage, diplopia and weakness subsided. On several occasions the patient was given a placebo instead of Mestinon® and developed marked symptoms of myasthenia gravis.

Because of the findings of myasthenia gravis, the patient underwent routine thyroid function investigation (14). The twenty-four hour I-131 uptake was 89 per cent and the protein bound iodine was 8.7 gamma per cent. In view of laboratory evidence of hyperthyroidism the patient was treated with 3 millicuries of radioactive iodine on December 16, 1957.

The unexplained eosinophilia persisted and a skin and muscle biopsy of the right deltoid was performed. This revealed epithelioid granulomata with multinucleated giant cells (Figure 2). There was no caseation necrosis present and no acid fast bacilli were seen. This was considered compatible with a diagnosis of Boeck's sarcoid. A Nickerson-Kveim test was performed and the skin biopsy which was done, fulfilled the criteria for sarcoidosis. A scalene node biopsy was negative and a chest film showed no evidence of pulmonary sarcoidosis or hilar lymphadenopathy. Lateral tomography of the chest revealed no evidence of a thymic tumor. However, chest x-ray showed evidence of old healed apical tuberculosis. Tuberculosis cultures of gastric material were negative. A liver biopsy revealed hepatic granulomata. There was no evidence of parotid or ocular involvement with Boeck's sarcoid.

The electroencephalographic left temporal focus was unchanged. It was felt that this might have represented a cerebral sarcoid lesion.

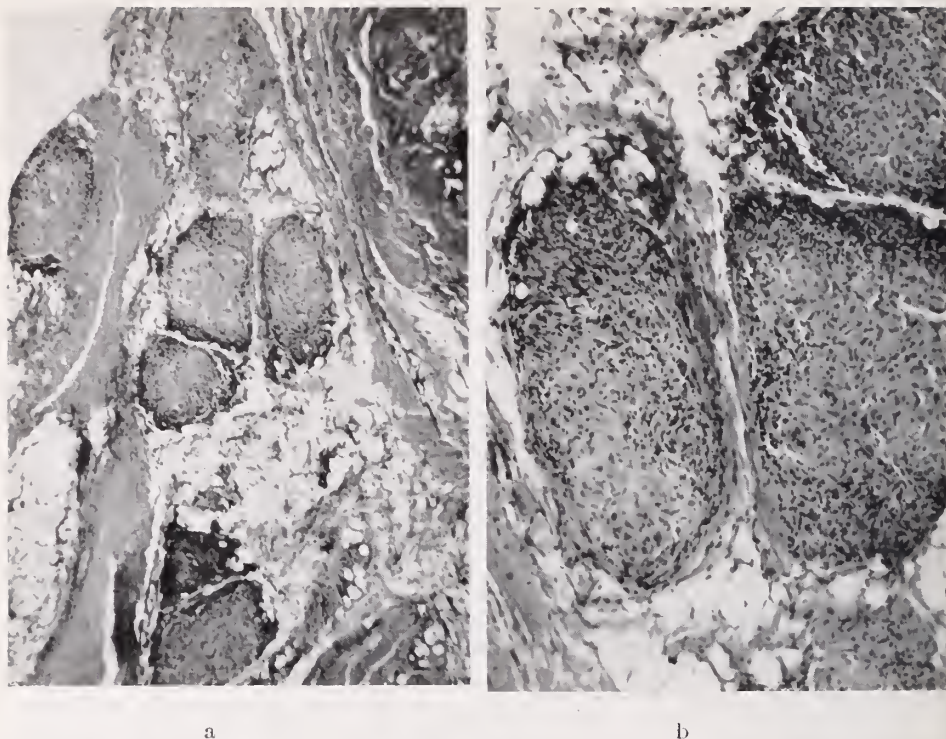


FIG. 2. Right deltoid muscle biopsy demonstrating non-caseating epithelioid granulomata with multinucleated giant cells; a, low power, b, high power.

During the hospital course, the patient developed diarrhea in early January 1958, at which time the stools were noted to contain cysts of *Entamoeba histolytica*. She was treated with a course of Diodoquin[®], 0.6 Gm. three times a day for 20 days.

Electromyographic studies were performed after substituting a placebo for Mestimon[®]. The response was typical of that seen in myasthenia gravis.

Eight weeks after treatment with radioactive iodine for hyperthyroidism the patient developed increasing weakness, dysphagia, and diplopia while receiving 225 mg. Mestimon[®] daily. A Tensilon test produced a myasthenic response and symptoms abated with an increase in Mestimon[®] dose to 360 mg. daily.

On February 28, 1958, I-131 24 hour uptake was 40 per cent. The symptoms and electromyographic evidence for myasthenia gravis persisted at that time.

Because of the evidence of muscle involvement with granulomata, a therapeutic trial of Prednisone[®] 25 mg. daily was started on March 6, 1958. After twenty-one days of steroid therapy, the Mestimon[®] was discontinued and although clinically no weakness could be demonstrated, the ergographic studies before and after Tensilon and electromyographic studies revealed the persistence of myasthenia gravis.

Three months following initial treatment with radioactive iodine, the protein bound iodine was repeated and was 10.4 gamma per cent. The twenty-four hour

radioactive iodine at that time was 77 per cent. Because of this evidence for persistent hyperthyroidism, in spite of lack of clinical thyrotoxicity, she was re-treated with 2.0 millieuries on May 5, 1958. Re-examination of the stools for ova and parasites revealed the presence of the ova of *Schistosoma mansoni*. There were no amoebae present.

After 55 days of Prednisone® therapy (45 mg. daily), Tensilon test was again repeated and response at this time showed no evidence for myasthenia. Steroids were discontinued on April 29, 1958. On May 9, a placebo was substituted for the Mestinon®. The patient showed no evidence of weakness, ergograms were normal, and there was no change after administration of Tensilon® (up to 10 mg. I.V.) Electromyography on May 15, 1958 revealed normal latencies and amplitude of response with no decline in response to repetitive stimulation. This was a normal EMG and strikingly different from the previous one done while the patient was clinically myasthenic.

A random right gastrocnemius muscle biopsy done April 11, 1958 revealed focal atrophic fibers with increase in sarcolemma nuclei. No evidence of lymphorrhagias or epithelioid granulomata was seen (15).

The patient was discharged from the medical service in a complete remission with no clinical or laboratory evidence of myasthenia gravis.

DISCUSSION

Since an etiologic agent for sarcoidosis is not known, diagnosis today depends on certain clinical and pathologic findings. A good working definition is that of Scaddings (16), "sarcoidosis is a disorder which may affect any part of the body but most frequently the lymph nodes, liver, spleen, lungs, skin, eyes, and small bones of the hands and feet characterized by the presence in all the affected organs or tissues of epithelioid cell tubercles, without caseation, with little or no round cell reaction, becoming converted in the older lesions into a rather hyaline featureless fibrous tissue."

The diagnosis may be presumed if at least two or more of the following findings are present: chest x-ray (showing parenchymal involvement with or without mediastinal or hilar lymphadenopathy), peripheral lymphadenopathy, hepatosplenomegaly, bony changes, skin nodules, uveitis, parotitis or hyperglobulinemia (17). The presence of epithelioid granulomata in liver and peripheral muscles may also be used as evidence for sarcoidosis.

Skin tests for tuberculosis are often negative in sarcoidosis. A negative tuberculin test was found in 64.8 per cent of Longcope's series (18).

Nelson in a comprehensive review of the Kveim reaction summarizes the experience of most investigators and believes a positive Kveim reaction may be expected in 50 to 90 per cent of patients with sarcoid with presumably false positive reactions to range from 0 to 6.5 per cent (19). He discusses the criteria for considering a Kveim test positive. It is generally agreed that biopsy of a papule six weeks after the intracutaneous injection of properly prepared antigen which histologically reveals epithelioid granulomata, is the best evidence for a positive test. Though it is of diagnostic help, the mechanism of the Nickerson-

Kveim reaction is not known. This patient had an unequivocally positive Niekeron-Kveim reaction according to the above criteria using an antigen with proved specificity as done by Dr. Louis E. Siltzbach.

The hyperglobulinemia which was present in this case is frequently reported in Boeck's sarcoid. Eosinophilia up to 35 per cent has been mentioned in the literature (20, 21) and was noted up to 42 per cent in this case, but Schistosomiasis could well explain this finding.

Cerebral manifestations of sarcoidosis have been well documented (22). The current patient manifested a persistent irritative focus in the left anterior temporal area on EEG which may have been due to sarcoid granulomatous infiltration. Sarcoid lesions of the skin and subcutaneous tissues were absent in this case. There was no evidence of either peripheral, hilar or mediastinal lymphadenopathy. The well known pulmonary changes associated with sarcoidosis were absent. There was no evidence of involvement of the cornea or uveal tract of the eye.

Erythema nodosum may be a manifestation of sarcoidosis as well as tuberculosis, post-streptococcal state, coccidioidomycosis and other granulomatous diseases. Erythema nodosum with hilar lymphadenopathy has been often shown to be a manifestation of sarcoidosis when sought for by liver biopsy. Mather, Dawson and Hoyle (23) found ten of eleven cases of erythema nodosum with hilar lymphadenopathy to have hepatic granulomata whereas there were none in the cases of post-streptococcal state. Smellie and Hoyle (24) found erythema nodosum to occur in 23 per cent of sixty-six cases of hilar lymphadenopathy due to sarcoidosis. Lofgren (25) in a series of 212 cases of bilateral hilar lymphoma syndrome (primary pulmonary sarcoidosis), found 113 cases with erythema nodosum of which 109 cases presented initially with erythema nodosum.

As a manifestation of tuberculosis or coccidioidomycosis, erythema nodosum is seen early in the stage of active disease. This patient's coccidioidin skin test was negative and although a positive tuberculin skin test in first strength was present, the only additional evidence for tuberculosis was an x-ray showing fibrotic strands in the right apex of the lung. An antistreptolysin-O titer at the time was less than 100 and there had been no acute respiratory tract infection. The presence of erythema nodosum in this patient may be explained as a manifestation of sarcoidosis.

The presence of granulomata without caseation in the specimen obtained on liver biopsy is also evidence for sarcoidosis. Mather, Dawson, and Hoyle (23) present their experience with liver biopsy in sarcoidosis and report an incidence of 63 per cent positive biopsies. Branson and Park (17) reviewed 117 cases of sarcoidosis autopsy material and noted that 66 per cent had conclusive histopathologic evidence for hepatic sarcoidosis. In sixty-three patients with presumptive evidence of sarcoidosis, 76 per cent had positive liver biopsies.

Other diseases in which hepatic granulomata occur such as brucellosis, berylliosis, and histoplasmosis were not present in this patient. Epithelioid granulomata in the liver do not have clearcut histologic differences that will distinguish between sarcoidosis and tuberculosis unless caseation has occurred. Miliary

tubercles in the liver may be associated with all stages of chronic pulmonary tuberculosis and in most instances is indicative of terminal dissemination, but also occur in acute miliary tuberculosis, pylephlebogenic tuberculosis and in splenic tuberculosis (26). The history, physical findings, negative tissue cultures, negative gastric washings suggest that the hepatic epithelioid granulomata were due to sarcoidosis. The presence of schistosomiasis *mansoni* leaves the possibility open that these hepatic granulomata were associated with this entity, but there was no evidence of schistosomal ova in the biopsy material.

Although it has been reported in the past (27) that the characteristic lesions of sarcoidosis may be found in skeletal muscle, it has been only recently that the prevalence with which this occurs has been pointed out. Phillips and Phillips (28) found granulomata in four out of five cases of sarcoidosis in whom random gastrocnemius muscle biopsy was performed. None of these patients exhibited muscle weakness. The authors point out that perhaps one of the reasons the reported incidence of muscle involvement is low pathologically is the failure to do routine examinations of skeletal muscle at autopsy., Wallace et al. (27) have reported forty-two cases with proved sarcoidosis in whom twenty-three had sarcoid lesions on random muscle biopsy. None of these patients had symptoms referable to the motor system. Maurice (5) points out the frequency with which sarcoid lesions are found in muscles with no clinical manifestations. He also reports a case who presented clinically an atypical picture of amyotrophic lateral sclerosis and was later found to have sarcoid lesions in the muscles as well as in other organs. Although the incidence of muscle involvement in sarcoidosis has not been established it seems to be not uncommon and may or may not be associated with the clinical counterpart of weakness and atrophy. Ammitzball (8) reports a case of extensive muscle involvement with marked weakness and dramatic response to steroids. Klotz (10) et al., also report a case of extensive nodular involvement of muscle with skin and lymph node lesions which responded strikingly to steroids. Electromyography was non-diagnostic in both cases and no evidence for myasthenia gravis existed.

Muscle biopsy in the present patient revealed typical epithelioid granulomata with no caseation or acid fast bacilli. The incidence of skeletal muscle involvement in tuberculosis is considered distinctly rare (5, 29). Muscle weakness and atrophy in sarcoidosis is not adequately explained. The presence of granulomata in cases with no atrophy or weakness speaks against strictly mechanical interference with contraction. Sarcolemmal degeneration or inflammation is not found in the surrounding muscle. In some cases (4) involvement of the nervous system with secondary degeneration and atrophy has been reported. As part of a generalized picture of fever, malaise and weight loss with multiple system involvement, muscle weakness could occur as in other illnesses without requiring specific involvement of the neuromuscular systems. No evidence exists for a possible humoral factor causing muscular weakness in sarcoidosis.

Although the presence of myasthenia gravis with sarcoidosis has not been previously reported, myasthenia gravis has been reported in association with other systemic diseases (30). The occurrence of weakness in thyrotoxicosis is

well known, and there have been several reports of a myasthenic picture, responding to anticholinesterase drugs (31-34). In some of these cases the underlying thyroid disease was surgically treated and there was a concurrent improvement in the weakness. An increase in myasthenic symptoms as hyperthyroidism is controlled, termed the "seesaw" effect has been also described (35, 36). A myasthenic syndrome in cases of bronchogenic carcinoma improving on neostigmine has been reported (37, 38). Two instances of dermatomyositis with myopathy and amelioration after treatment with prostigmine are noted in the literature (39). Cases of non-specific polymyositis with muscle biopsy showing fibrosis and atrophy responding to cholinergic drugs have been seen (40, 41). The diagnosis of myasthenia in these cases was substantiated only by response to anticholinesterase preparations, and no electromyographic studies were done.

Myasthenia gravis is considered to be a disease of voluntary muscle due to defects in neuromuscular transmission causing weakness. This is temporarily improved by the administration of Neostigmine® or more recently Tensilon® (edrophonium hydrochloride). Also noted is a characteristic electromyographic pattern (42, 43) consisting of rapidly progressive failure of muscle response on electrical stimulation of the motor nerve. This is considered to be the "myasthenic response." Eaton and Lambert (43) no longer hold the view that the myasthenic response to Neostigmine®, edrophonium or curare to be in themselves pathognomonic of myasthenia gravis since it may occur in other conditions as poliomyelitis and amyotrophic lateral sclerosis. However, the absence of other disease of the neuromuscular system and the presence of a demonstrated defect in neuromuscular transmission having the above characteristics fulfills the present criteria for the diagnosis of myasthenia gravis. Whether one chooses to term this myasthenia gravis or myasthenic syndrome, myasthenic-like, or myasthenia is not based on any clearcut criteria. There may be a valid distinction between these terms and this will depend upon the demonstration of the exact defect or defects in transmission and the variation from individual to individual presenting the same clinical picture.

In this patient a response to Tensilon® using suitable placebo controls was striking. On the day of recording the initial electromyogram, the patient was given Mestinon® placebos instead of her usual Mestinon® dosage. After omitting two doses, the patient was unable to swallow, could not handle her secretions, had diplopia and marked generalized weakness.

The patient had an elevated radioactive iodine uptake and protein bound iodine although clinically she did not seem hyperthyroid. Treatment with radioactive iodine did not seem to influence the status of the myasthenia gravis.

A course of steroid therapy was decided upon because of the good response in patients with symptomatic sarcoidosis. Myasthenia gravis has also shown amelioration with steroid therapy, (44) although there have been other reports noting an exacerbation of weakness following treatment with ACTH and cortisone (45, 46). Kane (47) discusses the rationale on which steroids were originally tried in myasthenia gravis. The best results with ACTH were noted in patients with thymic tumors, with an occasional remission in the myasthenic picture. The

present patient had no thymoma. Several deaths have been reported in steroid treated cases due to a sudden increase in anticholinesterase drug requirements (46).

The patient reported here was treated cautiously with Prednisone® 45 mg. daily for nine week period. Mestinon® was discontinued and there was no evidence of weakness. Tensilon® produced no augmentation to muscle power by ergographic measurement. Electromyography failed to show the myasthenic response previously seen.

One might speculate that myasthenia gravis in this patient was related in some way to her sarcoidosis, and with the use of steroids the underlying defect in neuromuscular transmission responded as did those cases of myasthenia associated with other systemic disorders as noted above. This is merely conjecture, and other explanations of this result would be acceptable, that is, the direct effect of steroids on myasthenia gravis itself (44, 48, 49). Spontaneous remission and exacerbations in myasthenia gravis are well known and therefore no conclusions can be drawn with regard to the effects of therapy in this case.

SUMMARY

A patient is presented who satisfies the criteria for the diagnosis of sarcoidosis and myasthenia gravis. Sarcoid granulomata were found in muscle and liver. A positive Nickerson-Kveim reaction was present. Myasthenia gravis with diplopia, dysphagia and generalized severe weakness responding to Tensilon® with typical electromyographic pattern was also present. The myasthenia gravis disappeared after a course of steroid therapy. The criteria for diagnosis and response to medication are discussed.

ACKNOWLEDGMENTS

We are indebted to Dr. Kermit E. Osserman, Chief of the Myasthenia Gravis clinic, The Mount Sinai Hospital, New York, for his criticisms and suggestions in the preparation of this report.

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INTERNAL HERNIA THROUGH THE FORAMEN OF WINSLOW

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A review of the literature up to 1953 reported by Lane Roberts (1) revealed that 64 cases of herniation through the foramen of Winslow into the lesser sac were on record. He added two personal cases. Of this group, 45 cases showed herniation of the small bowel, 16 herniation of the right side of the colon and the cecum and 5 cases of herniation of the transverse colon. A preoperative diagnosis has rarely been made, resulting in considerable delay in surgical correction. In the series reviewed above, there were 27 deaths. A correct diagnosis, presumably the first of its kind preoperatively, was made on roentgen examination by Hollenberg (2). The roentgen signs of this condition have also been summarized by St. John (3). There have been 10 additional case reports since the review by Lane Roberts (1, 5-12).

CASE REPORT

A 50 year old white female was admitted with the chief complaint of right upper quadrant pain of eight hours duration associated with vomiting. This pain was colicky in nature and radiated to the back. Over the previous ten years, the patient had had five or six similar attacks. The first episode ten years prior to admission had lasted for three weeks but the subsequent episodes were relieved after a short period of time on each occasion.

On admission, the patient was in distress but did not appear to be acutely ill. Examination of the abdomen showed tenderness and spasticity in the epigastrium and in the right upper quadrant. The remainder of the examination was not contributory. Blood pressure was 130/100, pulse 80, temperature 99.3°F. Hemoglobin was 13.7 grams per cent, total white count was 3,300 per cu. mm. with 70 per cent polys. Alkaline phosphatase was 3.9 Bodansky units. Urine was negative for bile or urobilin.

The tentative clinical diagnosis of chronic and acute cholecystitis was made. In an effort to confirm this diagnosis, intravenous cholangiography was done. This demonstrated good visualization of the gall bladder which was located in the right lower quadrant. There was no evidence of any filling defects within it. Several biliary radicles, the cystic and common duct were also opacified and did not appear to be distended. The common duct gave the impression of being somewhat stretched in its upper portion and was perhaps located unusually far towards the right (Fig. 1). In addition, overlying the upper lumbar spine, there was a large ovoid gas shadow within which there appeared to be multiple mottled densities (Fig. 1A). The upper margin of this shadow reached the level of the

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FIG. 1. A film taken during the course of intravenous cholangiography shows the elongated gall bladder low on the right side below the level of the crest of the ilium. There is no evidence of any filling defect within it. Several biliary radicles, the common hepatic and the common duct are also opacified and are not dilated. The common hepatic and common duct appear elongated and displaced towards the right, especially superiorly. Overlying the upper portion of the lumbar spine, there is an ovoid air-containing shadow (A) which extends as high as the central tendon of the diaphragm and which shows in its lower portion mottled densities. To the left of this, there is a vertical streak-like lucent shadow (B) which appears to parallel the left margin of the central lucent area.

diaphragm. To the left of this shadow was a streak-like vertical lucent shadow (Fig. 1B). The significance of these two lucent areas was not realized at the time of the examination.

The patient was treated symptomatically but continued to complain of abdominal pain. Roentgen examination of the abdomen four days after intravenous cholangiography (Fig. 2) showed persistent visualization of the gall bladder. There was a loop of cholegrafin opacified bowel on the right side of the abdomen



FIG. 2. Examination of the abdomen 4 days after intravenous cholangiography shows persistent visualization of the gall bladder (B). In the right lower quadrant, there is a cholegrafin opacified loop of bowel (C) which has the appearance and location of proximal transverse colon. The opaque material in it apparently was derived from the distended "viscus" (A) in the upper and left portion of the abdomen. A film of the abdomen taken three days previously had shown this "viscus" more completely opacified with no opaque material in the colon. On the medial aspect of this distended, air-containing viscus, there is a deep cleft which has the appearance of a haustral septum. There is no evidence of bowel in the ordinary position of the ascending colon or hepatic flexure. Air is seen in the descending colon, sigmoid and rectum. There are no distended loops of small bowel. (Incidentally, a gastric suction tube is also evident.)

extending to the midline which had a caliber larger than would be anticipated for small bowel. This portion of bowel showed suggestive haustration and its transverse course over the fifth lumbar vertebra seemed to be continuous with a gas collection on the left side in the distal transverse colon and splenic flexure. In the midline extending to the left a markedly distended gas-containing viscus was seen which also contained a portion of the cholecystographic opaque material.



FIG. 3. Film of the abdomen after barium swallow on the same day as the examination in Figure 2 shows that the distended viscus is not stomach. The large fluid level was located behind as well as medial to the stomach. Transverse colon (C) is still opacified by cholegrafin and is not distended. Review of Figure 1 now permits the vertical lucent shadow (B) to be identified as stomach.

In its medial aspect, there was a deep cleft which suggested an interhaustral septum and therefore that this viscus was a markedly distended portion of colon. Air was seen in the region of the descending colon and sigmoid but there was no evidence of gas or fecal material in the region of the cecum, ascending colon or hepatic flexure. No remarkable distention of any portion of small or large bowel was noticed. It should be noted that examination of the abdomen done three days prior to this had demonstrated a considerable amount of the cholecysto-

graphic medium in the distended viscus high on the left side of the abdomen without any opaque material elsewhere in the abdomen except in the gall bladder. It was therefore assumed that the loop of bowel on the right side of the abdomen was transverse colon which was distal to and directly continuous with the distended viscus in the upper left abdomen.

The suggestion was made at this time that the patient had a volvulus of the colon and that the markedly distended loop of bowel high on the left side of the abdomen extending to the midline was a twisted cecum. A barium swallow was given to the patient (Fig. 3) and an erect film showed that this viscus was independent of the stomach. A disturbing feature was the fact this air-containing viscus appeared to be located behind as well as medial to the stomach but the significance of this was not appreciated.

On exploratory laparotomy, a herniation of the right side of the colon including the distal part of the terminal ileum through the foramen of Winslow into the lesser sac was discovered. The foramen of Winslow admitted four fingers and there was no difficulty in reducing the herniated viscera into the general peritoneal cavity. There was no posterior fixation of the right side of the colon. The foramen of Winslow was closed by multiple sutures.

DISCUSSION

In the reported cases of herniation through the foramen of Winslow, an invariable finding has been distinct enlargement of this opening which normally admits only one finger (1). While it is possible that this is the result rather than an etiological factor, it appears likely that it represents a congenital anomaly. The ring is rarely sufficiently tight to cause strangulation. Other predisposing factors exist in individual cases: lack of fixation particularly of the right side of the colon, a long small bowel mesentery, small greater omentum or short transverse mesocolon. The gall bladder, with or without adhesions, may serve as a funnel-shaped arrangement to direct viscera towards the foramen of Winslow (2). For some unknown reason, herniation exclusively of small bowel appears to be much more common in males than in females. A remarkable clinical feature which has been noted in some cases has been the inability of the patient to lie on his back and the necessity of assuming a sitting, bent-forward position to obtain some relief of pain.

The preoperative diagnosis of this condition depends on the correct interpretation of the clinical and particularly the roentgen findings. These depend to some degree on the nature of the contents of the hernial sac but the essential features are the recognition of a distended portion of bowel occupying the region of the lesser sac located medial and posterior to the stomach (2-4). Superimposed on these findings are the features of intestinal obstruction, usually incomplete and located either in the distal small bowel or the right side of the colon. When the right side of the colon is herniated, its absence from its normal location is a very helpful diagnostic feature. If the actual site of obstruction can be localized, it corresponds to the location of the foramen of Winslow. In the case presented, the findings illustrated in Figure 1 suggest the correct diagnosis since the linear lucent

shadow (B) to the left of the spine represents displaced, compressed stomach and the location of the central lucent shadow with its mottled contents (A) is characteristic. Figure 2 demonstrates nicely the fact that the transverse colon fills directly from the incarcerated viscus which must therefore represent the right side of the colon. The transition between dilated colon and colon of normal caliber occurs in the region of the foramen of Winslow.

SUMMARY

A case of herniation of the right side of the colon through the foramen of Winslow is reported with a summary of the roentgen features which should suggest this diagnosis. Early diagnosis is necessary if surgical correction is to be successful. Gangrene of the herniated bowel is rare, so that simple reduction and closure of the foramen are curative.

ACKNOWLEDGMENT

Permission to report the above case was kindly granted by Dr. Samuel J. Glick.

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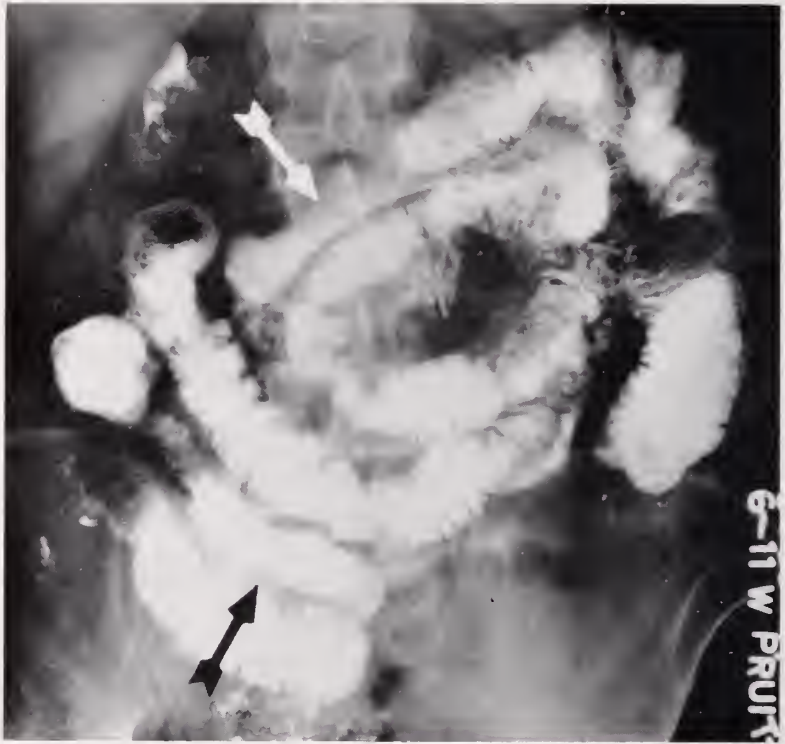
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Radiological Notes

BERNARD S. WOLF, M.D.

CASE NO. 69

This was the eighth admission of a 62 year old white male with the chief complaint of three days of abdominal pain, nausea and vomiting. The previous story included treatment for meningovascular lues, grand mal seizures, thoracotomy for a chronic lung abscess, drainage of a brain abscess of the left temporal lobe, and thrombophlebitis of the left calf five and two years prior to the current admission.



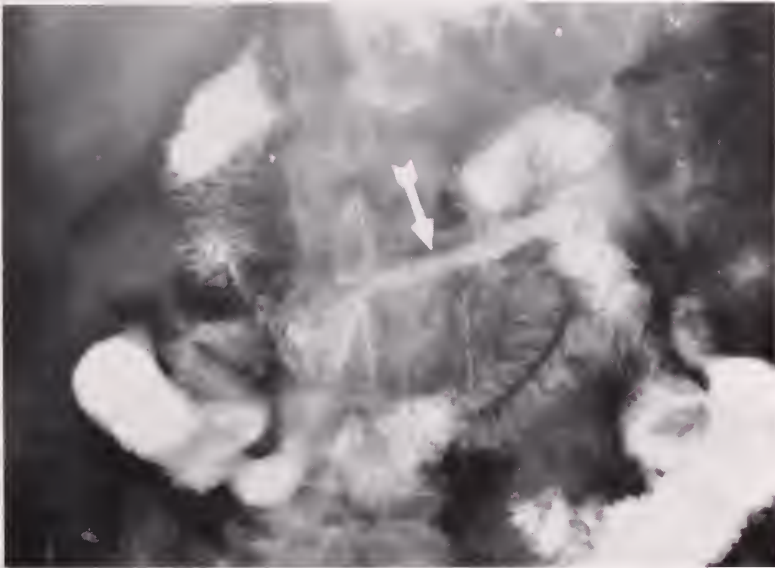
Case 69, Fig. 1A. Small bowel series shows a segment in the proximal jejunum (upper arrow) 4 to 5 inches in length with limited distensibility, effaced mucosal pattern, straightening of its course and thickening of its wall. There is no sharp demarcation from adjacent uninvolved proximal or distal bowel. A second similar segment (lower arrow) is present in the proximal ileum.

Three days before admission, the patient began to vomit, could retain nothing in his stomach, and complained of abdominal pain. He noted that his abdomen became progressively distended but, despite this, he continued to pass gas and had normal bowel movements. He could not describe the nature of his vomitus. On admission, the temperature was 100°F.. The abdomen was grossly distended

but did not appear to be tense and there were no signs of free peritoneal fluid. The liver edge was palpable, one fingerbreadth below the costal margin. There was some generalized tenderness to deep palpation throughout the abdomen with minimal rebound tenderness. No masses were palpable. The hernial sites were not remarkable. Bowel sounds were infrequent. The pupils were small and sluggish in their reaction to light. The knee jerks were diminished to absent. Soft stool which showed a 2 plus guaiac reaction was present in the rectum. Hemoglobin was 11 grams per cent, white blood count 20,000 per cu. mm., blood chemistries were not remarkable. Electrocardiogram showed evidence of old myocardial infarction.

Roentgen examination of the abdomen was interpreted as suggestive of incomplete small bowel obstruction. Since the patient did not appear to be seriously ill, he was treated by a long suction tube which drained only small amounts of cloudy fluid. He continued to have daily bowel movements. Three days after admission, the long tube was removed and the patient continued to do well on a soft diet.

Twelve days after admission, a small bowel series was done and repeated for confirmation two days later. On both of these examinations, the transit time of the barium through the small bowel was within normal limits and there was no evidence of remarkable dilatation. However, there was a segment in the proximal jejunum which was slightly narrowed with a completely effaced mucosal pattern (Figs. 1A, 1B). This segment was unusually straight, showed an absence of the normal sinuous course of a small bowel loop, and was relatively static since



Case 69, Fig. 1B. During the later portion of the same examination, barium persists in the proximal involved jejunal segment (arrow) which appears unchanged in appearance and location.



Case 69, Fig. 2. Small bowel series shows the segment in the proximal ileum to be composed of two loops (arrows) which show relative lack of distensibility, scalloped contours, absence of a valvular pattern and thickening of the wall as indicated by the increased space between these segments and the adjacent loops of small bowel.

barium was retained in this area for a considerable period of time. In addition to this segment, there was another loop or loops in the distal jejunum or proximal ileum which also showed slight narrowing and irregular scalloping of the contours with flattened or obliterated mucosal pattern (Fig. 2). The distance between these loops and the adjacent loops of small bowel was increased indicative of thickening of the bowel wall. Contractility of this second segment was also irregular and barium was retained longer than in adjacent areas.

The two portions of the small bowel described above were interpreted as showing evidence of segmental infarction as a result of mesenteric occlusion. It was anticipated that, unless operative intervention was performed, fibrosis and stenosis were likely to occur some time in the future. It was therefore recommended that this patient undergo laparotomy but he refused and he was discharged to the Out-Patient Department. He was seen about two months after discharge and had no complaints referable to the abdomen. Five months after discharge, however, he reappeared in the emergency room with another acute episode of abdominal pain, distension and vomiting with diffuse abdominal tenderness and rebound tenderness. He was operated on immediately and almost the entire small bowel was found to be gangrenous. A massive resection was done but the patient succumbed shortly post-operatively.

The roentgen features of segmental infarction have been previously described

(*Radiology*, 66: 701, 1956) and the findings in this case are quite typical. Since it takes months for fibrosis and stenosis to occur, the absence of these findings during the final episode of massive infarction in the present case is not surprising. It is of interest that the first episode of mesenteric occlusion resulted in obvious compromise of only short segments of the small bowel but that in the second episode the entire small bowel including the previously involved segments became gangrenous.

Final Diagnosis: SEGMENTAL INFARCTION OF THE SMALL BOWEL.

CASE NO. 70

SUBMITTED BY CLAUDE BLOCH, M.D.

New York, N. Y.

This was a re-admission of a 61 year old male who had been followed and treated for eight years because of polycythemia vera which was known to have



Case 70, Fig. 1A. Barium swallow shows no remarkable limitation of distensibility or abnormality in flow of barium through the esophagus and into the stomach. There is, however, distinct and constant irregular spiculation of the entire contour of the filled esophagus. The fold pattern in the small, contracted, direct type of hiatus hernia, however, is intact.



Case 70, Fig. 1B. With less filling of the esophagus, the markedly distorted bizarre mucosal pattern responsible for the serrations of the contours is evident. The process involves the entire length of the esophagus in uniform fashion. The small elongated hernial sac is evident below the inferior esophageal sphincter.

been present for at least 15 years. For four years, he suffered from secondary gout with pain in the toes, ankles and knees. Butazolidin furnished considerable relief. The current admission was because of persistent abdominal pain, nausea and a general deterioration of his condition. Marked anemia and leucopenia were found with many blast cells in the peripheral blood. Bone marrow aspiration and biopsy confirmed the clinical impression of a myeloproliferative syndrome with leukemic changes. He was immediately treated with steroids by mouth. Because of fever and a urinary tract infection, the patient was also given large amounts of penicillin, streptomycin and Chloromycetin.* Two and a half weeks after admission, he began to complain of dysphagia.

Roentgen examination of the esophagus (Fig. 1A, 1B) showed no delay in the

passage of barium through the esophagus or into the stomach. There was no remarkable limitation in distensibility but on all films the contours of the esophagus showed a fine irregular spiculation. The mucosal pattern showed a complete absence of the normal longitudinal folds which were replaced by irregular interlacing, fragmented short folds or areas of thickened mucosa. A small direct type of hiatus hernia was also present but the fold pattern in the hernial sac was intact.

The findings in the esophagus were quite unusual. There was no rigidity or limitation of distensibility or discrete filling defect or projecting ulcer crater and no remarkable spasm or irritability. The findings therefore did not suggest a neoplastic process or the usual type of peptic esophagitis. The chief and apparently the only feature was a very remarkable disturbance of the mucosa. The nature of this process became clear when it was discovered that the patient was suffering from a severe thrush involving the entire oral cavity and extending onto the epiglottis. It became evident that the process extended into and throughout the length of the esophagus.

There have been several case reports of monilia esophagitis in patients who have received antibiotic and steroid therapy usually during the course of chronic leukemia. The roentgen findings appear to be characteristic as long as the inflammatory changes remain very superficial. In more severe cases, marked spasm may be present and differentiation from other varieties of esophagitis may be impossible.

Final Diagnosis: MONILIA ESOPHAGITIS.

CASE NO. 71

This was the first admission of a 76 year old white female with a history of epigastric pain one month prior to admission which disappeared within a few hours. This was not associated with nausea or vomiting. However, occult blood was found in the stool and the hemoglobin was reduced to 6 grams per cent. The patient was treated with transfusions and iron by mouth after a gastrointestinal series had revealed a paraesophageal hernia. The patient was admitted for additional investigation and possible surgical intervention. Physical examination on admission was non-contributory. Hemoglobin was 10.5 grams per cent. White count was normal with a normal differential count.

Barium enema examination (Fig. 1A, 1B) showed no abnormality in the colon. Barium entering the appendix, however, outlined a peculiar crescentic collection which on close examination appeared to cap an ovoid soft tissue density about an inch and a half in its longest diameter. This appearance was interpreted as most likely due to a mucocele of the appendix. This was confirmed at exploratory operation; the appendix including the mucocele was removed. The patient was discharged for additional follow-up to determine whether repair of the paraesophageal hernia was to be done.

Final Diagnosis: MUCOCELE OF THE APPENDIX.



Case 71, Fig. 1A. Right side of the colon in the PA projection shows the base of the appendix to be normally located. The short narrowed segment near the base is angulated and directed behind the caput. Through the barium filling the caput coli, a crescentic density (arrow) can faintly be seen.



Case 71, Fig. 1B. In the right oblique projection, the crescentic collection (upper arrow) of barium within the appendix is projected free of the caput coli. The concavity of the inferior aspect of this collection appears to cap an ovoid soft tissue density (lower arrow) which is so faint that it cannot be clearly reproduced.



Case 72, Fig. 1A. Barium enema examination shows a sharply demarcated, punched-out circular filling defect located in the lower pole of the caput coli in its medial portion. There is no evidence of filling of the appendix.

CASE NO. 72

This was the second admission of a 52 year old white female who ten years ago had undergone appendectomy and hysterectomy. For some time the patient had been complaining of episodes of right lower quadrant cramp-like pain associated with loose stools but without nausea or vomiting. On occasion, the patient complained of rather vague episodes of abdominal distension. There had been no bleeding or melena.

Barium enema examination (Fig. 1A, 1B) showed a remarkably well-circumscribed, sharply demarcated, spherical defect in the lowermost pole and medial portion of the caput coli. The appearance was most suggestive of an inverted appendiceal stump although the possibility of a small polyp could not be entirely excluded.

This patient was explored and the remnant of an inverted appendiceal stump removed. Pathological report was "Polypoid cecal mucosa. Remnant of appendiceal lumen in the center."

Final Diagnosis: INVERTED APPENDICEAL STUMP.



Case 72, Fig. 1B. After evacuation, the defect in the caput coli (arrow) persists unchanged.

CASE NO. 73

This 56 year old female complained for many years of a feeling of a "lump" in the epigastrium although no masses had ever been palpated. She also complained that, at times, the right side of her abdomen became distended and that this feeling of fullness extended towards the right hip. She would occasionally become nauseous in the middle of the afternoon and this would persist until she would fall asleep at night. There had been a loss of about five pounds within one year. Gall bladder series had demonstrated Aschoff-Rokitansky sinuses in the gall bladder but no definite evidence of biliary calculi. A barium meal examination was said to have been negative. There was no history of any abdominal operation. Hemoglobin was 13.9 grams per cent, white blood count and differential count were normal as was the sedimentation time. Stools were negative for blood.

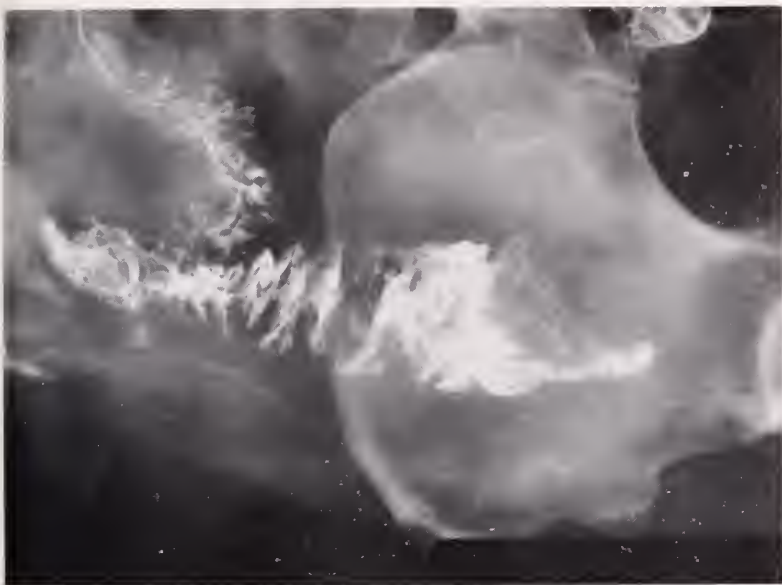
Barium enema examination (Fig. 1A, 1B) demonstrated a broad-based sharply demarcated filling defect projecting into the caput coli from its inferior pole. This defect was unchanging in size in different phases of distension of the colon. There was no evidence of filling of the appendix.

Examination of the ileocecal region after barium by mouth (Fig. 2) confirmed the findings of the barium enema and gave the impression of flattening of the infero-medial aspect of the caput coli as well as perhaps slight mesial displacement of the terminal ileum. At exploratory laparotomy, the appendix containing a large mucocele was found intussuscepting or inverting into the caput coli.

Final Diagnosis: INTUSSUSCEPTING MUCOCELE OF THE APPENDIX.



Case 73, Fig. 1A. Double contrast portion of the barium enema examination shows a sharply demarcated, broad-based filling defect (arrow) in the lower pole of the caput coli arising at the usual location of the base of the appendix. There is no evidence of appendiceal filling.



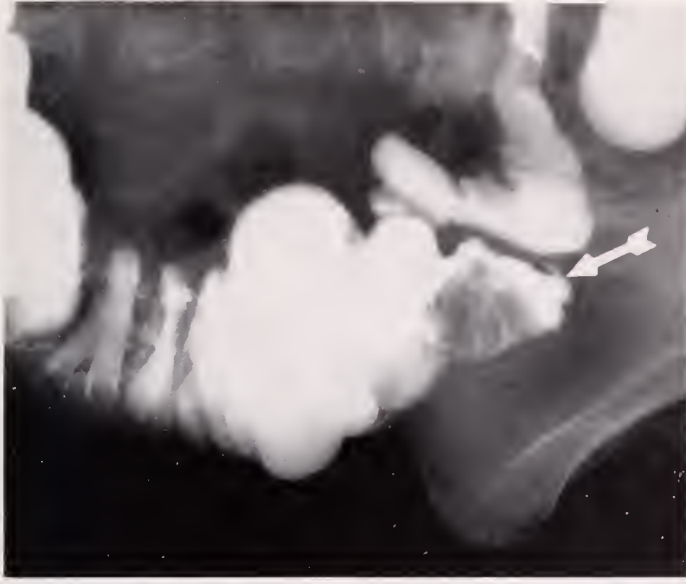
Case 73, Fig. 1B. Film taken after evacuation of the barium enema shows persistence of the filling defect with abrupt horizontal cut-off of the caput coli.



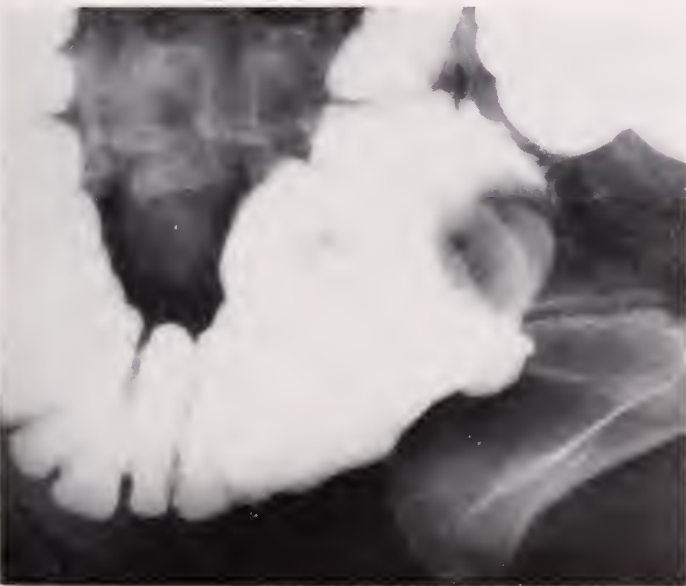
Case 73, Fig. 2. Ileocecal region after administration of barium by mouth shows findings similar to those seen on the enema. There is also evidence of flattening of the medial aspect of the caput coli and an arcuate course of the terminal ileum which suggests that it may surround an extrinsic component of the mass.

CASE NO. 74

This was the first admission of a 68 year old female who had complained of recurring heartburn for many years. One year prior to admission, she had developed congestive heart failure marked by ankle edema and pretibial edema. With treatment, she improved rapidly and in the year prior to admission had lost 35 pounds in weight due to loss of fluid. One month prior to admission, she noted bright red blood in the stool. Appendectomy was said to have been done many years previously. Physical examination was not contributory except for slight hypertension. Hemoglobin was 13 grams per cent. Sigmoidoscopy was not remarkable. Barium enema examination, however, (Fig. 1A, 1B) demonstrated a discrete, sharply demarcated, hemispherical filling defect in the caput coli. This seemed to arise from the lateral and inferior portion of the caput coli by a broad



Case 74, Fig. 1B. After evacuation, the mass seems more elongated and the defect smaller. In addition, the base of the appendix (arrow) at the apex of the caput with filling of the appendiceal stump is evident and is located a short distance from the mass.



Case 74, Fig. 1A. Barium enema examination shows a sharply demarcated, hemispherical, polypoid defect with slightly scalloped contours occupying the lateral and inferior portion of the caput coli. No definite evidence of ulceration.

base. There was a suggestion that after evacuation, there was some change in the configuration and apparent size of the defect. There was no evidence of mucosal ulceration.

The patient was admitted because of the findings on barium enema and exploratory laparotomy performed. A soft mass was found in the wall of the caput coli which was encapsulated and easily enucleated after incising the serosa. The mucosa was intact and did not appear to be stretched out over the mass which was located in the submucosa. On cut section, the mass had the typical appearance of a lipoma.

The appearance of the defect in the caput coli in this case is similar to Case No. 73 except for its location lateral to the base of the appendix. In both cases, the tumor—mucocele, lipoma—is intramural as indicated by the broad based, sharply demarcated, smoothly contoured, hemispherical appearance of the defect. The diagnosis of mucocele is based on location, at the base of the appendix, with failure to fill the appendix. A lipoma in this region is most commonly located on the ileocecal valve. In contrast to most lipomas of the colon which reach a large size (*J. Mt. Sinai Hosp.*, 21: 80, 154), there was no evidence of the formation of a pseudo-pedicle or stalk in the current case. This was fortunate since enucleation was feasible and colotomy was not required.

This case is presented through the courtesy of Dr. Albert Cornell and Dr. Bernard Friedman.

Final Diagnosis: SUBMUCOSAL LIPOMA OF THE CAPUT COLI.

Clinico-Pathological Conference

SEVERE HYPERTENSION AND BACK PAIN IN A YOUNG GIRL

Edited by

FENTON SCHAFFNER, M.D.

A 16 year old Negro female high school student was admitted to The Mount Sinai Hospital for the second time because of weakness, vomiting and confusion on November 12, 1957.

In the spring of 1956, the patient noted low back pain and ankle swelling but had no fever, sore throat or smoky urine. The patient was told that she had high blood pressure and kidney disease, and she was kept at home for one month. On a low salt diet she became asymptomatic until May, 1957 when she noted blurred vision. She was seen by an ophthalmologist and was admitted to The Mount Sinai Hospital for the first time on May 28, 1957.

Physical examination revealed her blood pressure to be 190/130 and she had retinal hemorrhages and exudates with nasal blurring of the discs. The thyroid was diffusely enlarged. The left ventricle was hypertrophied and the liver was felt two fingerbreadths below the right costal margin. A nodular 5 x 4 cm. mass was palpated 2 cm. to the left of the midline in the left lower quadrant. This mass had intrinsic pulsations or transmitted aortic pulsations. A mass of hard matted lymph nodes was present in the left axilla but there was no other significant lymphadenopathy.

Urinalysis showed a concentration of 1.010, 2+ albumin with occasional red and white cells and hyaline and granular casts. Hemoglobin was 10.6 Gm. %, and the white blood count was 5,100 cu. mm. with 8 to 18% eosinophiles. The sedimentation rate was 64 mm./hr. The BUN was 35 mg. %; albumin, 4.0 Gm. %; globulin, 3.6 Gm. %; phenolsulphonphthalein retention 5% in 15 minutes and 25% in 2 hours. L.E. and sickle preparations were negative. Serum electrolytes and the results of various hepatic tests were normal. Chest x-ray showed a density in the right paratracheal region which was either a lymph node or prominent innominate artery. The heart was enlarged. The aortic knob was prominent. On intravenous pyelography the kidneys were normal in size. There was prompt appearance of dye on the right side with suggestive evidence of a soft tissue density in the lower left lumbar region. Differential renal function studies were attempted with ureteral catheters in place; however, this was unsuccessful. Left axillary lymph node biopsy revealed caseating granulomatous lymphadenitis in which acid-fast bacilli were seen.

During her hospitalization the patient developed erythematous nodular lesions on both lower extremities. Biopsy of one of these lesions was reported as "skin and dermis with no significant change". A right renal biopsy was also performed. The patient was treated with isoniazid, paraaminosalicylic acid, streptomycin, Serpasil,[®] Apresoline[®] and two blood transfusions. Her condition was unchanged and she was discharged on August 1, 1957.

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

In November, 1957 she began to experience weakness, headache and shortness of breath. She was treated with Digoxin® with some improvement. On November 8, 1957 she experienced epigastric pain, nausea and began to vomit frequently. She became confused and on November 12, 1957 was admitted for the last time.

The patient was an acutely ill young negro female with mild orthopnea, a uremic odor and mental confusion. Blood pressure was 240/140 in both arms, pulse 100/min. and regular, temperature 98.6°F. and respirations 26/min.. There were several macular erythematous pretibial skin lesions 3 cm. in diameter. The mucous membranes were pale. Fundoscopic examination revealed hemorrhages, exudates and papilledema. Enlargement of the thyroid was again noted. The neck veins were distended and there was a positive hepatojugular reflux. The left axillary nodes were still palpable. The right lung base was flat with bilateral basilar subcrepitant rales. The point of maximum impulse was in the sixth left interspace in the anterior axillary line. A gallop rhythm was heard with a loud second aortic sound. The abdomen was markedly distended and the liver was palpable five fingerbreadths below the right costal margin. The left lower quadrant mass was unchanged. There was no peripheral edema.

Urinalysis showed 4+ albumin, many RBC's and an occasional granular cast. Hemoglobin was 7.0 Gm. % and WBC was 6,650 cu. mm. with a normal differential count. The BUN was 103 mg. %; CO₂, 15.3 mEq./L; chlorides, 78 mEq./L; sodium, 120 mEq./L; potassium, 7.2 mEq./L; albumin, 3.3 Gm. %; globulin, 3.0 Gm. %; and creatinine, 12.6 mg. %. An electrocardiogram showed left ventricular hypertrophy.

On the first hospital day, the patient was treated with intramuscular Serpasil®; however, her condition continued to deteriorate. Her urinary output was 100 cc. per day. When her potassium was reported as 8.2 mEq./L and tall T waves were noted in the precordial leads, she was given 50% glucose with insulin, potassium exchange resins and enemas with a fall of the serum potassium to 5.9 mEq./L. On the third hospital day, the patient experienced severe back pain. Several minutes later she expired.

*Dr. Lester R. Tuchman**: Ladies and gentlemen, this is my first clinical-pathological conference and I thought I might introduce an innovation. As you all know, the panel system has now taken over medicine. I thought that today we might try that method and see how it works in a clinical-pathological conference. I have, therefore, invited people into whose areas the problems which are presented seem to rest. I have asked Dr. Siltzbach to come and discuss with us those things which have to do with tuberculosis. Dr. Levitt has questions that deal with nephritis; Dr. Mendlowitz, hypertension; and Dr. Wolf has promised to come and talk to us about the x-ray findings.

You all know the salient facts. I think it must be clear to all of you where the problems lie, and with your permission I will address myself as moderator to the problems.

This is a 16 year old Negress, admitted with a marked hypertension and with what seemed to be unequivocal evidence of lymphadenitis of tuberculous origin.

* Attending Physician, The Mount Sinai Hospital, New York, N. Y.

She also had a renal lesion of marked extent with an enormous tendency to a rapid progression and death. It seems to be quite clear that there was a caseating lesion. Dr. Siltzbach, would you accept as tuberculosis the evidence of the biopsy which shows a caseating lesion and acid-fast bacteria?

*Dr. Louis E. Siltzbach**: I would think so.

Dr. Tuchman: You do not think there is any other acid-fast bacillus?

Dr. Siltzbach: I think, for the purposes of our discussion, such organisms as atypical acid-fast bacilli or nocardia need not be given much consideration. We can accept the axillary lymphadenopathy as tuberculous since we found both caseation and acid-fast bacilli. The axilla is not an uncommon localization for tuberculous nodes although the cervical region is more frequently affected.

Dr. Tuchman: What do you think of the mass in the left lower quadrant?

Dr. Siltzbach: That is a great puzzle. I have not seen the projected film but several thoughts suggest themselves. First, I do not believe that one ordinarily can palpate retroperitoneal nodes easily. A definite mass was felt in the left lower quadrant and, if this finding is on a tuberculous basis, one would rather think of mesenteric nodes or masses of omentum in peritoneal involvement by tuberculosis, but I doubt that these are present.

Dr. Tuchman: From the location as described in the chart, would you consider that this could be tuberculosis of the kidney?

Dr. Siltzbach: No, I do not think so. The findings of the urinary sediment are not characteristic of tuberculosis of the kidney. We are told that both kidneys were of equal size radiologically. Nor did this patient have increased frequency or burning on urination which occurs in kidney tuberculosis when the bladder is involved.

It is my guess that the mass which was felt in the left lower quadrant is not a tuberculous kidney even though patients with lymph node tuberculosis are more likely to have kidney tuberculosis than patients with the common variety of pulmonary tuberculosis.

Of course we might be dealing with a psoas abscess secondary to Pott's disease of the spine of tuberculous origin, but the bone films do not support this idea.

Dr. Tuchman: Can you conceive of any tuberculous lesion involving the area in the left lower quadrant as described in the protocol that would explain either the hypertension or the urinary findings?

Dr. Siltzbach: I am unwilling to connect tuberculosis in the lymph nodes or elsewhere to the hypertension and urinary findings. I think it is more likely, from the rest of the story, that the patient had some unusual vascular disease, but no doubt you will hear more about this from the other panelists.

Parenthetically, I do not recall seeing a patient with such severe hypertension in tuberculosis of the kidney, nor have I heard of any instance in which pressure of retroperitoneal tuberculous lymph nodes on a renal artery caused a so-called Goldblatt phenomenon.

In short, I think that the patient has two diseases, lymph node tuberculosis and some vascular disease.

* Associate Attending Physician, The Mount Sinai Hospital, New York, N. Y.

Dr. Tuchman: Would a tuberculous lymphadenitis be likely to develop into an amyloid disease to give a renal lesion of any kind and a renal lesion resembling this?

Dr. Siltzbach: I do not believe so.

Dr. Tuchman: May I recapitulate and see if I understand clearly what you have said? You are of the opinion that the tuberculosis has been established for the lymphadenitis but that it is not in any probable way related to the rest of the clinical picture.

Dr. Siltzbach: That is correct. I would feel more comfortable about the tuberculous nature of the lymphadenopathy if positive cultures for tubercle bacilli had been obtained, but even without this I think we can accept the diagnosis of lymph node tuberculosis.

Dr. Tuchman: Are there any questions you would like to address to Dr. Siltzbach?

Doctor: Was the erythematous lesion related to tuberculosis?

Dr. Siltzbach: I did not personally see the erythematous nodular lesions on both lower extremities. Generally, the erythema nodosa occurs six weeks after the first contact with the bacillus. In other words, it generally comes at about the same time the patient's tuberculin response converts from negative to positive. There are exceptions, of course, in that some tuberculous patients may have more than one attack of erythema nodosa particularly during a period of fresh hematogenous dissemination, but this girl's course was afebrile and I would rather relate the skin lesion to some vascular phenomenon rather than to classical erythema nodosa.

Dr. Tuchman: Dr. Mendolowitz, would you tell us how you feel about a young girl of 16 with blood pressure levels such as are described here? In what areas would you look for causes?

Dr. Milton Mendlowitz:* I think this case is very peculiar and unusual from several points of view. With reference to the hypertension, she had very high levels of blood pressure and eye ground changes that were extensive. In other words, this was a malignant, highly accelerated form of hypertension.

Now, the question is: what underlying disease was present in a girl at 16 years? I do not think it can be resolved from pure clinical examination alone from what we know about this case. However, I think we can guess in certain directions. We are told that there was prompt appearance of a dye on the right side on intravenous pyelography while there was no appearance of the dye on the left side. From this one would assume that this patient either had a congenitally small or absent left kidney or that she had a normal-sized left kidney to which the circulatory supply was obstructed—so-called Goldblatt kidney—or that she had some disease of that kidney which made it impossible for the dye to be visualized.

There were no arteriographic studies made, so we really do not know too much about what has occurred in the left kidney.

* Associate Attending Physician, The Mount Sinai Hospital, New York, N. Y.



FIG. 1. Intravenous pyelogram showing visualization of the right kidney and a normal-sized left renal shadow but with no dye.

Dr. Tuchman: Dr. Mendlowitz, I want to interrupt at this point. Dr. Wolf will tell us about the x-ray films.

Dr. Bernard Wolf:* In the pyelogram the right side is visualized with calyces and a renal outline which do not seem to be remarkable (Fig. 1). On the left side there is no visualization but there does seem to be a renal shadow which has the normal configuration and which is normally located. The psoas shadows are obscured by intestinal contents. In the bones there are no distinctive lesions.

Dr. Tuchman: Would you tell us what light this throws on the question as to whether there is any disease in the left kidney that has clinical importance for the facts as presented?

Dr. Wolf: There are many reasons for failure of visualization. These range all the way from a ureteral calculus with temporary kidney block to diffuse inflammatory processes in the kidney and also to various vascular lesions of the kidney, none of which can be recognized by the plain film or intravenous pyelogram, particularly if there is no visualization.

Dr. Tuchman: If this was a vascular lesion, how large a vessel would have to be involved to cause it?

* Director, Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

Dr. Wolf: It need not be a large vessel, assuming that there has been an acute process in the nature of renal infarct. If, however, there has been a chronic process related to vascular disease, it should involve a major, if not the main, renal vessel.

Dr. Tuchman: Is there anything here which would lead you to suspect that this would be tuberculosis?

Dr. Wolf: Since one cannot see any details of the collecting system, it is impossible to say. It is rare, however, for tuberculosis to involve the kidney to a point where there is no visualization and not cause some disturbance of the renal outline.

Sometimes one can see what looks like a renal outline when there is no kidney. For instance, after a nephrectomy, what looks like a renal outline is seen but, in reality, is the result of residual perinephric fat.

Dr. Tuchman: The mass as described is supposed to be in the left lower quadrant, two inches to the left of the midline and four to five centimeters in dimension. How do you relate that to the kidney?

Dr. Wolf: I certainly cannot see any evidence of the mass.

Dr. Tuchman: Dr. Levitt, how do you interpret these renal findings and the history and physical as given?

Dr. Marvin F. Levitt:* I think the most important features of this patient, when she came in, was the association of fever with striking renal disease and severe hypertension. The problem is to determine whether the hypertension was a consequence of primary renal disease or a so-called Goldblatt phenomenon or whether she had accelerating hypertensive disease.

What is important in helping to differentiate is the very first sentence that mentioned the fact that this girl had edema. I would like to know a little more about the nature of that edema seven to eight months before she came in.

There are three possible explanations for this edema. One is that she had congestive heart failure. It would be unusual for a young girl to suddenly develop congestive heart failure as the first manifestation of accelerated hypertension. I would like to know if she was short of breath, if there was swelling of the eyes, and something about the back pain. I cannot explain back pain on the basis of congestive heart failure. It is possible that she had congestive heart failure but I am not satisfied with that explanation for the edema.

It is possible that she had a nephrotic syndrome secondary to glomerulonephritis or possibly amyloid. For a patient with amyloid nephrosis to clear up by the time she gets into the hospital is extremely unlikely. Even if the edema were due to a nephrotic syndrome, I would like to see some persistence of the nephrotic syndrome when she entered the hospital. There was no massive albuminuria, no hypoalbuminemia and no hypercholesteremia. I am left with the possibility that she had an acute nephritis and that this was responsible for her edema and responsible for the back pain; the latter would not go hand-in-hand with congestive heart failure or nephrotic syndrome.

On the basis of the fact that her presenting symptom was edema, I think the

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most likely possibility is that she had acute diffuse glomerulonephritis nine months before her death.

Now, I am also very disturbed by the fact that the left kidney does not visualize. I do not believe we have enough evidence to draw any conclusions from that because I think the right side visualized only poorly and the left side visualization was maybe slightly poorer than the right side. The massive nodes may have been enough to obscure the kidney on the left. I think these lymph nodes would help explain an absence of visualization on the left without marked evidence of disturbed renal function on both sides.

Dr. Tuchman: What do you think of the diagnosis of nephritis?

Dr. Levitt: It appeals to me because it is the only diagnosis that would explain the edema nine months before admission.

Dr. Tuchman: How often have you seen a blood pressure of 240/130 in chronic nephritis?

Dr. Levitt: It occurs in the uremic phase or with the association of a superimposed glomerulonephritis. About the precise frequency, I would not be willing to hazard a guess, but I do not think it rules out the diagnosis of the chronic nephritis in the uremic phase.

Dr. Tuchman: Which do you favor between a vascular lesion and chronic progressive glomerulonephritis?

Dr. Levitt: I cannot explain the original onset of edema on the basis of accelerating hypertension. If she was in heart failure, why did it improve despite the progression of her disease?

Dr. Tuchman: Dr. Bank several years ago described some ten cases of hypertension of tremendous order with lesions which were reminiscent of periarteritis. How would you put this case in reference to the group described by Dr. Bank?

Dr. Levitt: I do not think she is one of them because those patients did not present with edema. Also, there is one other finding which may be deserving of some emphasis. On the first admission she did not have many red cells in her urine, which would have been present in large numbers in necrotizing arteritis.

Dr. Tuchman: It may not have been necrotizing at this time.

Dr. Levitt: I think it would have had to be.

Dr. Tuchman: At that time she did not have quite the present blood pressure level.

Dr. Levitt: She had diastolic pressures of about 130 mm. Hg. The finding that I am having trouble with is the edema. Edema, to me, is most impressive because I cannot think of any other explanation for its disappearance.

Dr. Tuchman: You agree with Dr. Siltzbach that tuberculosis had nothing to do with the renal lesion?

Dr. Levitt: To my recollection, tuberculous lymph nodes producing a Goldblatt phenomenon has never been described. However, when we first saw her, that was one possible explanation that worried us. That, also, would not explain the edema.

Dr. Tuchman: Thank you very much. I think one of the wittiest things that Stevenson ever said was that he felt that a moderator should be like the fan in

the fan dance; to call attention to the subject without obscuring the view. The important view here is Dr. Popper's findings and I will turn the meeting over to him.

*Dr. Hans Popper**: The case which we will present is rather complex both from the clinical history as well as from the pathological standpoint.

First, let me quickly review with you the pathological findings in the biopsy specimen from the right kidney which unfortunately was not of the best technical quality. The glomeruli were surprisingly well preserved at this time. Some thickening of the glomeruli was present at the vascular pole. There were moderate changes in some glomeruli but predominantly we saw some degree of nephrosclerosis. You have already read the negative report of the skin biopsy and we could only confirm this.

In looking at the biopsy of the lymph nodes, we found a granulomatous lesion. The granulomatous lesion extensively replaced the lymph node architecture. There was extensive hyalinization of the reticulum and a fibrosing tubercle was noted. Since acid-fast bacilli were found, we all will agree with Dr. Siltzbach that it had to be lymph node tuberculosis and it was generalized, at least at the time of autopsy. In the tracheobronchial lymph node, a large solidified focus of tuberculosis was found, and tuberculosis was also found in the periaortic and mediastinal nodes and around the pancreas. Markedly thickened reticulum with a high collagen content was present in all the nodes. The collagenization of reticulum and scarring are part of the healing process of tuberculosis. It occurs occasionally in sarcoidosis. The question arises as to what degree this influenced the general picture. The lungs were devoid of any pathological changes. The pulmonary arteries appeared entirely normal, as did the pleura.

The heart weighed 420 grams in this young girl 16 years of age. Cardiomegaly was more marked on the left than on the right side. In addition, pericarditis was found with adhesions which easily separated and hemorrhagic areas were seen, all in keeping probably with typical uremic pericarditis.

The myocardium appeared unaltered. As we inspected the cardiac chambers, we saw extensive left-sided hypertrophy. The aortic valve was perfectly normal. Though the heart was generally hypertrophied, it was only slightly dilated and nothing in the heart itself indicated that the increased pressure led to cardiac decompensation.

Extending out of the aortic valve, almost an arterial cirrhosis was present with significant arteriosclerosis for this age. We were interested as to whether hypercholesteremia was present in the young girl. It is not in the record but I have been told that the serum cholesterol, at least at the time it was determined, was normal. We have the type of arteriosclerosis in this age group which I would still like to connect with hypercholesteremia. In the media of the aorta, we saw edema. The elastica and the muscle fibers were distinctly separated by a material which did not show a chromotropic type of degeneration. There was also distinct edema of the aortic valve with separation of the elastica and the muscle fibers.

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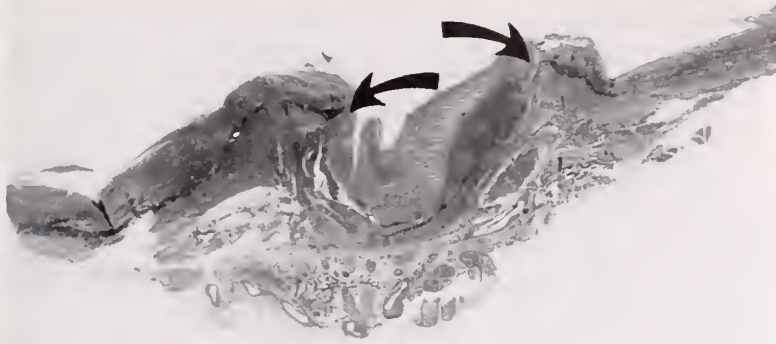


FIG. 2. Small aneurysm of abdominal aorta showing break in the elastica fibers (arrows). (Elastica stain $\times 4$).

In such areas without any cellular infiltration, the aortic structure was little distorted. The elastica was separated and the muscle fiber was not healthy because of the arteriosclerosis. This may not have been the result of medial edema with weakening of the wall. In looking further down into the descending part and thoracic part of the aorta, the picture very dramatically changed. We saw marked disfiguring of the intimal architecture which was associated with multiple outpouchings. One pouch was about a centimeter in diameter where the celiac axis originated. A thrombus was located above the celiac axis. Just above the bifurcation of the aorta into the iliac arteries, another pouch about three to four centimeters in diameter extended anteriorly and somewhat toward the left. Histologic examination of the aneurysm associated with the celiac axis showed some elastica still preserved and some broken. We found medial breakdown, medial necrosis, and finally elastica breakthrough (Fig. 2). It meant that the changes which were somewhat discrete and just suggestive in the thoracic portion in the arch of the aorta became dramatic with destruction of the elastica.

Chromotropic degeneration which characterizes classical medial necrosis and which typically occurs more in the upper portion of the aorta was absent but the elastica had broken into small bits and gave way, producing false dissecting aneurysms undermining the wall of the aorta. Actually, they were not quite dissecting but between true and dissecting aneurysms. The original wall of the aorta formed part of the aneurysmal lumen but there was also medial destruction and undermining. We could not call them true aneurysms because the original wall was not really preserved and we could not really call them dissecting aneurysms. In the broken-down and destroyed wall, fat was deposited and it was free of elastica. The lowest aneurysm broke through the posterior wall of the abdominal cavity (Fig. 3) but it did not break into the peritoneum, although 500 ml. of serous fluid was found in the peritoneum at the time of death. The earlier back pain could have easily been explained by the lesion. The severe back pain was ended by the profuse hemorrhage into the retroperitoneal space which extended along the ureters down to the bladder wall.

The etiology of the aneurysm was the next question. Tuberculous nodes were

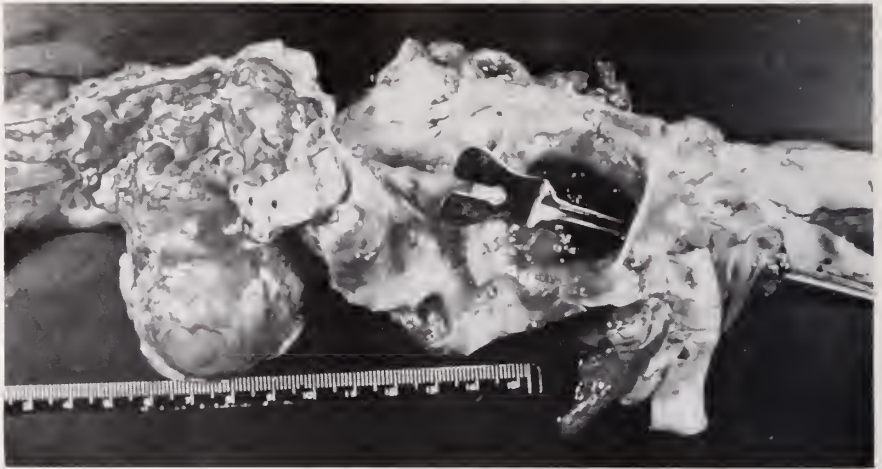


FIG. 3. Gross picture of abdominal aorta showing site of rupture of lowest aneurysm to the right and another saccular but intact aneurysm to the left.

near the ruptured aneurysm but with no real connection between the two. There were multiple aneurysms with infarcts, especially in the largest one, and with some periaortic lymph nodes containing tuberculosis nearby, but they did not necessarily reflect the etiology. We did not find any infiltration in the areas where breakdown of the elastica was recognized. I, therefore, do not think it was syphilitic. Furthermore, very few plasma cells were in the exudate in the wall of any of the aneurysms. It would be distinctly peculiar in this age group to find a syphilitic aneurysm. I was informed before the conference that at least one serologic test for syphilis was performed with negative results. This does not necessarily exclude syphilis because at the time when we saw syphilitic aneurysms in large numbers, serology was negative in thirty per cent. We found extensive thickening of the media of the vasa vasorum throughout the aneurysm extending into the aorta. I think possibly this constriction or obstruction of the arterial blood flow by the thickened arterial vessels might have been aggravated by the aneurysm in this particular situation. In the part of the aorta with only edematous foci, all of the vessels were also thick. These markedly thick vessels interfered with blood supply, probably one of the causes of the aneurysm formation.

In the arteries in the diaphragm, excessive hyperplasia of the media was extensive, as in other parts of the body such as in the submucosa and muscularis of the stomach. These vessels exhibited diffuse muscular hypertrophy through the entire wall associated with tremendous media thickening, probably the end result of spasm. The elastica was not constricted. Nowhere in the thickened vessels was the elastica altered.

The liver appeared normal except for the presence of the arteriosclerotic changes. The spleen was slightly enlarged and showed severe arterial changes. The adrenals were entirely normal.

The last organs which I want to bring to your attention are the kidneys. The left and right kidneys were small, weighing 80 grams and 60 grams respectively



FIG. 4. Gross picture of both kidneys, the paler one being the right kidney and the smaller darker one the left.

(Fig. 4). Large yellow irregular scars were on the surface and also reddish finer scars. The surface of the smaller left kidney was fairly smooth. Histologically, the architecture was moderately disturbed. Tremendous thickening of the arteries, especially the intima, and arteritis involving the left renal arteries were present. There was some arteriosclerosis but as a result of disturbance of the blood flow. There was also some interstitial fibrosis. The glomeruli were small and showed some sclerotic changes but most of them were well preserved. Some glomeruli were fibrosed (Fig. 5) due to the presence of a somewhat thickened

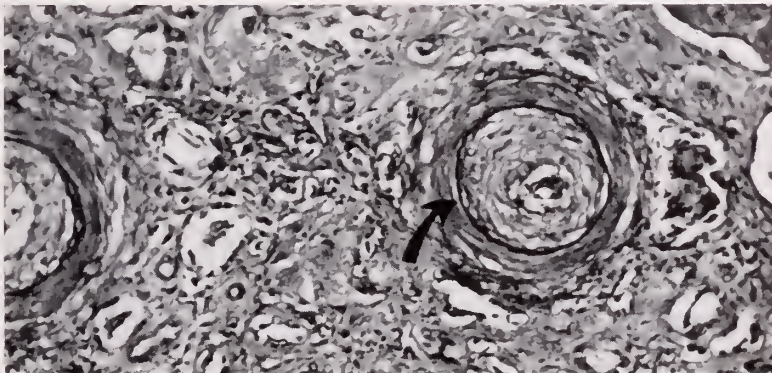


FIG. 5. Obstruction of lumen of interlobular arteries of left kidney by intimal proliferation, the internal elastic membrane being intact (arrow) (H & E $\times 120$).

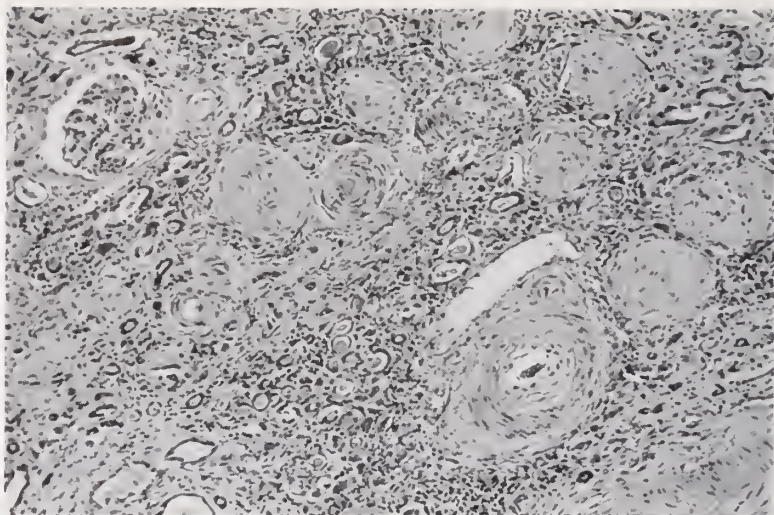


FIG. 6. Bunching of obliterated glomeruli and periglomerular scarring in left kidney (H & E $\times 63$).

media and a tremendously thickened intima obliterating the lumens of the artery branches (Fig. 6). These marked sclerotic changes gave rise to some scarring of the surface. The somewhat larger right kidney had many bigger scars than the left kidney which had only small scars. As we looked histologically in the right kidney, we saw an entirely different picture. There was very marked distortion of the architecture, probably with some compensatory hypertrophy. There was interstitial infiltration and fibrosis, perirenal fibrosis and large glomeruli with fibrotic changes. The glomeruli, in general, were large and scarred but the arteries were free. Peculiarly, the interlobular arteries were severely

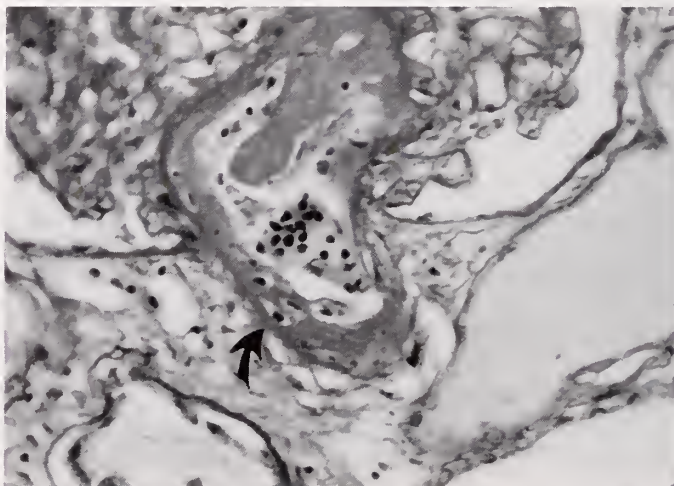


FIG. 7. Arteriolar necrosis in the right kidney with intramural hemorrhage of afferent artery (arrow) (PAS $\times 240$).

damaged on the left side but on the right side they were perfectly normal. There was no inflammatory component to any extent in this kidney but there were fatty cells, fibrosis and sclerosis. We saw sclerosis of part of the glomeruli. The glomerular poles were markedly fibrosed. This represents a severe and typical arteriolar necrosis in the right kidney (Fig. 7). It not only involved the arterioles but it also extended around the glomeruli and tubules. In some areas it even destroyed some of the tubules because of the disturbance of the blood supply. Was there any reason why the two kidneys were different? After inspecting the gross specimen once more, we saw that the left kidney and its renal artery were entirely normal. However, in the right kidney, the renal artery came from an aneurysm.

In trying to correlate the findings, we must remember that the right kidney was visualized and the left one was not, while the left one had architectural changes but a perfectly normal artery. Now, I think the explanation is not too difficult. First of all, the generalized lymph node tuberculosis with diffuse scarring was of little importance in the case. The patient had essential hypertension. The essential hypertension in view of the age of the patient must have led to a diffuse arterial spasm with very severe muscular hypertrophy of the arterial walls. This led to edema and then necrosis of the media of the aorta and to destruction of the elastica which led to multiple aneurysm formation. This probably accounted for the back pain and possibly to the eosinophilia found because of tissue destruction. The ankle swelling was the result of mechanical factors; the pressure from the aneurysm upon the vena cava inferior contributed to the conditions which produced the ankle swelling. How did we explain the peculiar renal changes? There were multiple aortic aneurysms and in the presence of severe arteriosclerosis, endarteritis developed in the left kidney because it was exposed to the high blood pressure without the protecting effect of the aneurysm. The aneurysm on the right side reduced the pressure effect upon the right kidney to a certain degree. Consequently, severe endarteritis developed in the left kidney and produced the changes of marked hypertension. Added to the essential hypertension was the Goldblatt phenomenon created in the left kidney as the result of endarteritis. Under the influence of the Goldblatt phenomenon, the blood pressure rose to astronomical levels. As it rose, it reached levels at which the protecting effect of the aneurysm on the right side did not make itself felt anymore. Malignant nephrosclerosis developed in the right kidney because the smaller arterioles were no longer protected by the endarteritis. By the same token the left kidney, having endarteritic changes involving its larger arteries, was protected from the development of the endarteritic necrosis. This is the only explanation whereby I can explain the two features—the protecting effect of the aneurysm which prevented the development of the endarteritis on the right side and produced severe early damage on the left side. Then, when the blood pressure rose to very high levels, severe arterionecrosis and complete breakdown occurred in the nonprotected right kidney.

Anatomical diagnosis: Rupture of abdominal aortic aneurysm. Multiple aortic aneurysms. Malignant nephrosclerosis. Hypertensive cardiovascular disease. Lymph node tuberculosis.

Important Notice

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THE JOURNAL OF
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SYMPOSIUM
ON
SYSTEMIC LUPUS
ERYTHEMATOSUS

George Baehr, M.D., and
Paul Klemperer, M.D.

Guest Editors

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PREFACE

The problem of systemic lupus erythematosus has held the interest of the medical staff of The Mount Sinai Hospital for the past thirty years; since the days when Dr. Emanuel Libman was Attending Physician to the institution.

Before Kaposi's original description of the disease in 1872 as a serious, acute, often fatal disease entity, lupus erythematosus had been regarded merely as a persistent but generally innocuous malady of the skin. Dermatologists almost exclusively were concerned with its diagnosis and empirical therapy. About the turn of the century its general medical implications became evident to clinicians. Various internists collaborated in attempts to define the obscure and puzzling clinical picture of the disease. The manifestations of joint, kidney and serous membrane involvement were clearly described and associated hematologic alterations were discovered in the laboratory. However, specifically characteristic pathologic-anatomic and histopathologic lesions first became known through Libman and Sacks' classical paper in 1924.

Since that time numerous additional microscopic observations were made which aided in clarifying the nature of the disease. These observations of altered structure of organs and tissues focused attention upon the obscure pathogenesis of the condition. The discovery of the lupus erythematosus cell by investigators at the Mayo Clinic coincided with the first cytochemical analysis of the hematoxylin stained bodies demonstrated in tissues by Dr. Louis Gross in our laboratory in 1932. Subsequent morphologic studies led to the establishment of dependable diagnostic criteria of systemic lupus erythematosus, and to hypotheses regarding the chemical mechanism responsible for the structural changes in the blood and tissue cells. Therapy was significantly advanced for the first time by the discovery of the corticoids. More recently, the disclosure of a L.E. factor in the serum of patients attracted the attention of immunologists and their studies have given new leads to the elucidation of the problem of etiology.

The history of systemic lupus erythematosus illustrates the path by which progress is achieved in medicine; exact observations made at the bedside and at the autopsy table led to research by means of the refined methods of fundamental biology.

A survey of the present state of our scientific knowledge of systemic lupus erythematosus seems timely and we have therefore invited a number of competent investigators to cooperate in summarizing current information on the subject. All are on the staff of The Mount Sinai Hospital or have been associated with us in the past.

GEORGE BAEHR, M.D.
PAUL KLEMPERER, M.D.
Guest Editors

SOME OBSERVATIONS ON THE PATHOLOGY OF SYSTEMIC LUPUS ERYTHEMATOSUS

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The historical development of lupus erythematosus as a systemic disease has been critically developed by Klemperer (1). In his brief review he traced the changing conception of this malady from that of a cutaneous disorder to one in which the entire organism is profoundly disturbed. This is now abundantly clear. It is also clear that, in any disease presenting such diverse and apparently unrelated manifestations, one must search for a catastrophe at a very basic level.

It is traditional, in developing a comprehensive concept of any discrete disease, to explain the alterations in form and function on a single pathogenetic principle. I am not sure that this is always the best starting point. It may be more profitable to assume, or we may even be forced to assume, that the many manifestations of systemic lupus erythematosus* reflect one or more derangements, associated or not, but always interdependent. One is impelled to make an acoustical analogy: the total tone characteristic for a given musical instrument consists not only of a fundamental tone but also of harmonic tones heard simultaneously with and over the fundamental tone. Although we have not yet identified the "fundamental tone" in systemic lupus erythematosus it is perhaps possible to sort out one or more harmonics.

It is not the purpose of this paper systematically to review the many organ changes apparent in systemic lupus erythematosus. The morphological manifestations have been fully documented in a number of papers (2-5). Before discussing the lesions to be found in S.L.E. one ought to re-emphasize the disappointing (and puzzling) paucity of anatomical change occasionally found on careful post-mortem examination of a patient dying after the most fulminating and severe clinical course.

The pathologic alterations in S.L.E. seem to fall into three groups. The lesions in the first group exemplify the "anatomical symptoms" of a widespread disturbance within the connective tissue system. The second group of lesions reflects injury to the nuclei of cells of mesenchymal origin, especially hematic cells, and perhaps other cells as well. The third group of alterations, granulomatous in character, follows from the first and second groups.

THE CONNECTIVE TISSUE LESIONS

The writer and his co-authors once expressed the idea that the morbid anatomical image in S.L.E. was a reflection of extensive damage in the connective

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* This recent term (and its rubric, S.L.E.) seems more appropriate than previous designations such as acute or disseminated lupus erythematosus.

tissues and that the underlying functional disturbance responsible for these changes was not evident (5). They further generalized that S.L.E. could be considered in common with a number of other conditions (scleroderma, rheumatic fever, rheumatoid arthritis, periarteritis nodosa, thromboangiitis obliterans, and serum sickness) as "collagen diseases" only in so far as all presented visible alterations in the connective tissue system, more or less similar, but each in a characteristic pattern (7). The expression "collagen disease" was devised as one of convenience, a sort of shorthand symbol to designate this group. Since its original use, the expression has been corrupted and abused to indicate disease of connective tissue, if indeed, there be such a thing. To others the term has become synonymous with the various syndromes of hypersensitivity. To still others, "collagen disease" evokes the idea of a single nosological entity having several manifestations, e.g., S.L.E., rheumatoid arthritis, scleroderma, etc. It is hoped that "collagen disease" will be considered in the sense of its original implication: that certain disorders, some related, some not, may have their morphologic expression in alterations of the connective tissues and that the latter comprise a system whose functions must first be defined chemically and physically before an understanding of its changes becomes possible. The accelerated pursuit of basic information regarding this most important system in recent years has been most gratifying. If "collagen disease" as a poor or even fallacious generalization has served no other purpose than again to call attention to the connective tissues as a functional system (8), it will have served well enough.

Connective tissue consists of fibroblasts, and collagen, reticulum and elastic fibers imbedded in and continuous with a complex, amorphous "ground substance." Structural changes in the "collagen diseases" may appear in some or all of these elements in variable degree and in different quality. One of the most striking changes in S.L.E. is so-called fibrinoid degeneration of the connective tissues. These alterations are now well known and can be demonstrated in variable frequency and intensity in the connective tissue of the heart and blood vessels, kidneys, serous membranes and skin, as well as in the less organized, dispersed, connective tissues (Figs. 1, 2, 3, 7).

Neumann first characterized fibrinoid degeneration as a particular kind of change in connective tissue fibres and possibly also in the ground substance: "dass eine mit Aufquellung und Homogenisierung verbundene chemische Veraenderung der Interzellulärsubstanz des Bindegewebes erfolgt, welche dieselbe einer Faserstoffmasse ähnlich macht" (9). Wolpers, employing electron microscopy, would have us believe that the collagen fibre is not in itself altered but merely suffused with precipitated tissue fibrin which causes the individual fibrils to become stuck to each other (10). He stressed particularly a peculiar granular change in the surrounding amorphous ground substance. These disturbances were noted in subcutaneous rheumatic nodules and in the experimental Arthus phenomenon. Rich and his co-workers, on the other hand, also having applied electron microscopy to collagen fibres from cutaneous Arthus lesions, would urge that the fibres themselves are altered, independently of any change in the surrounding ground substance (11).

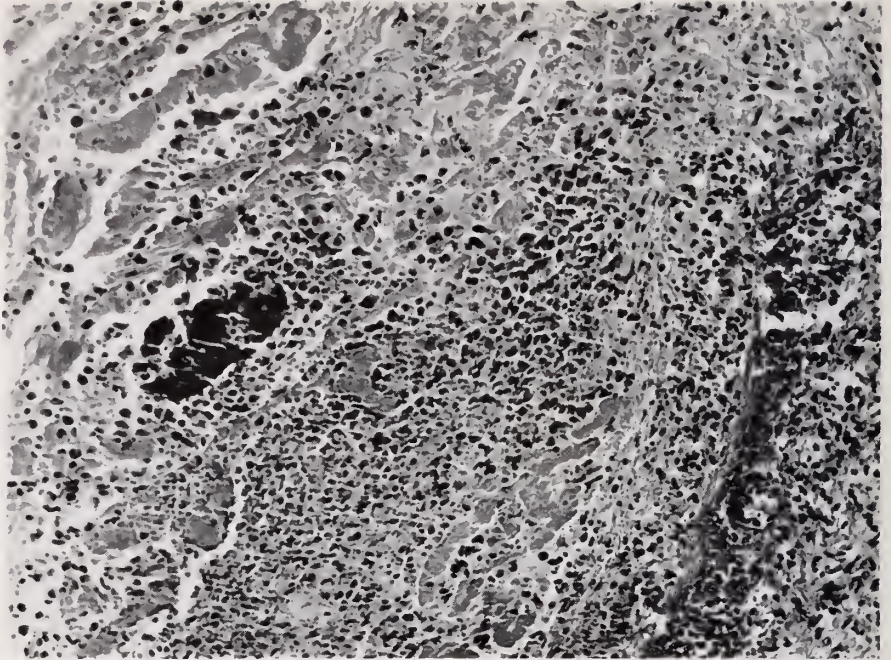


FIG. 1. Splenic capsule. Conglomerate of pyknotic nuclei and L.E. bodies, both discrete and coalescent (hematoxylin bodies), interspersed with masses of fibrinoid. $\times 165$.

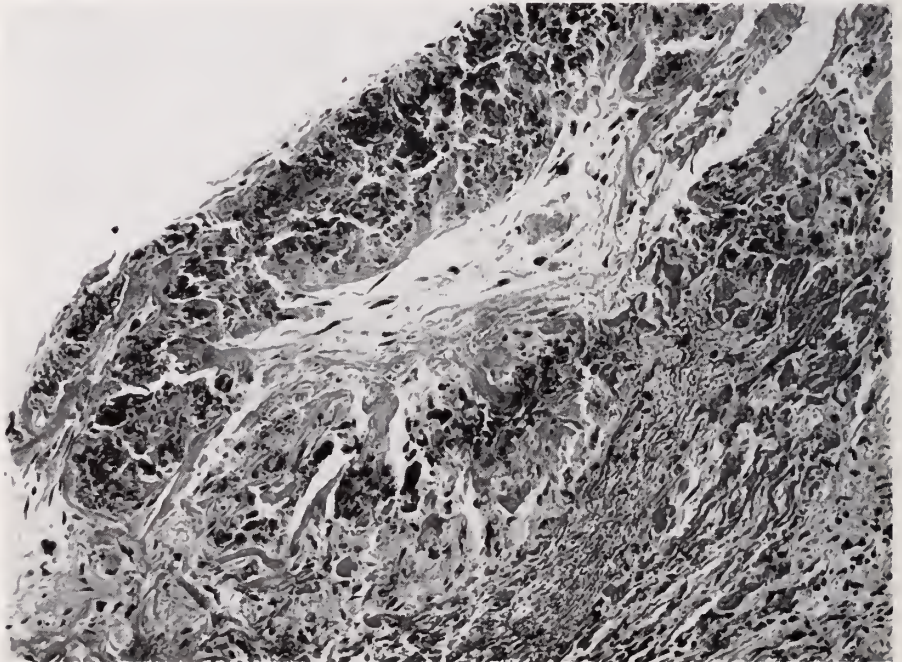


FIG. 2. Splenic capsule. Surface masses of fibrinoid and coalescent L.E. bodies (hematoxylin bodies); organization. Lesion essentially like that occurring in the endocardium. $\times 165$.

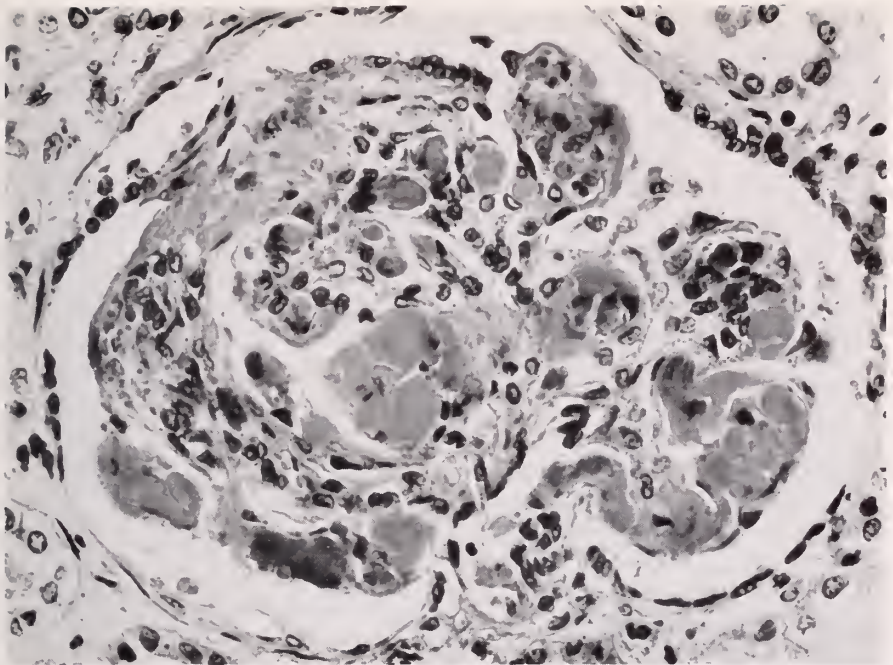


FIG. 3. Kidney. Fusion of endothelial and pericapillary fibrinoid masses. Focal loop necrosis (left). Adhesions. Discrete L.E. bodies in glomerular loops (upper right). Fibrinoid suffused with material of L.E. bodies (lower left). $\times 350$.

Klemperer and Altschuler and Angevine insist that the essence of fibrinoid consists, topographically at least, in a change occurring within the connective tissue ground substance (12, 13). If we assume that collagen fibres imbedded in the ground substance form together a continuum, the difficulties inherent in assigning a particular localization of this alteration fade considerably. It is reasonable, in the face of observational and histochemical evidence, to view fibrinoid as a change occurring in the ground substance and involving the collagen fibres or not.

Having accepted, for the moment, this particular localization of the fibrinoid change, how shall we regard it, of course, in the most general terms? There seem to be but two possible views. In the first of these, as expounded by Klemperer, fibrinoid represents a particular localization of abnormal proteinic material in the ground substance (14). In S.L.E. this is thought to be derived from products of degraded protein which are either precipitated locally, at the site of degradation, or transported by the blood stream, diffusing therefrom into the surrounding milieu. In this way fibrinoid might be found at any depth in the vascular wall, in the pericapillary basement membrane (wire-loops of glomeruli) and even within capillary loops where local hemodynamic disturbance might lead to intravascular concentration and precipitation of circulating abnormal material. In this way too has Klemperer explained the variable "histochemical appearance" of fibrinoid in S.L.E. by assuming more or less co-precipitation of DNA with the fibrinoid complex. This is, therefore, a unique kind of fibrinoid, pathognomonic

for S.L.E. Immunohistochemical manipulation of S.L.E. fibrinoid reveals that it contains gamma globulin (15, 16). This seems reasonable if we assume that anti-DNA or anti-nuclear immune bodies have been fixed to DNA which had previously suffused into and been precipitated in the specific S.L.E. fibrinoid. In extension of his argument, Klemperer would presume that there could be different varieties of fibrinoid, each possibly specific for a particular morbid state (and each awaiting pathogenetic characterization) (12). If this conception be broadened to include all eosinophilic, refractile, non-fibrinous material abnormally precipitated in the connective tissue ground substance then we might also include amyloid as another special kind of fibrinoid, more or less chemically discrete. One is rather loath to press ratiocination in this vein and looks forward to the time when descriptive terms such as fibrinoid, amyloid, paramyloid, and hyalin will, in the further course of experimental and chemical analysis, have become superannuated.

The essence of Klemperer's conception of fibrinoid is that it represents a substance which has been added to and deposited in the connective tissue. On the other hand, Altshuler and Angevine propose the second of the two possible views mentioned above, namely that fibrinoid represents a local alteration in the ground substance, and more specifically, that acid mucopolysaccharide in the presence of locally mobilized basic proteins is converted into fibrinoid.

In our present state of ignorance it is not begging the question tentatively to conclude that there are indeed different kinds of fibrinoid; that the fibrinoid of S.L.E. is quite pathognomonic in that it often contains DNA (12); and that although fibrinoid may in some states represent material brought to the ground substance and precipitated there, it may, in other states, be produced locally by physical and chemical alteration of some moiety of the ground substance.

Bearing in mind these provisional tenets, it is apparent that the term fibrinoid will be used most constructively for the present in its descriptive sense only, until more pathogenetic sorting out in clearly defined terms has taken place. Also, it would probably serve the cause of confusion less if we were not to identify this already complex problem with other tissue phenomena of similar appearance and even similar morphogenesis. Thus, the variety of pulmonary hyaline membranes in rheumatic fever, in uremia, in paranatal primary atelectasis, in various respiratory infections—these are problems in their own right whose solution is not advanced by the loose application of the term fibrinoid, even in its descriptive sense. Similarly, even should it be confirmed that intracapillary thrombi occurring in the generalized Shwarzman phenomenon do indeed represent precipitation of partially polymerized fibrin (17), the application of the term fibrinoid to these masses might inevitably suggest to some that fibrin is an essential of all fibrinoid.* This is very likely not true (13). Although arbitrary, it would seem best for the moment to reserve "fibrinoid" only for the characteristic change within connective tissue, with the understanding that surface or endovascular accumulations of this group of substances may have a similar pathogenesis.

* These authors imply that while fibrinoid is derived from fibrin, the particular fibrinoid precipitated in their experiments contains not fibrin but a fibrin-like material. We have happily been spared *fibrinoidoid!*

THE CELLULAR CHANGES

It was Gross who first noted a peculiar and pathognomonic cellular alteration in the endocarditis of so-called Libman-Sacks disease (2), now recognized as one of the more striking organ changes sometimes encountered in S.L.E. He described "hematoxylin-stained bodies" and believed them to represent "somewhat pyenotic and karyorrhectic nuclear masses." Eight years later Ginzler and Fox described similar bodies within areas of necrosis in lymph nodes and in addition, noted degenerated violaceous nuclei in the renal glomeruli of a young male with S.L.E. (4). Klemperer, Pollack, and Baehr made reference to and illustrated peculiarly degenerated and "bizarre" nuclei occurring most frequently in association with fibrinoid degeneration of connective tissue in the heart, blood vessels, serous membranes, and glomeruli (5). None of these authors fully appreciated the full significance of these cellular changes. Nor could they have.

The discovery of the "L.E. cell" by Hargraves, Richmond, and Morton (18) marked the beginning of a new phase in the slow unravelling of the pathogenesis of S.L.E. The immediate result of this observation was the realization of the relatively greater frequency of this disease than had been previously appreciated. Furthermore, the accelerated search for L.E. cells forcefully revealed the many clinical syndromes under which S.L.E. could masquerade. More important, however, has been the development of an appreciation of the relationship between "L.E. cells" and "hematoxylin bodies." We are indebted to Klemperer and his co-workers for noting the configurational, tinctorial, and histochemical similarity between "hematoxylin bodies" phagocytosed by histiocytes or polymorphonuclear leucocytes and the L.E. cells of bone-marrow aspirates (19). There now seems little doubt that these two structures reflect the same phenomenon, the one produced *in vitro*, the other occurring *in vivo*. It would seem both correct and convenient therefore to apply a single nomenclature to the several phases of this phenomenon, whether seen in the tissues or in isolated blood or bone marrow preparations. L.E. bodies (naked, swollen, amphophilic, leucocyte nuclei) are equivalent to hematoxylin bodies (naked, swollen, amphophilic, mesenchymal cell nuclei); L.E. cells represent L.E. bodies ingested by leucocytes or histiocytes.

It has been demonstrated that L.E. bodies are extremely frequent in the tissues of patients with S.L.E. The data of Klemperer et al., suggest that with careful search they may be demonstrated almost invariably (19). These authors found them most frequently in renal glomeruli and in the endocardium, less often in many other sites: serous membranes, synovia, lymph nodes, spleen, and the dispersed connective tissue.

There are two types of cellular change. In the most striking and obvious, naked nuclei are dispersed in large masses and present the alterations ordinarily characterized as pyknosis or karyorrhexis. These nuclei are small, dense, deeply basophilic, and appear to break down into small spherules and dust-like debris. In the periphery of such foci one may find occasional nuclei having a different appearance—swollen and translucent rather than dense and opaque, amphophilic

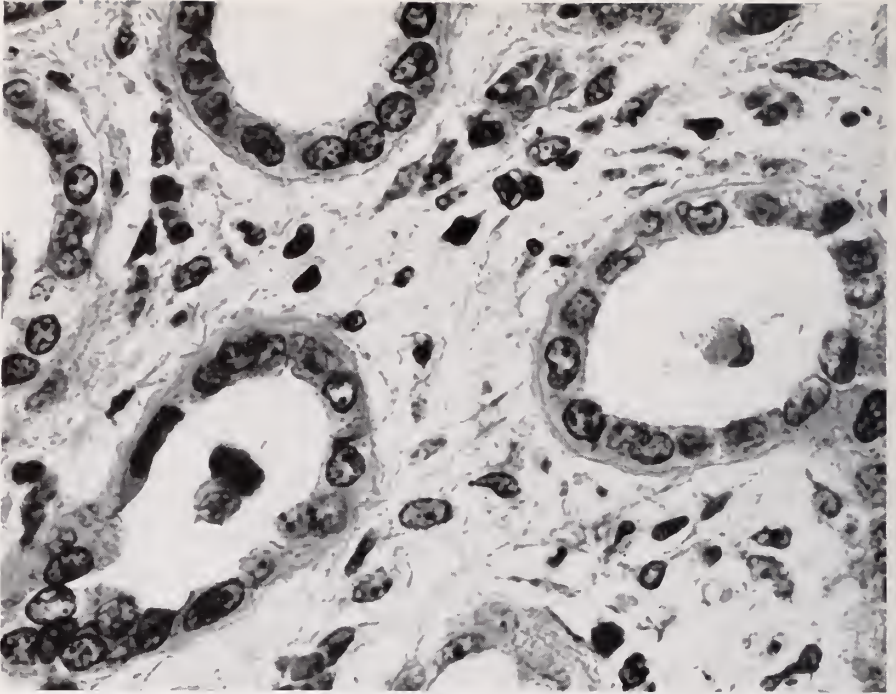


FIG. 4. Kidney. Tubule at left contains two L.E. bodies adherent to a desquamated epithelial cell. Tubule at right contains an L.E. cell. $\times 700$.

rather than basophilic. These altered nuclei, violaceous in hematoxylin and eosin preparations, can be equated with the L.E. bodies of bone-marrow aspirate or blood preparations. When phagocytosed by leucocytes in the tissues they are indistinguishable from L.E. cells. The tissue L.E. bodies are most often found as isolated forms in the endocardium, in blood vessels, in the skin, in renal glomeruli (Fig. 3), and in serous membranes, unassociated with masses of pyknotic nuclei as described above. When L.E. bodies occur in large, coalescent masses they constitute the hematoxylin bodies of Gross, pictured by him in the endocardium. They can occur, however, in other loci—e.g. in serous membranes (Figs. 1 and 2). The older L.E. bodies lose their Feulgen stainability and gain PAS reactivity (20). It has been suggested by Klemperer that S.L.E. fibrinoid represents aggregated L.E. bodies depleted of DNA (1). It is also possible, however, that DNA, leaching out of older L.E. bodies into the surrounding milieu of ground substance adds S.L.E. specificity to locally precipitated fibrinoid. It is of interest that L.E. bodies and L.E. cells formed in glomerular loops (either from fixed cells or from leucocytes) can be washed into the lower nephron (Fig. 4). Presumably they should be found in a concentrated urinary sediment, offering an additional aid to clinical diagnosis.

The L.E. phenomenon—i.e., the development of L.E. bodies, has not been described in any but mesenchymal cells (19). The writer, several times believing he saw the L.E. transformation in renal tubular epithelial cells, could not ex-

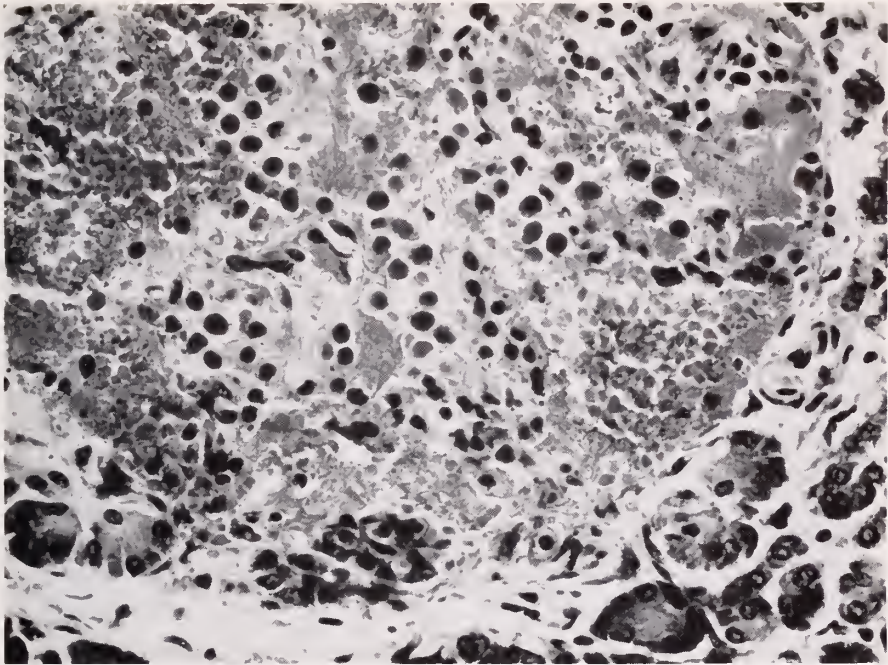


FIG. 5. Pancreas; islet of Langerhans. L.E. transformation of nuclei—probably epithelial. Capillary dilatation and hemorrhage. Fibrinoid masses on right. $\times 350$.

clude the possibility that these were L.E. bodies shed from glomerular loops. In a recently studied case of S.L.E., however, he found L.E. transformation of cells in the islets of Langerhans which appeared to be epithelial (Fig. 5). Many of the pancreatic islets showed occlusion of capillary loops by fibrinoid masses identical with those found in the renal glomeruli. This led to dilatation, engorgement and rupture of capillaries, and even to infarction of whole islets. These observations suggest that given a suitable concatenation of cell damage and local hemodynamic disturbance leading to concentration of antinuclear immune bodies (see below), any cell may suffer L.E. transformation. It is noted in this connection that complement fixation of specific L.E. gamma globulin can be carried out with a range of heterologous and unrelated cells (21).

Until recently it had been urged by Klemperer and his co-workers that the L.E. body, whether in tissues or in *in vitro* blood preparations, was produced by the depolymerization of DNA in the nuclei of mesenchymal cells. The studies of Kurnick et al., suggested that the serum of patients with S.L.E. contained a factor which served as the inactivator of intracellular DNAase inhibitor (22). It is interesting that even during the period of preoccupation with the idea of depolymerization of DNA, it was noted that the Feulgen-positive L.E. bodies also exhibited increased pyroninophilia. This presaged the next steps in our understanding of the L.E. phenomenon when vital data was forthcoming from two directions—chemical and immunological.

Godman and his co-workers showed in a series of brilliant, systematic, cyto-

chemical studies of the L.E. phenomenon that depolymerization of DNA is not the basis for the peculiar appearance of altered nuclei in S.L.E. (23-25). They postulated that protein, not normally found in nuclei, enters the latter, displaces histone, and combines with DNA. Reduction in methyl green complexing by DNA in the L.E. body is more apparent than real since stainable anionic sites are either preempted or masked by competing non-nuclear, inflowing protein. Destruction of basic groups in the latter by acetylation frees the dye binding sites and reveals undiminished, fully polymerized DNA.

At the same time, it was suggested by immuno-histochemical techniques that gamma globulin was fixed in phagocytosed L.E. bodies (26). From here it was a short but rational step to the assumption that the "L.E. factor" in abnormal serum is, in fact, an antibody, capable of being specifically complexed to nuclear material. Employing orthodox complement-fixation and absorption methodology Robbins et al, found that when sera from patients with S.L.E. exhibited the L.E. phenomenon they often reacted *in vitro* with homologous and heterologous nuclei and with various DNAs in accordance with the generally accepted criteria of antigen-antibody reaction (21). Although more proof of this interpretation is required, the evidence is strongly suggestive that the L.E. phenomenon, whether *in vivo* or *in vitro*, indicates "specific" complexing of nuclear material with immune serum protein in the sense of antigen-antibody interaction. The present writer has several times observed a remarkable dissociation between the clinical L.E. test and the post-mortem demonstration of L.E. bodies. In these instances the L.E. test was repeatedly negative when, at the time of death, an extraordinary degree of L.E. body formation was observed in the tissues. This apparent paradox can probably be explained by assuming that massive intravital nuclear fixation of circulating antibody left little or none available for *in-vitro* demonstration.

It is incumbent on us to reconcile the immunologic explanation of the L.E. phenomenon with the observed anatomical changes. If for the moment, we limit ourselves to a consideration of the cellular alterations only, we find no precedent in general pathology for a phenomenon similar to the L.E. body in form and genesis. It is, indeed, this very uniqueness which stretches credibility. One hopefully searches the considerable literature of transplantation immunity. The rejection of homografts seems fairly well founded in antibody response to antigenic material identified or associated with desoxyribonucleoproteins in the engrafted tissues (27). There has been no description in rejected homografts of any cellular change comparable to the L.E. body. It is of course possible that such alterations have been overlooked.*

THE GRANULOMATOUS MANIFESTATIONS

In 1945 Teilum described two fatal cases of systemic lupus erythematosus in which he found epithelioid cell granulomas and nodular necrosis in serous membranes, lungs, and lymph nodes (28, 29). These changes were very minute,

* How often must we ruefully observe with Goethe, "man sieht nur, was man weiss." Many pairs of eyes had scanned L.E. bodies in tissues many thousands of times without arrest until the discovery of the L.E. phenomenon invited a more searching and imaginative reexamination.

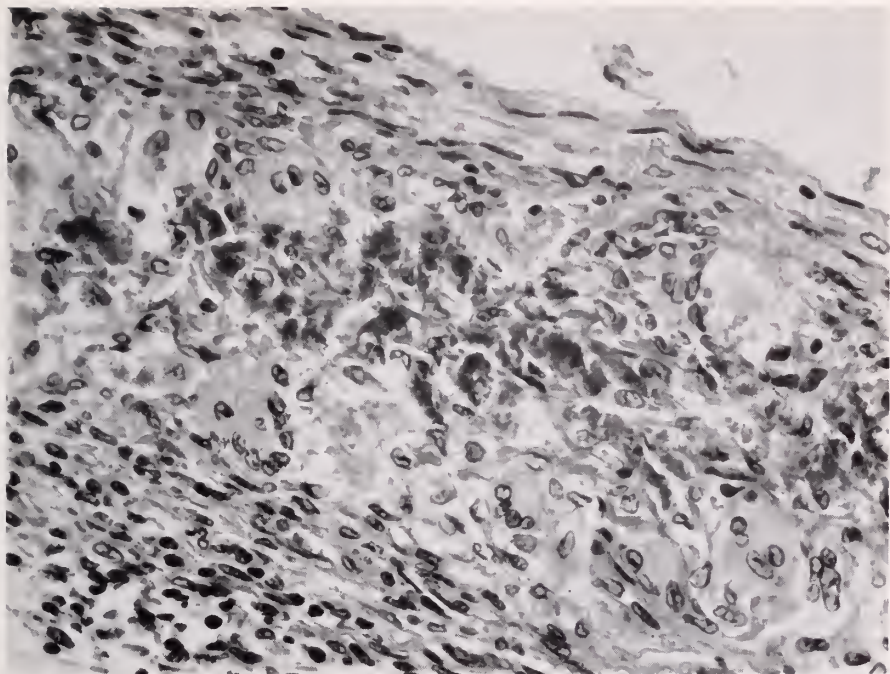


FIG. 6. Splenic capsule. Epithelioid and giant cell granuloma with central coalescent L.E. bodies and fibrinoid. $\times 350$.

though grossly visible, and consisted of foci of "fibrinoid necrosis" surrounded by large, pale, epithelioid cells without caseation, and without eosinophiles. He believed these lesions to be not only characteristic but also indicative of the allergic nature of lupus erythematosus. He also pointed out that they had not been singled out by previous students of the disease. And for good reason—for this particular tissue expression is most unusual in S.L.E. It may be however, despite its rarity, a significant stigma of hypersensitivity. The writer has observed such lesions in serous membranes and their connective tissue adhesions (Figs. 6, 7), and in the mediastinal and esophageal connective tissues (Figs. 8, 9, 10) in S.L.E. They consist of histiocyte-epithelioid cell nodules, with or without giant cells, which may or may not enclose masses of fibrinoid, occasionally compounded with coalescent L.E. bodies (Figs. 6, 9).

Save for the little understood granuloma of Boeck's sarcoid, tuberculoid lesions generally appear as a local tissue reaction to toxic, or infectious, or foreign material. Although tuberculoid lesions of one configuration or another have been noted in hypersensitivity in man (30, 31) and in experimental serum sickness (32, 33), there is no evidence that such lesions are in themselves a primary expression of hypersensitivity. Indeed, it is questionable if even the tubercle of tuberculosis is an allergic lesion (34). It appears to the present writer that tuberculoid lesions present themselves in hypersensitivity only when antigen-antibody interaction culminates in precipitation of large, insoluble aggregates which may also include the degraded products of concomitant local tissue destruc-

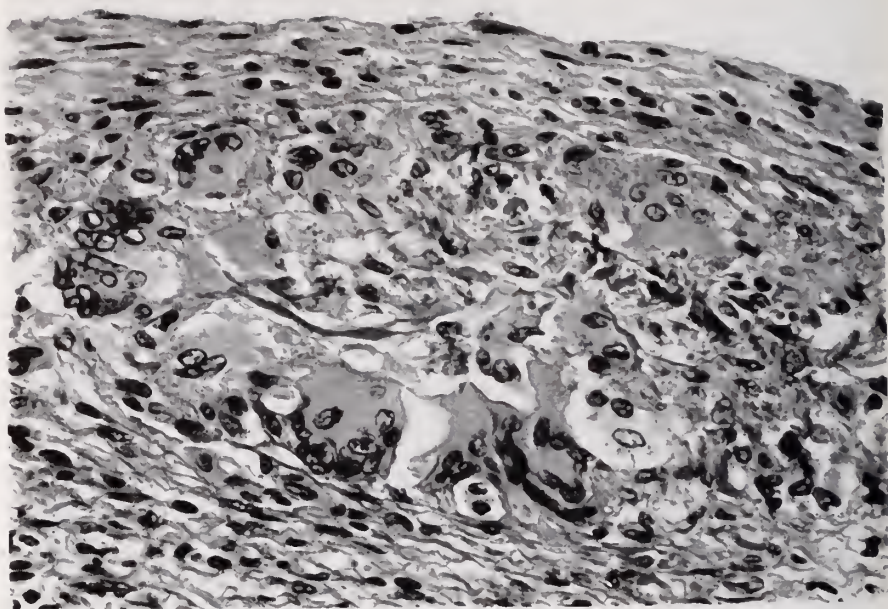


FIG. 7. Splenic capsule. Nodular granuloma with giant cells, some of Langhans type. Fibrinoid strand (left, center) with basophilic cast. Fragmented L.E. bodies (upper center). Resemblance to foreign body reaction. $\times 350$.

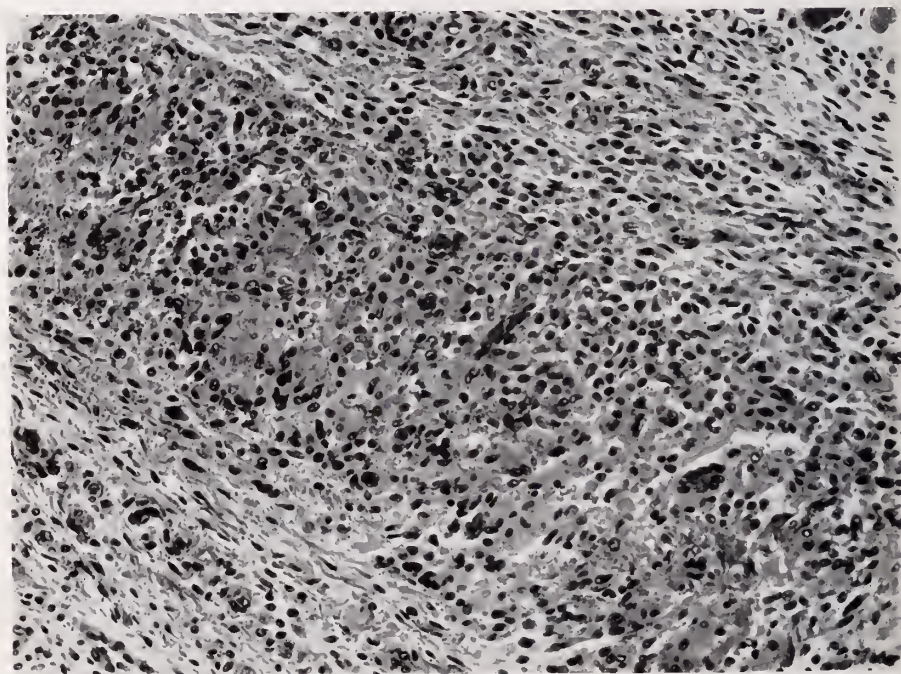


FIG. 8. Esophagus. Tuberculoid, histiocyte-epithelioid cell granuloma in adventitia of esophagus. $\times 165$.

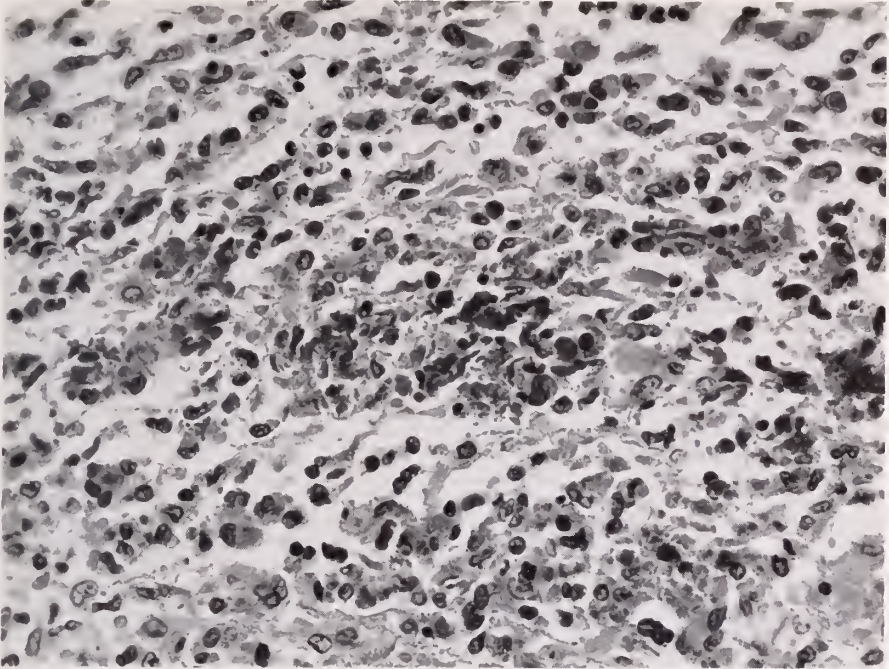


FIG. 9. Esophagus. Histiocyte-epithelioid cell reaction to coalescent L.E. bodies and fibrinoid. $\times 350$

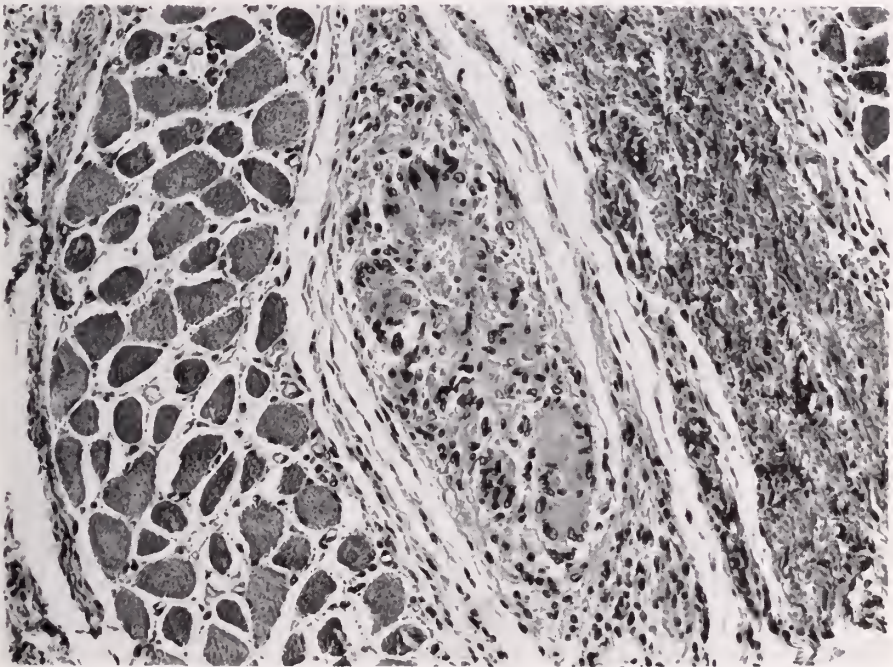


FIG. 10. Esophagus, interstitial tissue. Tubercloid, epithelioid-giant cell nodule showing traces of L.E. substance in center. $\times 165$.

tion. Such conglomerates may thus, because of their unnatural physical or chemical constitution, provoke a foreign body response—i.e., a tuberculoid reaction. There are some indications that the nature of the local response to antigen-antibody interaction is conditioned by the size and complexity of the precipitated aggregates in passive serum sickness (35). There are other observations which suggest that fixation of complement during certain antigen-antibody interactions results in the activation of ferments from proenzyme complement fractions (36). If such observations can be confirmed and extended, a rational mechanism for the development of such tissue changes as “fibrinoid necrosis” may be elucidated.

CONCLUSION

At the time of the discovery of the L.E. phenomenon ten years ago, the constellation of structural changes in S.L.E. had already been fairly well circumscribed and a clinico-anatomical entity well established. Despite a mass of accumulated information, no reasonable clue to the pathogenesis of this malady presented itself. It was persistently urged in some quarters, however, that S.L.E. was a disease of hypersensitivity. This was based particularly on the frequent occurrence of so-called fibrinoid degeneration in the connective tissues, a supposed pathognomonic stigma of allergic inflammation. There is not yet any incontrovertible evidence that S.L.E. is initiated by hypersensitivity. There is, however, a rapidly growing body of fact which would seem to indicate that whatever the unknown primary derangement in S.L.E., the major, overt, structural manifestations are secondary and based on antigen-antibody interaction.

Reference has already been made to the occasional finding of rather massive destruction of cells in many tissues, particularly serous membranes, lymph nodes, and spleen, in which individual nuclei present the conventional aspect of karyorrhexis rather than the L.E. alteration. The pathogenesis of these changes is not apparent. Whatever the cause, be it enzyme or metabolic disturbance, or infection (37) it is not inconceivable that these nuclear changes reflect a pool of unique antigenic material with complex haptenic groups (including DNA and other nuclear substances) available for autosensitization.

I would beg forgiveness for interpolating here another speculation: that the patient with S.L.E. has somehow become host to a heterophile system whose antibody has an unfortunate, fortuitous affinity for his own nuclear material.

These lucubrations are consonant with the ideas expressed by Miescher and Vorlaender who consider S.L.E. a disease of unknown cause (38). They do not regard it as an allergic disease proper. Nevertheless, certain manifestations appear, having the nature of autosensitization, in which antinuclear immune bodies interact with the nuclei not only of leukocytes but also of other cells, giving rise to the L.E. bodies in blood and to hematoxylin bodies in tissues. As the primary cause of the disease is obscure, so also is the mechanism of sensitization.

It is obvious that one of the most immediate tasks in our understanding of

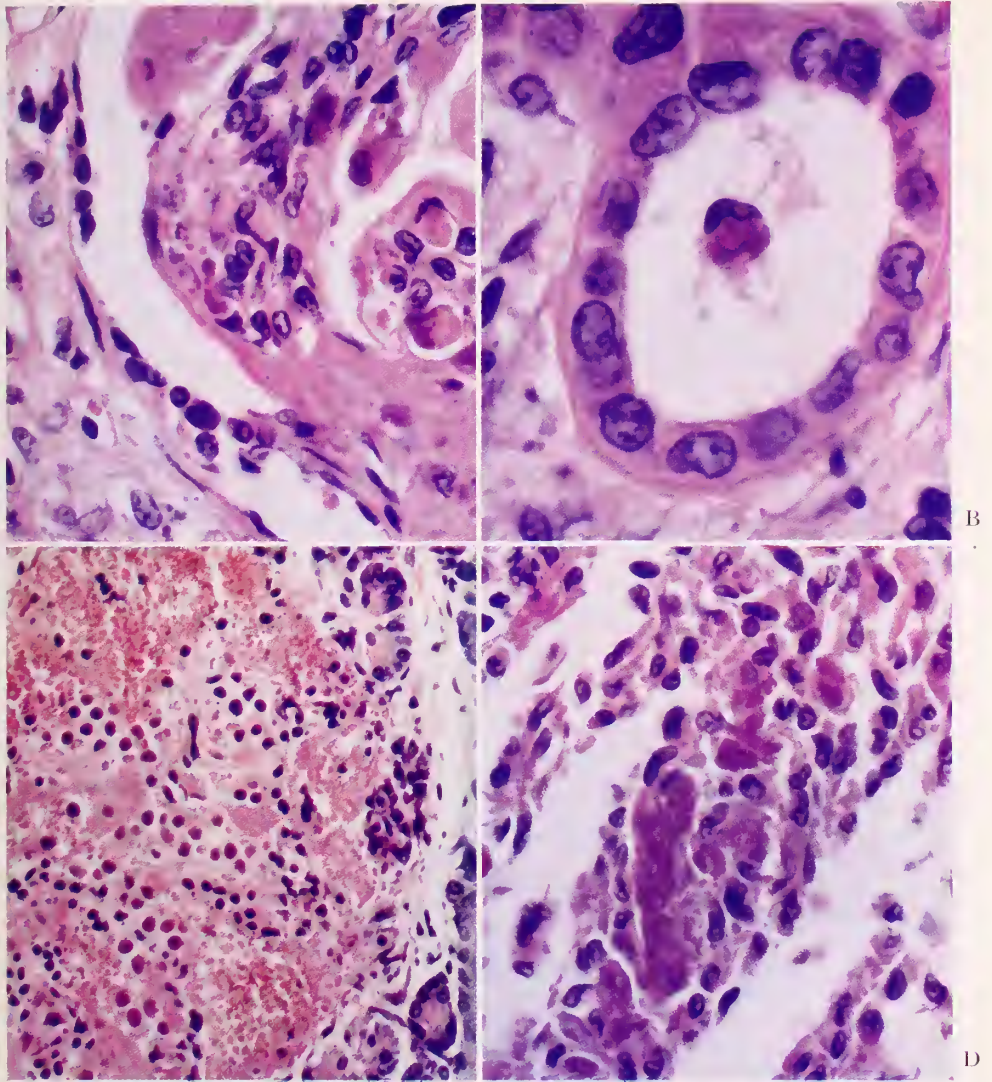


PLATE I

A. Kidney. Lower left portion of glomerulus shown in Fig. 3. Discrete and fragmented L.E. bodies against a background of endovascular and pericapillary fibrinoid masses. Latter is suffused by the stuff of the L.E. bodies. The L.E. bodies are amphophilic or violaceous in contrast to the distinctive basophilia of neighboring intact nuclei. H and E.

B. Kidney. Portion shown in Fig. 4. Lumen of convoluted tubule contains a phagocytosed L.E. body. The latter is characteristically violaceous and smudgy, identical in appearance with *in vitro*-prepared L.E. cells. H and E.

C. Pancreas. Islet of Langerhans as in Fig. 5. Cells showing the L.E. transformation are probably epithelial. H and E.

D. Skeletal muscle. Intermuscular connective tissue septum shows coalescing, fragmented L.E. bodies (hematoxylin bodies) with histiocytic and epithelioid cell reaction similar to lesion depicted in Fig. 9. H and E.

S.L.E. is a search for and characterization of the antigen responsible for the immune phase of this disease.

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THE NATURE AND PATHOGENETIC SIGNIFICANCE OF THE L.E. CELL PHENOMENON OF SYSTEMIC LUPUS ERYTHEMATOSUS

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INTRODUCTION

Many detailed descriptions of the L.E. cell and numerous accounts of its diagnostic significance in systemic lupus erythematosus have been published since its discovery by Hargraves et al., (1). It soon became obvious that the hematoxylin stained bodies of the tissues first depicted by Gross (2) and Ginzler and Fox (3) as material of nuclear origin were entirely analogous to the L.E. bodies found *in vitro*. These anatomic observations, which drew attention to a reaction centered in the nucleus, have formed the basis for most of the subsequent research into the pathogenesis of systemic lupus. The early characterization by Haserick et al., (4) of a factor in the serum of patients with systemic lupus capable of provoking the L.E. phenomenon in susceptible cells, and the anatomical and histochemical analyses of the hematoxylin bodies in this disease by Klemperer and his associates (5, 6) gave the prospect of new insight into the nature of this hitherto obscure disease.

These earlier histochemical analyses of the composition of the lupus body, and therefore hypotheses which depended on them, were based in large part upon histochemical dye-binding methods whose interpretation has since been found more complicated than was assumed in 1950. The L.E. bodies as well as other tissue lesions in lupus have been re-examined using these and other histochemical techniques, and the process of their formation more closely observed, with consequent revisions of many of our ideas. Presently, new insights are being gained in several laboratories from immunological and chemical study of the L.E. serum factor and its interaction *in vitro* with various cellular constituents. It is therefore timely to review our knowledge concerning the origin, development and composition of the L.E. body as a key to pathogenesis in systemic lupus erythematosus.

MORPHOGENESIS OF THE L.E. BODY AND L.E. CELL

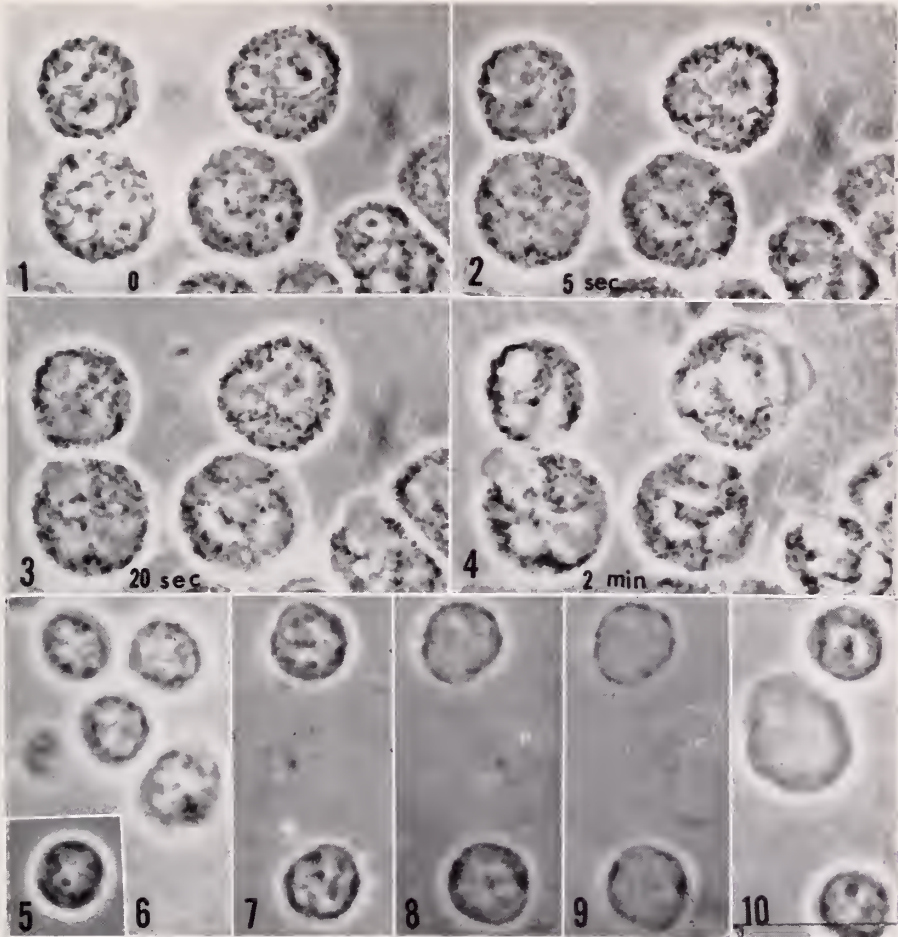
It is now generally held that the nuclei of both mature granulocytes and lymphocytes, normal or leukemic (7-9), as well as the cells of other tissues (10) can undergo the peculiar alteration characteristic of the L.E. body. The cells of other mammalian species are also susceptible to this change (11-13). The appearance of the typical L.E. cell in conventional preparations, its morphological differentiation from other bodies of somewhat similar form, and the conditions for obtaining these cells for diagnostic use have been documented in an

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ample literature, and are dealt with elsewhere. Of interest in the present context, and ancillary to an understanding of their chemical composition is an accurate account of the morphological changes which formation of the L.E. cell involves, and the time sequences in which they occur.

In the presence of the L.E. factor of the serum, nuclei of susceptible cells of isolated nuclei (14) or certain deoxyribonucleoprotein preparations (15) first undergo a peculiar and characteristic alteration, and these are subsequently engulfed by active phagocytes, almost always polymorphonuclear leukocytes, if the latter are present. This two-stage sequence was observed by Rebeck and Berman (16) in a consecutive study of the cells on coverslip windows applied, with L.E. serum, to the abraded skin of normal human subjects, and has been described in supravital preparations by Rohn and Bond (17-19). These authors, using supravital stains to assist light microscopy, observed that the affected nuclei of mature polymorphonuclear leukocytes first showed swelling and then dissolution of the chromatin pattern, with conversion of the nucleus to an amorphous mass within the original cytoplasmic envelope. They noted that phagocytosis did not occur until this surrounding cytoplasm was at least partially dissolved. In excellent cinematomicrographs recorded through the phase microscope by Robineaux (8, 20, 21), the L.E. phenomenon was studied in greater detail. The nuclear change, which sometimes affected only one lobe, was characterized by loss of the chromatin pattern usually within an intact membrane; this was usually accompanied by isolation of the surrounding cytoplasm. Rifkind and Godman (9) following the sequence of events in the same cells during the L.E. phenomenon, with particular reference to its primary phase, found that within 5 to 15 seconds of the addition of L.E. serum to susceptible substrate polymorphonuclear leukocytes, a sudden uniform loss of their chromatin pattern (homogenization) of the nuclei occurred, followed at once by marked swelling and increased density and often at least partial extrusion of the swollen lobes from the cytoplasm (Figs. 1-4). The nuclear membrane remained intact; in the material of these observations the swollen nuclear lobes maintained their identity, each tending to form an L.E. body (Fig. 4), although it has been noted by Robineaux, that fusion of the altered nuclear substance into a large amorphous mass sometimes took place in his specimens. Lymphocyte nuclei underwent similar changes following exposure to L.E. serum (Figs. 5-10), although more slowly. The surrounding cytoplasm in all cases was passively displaced by the altered expanding nucleus or L.E. body, and took no visible part in and made no contribution to the formation of the L.E. body; the phenomenon appeared to concern only the nucleus.

Phagocytosis of the L.E. body can occur only after some of the altered nuclear material is presented to the active phagocytic cell at least partly free from its surrounding cytoplasmic envelope (8, 19), whether through extrusion of lobes as pictured by Rifkind and Godman (Fig. 4), or lysis of the cytoplasm. The material of the L.E. bodies is strongly chemotactic for polymorphonuclear leukocytes. The photographs of Robineaux et al., (8) show clearly that the phagocyte ingests the altered nuclear material alone, and not the residual cytoplasm. It



FIGS. 1 to 10 represent phases of the L.E. phenomenon made with the technique of Davis and Eisenstein (26). All are phase contrast photographs made at a magnification of $\times 1500$.

FIG. 1. Polymorphonuclear leukocytes at the instant of addition of L.E. serum showing normal nuclear and cytoplasmic structure.

FIG. 2. Same field; 5 seconds after addition of L.E. serum. Nuclear homogenization and early nuclear swelling have occurred.

FIG. 3. Same field; 20 seconds after addition of L.E. serum. Further nuclear swelling with extrusion of nuclear lobes from cells at lower left and lower right, forming L.E. bodies.

FIG. 4. Same field; 2 minutes after addition of L.E. serum. Further swelling and extrusion of L.E. bodies. The cell at the lower right hand corner has lost its L.E. body and remains as a cytoplasmic remnant of the original cell.

FIG. 5. Lymphocytes in a control dried buffy coat preparation incubated with normal serum for 20 minutes. Lower left inset is a normal freshly isolated lymphocyte.

FIGS. 6 to 9. L.E. body formation in lymphocytes of a Davis preparation after 5 seconds, 1 minute, 2 minutes and 3 minutes incubation with L.E. serum. There is progressive loss of nuclear structure and formation of a homogeneous body with a thin cytoplasmic rim.

FIG. 10. Large lymphocyte-derived L.E. body after 10 minutes incubation in L.E. serum. Fine cytoplasmic tags are seen at lower left of L.E. body. Two unaltered lymphocytes are in the field.

has been commented upon (4, 6) that the L.E. transformation *in vitro* may take place within some minutes, indeed the very great rapidity with which the nuclear changes can occur under the influence of the L.E. factor is noteworthy: once initiated, the whole transformation of the polymorphic nucleus to the completed L.E. body may require no longer than 30 to 60 seconds (9).

It has usually been considered necessary to injure or alter in some way cells intended as substrate for the action of L.E. factor in order to produce good yields of L.E. cells. Most of the different procedures devised for improved clinical diagnostic tests have had as their basis various methods of effecting such injury, e.g., clotting (22, 23), rotating with glass beads (24), drying (25, 26). Robineaux et al., (8, 21) however, have reported the successful use of living leukocytes washed with a physiological saline solution as substrate cells for the L.E. transformation. While the mere withdrawal of blood into glass vessels or the anoxia prevailing in coverslip chambers, might in itself be thought to effect a minimal injury to some leukocytes, the reported L.E. transformation of the nuclei of presumably viable cells is of considerable interest, both in its implications for the *in vivo* formation of such bodies in lupus, and in posing the problem of how the active gamma globulin factor might gain access to the living nucleus.

In permitting detailed visualization of the entire sequence of the L.E. phenomenon, the stages of which could be compared with the appearance of stained preparations, phase microscopy has provided valuable information. However, it remains useful chiefly as a modality for investigating the cellular phenomena themselves and offers no apparent advantage over conventional L.E. preparations for more routine diagnostic purposes. Phase microscopy alone has been applied by some (21, 27) where the more easily observed stained preparations would have afforded more readily interpretable information.

COMPOSITION OF L.E. AND HEMATOXYLIN BODIES

Some observers of the L.E. phenomenon have referred to the nuclear changes as a "lysis" (16-18, 8, 20), a visual impression which was consonant with our previously held conception of the chemical nature of the L.E. bodies. The hematoxylin bodies were known to have originated from cell nuclei soon after their discovery (1, 2) and the finding that they, and L.E. bodies, contained deoxyribonucleic acid (DNA) was confirmed by ultraviolet absorption and the Feulgen reaction in the histochemical analyses reported in 1950 by Klemperer and co-workers (5, 6). These investigations depended on measurement of the manner in which the DNA of the hematoxylin bodies bound the basic dye methyl green, which, under certain conditions can bind selectively and stoichiometrically to DNA (28-38).

In the experiments of Kurnick (30) and Kurnick and Mirsky (31) on DNA samples *in vitro* it was shown that depolymerization of the DNA reduced its affinity for methyl green. On this basis, because of the reduced stainability of the hematoxylin bodies in the tissues with methyl green as compared with normal nuclei, their DNA was regarded as having undergone a change in the nature of depolymerization. This interpretation of the significance of methyl green uptake

has since been modified: the binding of this dye by nucleic acid in tissue specimens is now known to be influenced principally by such factors as fixation (34-36), the presence of cations (30, 31, 35, 37), pH (37), and most important, it is impaired by competitive interference of protein associated with DNA (34, 38, 39). Control of some of these variables permits us to make use of quantitative measurement of methyl green binding to gain information on the amount of DNA and its relationship to protein (39).

In more recent microspectrophotometric measurements (40-42), it was confirmed that methyl green staining of L.E. bodies and hematoxylin bodies was uniformly depressed as compared with control nuclei. To assess the effect of protein on methyl green binding by DNA in hematoxylin and L.E. bodies, methyl green uptake in the same bodies was measured before and after destruction by acetylation of the basic groups of protein which compete with basic dye for the phosphoryl groups of DNA. In contrast to the small increase in methyl green stainability effected by acetylation of protein basic groups in normal control nuclei, this procedure resulted in almost a 100 per cent increase of the apparent amount of methyl green which the DNA of L.E. bodies was capable of binding (Table I). It would thus appear that about half of the stainable sites of DNA in lupus bodies were masked by protein. The Feulgen reaction for the deoxy-pentose moiety of DNA, which is relatively insensitive to those changes in degree of polymerization of DNA or to its relation to proteins which affect methyl green staining, is therefore useful as a reference against which to compare such staining properties of DNA as its methyl green uptake. In most normal nuclei, such as those from which L.E. bodies originate, the ratio of the amounts of methyl green to Feulgen revealed DNA is about 1.0. The amount of methyl-green-stained DNA

TABLE I

Mean amount of methyl green and Feulgen dye bound in L.E. bodies derived from lymphocytes

Measurements of free (non phagocytosed) L.E. bodies in L.E. preparations made with lymphocytes from a patient with chronic lymphatic leukemia. The data illustrate the effect of competing protein groups, which are destroyed by acetylation, upon the binding of methyl green by DNA in lymphocytes and L.E. bodies respectively. Acetylation results in similar Feulgen: post-acetylated methyl green ratios for both, indicating that DNA is not depolymerized in L.E. bodies.

	Lymphocytes	L.E. Bodies
(No. measured)	(20)	(20)
Methyl green	16.7 ± 0.5	11.9 ± 0.3
Me Gr after acet	17.8 ± 0.8	23.1 ± 0.6
Feulgen	19.9 ± 0.4	21.3 ± 0.5
<u>Post-acet Me Gr</u>		
Me Gr	1.06	1.94
<u>Feulgen</u>		
Me Gr	1.19	1.79
Feulgen		
Post-acet Me Gr	1.12	0.92

TABLE II

Mean amounts of DNA and protein in L.E. bodies derived from lymphocytes

Measurements of free (non-phagocytosed) L.E. bodies in L.E. preparations derived from lymphocytes. The Feulgen data show that DNA is not lost in the course of the L.E. transformation. The marked increase of naphthol yellow S binding and Millon staining indicate the marked increase in total protein content in the formation of L.E. bodies. The decline and disappearance of alkaline fast green and in Sakaguchi staining in L.E. bodies suggests a loss of histone.

	A Lymphocytes	B Early L. E. Bodies	C L. E. Bodies	Ratios	
				B A	C A
Feulgen	15.4 ± 0.4	18.0 ± 0.5	17.7 ± 0.4	1.17	1.15
Naphthol yellow S	14.5 ± 0.6	23.8 ± 1.1	36.5 ± 1.1	1.64	2.54
Alk. fast green	19.0 ± 0.4	5.5 ± 0.6	*	0.29	—
Sakaguchi	3.1 ± 0.2	1.5 ± 0.1	*	0.48	—
Millon	2.2 ± 0.2	—	5.7 ± 0.4	—	2.75

* Indicates below measurable limits.

after acetylation of competing protein groups, compared with the amount of DNA measured in the same bodies by means of the Feulgen reaction (i.e., the Feulgen:postacetylated methyl green ratio) would indicate whether there is any residual decrease in methyl green uptake by DNA, i.e., which cannot be accounted for by the presence of competing protein. If there were, this ratio would be reduced in comparison to control nuclei. Measurements showed that the Feulgen:postacetylated methyl green ratios of both L.E. bodies and control nuclei tended to approach 1.0 (Table I). Thus, the decreased methyl green stainability of L.E. bodies could be satisfactorily accounted for by the effects of protein interference resulting from an association of a protein with the DNA of L.E. bodies not manifest in normal nuclei. The data gave no evidence of an altered state of the DNA itself, such as depolymerization. Entirely analogous results were obtained with hematoxylin bodies, the tissue counterparts of L.E. bodies (42). Moreover, comparison of the total relative amounts of Feulgen-revealed DNA in L.E. bodies with those of normal nuclei of the type from which they were derived (lymphocytes) showed that there was no significant loss of DNA in the process of the L.E. transformation (Table II).

It was thus evident from these data that in the nuclear alteration of lupus, the protein component of the affected nuclei rather than the DNA itself was changed in kind and/or amount. The "total amount" of protein present in objects such as L.E. bodies and nuclei can be estimated by microspectrophotometric measurement of the colored complexes resulting from naphthol yellow S binding and from the Millon reaction. The anionic dye naphthol yellow S (dipotassium flavianate) has been shown by Deitch (43) to combine stoichiometrically with the available ϵ -amino groups of lysine, the guanidyl groups of arginine, and the imidazole group of histidine residues in fixed protein, thus affording a valuable measure of the number of protein basic groups free to accept the dye in

any site. Application of this procedure made it evident that the number of such groups was more than doubled in the L.E. body as compared with the lymphocyte nucleus from which it originates. Quantitation of the product of the cytochemical Millon reaction (for histone plus nonhistone proteins (44)) gives a relative measure of the tyrosine residues of protein. Since this reaction reveals another grouping, and is independent of some of the ionic and electrostatic interferences attendant upon acid and basic dye binding, it is a valuable complement to other cytochemical estimates of the amount of protein present. With this procedure a more than two-and-one-half fold average increase in protein tyrosine residues was measured in the formation of an L.E. body from a nucleus. These data, which show increases in reactive groups, suggest an augmentation of the total amount of protein in such transformed nuclei. That this is indeed the case has been demonstrated by Rifkind and Godman (9) by means of interferometric microscopy in which it was determined that L.E. bodies had an average anhydrous mass (52.8×10^{-12} gm.) two-and-one-half times greater than that of control lymphocyte nuclei (21.7×10^{-12} gm.).

These determinations established that a marked augmentation in total amount of protein occurs in the L.E. transformation of nuclei. Further differences in protein composition between nuclei and the L.E. bodies were disclosed by the cytochemical test for histone proteins (41). These basic proteins are normally closely linked to DNA in all intact cells, where, owing to their high isoelectric points, they can be selectively demonstrated and quantitated (after removal of nucleic acid) by staining with the anionic dye fast green FCF, at high pH. The phagocytosed bodies of the L.E. cells and of hematoxylin bodies were almost always devoid of stainable histone, while the free L.E. bodies varied from diminished stainability to complete absence of coloration. Microphotometric estimations of total histone in nuclei in the course of the L.E. change showed this diminution to occur very early. These results were interpreted to indicate that the L.E. change entails either a loss of histones or else a masking of their available basic groups by some substance not normally present in nuclei. Arginine residues as determined by the Sakaguchi reaction (which is not subject to the same ionic electrostatic or steric factors affecting acid or basic dye-binding), are reduced nearly in half in the earliest L.E. bodies, and much further in the mature L.E. bodies. This fact would tend to favor the hypothesis that histones are displaced from their link with DNA by a protein normally foreign to the nucleus, and thence more easily lost. However, there is said to be no apparent increase in arginine in supernatant L.E. serum over substrate leukocytes (47), and since some histone stainability may sometimes be detected in L.E. bodies, the hypothesis must also be entertained that the histone remains, but that its combining groups are preempted or shielded and so prevented from accepting the dye, a condition analogous to that of the DNA. Hematoxylin bodies of the tissues invariably contained no basic protein of the histone type as detected by these methods (42). From these results it was concluded that:

1. The DNA of the L.E. body is not detectably depolymerized or significantly reduced in amount in the formation of the L.E. body from the leukocyte nucleus.

2. There is a more than twofold increase in total measurable protein and hence anhydrous mass in the formation of the L.E. body due to influx from without (i.e., L.E. serum) of a protein normally foreign to the nucleus.

3. Consequent on the entry of this protein, histones are possibly displaced from their normal combination with DNA, and subsequently either lost or masked by protein, and the DNA becomes associated (combined) with the new protein.

4. The nucleoprotein masses (L.E. bodies) formed in this way in systemic lupus are deposited in the tissues as the so-called hematoxylin bodies.

Insight into the nature of the incurrent protein reacting with cell nuclei was afforded by studies in at least two laboratories of the L.E. cells and free bodies by means of the immunohistochemical techniques of Coons and his collaborators (48). In these investigations fluorochrome-labelled antisera to normal human gamma globulin were allowed to react with L.E. cells, the sites of brilliant fluorescence then representing the localization of gamma globulin in the cells. In such preparations nuclei undergoing the L.E. change (free L.E. bodies), and the L.E. cell inclusions (phagocytosed bodies) fluoresced brilliantly, while normal nuclei, nuclei incubated with control (nonlupus) sera, or those stained with heterologous nonhuman antigamma globulins or in which the antigen (globulin) had been blocked failed to fluoresce, thereby indicating the presence of gamma globulin in the nuclei which have undergone the L.E. transformation (49, 50).

That the L.E. serum factor has an affinity for nuclear nucleoprotein is further suggested by the immunohistochemical technique, which showed the nuclear localization of fluorescent anti-human gamma globulin in the nuclei of normal autologous, homologous and heterologous tissues which had been exposed to L.E. serum (51-53). The nonspecificity of the substrate nuclear material is in accord with the same nonspecificity of substrate cells in eliciting the L.E. cell phenomenon. It has been further shown by Friou (54) that the fluorescent L.E. globulin from all cases of lupus erythematosus, irrespective of its L.E. cell forming capacity, is bound to either extracted or artificial nucleohistone preparations. The demonstration of gamma globulin in L.E. bodies strongly suggests that this protein, putatively that measured by Godman and Deitch (41), which enters the nucleus from L.E. serum to bring about the L.E. change, might be antibody. But it does not by itself constitute final proof that the gamma globulin in this site is indeed immunologically reactive.

NATURE OF THE INTERACTION OF L.E. FACTOR AND NUCLEAR CONSTITUENTS: THE SEROLOGY OF SYSTEMIC LUPUS.

At first, following the previously held concept that the L.E. and hematoxylin bodies contained partially depolymerized DNA, it was hypothesized that in systemic lupus the supposed depolymerization of DNA was effected by an intracellular deoxyribonuclease (since serum DNase could not be implicated) released from an intracellular inhibitor (55) by the entry of a serum protease, whose penetration into the cells was presumably facilitated by the postulated action of the L.E. factor on the cell surface (56-58). The bases of this group of hypotheses

which may be referred to as the "enzyme theory" are not tenable because more recent evidence has corrected the earlier idea and has shown that the DNA of L.E. bodies is not detectibly depolymerized (40-42), but also because it is now well established that the L.E. factor (not itself a depolymerase) reacts directly with the nuclear constituents.

Miescher and Fauconnet (59) first showed that the L.E. cell-forming factor of L.E. serum and globulin was absorbed by isolated homologous and heterologous nuclei, and that nuclei charged with this factor could be identified in the antiglobulin consumption test and by phagocytosis (14). The absorbed L.E. factor could be at least partially eluted from nuclei and not unexpectedly was found to be a gamma globulin with L.E. activity (14, 15, 59). The nucleoprotein (nucleohistone) extractible from nuclei by 1 M NaCl also reacted with the L.E. serum factor, but neither nuclei nor nucleoprotein could do so if their DNA had been removed by deoxyribonuclease (DNase) treatment (15). These evidences that a factor in L.E. gamma globulin which is absorbed by nuclei reacts with DNA were further reinforced by the finding of definite precipitin and complement fixation reactions obtained with lupus sera (but not others) and "purified" DNA (60-64). These precipitation reactions, which were obtained equally with DNA of human, animal and bacterial origin, could be demonstrated by Seligmann (64) with very dilute solutions by the Ouchterlony gel-diffusion method, the ring test, the method of passive hemagglutination, and in immunoelectrophoresis. Between 3 and 15 gamma of DNA per ml. L.E. serum was necessary to exhaust the precipitin. The precipitation reaction was specific for preparations of DNA and did not react with RNA; in L.E. sera giving this reaction complement fixation could almost invariably be found (61, 64). L.E. sera are also apparently capable of inhibiting bacterial transforming principle (i.e., DNA) from acting (66). The DNA precipitating and complement fixing "antibody" of L.E. serum has been characterized by both Seligmann (64) and Deicher, Holman, et al., (63b, 65) as capable of giving a precipitin-curve with a prozone, equivalence zone, and zone of antigen excess; it appears to move as a fast (gamma 1) globulin (66) and to come down with the 7S fraction in the ultracentrifuge.

From the nature of these reactions it seemed reasonable to assume that one was dealing with an antibody directed against DNA (61, 64, 65). The serum factor giving precipitation and complement fixation tests with DNA was a gamma globulin. It did not resemble a histone (64), and precipitation with DNA was conducted at a high pH in which nonspecific electrostatic or saltlike combination could be minimized (65). The objection that the serum factor might be reacting with protein impurities which accompany most ordinary preparations of DNA was answered by the extinction of the precipitin and complement-fixing reactions after DNase treatment, by positive reactions with DNA preparations from many varied sources, and by the fact that the reactions are elicitable with very small quantities of DNA (64). However suggestive the evidence in favor of the antibody hypothesis, final proof of the immunological nature of these reactions should include faithful reproduction of similar phenomena in animals. Animals immunized with leukocytic components (67-70), nuclei (68, 69, 71, 72) and nucleo-

protein, (65, 72) have not developed serological patterns quite characteristic of lupus or antibodies reacting with DNA alone, nor have the sera of rabbits immunized with leukocytes given rise to appearances generally acceptable as typical L.E. cells, although interesting ("pseudo L.E." (73)) phagocytic phenomena have been observed. However Miescher (71, 72) has claimed production of nuclear changes closely resembling the L.E. alteration with immune sera against nuclei or nucleoproteins. Moreover, although it has been reported that DNA may act as an antigen (74, 75) these results have not been satisfactorily reproduced by other investigators (64, 76) and it remains doubtful that DNA per se can act as an antigen, or that experimental immunization with nucleoprotein produces antibodies to DNA.

More extensive experience with the complement fixing reactions of L.E. serum and nuclear components indicated that the L.E. cell forming factor appeared to be different from that responsible for DNA fixation (63); subsequent research chiefly in Kunkel's laboratory by Holman, Deicher and Robbins (65) has shown that whole groups of complement fixing serum factors, reacting with different nuclear constituents may appear in systemic lupus, and that these groups may have different patterns in different patients. These factors may be variously directed against whole isolated nuclei, nucleohistone, DNA preparations, histone, and/or saline non-nucleoprotein extracts of nuclear material: different patients with systemic lupus possessed differing capabilities of reacting with these various constituents. The sera of some patients, capable of forming L.E. cells, could reportedly react with nuclei, nucleoprotein and histone, but not with DNA, while sera of other patients could fix complement with nucleoprotein and DNA, but not with histone (65).

Some information about the relationship of some of these antinuclear serum factors has been afforded by absorption and elution experiments. The relationship of the complement fixing factor reacting with DNA to the L.E. cell forming factor is of particular interest. The available evidence has indicated that these are not identical. After exhaustion of the precipitins of L.E. sera by addition of DNA it still remains possible to elicit the L.E. phenomena (27, 56, 63-65, 77). As noted, the sera of certain patients giving the L.E. cell phenomenon contained no demonstrable precipitin (64), or complement fixing factor (65) for DNA.

Eluates obtained by treatment of the L.E. serum-DNA precipitates with 2 M NaCl or with deoxyribonuclease were alleged by Seligmann and Robineaux (27) to contain the anti-DNA precipitin and also to be capable of inducing the L.E. phenomenon, but only when mixed with normal serum. Holman, Deicher, et al., (65) have been unable to duplicate these results and are unable to verify that the L.E. cell forming factor is one which can combine with DNA alone. They note, as do Hijmans and Schuit (77), that nucleoprotein, but not DNA alone, was capable of completely absorbing the L.E. cell forming factor from L.E. sera in a reaction which did not necessarily fix complement: both the DNA and histone were found necessary for this reaction, nor was histone released by the new combination. The discrepancy might be explained by the possibility that Seligmann's DNA preparations contained small quantities of protein. The

end point of Seligmann and Robineaux (27, 64), in which the L.E. change is routinely detected in fresh cells with the phase microscope, should also be checked with histochemical methods to verify the nature of the changes, and to permit comparison. The L.E. serum-nucleohistone precipitate yielded complement fixing gamma globulin factors, but little L.E. cell forming factor after DNase digestion. The L.E. cell forming globulin could be released from the remaining residue or from L.E. serum absorbed on nuclei by heating it to 56°C. (65). These properties would seem to differentiate the L.E. cell factor from the other anti-nuclear factors of lupus, especially in its dependence upon the DNA-protein link for reaction, since it apparently does not react with DNA alone.

The L.E. cell factor of the serum, correctly identified by Haserick et al., (78) as a gamma globulin, was supposed by them to be "immunologically distinct" from other gamma globulins. Seligmann and Hanau (79) and Hijman and Schuit (77) have taken exception to this interpretation. Indeed, present evidence would agree that the L.E. cell factor is itself antigenically like other normal antibody gamma globulins. It is said to reside in the Cohn II fraction of plasma (80). Larson (47), using the separation methods made possible by the cellulose cationic exchange column has isolated a gamma globulin which apparently is immunologically (as judged by gel-diffusion band) and electrophoretically homogeneous, moves as a 7S fraction in the ultracentrifuge, and which is capable of giving the L.E. cell phenomenon and a positive latex test (agglutination with nucleoprotein coated latex). This globulin is said to be chemically differentiable from other gamma globulin by its markedly low N/P ratio (47).

The possibility that the reactions described are combinations with an unusual globulin, but lacking immunological specificity, although remote, has yet to be completely excluded. With these objections in view, the hypothesis of the occurrence in systemic lupus erythematosus of a group of serum antibodies capable of reacting with the constituents of cell nuclei would nevertheless appear at present to be the most reasonable, factually consistent and heuristic conception.

PATHOGENIC SIGNIFICANCE OF THE SEROLOGICAL ALTERATIONS IN LUPUS AND OF THE L.E. BODY

While the idea of a disordered immune state as a mechanism in the pathogenesis of systemic lupus had previously suggested itself, interest in this possibility was renewed by recognition of the frequent occurrence of biological false positive serological tests for syphilis (13), and especially by attention to certain hematological manifestations which are seen in some cases of lupus. In particular, the occurrence of hemolytic anemia, with red blood corpuscle autoagglutinins and positive Coombs test (13, 81-83), thrombocytopenia and purpura (13, 83-88) and leukopenia (13) have been recorded, and the remarkable readiness with which some patients with S.L.E. develop antibodies against blood corpuscle antigens, and the frequency of transfusion reactions in them have been the subject of comment (13, 89, 90). The presence of thromboagglutinins (87, 88), precipitins (64), and complement fixing factors to platelet extracts (64), and the existence of leukagglutinins (72, 87, 91-94), positive Coombs (antiglobulin

consumption) tests (14, 94, 95), leukoprecipitins (64, 94, 96), and antileukocyte complement-fixing factors (94, 97) against leukocyte cytoplasmic antigen in lupus patients who had not been transfused have been documented in detail. These manifestations, which are invoked to explain the hematological signs of the disease, have been taken, together with the L.E. phenomenon, as evidence for the autoantibody or autoimmune theory of lupus (81, 64, 98-102). It is most often postulated that in some manner the patient's own cell constituents become antigenic and gain access to the antibody-forming cells, with the production of a variety of circulating antibodies directed against constituents of the patient's cells. A number of "antibodies" to nuclear nucleoprotein and protein are apparently formed among which the L.E. cell factor, albeit the most constant, is one.

While iso- and autoantibodies to cells, particularly hematic elements, are known to occur in several conditions, it was thought that the antinuclear factor was specific to systemic lupus erythematosus. Many of the reports which have appeared describing L.E. cells in other diseases (101, 103-105) have been doubted especially with regard to the validity of the diagnosis of the L.E. cell. This issue cannot be discussed in detail here, but it should be remarked that confusion might be avoided if these cells were examined not only in conventional preparations, but also with some histochemical methods, such as methyl green affinity and alkaline fast green staining. The occurrence of the L.E. cell phenomena in certain cases after administration of hydralazine (106-108) and in rheumatoid arthritis (109-113) remain problems; in certain cases of chronic hepatitis (lupoid hepatitis) with characteristically elevated globulins, it seems to have been more convincing (114-117) [but see (118)].

This finding is of nosological interest in the light of the recent report by Gajdusek (119) of complement fixing reactions between normal tissue antigens or "reagins" and gamma globulin of some patients with systemic lupus erythematosus (in 9 of 11 cases), lupoid hepatitis (in 3 of 4 cases), macroglobulinaemia, (in 2 of 5 cases), and chronic hepatitis (in 11 of 25 cases). Besides the fixation of complement, the participation of gamma globulin, the stability of the reaction at 56°C., and the occurrence of apparent prozones in antigen titrations were adduced as evidence for the immunologic nature of these reactions (119). It is, however, necessary to bring even more rigorous proof in order to exclude the occurrence of some nonimmunologic reactivity. These reactions could not be elicited against autologous antigens prepared with the patient's own tissues removed at biopsy (120), a fact which has been interpreted by Mackay, Larkin and Burnet to signify that the part of the antibody population of these patients having 'specificity' (highest affinity) for the autologous antigen have been absorbed out of the circulation, and that somehow a spectrum of homologous reactivity persists in the serum. However, it also seems possible that autologous tissue antigens failed to react *in vitro* because they had already been saturated with antibody *in vivo*.

From these varied data there emerges the tentative concept of a category of disease, of which lupus would be one, characterized by the presence of a spectrum of globulins having many characteristics of immune bodies, which have

autologous and heterologous affinity for various tissue constituents the sources and natures of which may differ in individual cases. Whether or not such a category of disease will prove to have reality, and whatever the relationship of systemic lupus to the other disorders named in this connection, it remains clear that in systemic lupus serum globulin is formed having a range of reactivities with tissue components most constant and characteristic of which, so far revealed, are the constituents of the nucleus. Both the origins and reason for this disorder, and its pathogenetic consequences remain obscure. We do not know precisely what relation all the manifestations of disease, clinical, serological and anatomical bear to one another. In considering the serological changes, the L.E. cell phenomenon which depends upon it, and some resulting tissue changes, we are dealing with but two links in a probably long chain of events, the other parts of which remain to be discovered.

To explain the occurrence of globulins, presumptively antibodies, which react with nuclear and/or other cellular constituents, it has been conjectured that:

1. autologous tissue components may become antigenic through some modification (somatic mutation of a mesenchymal cell (120)) involving loss of "recognition units" (100, 119); alteration by combination with foreign substances (? haptens) has also been postulated;

2. these antigenic materials gain access to antibody producing sites;

3. antibody populations or gamma globulins of varied nature, not conforming to standard pattern, are released which could combine with other autologous, homologous or heterologous tissue constituents (120).

Other theories involve immunization by foreign nucleoprotein and formation of cross-reaction antibodies (53).

Concerning these speculations there is little exact knowledge; we do not know why patients with lupus respond to antigenic stimuli so readily, what qualitative differences there are in their antibodies or why females are so much more apt to develop this disease than males. (Dameshek believes that sensitization occurs during menstruation (102).) The mere presence of the L.E. cell factor per se in the circulation, and in all probability also the precipitating and complement-fixing factors already referred to, is seemingly not pathogenic, at least for a limited time. Its transplacental passage and its appearance in the blood of the infant for periods up to seven weeks, with well-marked capacity for L.E. cell formation in the infant's blood, resulted in no apparent disease (121-123).

The relationship of the serologic alterations and of the L.E. cell phenomenon to some of the lesions in the tissues of patients with systemic lupus erythematosus as classically described by Gross (1) and especially Klemperer, Pollack, and Baehr (124) while still unclear, have been somewhat more enlightened by recent studies. The nuclear alteration of the L.E. change is regarded by most clinical observers not only as specific, but also as demonstrable at some time in almost every case of systemic lupus (101). That the L.E. phenomenon takes place *in vivo* is suggested by the finding of L.E. cells in freshly drawn untreated blood of patients (125, 126), in the tissues at autopsy in one case (127), and in the observations of its occurrence in viable cells (8, 21). Hematoxylin bodies, which are discrete or conglomerate deposits of the altered nuclear material, have been shown experi-

mentally by German (128) to be capable of deriving from embolization of swollen leukocytes which have undergone the L.E. transformation. It is also very likely that some are formed in situ from fixed tissue cells. It is obvious from a comparison of the chemical characteristics of the fresh L.E. body and of the hematoxyphil masses that the latter have undergone considerable change during their sojourn in the tissues. For example, fresh L.E. bodies stain metachromatically and fail to react with the PAS procedure (40, 42), while hematoxylin bodies are not metachromatic (42), may show diminished Feulgen stainability and are strongly stained in the PAS reaction (42, 129-131), changes which point to the probable addition of protein and of a PAS-demonstrable carbohydrate, and to subsequent loss of nucleic acid from the original nucleoprotein material.

Klemperer (127), and Gueft and Laufer (129) have postulated that with the degradation of these bodies and further loss of DNA from them, the protein residues remain as masses indistinguishable from the fibrinoid or hyaline deposits. From these authors' evidences, this interpretation of the origin of the fibrinoid would appear to be rather more applicable to the thrombotic intravascular masses especially in the glomerular loops than to the material in other loci designated "fibrinoid". In systemic lupus, such eosinophilic materials of arterioles and glomeruli without basophilic smudges containing DNA have in common with each other and with L.E. and hematoxylin bodies the presence of gamma globulin (49, 50, 132). There is no other compelling reason to suppose that all these materials called fibrinoid in lupus have an identical origin. Immunohistochemical (see 132), histochemical (133, 134) and pathological (135) studies of lesions associated with fibrinoid change in various diseases indicate that they are not chemically identical in all cases. Plasma proteins, in lupus, gamma globulin, evidently take part in the formation of fibrinoid substances. Of their possible reactivity with extracellular components of the connective tissues, where these masses are often found, nothing is specifically known, but the possibility that a transudation of some protein from the blood and its reaction with materials of the ground substance accounts for fibrinoid alteration of the connective tissue has been put forward (135, 136). It is not improbable that among the various tissue-reactive components in lupus serum, some will be found which combine with some of the still incompletely defined protein and polysaccharide materials constituting the connective tissue ground substances.

The significance of these serological and histological changes for the understanding of the whole morbid process in lupus remains to be elucidated (137), but it is already clear that disclosures made in pursuit of an understanding of the L.E. phenomenon and the tissue lesions of systemic lupus erythematosus have assumed a more general importance in pathology, and promise to have ever-widening implications in lupus and in other related systemic diseases.

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THE BLOOD IN SYSTEMIC LUPUS ERYTHEMATOSUS*

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Alterations of cellular constituents of the blood during the course of systemic lupus erythematosus have been recognized since the earliest descriptions of the disease. Changes in the plasma proteins were not recognized until much more recent times, and it is only since the description of the L.E. cell phenomenon that the possible pathogenetic importance of the plasma protein abnormalities has been emphasized.

Several excellent recent reviews have discussed the blood changes in S.L.E. Complete compilations of the world literature may be found in several recent monographs (1-5). No effort to duplicate these contributions will be made here. Rather, the present communication will limit itself, on the basis of the pertinent literature, and personal experience, to discussion of those changes in the blood proteins and formed elements which have particular clinical or pathogenetic importance.

RED CELLS

Historically, anemia was the first hematic manifestation of S.L.E. to be recognized; it is mentioned in the earliest clinical descriptions of the disease by Kaposi (6). Most patients with S.L.E. are more or less anemic when first examined. Anemias associated with S.L.E. can be broken down pathogenetically into three types; in a given patient at a given time, one, two, or all three mechanisms may be at work. The first type, which is almost universally operative, is normochromic or slightly hypochromic, mild or moderately severe with normal or diminished reticuloocytes and an apparently active bone marrow. Although no physiologic studies of this anemia have been published, there seems no reason to believe that it differs in any respect from the anemia associated with other systemic diseases (arthritis, cirrhosis, tuberculosis, neoplastic disease) (7). Bone marrow depression, due in large part to a disturbed protein metabolism and diminished hemoglobin synthesis associated with constitutional illness, is the major cause of this anemia. There is also a hemolytic component; red cell life span averages $\frac{1}{2}$ to $\frac{2}{3}$ of normal.

A second cause for anemia in S.L.E. is the more specific bone marrow depression associated with azotemia. This is ordinarily a feature of late stages of the

* Aided by a grant (A-221) from the USPHS, National Institute of Arthritic & Metabolic Disease, and in part by the Albert A. List, Frederick Machlin and Anna Ruth Lowenberg Funds.

† Aided by a Stipend of the Altru League, Inc., Brooklyn, N. Y.

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disease, when advanced renal disease has become prominent. Recent studies suggest that the bone marrow hypoplasia of azotemia may be due to lack of production of the specific erythropoietic stimulating factor ("erythropoietin"); here too, there is a hemolytic component to the anemia (8).

Finally, the full-blown picture of acquired hemolytic anemia may occur. This is usually an early manifestation of the disease, and is in fact, the presenting manifestation in about five per cent of cases. It does not differ clinically or in pathologic physiology from other acquired hemolytic anemias, with jaundice, splenomegaly and severe anemia as outstanding features. In almost all cases it is possible to demonstrate globulin "coating" of the patient's red cells by means of the direct anti-globulin technique; "autoantibodies", usually of the "warm" type, may be demonstrable in the serum. These patients, despite extremely active hemolysis, do not have hemoglobinuria. Very rarely another type of hemolysis occurs in which no serologic mechanism can be demonstrated, and in which hemoglobinuria is prominent.

Treatment of anemia in a patient with S.L.E. is only important when the anemia is the major manifestation of the disease; this in fact only occurs either in the chronically anemic patient or in one with a severe hemolytic process.

In the case of the anemia of azotemia, no treatment other than blood transfusion is apt to be effective at the present time. Erythropoietin is not available in a form suitable for administration to humans; if and when such a preparation becomes available, it may be of great value in this situation.

Blood transfusion in any patient with S.L.E. should only be resorted to only under the most pressing indications. A tendency to form antibodies to blood group substances which are not usually strongly antigenic (i.e., factors like those in the Kidd and Duffy systems and the minor Rh types) is characteristic of this disease (9-10). The number of stimuli by these substances should therefore be kept at a minimum for each patient.

In the patient with hemolytic anemia, treatment with ACTH or corticosteroids is usually very effective, with rapid decrease in the rate of hemolysis and improvement of hemoglobin level. Blood transfusion here must be restricted to the patient whose hemoglobin is dangerously low. In addition to the considerations discussed in the preceding paragraph, the rate of hemolysis in the actively hemolyzing patient is directly related to the concentration of red blood cells, so that transfusion often defeats its own purpose.

WHITE CELLS

Persistent leukopenia is mentioned prominently in most discussions of hematic changes in S.L.E. Reduction in the number of white cells is, however, rarely of high degree. Neutropenia is uncommon, most of the reduction being effected by a marked lymphopenia. Leukocytosis occurs in response to infections, pregnancy and other unknown stimuli. Before the advent of the L.E. cell phenomenon the leukopenia of S.L.E. was of diagnostic importance; nowadays a low white blood count would be, at best, a lead pointing toward S.L.E.

Reliable information as to the mechanism of the white cell depression of S.L.E. is lacking. Several investigators have found evidence, by one or another

immunologic technique, of "antileukocytic antibodies" in the sera of patients with S.L.E. (11, 12). Lapin, using an extremely meticulous technique, finds a very high incidence of an unidentified substance which is capable of immobilizing and killing white cells (13, 14). One difficulty in correlating the studies of these workers with the clinical facts is that all of them have used polymorphonuclear leukocytes as substrate cells, while the striking cytopenia of S.L.E. involves the lymphocytes.

In summary, leukopenia (lymphopenia) is very common in S.L.E., but is of little physiologic importance, of limited diagnostic value and of unknown origin.

PLATELETS

Slight to moderate thrombocytopenia is common in S.L.E. Fifty per cent or more of patients show some degree of platelet depression at some time during their course. Severe thrombocytopenic purpura is not common; the incidence in The Mount Sinai Hospital series is only 5 per cent. It may, however, be the presenting manifestation of the disease; such was the case in one of our patients.

The mechanism of thrombocytopenia in S.L.E. is not clear. Bone marrow examination invariably demonstrates increased numbers of megakaryocytes showing poor platelet formation, exactly as in idiopathic thrombocytopenic purpura (ITP). Since several studies have put the humoral theory of ITP on a firm footing, attempts have been made to demonstrate anti-platelet "antibodies" in S.L.E. as well (15, 16). Agglutination and anti-globulin techniques, although successful in the hands of some workers, have been difficult to apply and have given equivocal results. The more recent use of anti-globulin consumption tests, and precipitin and complement fixation techniques has given convincing demonstrations of the presence, in S.L.E. serum, of substances capable of reacting specifically with human platelets (11). Clarification of the possible role of such substances in causing thrombocytopenia in living patients has yet to be made.

Severe thrombocytopenic purpura, although not common, may occur at any time during the course of the disease and may, on occasion, be the dominant clinical manifestation. The management of thrombocytopenic purpura secondary to S.L.E. is essentially the same as the management of idiopathic thrombocytopenic purpura. A good response to adrenocorticomimetic hormones may be anticipated. For the occasional patient with severe purpura with few other manifestations of S.L.E. it is worth noting that splenectomy is usually an effective therapy. A recent report suggests that splenectomy may accelerate the course of S.L.E. but such has not been the general experience (17, 18). At The Mount Sinai Hospital in the past ten years, there have been three splenectomies for thrombocytopenic purpura secondary to S.L.E. In all three cases, permanent remission of thrombocytopenia occurred. One patient died four years after splenectomy; the other two are under treatment for S.L.E. four and eight years respectively after operation.

PLASMA PROTEINS

It has become increasingly apparent in recent years that alterations of the plasma proteins are of great significance in S.L.E. These alterations involve,

in ascending order of probable importance, fibrinogen, albumin, alpha globulins and gamma globulins.

Fibrinogen

Increased circulatory concentration of this protein occurs in most inflammatory conditions. S.L.E. appears to be no exception. Hyperfibrinogenemia is probably the major contributing cause of the rapid erythrocyte sedimentation characteristic of the disease; other clinical or pathogenetic significance is doubtful.

Albumin

In the later stages of S.L.E., and especially in the presence of significant renal involvement, a reduction of the plasma albumin is noted. This is frequently severe enough to be associated with edema; the nephrotic syndrome in the course of S.L.E. is discussed elsewhere in this series of papers (19).

Hypoalbuminemia in S.L.E. probably represents a combination of two lesions: failure of synthesis associated with the ravages of a chronic disease, and loss into the urine.

Alpha globulins

It is possible with present day techniques, to distinguish thirteen individual alpha globulin fractions in human serum, but the significance of pathologic variations among these is unknown (20). Many of these alpha globulin components contain high percentages of carbohydrate and hence belong to the group of "glycoproteins" or "mucoproteins."

There is little question that there are profound disturbances among this group of proteins in S.L.E. Reiner was among the first to notice elevation of the alpha-2 globulins (21). This finding has subsequently been confirmed by others; alpha-1 globulin increase has also been prominent. Greenspan has found a high level of "mucoprotein" in patients with S.L.E.; Boas & Soffer found high serum hexosamine levels (22, 23). Both of these latter findings probably involve substances in the alpha-globulin group.

The single most important quantitative component of this group is the serum haptoglobin- a protein (or, more probably, series of proteins) whose variations in disease have been studied by Jayle and by Allison and Blumberg (24, 25). This is a glycoprotein which has the ability to bind hemoglobin; it has been found by these writers to be elevated in a variety of pathologic states. The serum haptoglobin has been found to be elevated in twelve out of fourteen cases of S.L.E. (26).

It is possible that these alpha-globulin deviations in S.L.E. may prove to be of great significance; at present it can only be noted that they exist.

Gamma globulins

Profound changes in the plasma gamma globulins occur during the course of S.L.E. These changes are quantitative and qualitative. There is usually, at the time of diagnosis, a definite elevation of the gamma globulin level; as the disease progresses, there is a tendency for further rise (3, 27). Evidence is accumulating

that these gamma globulins are composed of numerous varieties of proteins resembling antibodies but having unusual and abnormal specificities.

Disturbances of the gamma globulins in S.L.E. have both practical and theoretic importance, and so deserve consideration at length here.

Quantitative Changes

Characteristically, the gamma globulin level is high (27). This may be detected clinically by electrophoresis or by Kunkel's zinc sulfate turbidity (28). The finding is almost universal and so of some diagnostic importance. Occasionally, however, normal or low gamma globulin is found. This usually, if not always, is associated with considerable renal involvement. It is possible that hypogammaglobulinemia in S.L.E. with nephropathy is due entirely to urinary loss of gamma globulin; however, observations on one patient lead us to believe that this simple explanation is inadequate.

Elevation of gamma globulin, as well as hypoalbuminemia and hyperfibrinogenemia, contributes to the rapid rate of erythrocyte sedimentation which is usually found in this disease. This constellation of plasma protein changes is probably also responsible for the abnormal "liver function tests" (cephalin-cholesterol flocculation and thymol turbidity) which are characteristically found (29). The p-toluene sulfonic acid test recently described by Jones & Thompson is another flocculation reaction which probably has the same degree of specificity (30, 31).

Qualitative Changes

When tested by ordinary physico-chemical methods, the plasma gamma globulins of S.L.E. do not behave abnormally. Electrophoretically and chromatographically, they are normally heterogeneous (32) in contrast with the homogeneous paraproteins of myeloma or Waldenström's syndrome. In the ultracentrifuge, the vast preponderance sediments with a Svedberg number of 7 and usually only a normally small proportion has a sedimentation constant of 19 (33). Despite an early report suggesting that S.L.E. gamma globulins have specific antigenicity subsequent efforts by several groups to demonstrate this have failed (33-35). It now seems most likely that S.L.E. gamma globulin cannot be distinguished from other human gamma globulin by its antigenicity for other animals.

With regard to their antibody content, however, S.L.E. gamma globulins exhibit the most striking, unusual and abnormal behavior. Chief among the antibody (or antibody-like) activities which have been studied is, of course, the L.E. cell factor. In addition, patients with S.L.E. exhibit several other gamma globulins which act like abnormal auto-antibodies. Finally, there is suggestive evidence of a distortion of antibody response to antigens of external origin.

These qualitative abnormalities of the gamma globulins in S.L.E. will be discussed in some detail, since they have considerable interest both for the clinician and for the investigator.

L.E. CELL PHENOMENON

In 1948 Hargraves and his associates reported the presence of an abnormal leucocyte in the bone marrow aspirate from patients with S.L.E. (36). The cell

was a phagocyte containing a homogeneous inclusion body which stained reddish blue with azure-eosin. Because of its unique appearance, the frequency with which it was found in S.L.E., and its apparent specificity, the cell and its inclusion body was named the "L.E. cell."

The L.E. cell phenomenon, more than any other clinical or laboratory characteristic of the disease commands the attention of physicians and research workers for three reasons. First, because it is of great diagnostic value. Second, it is a phenomenon reproducible *in vitro* and thus easily amenable to laboratory analysis. Finally, the factor responsible for L.E. cell formation may play a role in the clinical course of the disease.

Description of the L.E. Cell

The morphologic and tinctorial criteria are as follows: The presence of one or more inclusions in a phagocyte, usually a neutrophilic leucocyte. The inclusion body is round or oval, completely homogeneous and compresses or displaces the phagocyte nucleus to the periphery. When stained with azure-eosin the inclusion body is a pale blue with a more or less pink component. It must be distinguished from nucleophagocytosis in which the inclusion may be an intact nucleus or an entire cell, and in which the nuclear inclusion takes a deep blue stain with identifiable chromatin structure. It must be distinguished from erythrophagocytosis in which the inclusion body has no blue color (the use of dark blue filters can make this distinction difficult).

Associated constantly with L.E. cells in positive preparations are two other phenomena, "rosettes" and "free L.E. bodies." Rosettes are aggregates of leucocytes which surround a degenerating cell or a portion of nuclear material. "Free L.E. bodies," or "globs," are extracellular fragments varying in diameter from about three microns up to ten to fifteen microns and having the appearance and staining characteristics identical with those of the inclusion body of the L.E. cell. In deciding whether or not a given L.E. cell preparation is positive, although "rosettes" and "globs" are suggestive, they are not sufficient by themselves since a variety of non-specific artefacts can produce them.

Incidence of Positive L.E. Cell Preparation in S.L.E.

The L.E. cell phenomenon has been demonstrated in from forty to one hundred per cent of patients with S.L.E. (37). The more recent series, however, list figures well over ninety per cent. The higher percentages are in part the result of technical factors: improved methods and more tests per patient. They may also, in some instances, reflect the clinician's increasing dependence upon the test as a criterion for the diagnosis. Thus any assessment of the frequency of the L.E. cell phenomenon in S.L.E. is limited by the fact that there is no other absolute criterion by which a diagnosis of S.L.E. can be made.

Clinical remissions, whether spontaneous or induced by steroid therapy, are generally, but not always associated with a reduction in the degree of positivity of the L.E. cell phenomenon. However, the positivity or negativity of the preparation is a poor index of the clinical status of the patient and is of unreliable prognostic value.

L.E. Cell Specificity

The early literature on the L.E. cell mentions many different diseases associated with positive L.E. cell preparations. As experience with the test increased, the number and variety of false positive tests diminished, and one must assume that the early instances of nonspecificity were probably the result of inadequate experience with the test or, more rarely, the coincidence of another disease and unrecognized S.L.E.

At the present time the problem of "false" positivity is restricted to a few diseases and the observations are made and reiterated by experienced physicians. Positive L.E. cell preparations have been reported in liver disease, chronic hydralazine toxicity and rheumatoid arthritis.

Liver Disease

A search of the available literature reveals less than fifteen cases of positive L.E. cell preparation in patients with chronic liver disease proved by biopsy (Laennec's cirrhosis, postnecrotic cirrhosis and active chronic hepatitis (37-42). Four of the reported cases presented clinical or postmortem evidence of S.L.E. Another three cases failed to disclose evidence of S.L.E. on postmortem examination. Of these, however, one was found to have diffuse myelomatosis; no histo-chemical studies were performed to determine if the L.E. cell inclusions were nucleoprotein or amyloid. In another case the photograph of the L.E. cells was not convincing.

Until further follow-up reports are available and histochemical and serologic studies are performed, the occurrence of the L.E. cell phenomenon as a manifestation of liver disease must be viewed with skepticism.

Hydralazine

On occasion, the syndrome of chronic hydralazine toxicity is indistinguishable from S.L.E. (43). In all cases reported cessation of drug therapy was followed by remission of the syndrome. No spontaneous exacerbations are reported; no postmortem examinations are reported. In some, but not all of the cases there was a history prior to drug therapy suggestive of S.L.E.

The L.E. cell phenomenon in these cases of hydralazine toxicity is indistinguishable by conventional methods and also by serological and histochemical techniques, from the L.E. cell phenomenon in S.L.E.

In an attempt to reproduce the syndrome in laboratory animals, Comens administered the drug to seven dogs (44). Six of the animals are reported to have developed positive L.E. cell preparations and on postmortem examination glomerular lesions were found. Examination of the photographs does not allow the unequivocal conclusion that the cells are L.E. cells. It would be of great interest to repeat the experiment in order to study the sera and tissues of these dogs by the latest histochemical and serologic methods.

Rheumatoid Arthritis

The L.E. cell phenomenon is positive in from zero to twenty-seven per cent, of patients with rheumatoid arthritis (37, 45-47). Analyses of reported series shows that those series with a high percentage of positive tests contain more cases which clinically show evidence of systemic disease suggestive of S.L.E. Those with a lower percentage contain more cases of rheumatoid arthritis with

few or no signs of extra-articular disease. It appears that between the extremes of mild rheumatoid arthritis and acute fatal S.L.E. there exists a spectrum of cases which display, to variable degrees, the characteristics of both diseases.

In rheumatoid arthritis, absolute diagnostic criteria are lacking. Typical rheumatoid arthritis may occur as a manifestation of S.L.E.; and, conversely, cardiac, renal, and serous membrane lesions have been described in rheumatoid arthritis.

There is a converse to the existence of "false positive" L.E. cell tests in rheumatoid arthritis. Blood from patients with S.L.E. sometimes shows the presence of the "rheumatoid factor." The "rheumatoid factor," widely held to be specific for rheumatoid arthritis, has been shown by Franklin and associates to be a gamma-one macroglobulin (22 Svedberg units) (48). The same or similar protein has been shown to occur in sarcoidosis, kala-azar and liver disease (49). It thus differs from the abnormal gamma globulins of S.L.E. under discussion and belongs to a different class of proteins. Its biological significance is obscure. Present methods for its identification vary widely in different laboratories. Whether positive tests for rheumatoid arthritis in cases of S.L.E. are due to the same "rheumatoid factor" as found in cases of rheumatoid arthritis is not clear.

Thus, interrelationships between S.L.E. and rheumatoid arthritis exist on several planes: their significance cannot yet be evaluated.

L.E. Cell Techniques

Many methods for demonstrating L.E. cells have been published. Each technique has its proponents who believe it more sensitive and reliable. Comparisons of techniques have yielded conflicting results and there is no unequivocal evidence that one is better than another. Improperly employed, all methods will fail. Without begging the issue, it must be concluded that experience and facility in performing the test and discrimination in reading the test slide are more important at present in determining reliability and sensitivity than is the particular technique employed.

Certain essentials must be met by any method. Deliberate traumatization of the substrate cells, either chemical or physical, increases the number of L.E. cells. If L.E. plasma is employed minimal amounts of heparin should be added since excessive concentrations of heparin depress or prevent the formation of L.E. cells.

Mechanism of the L.E. Cell Phenomenon

Within a short period of time after the original observation of the L.E. cell phenomenon (36), it became apparent that the phenomenon could be demonstrated by simple *in vitro* techniques and that the essential factor contributed by the patient with S.L.E. was a blood gamma globulin substance (50, 51). It is now known that the L.E. cell phenomenon depends upon three components. Blood serum or plasma of a patient with S.L.E. containing a specific gamma globulin fraction, the *L.E. cell factor*, when incubated with *substrate leucocytes*, converts the nuclei into swollen amorphous masses that are then engulfed by *viable phagocytes* to produce L.E. cells.

By systematically altering the components participating in the reaction, it was possible to define the necessary conditions for the formation of the L.E. cells.

L.E. Cell Factor

The L.E. cell factor is a gamma globulin. On starch block electrophoresis the factor migrates with the faster fraction of the gamma globulin. On ultra-centrifugation the factor sediments with the bulk of the normally occurring gamma globulin (7 S), (33). Chemical separation of the factor from serum is achieved by employing the routine methods for gamma globulin precipitation; however, unless the method is a "mild" one the separation is attended by loss of activity. The factor is heat labile; heating serum at 56°C. for one hour destroys all activity. The factor is stable indefinitely once frozen but activity is quickly lost on repeated freezing and thawing of L.E. serum.

Substrate Leucocyte

Human white cells and dog bone marrow cells are used most frequently although cells from a number of species are sensitive to the factor. Hematoxylin body formation, which is the analogue in tissues of the L.E. cell phenomenon, has been observed in postmortem material to involve all types of cells of mesenchymal origin (52). Epithelial cell nuclei, both normal and neoplastic, have been shown to be susceptible to the L.E. cell factor (53, 54).

Evidence strongly supports the hypothesis that an intact viable leucocyte is resistant to the factor since chemical or physical trauma deliberately inflicted increases the rapidity of L.E. cell formation, the number of L.E. cells per total leukocyte population and the sensitivity of the test. Types of trauma include: freezing and thawing, mechanical crushing and sieving of a blood clot, mechanical disruption by glass beads, air drying on a microscope slide and chemical trauma with quinaerine (54-60). In those techniques in which there is no deliberate trauma, the long incubation period probably accounts for cell alteration because of an unfavorable metabolic milieu.

Phagocytes

Substrate cells once acted upon by the factor are engulfed by viable phagocytes. Nothing is known as to the nature of the stimulus for phagocytosis except that it resides in the substrate-serum factor complex. Washed free of the L.E. serum the substrate cells will still undergo phagocytosis when placed in contact with suitable phagocytes.

Biochemical Basis of the L.E. Cell Phenomenon

The L.E. cell phenomenon demonstrates the existence of an abnormal gamma globulin which is able to produce morphologic changes in leucocytes. The nature of these changes and the mechanism by which they are produced have been the subject of extensive investigation. These investigations have been conducted in two fields: histochemical and serologic.

The histochemical studies are extensively reviewed in another paper in this series; they will only be summarized very briefly here.

In their first report on the L.E. cell, Hargraves and his associates stated that the inclusion body was Feulgen positive and hence contained desoxyribose nucleic acid (DNA) (36). Later studies of the tissue hematoxylin bodies by

Klemperer and his associates and of the L.E. cell inclusion by Lee, Michael and Vural were interpreted as showing that the DNA of these bodies was partially depolymerized (51, 61). Gueft and Laufer then found that the protein content of the L.E. bodies was different from that of normal nuclei (62). The histochemical studies have now culminated in the work of Godman and Deitch (63, 64). They have shown that leucocyte nuclei contain increased amounts of protein following incubation with L.E. cell serum; that there is no histochemical evidence of depolymerization of DNA; and finally that as incubation of S.L.E. serum with nuclei proceeds nuclear histone seems to disappear.

The earliest serologic studies after the demonstration of the L.E. cell factor by Haserick and Bortz proceeded from the *supposed* histochemical evidence of DNA depolymerization (50). These studies which dealt with possible relationships between L.E. cell factor and depolymerizing enzymes (DNA-ase) are now only of historical interest (65, 66).

The modern era in the serologic investigation of the L.E. cell phenomenon was ushered in by the studies of Miescher and Fauconnet (67). By incubating S.L.E. serum with large quantities of leucocyte nuclei prior to performing the L.E. cell test, they were able to inactivate the serum. They further demonstrated that during incubation with nuclei detectable amounts of gamma globulin were lost from the serum. These findings directed Miescher to apply to this system the "antiglobulin consumption" test (68). With this technique, material eluted from nuclei previously incubated with serum containing the L.E. cell factor was shown to contain gamma globulin. Thus the gamma globulin lost from the serum was demonstrated to have been bound to the nuclei.

Holman and Kunkel showed that the material bound to the nuclei incubated in S.L.E. serum was itself capable of inducing the L.E. cell phenomenon after elution from the nuclei (33). They further found that the reaction between S.L.E. gamma globulin and nucleoprotein fixed complement.

Seligmann employing the Ouchterlony agar diffusion technique, observed precipitin lines when S.L.E. serum diffused into purified DNA from nucleoprotein (69).

Thus it became increasingly evident that the application of immunologic methods provided a fresh and fruitful approach to the analysis of the gamma globulin dysproteinemia of S.L.E.

Subsequent studies, employing serologic and precipitin techniques demonstrated that S.L.E. gamma globulin may contain several components characterized by their affinity for different substrates (11, 35, 70-74). One component is readily absorbed to nuclei and nucleoprotein; one to DNA, and a third to histone. The affinity for nuclei, nucleoprotein and DNA is not restricted to leucocyte substance but can be demonstrated with nuclei from a number of organs as well as from different species. The components are not all constantly present in every S.L.E. serum but vary from patient to patient.

The L.E. cell factor is associated with the gamma globulin component which is strongly adsorbed to nuclei and nucleoprotein. It is possible that the L.E. cell factor is not a single physically and chemically homogeneous protein but

rather a group of proteins that have a strong affinity for nuclear material. Whether it can be bound by native DNA in the absence of the protein moiety remains to be tested. Strong evidence argues against the possibility that deoxyribonuclease participates in the reactions.

OTHER ABNORMAL ANTI-BODY-LIKE GLOBULINS

False Positive Serologic Tests for Syphilis (S.T.S.)

Until the recent development of serologic reactions using *Treponema pallidum* as the antigen, the serologic diagnosis of syphilis was based on the reaction of serum with an antigen derived from beef heart. The common occurrence of false positive reactions to this latter antigen in sera from patients with S.L.E. was first recognized by Coburn and Moore in 1943 (75). They demonstrated by electrophoretic separation that the factor in S.L.E. blood was predominately in the gamma fraction with only a small component migrating with the beta globulin fraction. A further distinction was noted when upon heating to 56°C. the luetic antibody decreased in potency, while the factor in S.L.E. blood gained in potency. The clinical application of the *Treponema Pallidum* Immobilization test (T.P.I.) now provides a simple and certain means to verify this difference.

The reported incidence of false positive S.T.S. in S.L.E. is variable, depending in part how vigorously the search is pursued. When batteries of tests are performed and the T.P.I. test employed to exclude syphilis, the incidence ranges between twenty and thirty per cent.

In the latest available long term follow-up of individuals who have the false reactor substance, there were reported 148 cases followed from one to twenty years (76). Ten per cent of the number developed S.L.E.; seven per cent developed rheumatoid arthritis; and forty-five per cent had evidence of S.L.E. or a "collagen vascular disease". Stress is laid upon the observation that an individual may develop a false positive S.T.S. years before there is clinical or laboratory evidence of S.L.E.

Circulating Anticoagulant

Many reports have noted the appearance of a bleeding disorder in S.L.E. distinct from thrombocytopenia. In all the reported cases this has been due to the presence of a substance in the affected plasma which inhibits the second stage of blood coagulation, namely the conversion of prothrombin to thrombin by thromboplastin (77-81). The abnormality appears to reside in the gamma globulin. Whether it combines with thromboplastin or prothrombin to accomplish its end is not clear (78, 79). Possibly anticoagulants in different patients have somewhat different specificities. In any case, this material appears to be another of the abnormal antibody-like substances which characterizes S.L.E.

The circulating anticoagulant of S.L.E. occurs most frequently in minimal sub-clinical concentration. In The Mount Sinai Hospital series, over twenty per cent of patients tested showed some abnormality. In only one case however, could clinical bleeding be ascribed definitely to its presence. An anticoagulant

of this specific type is, however, of diagnostic importance, since it has very rarely been reported in other conditions.

Anti-RBC, WBC and Platelet Substances

These have been discussed in the section on hemocytologic changes. They occur with great frequency in S.L.E., but so far have not been differentiated from similar activities occurring in other diseases.

DISCUSSION

The manifestations of S.L.E. in the blood are thus seen to be manifold and profound. All cellular components and most of the protein fractions are sometimes or always involved. Which, if any of these disturbances are of fundamental importance?

The cytologic disturbances can be dismissed in this regard, since they are always symptomatic. Hyperfibrinogenemia and hypoalbuminemia likewise can be ascribed to known or suspected mechanisms and hence placed in their roles as secondary phenomena. Alterations of the alpha globulins may be of very great importance pathogenetically, but what we know of them so far indicates that in S.L.E. they follow a pattern similar to that seen in some other chronic diseases: lymphomas, tuberculosis, rheumatoid arthritis.

Gamma globulin abnormalities characteristic of S.L.E. are, however, unique; it is possible to establish the diagnosis from a sample of blood entirely on the basis of its content of specific abnormal "auto-antibodies". So far, the list of anti-substances includes proteins active against DNA, DNA-histone, histone, cell nuclei, leukocytes, platelets, red blood cells, thromboplastin, and beef heart antigen. This profusion of antibody-like activities directed against "antigens" which, for the most part, are normal body constituents, gives rise to speculation in two distinct directions.

First, the clearly demonstrable *in vivo* effects of the "auto-antibodies" so far described are very few and relatively unimportant. Such relationships as the anti-RBC factor in hemolytic anemia, anti-platelet factor in thrombocytopenia and anti-coagulant in hemorrhagic disorders are fairly clear but of peripheral interest. The L.E. cell factor (or factors) has not been shown to have any physiologic effects *in vivo*. Nevertheless, the existence of this multitude of anti-substances leads one to suspect that many other analogous proteins may exist. A circulating substance active specifically against glomerular basement membrane might, if it could be demonstrated, provide a partial explanation of the nephropathy of S.L.E. Similarly, an antisynovial membrane, or anti-hyaluronic acid might define the arthropathy of this disease. Attempts to demonstrate these or other activities which might have important pathogenetic effects should clarify the question of whether the "auto-antibody" theory of S.L.E. has any validity.

The second line of speculation concerns more fundamental matters. If one accepts, for the moment, that "auto-antibodies" are the immediate causes of the manifestations of S.L.E. (a statement clearly not proved on the basis of present

knowledge alone) the real problem in S.L.E. concerns the production of "auto-antibodies." It has been suggested that repeated stimulation by bacterial infection may eventually give rise to a spectrum of anti-bacterial antibodies among which may be an anti-bacterial-DNA; and that with further stimulation the anti-bacterial-DNA develops broader specificity so that eventually an anti-any-DNA is produced (11). Broadening of antibody specificity with hyperimmunization is something which has been demonstrated in animals. An alternative hypothesis would invoke a metabolic defect of the antibody-forming tissues which results in subtle distortions of antibody response. A streptococcal antigen might, because of faulty ribose nucleic acid synthesis in the host, invoke an antibody not against the streptococcus itself, but against something quite different—thromboplastin, for instance.

A number of hypotheses intermediate between these extremes might easily be tailored to fit the pitifully few facts available. The design of experiments which might help to define the problem more clearly is difficult, since so little is known of mechanisms of normal antibody synthesis. One problem which demands investigation, however, concerns the response of S.L.E. patients to selected heterologous antigens.

In conclusion, numerous studies over the past eight years have demonstrated that in S.L.E. a large variety of antibody-like substances occur which have individual specificities against many different normal body constituents. That these antibody-like proteins are the direct cause of the important clinical and anatomical manifestations of the disease is an attractive hypothesis for which proof is so far lacking. Finally, should overwhelming evidence for this hypothesis be forthcoming, the fundamental problem in S.L.E. will be the discovery of the reason for abnormal antibody production.

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THE CLINICAL FEATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS

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INTRODUCTION

This essay is devoted to the clinical depiction of systemic lupus erythematosus (S.L.E.). Discussion concerning the pathology, the hematic disturbances and the treatment will be presented by other contributors in the present symposium.

Systemic lupus erythematosus is a serious constitutional disorder which in fullest efflorescence usually affects the skin, mucosae, serous membranes, small blood vessels, endocardium, connective tissue, kidneys, brain and blood. Untreated cases ordinarily are fatal; a few go into spontaneous remission.

The cause of S.L.E. is unknown. During the twelve and a half decades which have elapsed since the earliest descriptions, the disease passed from the realm of dermatology to the more comprehensive realm of internal medicine and morbid anatomy. At present, the most promising studies are those of cytopathologists and cytochemists (1), who seem likely to reveal either the basic cause or some of the fundamental mechanisms. Discovery of the cause will inevitably make possible a more exact delimitation of the disease than can be given today and will authoritatively resolve the question of the relation between S.L.E. and discoid lupus as well as the relation between S.L.E. and other diseases in which connective tissue is systematically affected.

DISCOID LUPUS

Inasmuch as there are competent observers who maintain that S.L.E. is in some way akin to discoid lupus, the latter condition will be described here, although it is properly outside the scope of the present discussion.

Chronic discoid lupus erythematosus is a disease which appears in the form of one or more mildly indurated scaly reddish plaques. Often these clear in the center but extend at the margins. The central cleared area tends to become atrophic and to show telangiectasia. When the silvery scale is lifted it typically brings with it adherent keratotic plugs. Obstruction of hair follicles and sweat ducts is highly characteristic. The lesions show marked chronicity but may heal and leave a pigmented residue. The commonest site of occurrence is the face, especially the cheeks, but also the nose, ears, and lower lip. Lesions may occur symmetrically on the cheeks and may extend over the bridge of the nose, producing a conformation like the shape of a butterfly. The term *vespertilio* is often used in European descriptions and provides a welcome alternative designation for those who are becoming tired of the conventional lepidoptera. The scalp is commonly affected, alopecia being a frequent consequence. The lesions of chronic discoid lupus may spread over the chest, back and extremities, producing the so-called chronic disseminated lupus erythematosus. This is less common

than the circumscribed variety. The lesions retain the traits of the chronic discoid form.

Dermatologists also recognize special types of lupus known as lupus erythematosus profundus and tumidus. These have been attributed to localization of the infiltrate in the deeper and intermediate layers of the skin respectively (2).

Constitutional symptoms are rare in chronic discoid lupus. In chronic disseminate lupus symptoms are mild and consist mainly of arthralgia and lassitude. Since chronic discoid and chronic disseminated lupus tend to be ignored by internists and research workers, little fundamental information is available as to whatever physiological and biochemical disturbances may accompany these diseases. Montgomery has made the important observation that in one third of a series of thirty cases of acute disseminate lupus erythematosus the disease started as the chronic discoid type (3). Lejhane and Lejhane reported a case of what was probably discoid lupus which underwent acute exacerbation (4). Autopsy disclosed lesions similar to those often encountered in S.L.E., viz., pneumonitis, fibrinous pleuritis, and verrucous endocarditis. In some cases of discoid lupus Rein and Kostant found hyperglobulinemia and biologic false positive reactions for syphilis; these facts lend additional support to the belief that discoid lupus may be related to S.L.E. (5).

SYSTEMIC LUPUS ERYTHEMATOSUS

Incidence

S.L.E. most often occurs in young women but it has been found also in children and middle-aged persons, and it may occur in males. It has been observed repeatedly in Negroes of either sex (6).

There is a marked tendency for the disease to appear or to recur after the patient has been exposed to sunlight. Hence acute cases tend to be relatively common in spring and summer. Exacerbation may also occur after exposure to artificial ultra-violet rays. Focal infection has been incriminated but not convicted. Allergic persons show no special predisposition to S.L.E. Haserick has reported a few examples of familial occurrence (7-9).

The Quarterly Cumulative Index Medicus lists reports of the disease from almost every country which contributes to the medical literature, but no recent worldwide analysis of geographical distribution is known to the present author. It would seem, for reasons already given, that such analysis should emphasize the parameters of solar radiation, cutaneous pigmentation, and perhaps altitude. Study of a generous sample of case reports from foreign countries reveals no regional peculiarities in the clinical picture.

Twenty years ago systemic lupus erythematosus was regarded as a rarity and cases almost always found their way to staff meetings and clinico-pathological conferences. During the last two decades, and especially during the last five years, the disease has been recognized with greater accuracy and ease than ever before. Diagnosed cases may now be found in the medical service of any large general hospital in the United States.

At any time, months or years after its debut, discoid lupus may flare into

acute S.L.E. (10, 11). This fact fortifies the opinion that the two diseases are related. At present it is not known whether *all* cases of discoid lupus are susceptible to acute exacerbation. Indeed, the transformation is uncommon. Actinic radiation, chrysotherapy and surgical operations are usually incriminated as precipitating causes of the abrupt changes (12).

Clinical Features

Since S.L.E. is a systemic affliction in which lesions may occur in many different organs and organ systems, individual cases show great diversity in onset and evolution. Often the presenting symptoms are malaise, lassitude, low fever, and chilliness or true chills. The case thus may be classified among fevers of unknown origin. Another common mode of onset consists of fever and arthralgia, or of fever, arthralgia and pleurisy. In other cases the initial symptoms may assume the guise of nephritis or thrombopenic purpura or hemolytic anemia or even idiopathic epilepsy. Skin lesions may make their appearance at any point in the course or may be absent during the entire illness. Fever is rarely absent in the untreated case and is a rough index to the acuteness and severity of the morbid process.

A few persons have been found who appeared to be in good health but who had a positive Wassermann or Meinelke test without history or physical signs of syphilis and with negative response to the treponema immobilization test. It has been shown that some of these persons later developed the clinical signs of S.L.E. (13).

Although the fully developed case of S.L.E., like the early case, may show a predominance of symptoms and signs referable to one organ system, involvement of several systems is almost invariable in late stages. The unfortunate victim usually has high fever, pleurisy or pericarditis, pneumonitis, widespread cutaneous eruptions, mucosal ulceration, anemia, and azotemia. To this complex agony a bacterial complication such as sepsis or bacterial endocarditis may be superadded not long before the end.

In the pre-steroid era there were a few patients in whom the decline of the fever and the fading of the eruption heralded a remission which might last for many years. Such remissions can occur repeatedly in a single patient. It was usually thought that a person who had acute S.L.E. was unlikely to live more than eighteen months, whereas subacute cases might be protracted to about three years. Both estimates were defeated by occasional favorable cases. At the present time it is believed that steroids will force acute symptoms into clinical quiescence but there is no unanimity as to whether these drugs prolong life. It is my impression that they do. An especially interesting study of the prognosis of S.L.E. will be found in the paper of Merrell and Shulman (14)

Skin and Mucosae

The cutaneous lesions of S.L.E. are extremely varied; this fact contributes alike to the interest of the problem and to the perplexity of the physician. The most typical lesion is an elevated, sharply margined erythematous area situated on the malar eminences and the bridge of the nose. Confluence of

these areas produces the familiar butterfly or bat contour. In acute cases the erythematous areas often lack sharp delimitation, especially at onset. Erythematous lesions frequently appear on the forehead, ears, eyelids, chin, and the so-called flush area of the neck and manubrial region. The redness tends to stop at the frontal hair-line and at the orbital margins. The arms, forearms, trunk, palms, and soles may be affected. The erythema often presents a distinct violaceous or lilac hue, especially on the face. The appearance may be that of persistent intense redness, hence the terms *erysipelas perstans faciei* and *erythema perstans faciei*, used by the great dermatologists of the past. The skin of the fingertips and that around the nailbeds tends to swell and turn red or purple. Deep tender macules may appear on the palmar surfaces of the terminal phalanges and elevated red patches are formed on the dorsa of the fingers. The erythematous involvement of the fingers is usually greatest at the distal end.

Petechiae or even large hemorrhages may be found, especially on the extremities. Occasionally vesicular or bullous lesions complicate the scene. It is not rare for the eruption to have the characteristics of urticaria or erythema multiforme (15). Tumulty has reported cases of S.L.E. in which typical erythema nodosum was present and several which resembled scleroderma (16). Variety is characteristic of any group of cases and of many individual cases. Instances have been reported in which the skin presented nodular lesions like papulonecrotic tuberculids (17, 18). The scalp may be affected in S.L.E., but this is rare (19).

The skin lesions itch in a minority of cases. Scaling occurs but is neither frequent nor prominent.

Subsidence of the eruption is apt to leave a brownish stain, especially on the face. Atrophy and telangiectasia occur, but are less common and less severe in S.L.E. than in discoid lupus.

It is important to recognize that involvement of the skin provides no index to the intensity of the visceral disease. The skin may be clear even in cases which end fatally (20).

In cases of moderate or great severity the mucous membranes are usually affected. Most often the changes take the form of shallow ulcers on the palate, fauces, pharynx, or, much less often, the tongue; erythema, hemorrhage and telangiectasia may be present at the same time. The ulceration may be complicated by moniliasis. The lips tend to become swollen, sore and crusted. Epistaxis is not unusual. The ulcers greatly augment the suffering and also impede the administration of food and fluids. Ulceration of the genitalia occurs and is often overlooked.

In a small number of cases one or more indolent lesions of discoid lupus, of the type described in a previous paragraph, may be present for years before the constitutional symptoms of S.L.E. make their debut. In such cases the discoid lesions tend to become bright red and engorged when the acute stage supervenes.

Joints

Most lupus patients have arthralgia at one time or another. Pain in the joints is often the first symptom and may appear years before any other com-

plaint; it is apt to be accompanied by mild stiffness, especially of the fingers and knees. Pain is common during the onset of acute and subacute stages of the disease. Frequently the joints ache without tenderness even when the disease appears to be in remission. In the severe cases redness and synovial effusions develop; hence the erroneous diagnosis of acute rheumatic fever may be offered. Periarthritis, tenosynovitis, and myositis are common.

Harvey, et al., have noted that even the temporo-mandibular joint may be involved (21). This detail should be of special interest to old clinicians who regard temporo-mandibular arthritis as evidence of Neisserian infection.

The appearance of the joints presents no special traits by which the diagnosis of S.L.E. can be made. The synovial fluid may yield a positive L.E. test. Suppuration and ankylosis are not part of the clinical picture.

In a few who suffer from S.L.E. the joints acquire the appearance typical of rheumatoid arthritis. In such cases it may be impossible to decide whether the patient has one disease or two.

Serous Membranes

Lesions of the major serous membranes are conspicuous in the morbid anatomy of the S.L.E. and are an important determinant of the clinical picture. Acute fibrinous pleuritis with pain and dyspnoea occurs in a large proportion of the severe cases. Effusion is common. Pericarditis, somewhat less frequent than pleuritis, may produce small or large effusions, which are sometimes loculated. Both pleural and pericardial fluid may yield a positive L.E. test (22).

The abdominal serous membranes are not exempt from the disease. To this fact is ascribed the ill-defined abdominal pain which so often occurs. In some cases the morbid process manifests itself as perisplenitis or perihepatitis, characterized by pain and tenderness in the upper abdominal quadrants. Acute surgical disease of the abdominal viscera may be simulated.

Lymph Nodes, Spleen, Blood

General adenopathy is frequently but not invariably present. The nodes usually are not tender, matted, or indurated. The adenopathy may occur with or without mild degrees of splenomegaly. When these signs are accompanied by hemorrhagic phenomena the false diagnosis of primary blood dyscrasia may be hard to resist.

As previously stated, some persons whose troubles start with thrombopenic purpura later develop characteristic manifestations of S.L.E. In such cases splenectomy may be of temporary benefit but is certainly not curative. Thrombotic thrombopenic purpura has been suspected of being a congener of S.L.E. (23, 24).

Leukopenia, definite but not extreme, is typical of S.L.E. The differential white count may be normal or may be shifted to the left. Haserick observed that in the severe untreated case of S.L.E. eosinophiles are few or absent in the peripheral blood and that these cells appear after treatment with steroids is begun (7). Leukocytosis usually signifies intercurrent infection such as pneumonitis, bacterial endocarditis, or pyelonephritis. Moderate thrombocytopenia

and hypochromic anemia are regularly present. The sedimentation rate is characteristically elevated and is apt to reach extreme levels in acute cases. The Wassermann and Kahn reactions give falsely positive results in a large minority of cases. Indeed these reactions are sometimes positive long before the advent of any clinical evidences of S.L.E. Hypoalbuminemia and marked hypergammaglobulinemia are characteristic. Transfusion reactions are common. These and other peculiarities of the blood (including the highly specific L.E. test) are described in detail elsewhere in the present symposium (25).

Cardioroscular System

A variety of troubles may beset the heart of the patient with S.L.E. Inevitably the fever is accompanied by simple tachycardia, but at times the heart rate is rapid even when the temperature is little elevated. Cardiac failure is unusual but may occur as a by-product of steroid treatment. The pleural effusions which so frequently supervene are due to inherent disease of the serosa and not to passive congestion. Myocarditis and pericarditis occur, the latter being the commoner. The pericarditis of lupus presents the usual clinical phenomena, substernal pain, dyspnoea, a tendency to sit with the trunk bent forward, and the usual physical and electrocardiographic signs. Suppuration and calcification do not occur.

A blowing apical systolic murmur occurs in many cases of S.L.E. Careful retrospective studies have shown that this murmur cannot be correlated with the presence of non-bacterial verrucous endocarditis, i.e. with the cases which were formerly segregated under the designation of Libman-Sacks syndrome but which are now known to belong under the rubric of S.L.E. (26). The murmurs and lesions of rheumatic heart disease are not rare in cases of S.L.E., but this appears to be nothing more than a confusing coincidence.

In a small number of cases S.L.E. is complicated by acute or subacute bacterial endocarditis. Such patients run a fulminating course, with swinging "septic" fever, petechiae, splenomegaly, infarction of viscera, and positive blood culture. With the advent of antibiotics and steroids such cases, never very common, are presumably becoming rare.

The blood pressure in S.L.E. is usually normal unless such complications as pericardial effusion or uremia are present. Raynaud phenomena may occur during acute S.L.E. or may have been among the patient's previous illnesses long before the emergence of the S.L.E. syndrome.

Lungs

The lungs are frequently involved in S.L.E. Often the picture is that of persistent or migratory, patchy lobular pneumonia, usually accompanied by pleuritis and effusion. Ordinarily the pleuritic signs and symptoms predominate over the pulmonary but this rule has been broken in several reported cases (27).

Dyspnea is extremely common. The lungs may present widespread consolidation or focal infiltrative lesions, and the physical signs vary accordingly. Commonly the lesions discovered at autopsy are more extensive than the physical

signs had indicated. Roentgen films not infrequently reveal mottled and streaked shadows interpreted as subpleural infiltrates accompanied by areas of atelectasis. The pleurae may show local thickening and small or large effusions. Ordinarily involvement is greatest at the bases. Roentgenologists have learned to suspect the presence of S.L.E. where pleural and subpleural lesions are present simultaneously (28). Before the advent of steroids the pneumonic lesions of S.L.E. were tenacious and migratory. When pulmonic infiltrates are discovered in a case of S.L.E. it is extremely and obviously important to exclude tuberculosis as the cause; occasionally the clinical and roentgen appearances have been indecisive. Ordinary bacterial pneumonia may occur in S.L.E. as in other chronic diseases.

Gastrointestinal Tract, Liver

Little is known about the behavior of the gastrointestinal tract in S.L.E. It is usual for lupus patients to have nondescript abdominal pain; a good many have intermittent diarrhea. In some instances the pain is almost certainly due to lesions of the peritoneum; in others the intestinal vasculature is probably culpable. Infarction may occur, and the use of steroids has brought with it occasional instances of perforation. Usually abdominal and gastrointestinal symptoms in S.L.E. are overshadowed by other troubles. Harvey, et al., have described ulcerative and diphtheritic esophagitis in lupus (21).

Hepatic symptoms are not prominent. Moderate degrees of hepatomegaly are common, jaundice is rare. Tests for hepatic function are apt to be vitiated by the hyperglobulinemia which is characteristic of the disease, hence the physician must use his own naked judgment. Persistent pain and tenderness in the hepatic region are more suggestive of periarteritis nodosa than of S.L.E.

Kidneys

The kidneys are frequently attacked by the morbid process. Most patients show at least albuminuria and microscopic hematuria. Alternatively the syndromes of acute nephritis or nephrosis present themselves. In severe cases renal function suffers major damage, which leads to typical uremia and death. As in any serious constitutional disease, pyelonephritis may appear, an unwelcome addition to the burden of the patient and the physician. The ocular changes which may accompany renal disease are discussed below.

The renal component of S.L.E. is of major importance because it is refractory to treatment, even by steroids, and because it is a principal immediate cause of death.

Nervous System

A variety of neural and psychic disturbances may occur in S.L.E. The commonest are epileptiform convulsions, delirium, and psychotic states, especially schizoid reactions and mania. The ingenious discovery of the L.E. test has made it possible to recognize S.L.E. as the underlying ailment in occasional persons who appeared to have ordinary idiopathic epilepsy. It is probable that

conscientious surveys of epileptic and schizophrenic patients will disclose small numbers of additional cases. It is also not unusual for convulsions to occur in patients with S.L.E. under treatment with steroids. Such cases understandably confuse the physician, who may be at a loss to decide whether the convulsions are caused by the disease or the drug. At the present time opinion inclines toward continuing the steroid treatment, especially if the brain is not the only organ affected by the disease, but anticonvulsant drugs must often be added to the regimen.

Other neural disturbances observed in S.L.E. include peripheral neuritis (29), infarction of the spinal cord (30), and meningitis, especially the tuberculous variety.

Eyes

The commonest ophthalmoscopic findings in S.L.E. are hemorrhages and the so-called cotton-wool exudates. The hemorrhages tend to occur around the retinal vessels and to be flame-shaped. Hemorrhages in the vitreous humor have been reported. Cotton-wool exudates are well defined, fluffy, yellowish-white deposits situated usually in the posterior half of the fundus. Cyclical changes in these lesions have been reported (31). Cotton-wool exudates may occur independently of uremia; they are apt to appear in lupus patients who have cerebral signs. Papilledema occurs in S.L.E. but is rare; peripapillary edema is common.

Special Problems

S.L.E. may occur coincidentally with many other diseases. In some instances the apparent coincidence is merely a matter of erroneous diagnosis; in others the difficulty proceeds from our present inability to define the concept of S.L.E. with satisfactory precision. Thus, as has been stated in a previous paragraph, in cases where S.L.E. appears to be coincidental with rheumatoid arthritis, the problem may be impossible to resolve. The difficulty is almost as great in cases of rheumatic fever. Indeed the case of a young negress has been reported in which Sydenham's chorea was followed within six weeks by S.L.E. Autopsy revealed lesions of both diseases (32). Other ailments which have been reported to accompany S.L.E. are neoplasms, Sjögren's syndrome (33), meningitis, and tuberculosis. The latter is a constant but not insuperable danger during steroid treatment. As previously stated, S.L.E. may be complicated by bacterial endocarditis and also by visceral or peripheral thrombosis and embolism, otitis media, abscesses of the skin, and parotitis.

It has been demonstrated that sufferers from S.L.E. may undergo major and minor surgical operations safely (34). Splenectomy has often been performed without immediate ill effect. Post-operative problems in S.L.E. are as likely to be caused by the steroids as by the basic disease.

Much has been written about pregnancy in cases of S.L.E. but most of the information available dates from the pre-steroid era. In a few cases the skin lesions disappeared during pregnancy but reappeared after parturition (35).

It is the general opinion that in most cases acute S.L.E. is affected favorably by pregnancy but that the risk of fetal death is high. Most authors regard abortion as unwarranted.

DIAGNOSIS

The diagnosis of S.L.E. is beset with numerous difficulties. These have been alleviated but not dispelled by the discovery of the L.E. test, which is discussed elsewhere in the present symposium.

As in so many other areas of clinical medicine, the first diagnostic act should be *to suspect*. A large variety of circumstances should lead the physician to think of S.L.E. These include: (a) thrombopenic purpura or hemolytic anemia not attributable to drugs or poisons; (b) biologic false positive reaction for syphilis; (c) continued fever of unknown origin; (d) arthralgia, especially when accompanied by fever, pleuritis, pericarditis, pneumonia, cutaneous eruptions, or abnormal urine; (e) persistent or otherwise exceptional cases of pneumonitis. It would be well to add to this list cases of rheumatoid arthritis, dermatomyositis, scleroderma, idiopathic epilepsy, and schizophrenia. All these suspicions are fortified if the patient is a young woman or has recently been exposed to actinic radiation or has been given injections of gold salts. Suspicion should also attach to persons who have sunburn which has failed to clear in the usual time. Any unexplained deviations in persons who have discoid lupus should of course be subjected to careful study.

The L.E. test, properly performed, rarely yields a false positive result. Such conditions as pernicious anemia, dermatitis herpetiformis, myeloma, and tuberculosis have been reported in this connection but not all such instances can be accepted unreservedly (36). The principal difficulty is provided by cases of hydralazine toxicity, since in these the patient may have fever, abdominal pain, polyserositis with effusion, pneumonitis, arthritis, and even a cutaneous eruption and hyperglobulinemia. "Hydralazine disease" astonishes rather than perplexes the clinician, since the use of the drug can usually be recognized; moreover hypertension is not characteristic of S.L.E. Another source of trouble is the patient to whom steroids have been given or are being given without a definite diagnosis. It is now well known that the use of steroids makes L.E. cells hard to find; indeed some physicians maintain that L.E. cells disappear during steroid treatment. In such cases diagnosis may be difficult or impossible unless the use of steroids can be interrupted.

There are also untreated cases of S.L.E. in which lupus cells are few or appear intermittently. In such cases the hyperglobulinemia and the abnormal urine may provide sufficient clarification until a positive test can be obtained.

Biopsy of the skin, muscles, and kidney possesses only moderate reliability. Apart from the obvious facts that the procedure is no more reliable than the pathologist who executes it, and that not all pathologists can be depended upon to recognize the histologic picture, the microscopic changes of S.L.E. are difficult to detect. These changes are discussed authoritatively in another part of the present symposium. Biopsy is helpful—not invariably—in cases where the diag-

noses of scleroderma, periarteritis, and sarcoid must be excluded. Microscopical examination of spleens excised in cases of thrombopenic purpura or hemolytic anemia occasionally yields definite evidence of S.L.E.; hematoxylin bodies, "onion-skin lesions" (periarterial fibrosis) and peri-splenitis should be looked for diligently.

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SYSTEMIC LUPUS ERYTHEMATOSUS IN CHILDHOOD

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INTRODUCTION

The incidence of systemic lupus erythematosus (S.L.E.) in children under the age of fifteen years is difficult to assess. Descriptions of large series of cases of this syndrome in adults indicate an incidence of approximately four to ten per cent in children in this age group (1, 2). Individual case reports are few (3-9); a group of eleven children, however, has been described (10). During the years between 1947 and 1958, fifteen patients with an onset of S.L.E. prior to the age of fifteen years were studied at The Mount Sinai Hospital.

The purpose of this report is to describe the syndrome as it appears in this age group and to discuss its course, prognosis and treatment. Differences, if any, between the syndrome in these children and in adults will be examined and features important to its differential diagnosis will be emphasized.

The discovery of the L.E. cell phenomenon (11) and the refinement of its use as a diagnostic technique have facilitated the recognition of this syndrome (12-15). The availability of antimicrobial drugs and hormonal agents has apparently prolonged the life of some patients with this disease. Accordingly, a greater familiarity with the clinical spectrum of S.L.E. as it pertains to children is essential to pediatricians.

CLINICAL MATERIAL

The fifteen cases of S.L.E. reviewed in this report include fourteen females and one male. The age of onset varied from five to fifteen years. All children were of the white race. Nine were Jewish and four were of Puerto Rican descent, this being a reflection of the patient population at The Mount Sinai Hospital.

Two patients were sisters who contracted the disease within two and one-half years of each other. Diagnosis in every case was not accepted until several positive L.E. cell preparations were obtained. Table I lists the essential findings in each patient.

CLINICAL FEATURES

The initial sign or symptom of these children is tabulated in Table II. The most frequent complaints included arthralgia, both with and without objective findings, rash, and fever. These symptoms are all similar to those of other "collagen" diseases. Four of the children had early symptoms not at all suggestive of this syndrome. These included menorrhagia, convulsions and edema. It is also of significance that a rash was present initially in only three of the patients.

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TABLE I
Clinical Data of 15 Children with Systemic Lupus Erythematosus

Case No.	Age at Onset (Yrs.)	Sex	Initial Symptom	Major Early Signs & Symptoms						Major Systems Involved					Duration of Follow-Up (Yrs.)	Present Status	
				Arthralgia	Fever	Rash	Weight loss	Weakness	Pallor	Chest pain	Lid edema	Reticulo-endothelial	Renal	Cardiac			C.N.S.
1	5	F	Convulsions	+	+				+							1 $\frac{1}{3}$	Remission
2	8	F	Pallor		+	+			+							2 $\frac{1}{2}$	Dead
3	8 $\frac{1}{2}$	F	Fever	+	+		+	+	+							3 $\frac{1}{2}$	Dead
4	9 $\frac{3}{4}$	F	Fever		+	+										2 $\frac{1}{2}$	Remission
5	10	F	Arthralgia	+	+		+									5	Remission
6	10	F	Rash	+	+	+			+							8 $\frac{1}{2}$	Incomplete remission
7	10 $\frac{1}{2}$	F	Rash	+	+	+	+		+							2	Dead
8	10 $\frac{1}{2}$	F	Arthralgia	+	+		+	+								$\frac{3}{4}$	Remission
9	10 $\frac{3}{4}$	M	Arthralgia	+	+	+										$\frac{1}{4}$	Remission
10	11 $\frac{1}{2}$	F	Arthralgia	+		+	+									2 $\frac{3}{4}$	Dead
11	12	F	Edema	+		+	+	+		+	+					2 $\frac{1}{2}$	Dead
12	12	F	Rash	+	+	+	+	+								2	Dead
13	14	F	Menorrhagia	+					+				+			$\frac{1}{3}$	Remission
14	15	F	Arthralgia	+	+	+	+	+								1 $\frac{1}{2}$	Remission
15	15	F	Arthralgia	+		+										1	?

TABLE II
Initial Sign or Symptom in 15 Children with Systemic Lupus Erythematosus

Sign or Symptom	No. of Children
Arthralgia.....	6
Rash.....	3
Fever.....	2
Pallor.....	1
Menorrhagia.....	1
Convulsions.....	1
Edema.....	1

Figure 1 is a graphic summary of the various signs and symptoms seen during the early stages of the disease. It also depicts the frequency of major organ systems eventually involved during its course.

The most common sign, both at onset and during the progression of the disease, was joint involvement. The joint symptoms were usually acute. Pain with or without local swelling and redness, was the chief manifestation. There was no predilection for specific joints, the interphalangeal joints being involved as frequently as knee, hip and elbow joints. Back pain occurred in two children and this was assumed to be due to intervertebral joint involvement. Character-

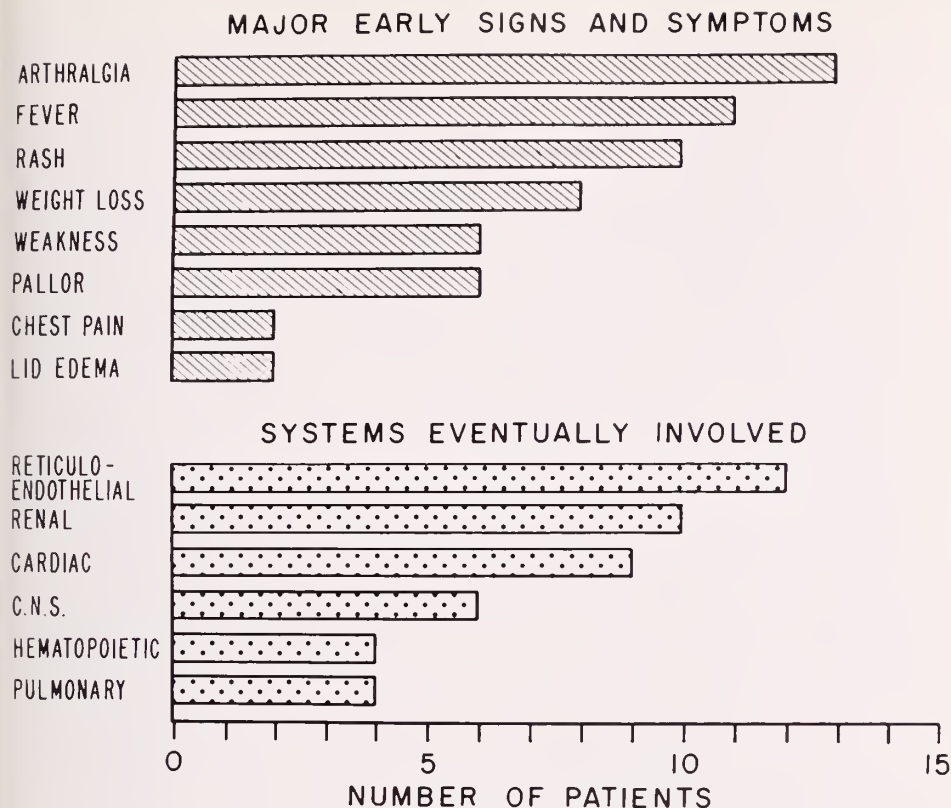


FIG. 1

istic of the arthralgia, however, was the rarity of development of any permanent deformity regardless of the severity or the duration of the disease. This may serve to differentiate this joint involvement from that of rheumatoid arthritis. Only one patient developed such a deformity. One patient, interestingly, developed a transient nodule on the dorsum of a wrist.

The fever pattern in these children was variable. It varied from daily low-grade levels of 101° F. to daily spikes of 103° to 104° F. The fever was intermittent with recurrences usually heralding an exacerbation of the disease. In no child did it spike to 105° or 106° F., as may be seen in rheumatoid arthritis.

Although the cutaneous manifestations of S.L.E. were present in only three children as an initial sign, they appeared sometime during the course of the illness in two-thirds of the patients. In the majority, there was the typical "butterfly" sunlight sensitive eruption involving the face. In two of the children a generalized non-specific maculo-papular eruption occurred on the trunk and extremities. Three patients had oral lesions; two demonstrated vesicles and ulcers resembling herpetic stomatitis; one had ulcerated lesions secondary to hemorrhage into the mucous membrane.

An outstanding sign which occurred early in more than one-half of the patients

was weight loss. It usually was accompanied by prominent anorexia. Weakness and pallor were also frequent in these children. Chest pain occurred in two patients as did "puffy" eyelids.

Although perhaps not present at the onset, several major systems became involved as the syndrome progressed. The "reticulo-endothelial system" was implicated in eighty per cent of the children. The majority had generalized lymphadenopathy either at the onset or during the course of the disease. One-third had hepatomegaly or splenomegaly, usually not at the onset. Only one child had clinical icterus.

Two-thirds of the children have had renal involvement. This figure is probably closer to one hundred per cent since none of the five children who, thus far, are free of renal findings have been followed for more than one and a half years. Several children had albuminuria early in the course of the disease. Two had edema, either periorbital or ankle, at the onset. Seven of the ten children who have been followed for more than one and a half years have thus far developed a typical nephrotic syndrome. In all who died, chronic renal disease was a contributing cause of death.

Cardiac manifestations varied from a persistent systolic murmur as an isolated sign to such findings as ECG changes indicative of myocardial damage, hypertension and pericardial friction rubs. In five of six fatal cases cardiac findings progressed to advanced myocardial involvement which in turn led to heart failure as a contributing factor in the deaths.

Six children had central nervous system manifestations. These included grand mal seizures at the onset of the disease in two children, blurred vision in two, ankle clonus in one child and an abnormal EEG in the sixth.

Four of the children have thus far had hemorrhagic tendencies. One presented with menorrhagia as the initial symptom of the disease. The other three had bleeding episodes involving the nose, oral cavity and skin.

Table III is a listing of other diagnoses considered in these children prior to the confirmation of S.L.E. A perusal of these conditions associated with the previous discussion of the diverse signs and symptoms is a testament to the protean and frequently confusing picture presented during the early months of this illness. In fact, review of the histories reveals a significant delay in time between the onset of symptoms and definitive diagnosis. In only three children was the diagnosis made during the initial contact. The diagnosis was made in seven children within six months after initial examination but it was delayed from one to three and a half years in five. The average duration of "lag" was

TABLE III

Other Diagnoses Considered in 15 Children with Systemic Lupus Erythematosus

Acute glomerulonephritis	Infectious mononucleosis
Acute hemolytic anemia	Rubella
Acute leukemia	Rheumatic fever
Allergic rash	Infectious arthritis
Epilepsy	Traumatic arthritis
	"Viral" infection

ten months. Several of the patients were treated for allergy, infection, traumatic or infectious arthritis and epilepsy prior to the eventual recognition of the underlying disease.

LABORATORY FINDINGS

Except for the finding of the L.E. cell phenomenon, no individual laboratory test was of diagnostic significance. The L.E. cell test as performed in our laboratory (16) was positive in all patients once the diagnosis was considered.

The majority of the children had a depression of their hemoglobin levels either at the onset or during the course of the disease. As previously indicated, in only four could this have been due to actual blood loss. Eight of twelve patients, in whom this test was performed, demonstrated a positive Coombs reaction. Platelet counts were depressed in approximately one-half of the patients.

All of the patients had a leukopenia varying from 3000 to 6000 cells per cu. mm. during the course of the disease; nearly all had a polymorphonuclear leukocytosis.

The sedimentation rate was elevated in all of the patients, although in three it did not rise until several months had elapsed. The Wassermann reaction was positive in only two of seven patients in whom it was performed. The albumin/globulin ratio was reversed in one-half of the patients at the onset of the disease, even before kidney involvement was evident.

Although albuminuria was present in nine of the patients at the onset, other laboratory signs of renal impairment such as the appearance of urinary formed elements, elevated blood urea nitrogen, elevated serum cholesterol and depressed clearance tests and PSP excretion did not appear until the disease had progressed.

Gamma globulin elevation was noted in four of six patients in whom serum protein patterns were studied by electrophoresis; in two patients the level was below normal.

COURSE AND PROGNOSIS

The present status of fourteen of the fifteen patients is known. Only ten children have, thus far, been followed for more than one and a half years after onset; six have succumbed.

The course of those who died was characterized by repeated exacerbation with additional systemic involvement and increased severity occurring with each recrudescence. Death occurred, on the average, two to three years after onset and was due usually to a combination of cardiac and renal failure. Three patients had autopsy examinations. Pathologic features well described in adult series were found, i.e., the typical "lupus nephritis" accompanied by endocarditis and myocarditis (17, 18). Of interest is the fact that three children are living in remission despite the fact that their disease began two and one-half, five and eight and one-half years ago.

TREATMENT

Therapy in children does not differ from that employed in adults. Supportive measures include an adequate diet with vitamins, anti-pyretics, transfusions,

digitalis and, especially, antibiotics. Steroids are reserved for periods of severe symptomatology not ameliorated by the above measures. The initial dosage should be large enough to control symptoms quickly, usually 200 to 300 mg. of cortisone or 40 to 60 mg. of prednisone. Efforts are then made to reduce the drug to a maintenance level sufficient to keep the signs and symptoms quiescent, usually 75 to 100 mg. of cortisone or 15 to 20 mg. of prednisone daily. Intermittent attempts to wean the patient from the steroid are also made; the drug is reinstated when severe symptoms reappear. It is of interest that the nephrotic syndrome secondary to S.L.E. does not respond with either immediate diuresis or prolonged remission to steroids as does the idiopathic form of nephrotic syndrome of childhood.

Recently, analyses of large series of cases of S.L.E. in adults, have led to a somewhat more optimistic outlook concerning the prognosis (19, 20). Harvey has stated that more than fifty per cent of ninety-nine patients have survived for four or more years (2). Although there have been no extensive follow-ups in children, the conclusion has generally been accepted that survival in this age group is shorter. In the present series, three of the children survived from two and one-half to eight and one-half years after the onset of their symptoms. It would appear therefore that appropriate therapy with antimicrobial drugs and hormonal agents may serve to ameliorate symptoms and prolong life.

DISCUSSION

As has been discussed, the clinical manifestations of S.L.E. are protean and the organ involvement is multiple. It should be emphasized that the diagnosis can be made in the early stages only if it is considered.

The early presence of the typical "butterfly" eruption is the best clue to diagnosis. Rashes of varying types however, have been described (21); in the present series the diagnoses of rubella, infectious mononucleosis and allergy were considered in three children. Of importance is the observation that five children had no rash of any type during the course of their disease. When, in addition to the three most common early symptoms (arthralgia, fever and rash), the disease has progressed to include renal involvement, hemorrhagic manifestations, or polyserositis, recognition presents no problem. Most important is its diagnosis during the early stages, during the period when intermittent arthralgia or recurring fever are the cardinal symptoms.

Several clinical features gleaned from analysis of the fifteen children in this series may be of aid in establishing the early diagnosis of S.L.E.:

A. The early accompaniment of arthralgia and fever by anorexia and weight loss;

B. The early appearance of generalized lymphadenopathy and/or hepatomegaly and splenomegaly;

C. Renal involvement as evidenced only by albuminuria or hematuria (the diagnosis of acute glomerulonephritis was entertained for several weeks on patient number 4 before S.L.E. was considered);

D. Central nervous system signs, especially convulsions (patient number 1

presented with grand mal seizures and was considered to be an epileptic for one year prior to the appearance of other manifestations);

E. Hemolytic anemia.

Although, as has been pointed out, none of the routine laboratory tests are specific, the coexistence of an elevated sedimentation rate, leukopenia with polymorphonuclear leukocytosis and an elevated serum globulin level would be highly suggestive. A positive Coombs test and/or a positive serologic test for syphilis may also be found. As has been stressed by many workers only the repeated performance of the L.E. cell test in all patients presenting any of the suggestive signs and symptoms will ferret out cases in the early stages of the disease (19, 22).

SUMMARY

A group of fifteen children with S.L.E. beginning prior to the age of fifteen years is described. Early signs and symptoms, subsequent visceral involvement, laboratory findings, course, treatment, and outcome are analyzed. Features pertinent to the early differential diagnosis are emphasized.

It appears that the clinical picture in this age group does not differ markedly from that described in adults. It also is evident that the course and prognosis in the two age groups are similar. It is concluded that an early diagnosis of this syndrome can be established by greater awareness of the varied clinical picture and with the more frequent performance of L.E. cell preparations.

ACKNOWLEDGEMENT

The authors wish to thank Drs. George J. Ginandes, Samuel Karelitz and Stanley L. Lee for granting permission to include their private patients in this series.

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THE THERAPY OF SYSTEMIC LUPUS ERYTHEMATOSUS

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The advent of corticotropin and the adrenal glucogenic steroids constituted the first significant advance in the therapeutic management of systemic lupus erythematosus (1, 2). During the course of the decade that these agents have now been employed, they have proven to be quite effective in the control of most of the clinical manifestations of this illness (3-9). This is somewhat less true of other collagen diseases such as polyarteritis nodosa and dermatomyositis, while their ability to subdue the progression of scleroderma is at best meager.

Systemic lupus erythematosus is a disease of protean complexity but is often characterized by fever, joint pains, rash, lymphadenopathy, involvement of the serous cavities, hepatomegaly, splenomegaly, various blood dyscrasias, and impaired renal function. In Tables I and II are listed the symptoms and physical signs that we encountered in our group of fifty-five patients with lupus, while in Table III are recorded the laboratory data obtained in these patients. With the exception of the impairment of renal function, most of the other manifestations are promptly brought under control with either corticotropin or the adrenal steroids. Following administration of the hormone in adequate amounts, the temperature usually returns to normal levels within twelve to thirty-six hours, the arthralgias and arthritis subside appreciably within one or two days, while the rash disappears almost entirely, except for a faint brown sealiness, within a week. Pleural and pericardial collections of fluid are absorbed, the latter somewhat less rapidly than the former (Table IV). The enlarged liver, when not due to congestive heart failure, seldom returns to normal but generally does become somewhat reduced in size. Essentially the same is true for the splenomegaly. A previously false positive serology becomes negative in twenty to thirty per cent of those patients whose serology was previously positive.

In no instance in our group have the L.E. cells entirely disappeared from the peripheral blood. Their abundance is significantly decreased when the disease is brought under control, but we have never failed to find them with patient and careful search. Thrombocytopenia and hemolytic anemia occurring during the course of the illness respond most satisfactorily to treatment with the hormonal agents. Indeed, the response to treatment of the latter manifestation, which in the past represented such a dire hazard to the patient with systemic lupus erythematosus, is most dramatic in the promptness of remission. It is interesting to observe, however, that although the hemolytic phenomena cease, the positive Coombs' test remains unaltered (Table V). In patients with thrombocytopenia, the blood platelets rapidly increase in number, and purpura, when present, subsides.

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Aided by a grant from the National Institutes of Health, The United States Public Health Service.

TABLE I

Incidence of Symptoms in 55 Patients with Acute Systemic Lupus Erythematosus

Symptom	Patients	
	Number	Per cent
Arthralgia.....	52	95
Fever.....	50	91
Weight loss.....	36	65
Rash.....	34	62
Arthritis.....	34	62
Chest pain.....	20	36
Chills or chilliness.....	17	31
Abdominal pain.....	11	20
Convulsions.....	11	20
Alopecia.....	10	18
Lymphadenopathy.....	9	16
Light sensitivity.....	6	11
Bleeding tendency.....	6	11
Paresthesia.....	1	2

TABLE II

Incidence of Physical Signs in 55 Patients with Acute Systemic Lupus Erythematosus

Physical Sign	Patient	
	Number	Per cent
Lymphadenopathy.....	39	71
Rash.....	34	62
Mucous membrane lesions.....	19	35
Joint abnormalities.....	28	51
Hepatomegaly.....	26	47
Cardiac abnormalities (total).....	20	36
Hypertension.....	7	13
Significant murmur.....	6	11
Gallop rhythm.....	5	9
Pericardial friction rub.....	4	7
Pericardial effusion.....	4	7
Pulmonary abnormalities (total).....	18	33
Pleural effusion.....	7	13
Friction rub.....	6	11
Splenomegaly.....	14	25
Psychiatric abnormalities.....	13	24
Edema.....	12	22
Finger-tip skin lesions.....	9	16
Fundal abnormalities.....	9	16
Petechiae.....	6	11
Neurological abnormalities.....	5	9

TABLE III

Laboratory Data in 55 Patients with Acute Systemic Lupus Erythematosus

	Patients	
	Number	Per cent
Positive L.E. test.....	55	100
Elevated sedimentation rate.....	51	93
Hyperglobulinemia.....	39	71
Cephalin flocculation test (2+ to 4+)*.....	30	68
WBC less than 5000/cu. mm.....	35	64
Urine		
Sediment, occasional to many WBC.....	32	58
Sediment, occasional to many RBC.....	22	40
Sediment, occasional to many casts.....	14	25
Albumin, 1+ or more.....	27	49
Hemoglobin less than 10 gm./100 cc.....	29	53
Abnormal EEG**.....	8	50
Abnormal chest x-ray.....	20	36
Azotemia.....	17	31
Creatinine greater than 1.5 mg./100 cc.†.....	12	41
False positive serologic test for syphilis.....	15	27
Abnormal ECG.....	12	22
Prolonged bleeding time‡.....	4	22
Platelets less than 100,000/cu. mm.....	9	16
C-reactive protein test, 1 or more††.....	8	67
Differential sheep cell agglutinin test, titer greater than 1:16§.....	1	14

* 44 patients

** 16 patients

† 29 patients

‡ 18 patients

†† 12 patients

§ 7 patients

In our group, the sedimentation rate returned to normal levels in over half of the cases. The persistence of an elevated sedimentation rate was usually associated with inadequate treatment, the presence of significant impairment of renal function, or the existence of some underlying complication or infection. Similarly, reduction in the preexisting hyperglobulinemia occurred in only slightly more than half of the patients. Patients with systemic lupus erythematosus almost always develop a normochromic anemia of varying intensity. The anemia responds slowly to steroid or corticotropin therapy. The hemoglobin and peripheral red blood cell count returned to normal levels in approximately half of our group. Most of our patients, however, did show an increase in the peripheral white blood cell count with a return of the presence of more mature granulocytes.

The major continuing threat to life of patients with systemic lupus erythema-

TABLE IV

Effect of Treatment on the Clinical Manifestations of Acute Systemic Lupus Erythematosus

Clinical Manifestation	Total No. of Patients	Total Improved (per cent)
Fever	47	100
Arthralgia	50	100
Weight loss	35	66
Lymphadenopathy	36	56
Rash	32	91
Mucous membrane lesions	19	74
Hepatomegaly	25	20
Cardiac abnormalities	20	35
Hypertension	7	0
Gallop rhythm	5	60
Pericardial friction rub	4	50
Pericardial effusion	4	50
Significant murmur	6	0
Pulmonary abnormalities	18	94
Pleural friction rub	6	100
Pleural effusion	7	71
Chest pain	20	90
Psychiatric abnormalities	13	62
Finger-tip skin lesions	9	44
Abdominal pain	11	73
Edema	12	58
Splenomegaly	14	14
Alopecia	9	44
Fundal abnormalities	9	67
Neurological abnormalities	5	20

tosus, despite adequate steroid therapy, is the development of persistent and progressive renal disease. Approximately half our patients showed some renal function abnormalities, as evidenced by the presence of red blood cells in the urinary sediment and varying degrees of albuminuria. In slightly over one-third of the group the blood urea nitrogen was elevated (Table III). Renal function studies, such as urine concentration tests, phenolsulphonthalein excretion, and urea and creatinine clearance, were determined in slightly more than half of the patients. These studies revealed several points of interest. The urine concentration test proved to be the least sensitive indicator of the status of renal function as observed in this group. On the other hand, the fifteen-minute excretion of phenolsulphonphthalein and the urea clearance yielded the most useful information in terms of appraisal of the renal status.

Renal involvement in systemic lupus is the least responsive of all the clinical manifestations of the disease to the adrenal glucogenic steroids or corticotropin. Of fifty-five patients studied in our clinic between 1948 and 1955, seventeen died. Of these, thirteen succumbed to progressive renal failure despite intensive and prolonged therapy. The nephrotic syndrome often encountered in this illness

TABLE V

Effect of Treatment on the Laboratory Data in Acute Systemic Lupus Erythematosus

Laboratory Test	Number of Patients Before Therapy	Percentage of Patients Improved
Positive L.E. test.....	55	0
Elevated ESR.....	49	57
Hyperglobulinemia.....	37	46
WBC less than 500/cu. mm.....	32	72
Hemoglobin less than 10 gm./100 cc.....	28	54
Urine		
Sediment, occasional to many RBC.....	22	32
Sediment, occasional to many WBC.....	32	50
Sediment, occasional to many casts.....	14	36
Albumin, 1 plus or more.....	27	26
Abnormal chest x-ray.....	20	60
False positive serologic test for syphilis.....	14	29
Azotemia.....	17	35
Shift to left (nonsegmented forms greater than 10%.....	32	41
Abnormal EEG.....	8	0
Reticulocytes greater than 0.7%.....	19	37
Cephalin flocculation greater than 1 plus.....	29	14
Abnormal electrocardiogram.....	12	42
Prolonged bleeding time.....	4	75
C-reactive protein test greater than 1 plus.....	8	25
Platelets less than 100,000.....	8	63
Positive direct Coombs' test.....	8	0
Hemolysis.....	4	100

may show a gratifying temporary response to salt and fluid restriction and hormone therapy. But, unfortunately, the underlying renal disease progresses inexorably.

During an acute relapse of the illness, when the temperature is considerably elevated, albuminuria, the presence of cellular elements in the urine, and an elevation of the blood urea nitrogen are not infrequently found. With the subsidence of the acute disease process, the abnormal urinary constituents will often disappear and the blood urea nitrogen value will return to normal levels. Whether this represents actual renal disease, characteristic of systemic lupus erythematosus, or is a manifestation of the general toxicity associated with the acute exacerbation of the illness, is uncertain. In any event, evidence of persistent and significant impairment in renal function was almost invariably encountered in those individuals who succumbed to the disease. It is our opinion that the renal status, after prolonged and adequate therapy, is the single most important factor in determining the prognosis of the individual patient. Evidence of persistent or progressive impairment of kidney function must, in general, be regarded as an ominous sign.

In more recent studies our data would tend to indicate that those patients

TABLE VI

Comparative Effects of Adrenal Steroids on Sodium Retention, Potassium Diuresis, Protein and Carbohydrate Metabolism (16)

Hormonal Agent	Sodium-Retaining Effect	Potassium-Diuretic Effect	Effect on Protein and Carbohydrate Metabolism
Cortisone.....	1	1	1
Cortisol.....	1.25	1	1.25
Prednisone.....	none	slight	3-5
Prednisolone.....	none	slight	3-5
6-Methylprednisolone.....	none	slight	4-6
2-Methylcortisol.....	80-100	5-10	4-5
Desoxycorticosterone acetate.....	30-50	5	0
Aldosterone.....	300-900	10-25	0
9 α -Fluorocortisol.....	300-900	10-25	10-15
9 α -Fluoroprednisolone.....	300-900	10-25	50
2-Methyl-9 α -fluorocortisol.....	1000-2000	?	9
9 α -Fluoro-16-hydroxyprednisolone (triamcinolone).....	none	?	4-6

who have impairment of renal function generally manifest this early in the course of the illness (10). The longer the disease remains established without development of this complication, the less likely is it to occur.

The treatment of systemic lupus erythematosus consists of vigorous administration of hormone and, where cortisone, cortisol, or corticotropin is employed rigid restriction of the daily salt intake. Such sodium restriction is much less necessary when certain of the newer adrenal steroid analogues are used (Table VI). When prolonged steroid therapy is contemplated, it is essential that the patient receive daily supplemental potassium. Two to three grams of potassium chloride a day is usually adequate to prevent development of hypokalemia. The newer steroids, such as prednisone, prednisolone, 6-methyl prednisolone (Medrol®), and perhaps some of the even more recent analogues, tend less to induce a potassium diuresis than do corticotropin, cortisone, and cortisol (11, 12).

The acute toxic manifestations of the disease are promptly brought under control when an *adequate* amount of hormone is administered. In Table VII are listed the usual initial and maintenance doses of the various steroids, with which we have had experience, required to return the elevated temperature to normal levels and suppress the toxic manifestations.

It should be emphasized that the therapeutic hormonal requirements of the individual patient may vary considerably from the mean. Where the acute exacerbation does not respond promptly to the usual initial dosage there should be no hesitancy in increasing it to whatever level is necessary to induce an adequate remission.

When corticotropin is employed, several alternative routes and agents are available: (a) aqueous corticotropin administered intramuscularly, in a dosage of twenty-five to fifty units every six hours around the clock; (b) intravenously in a dosage of twenty to forty units administered in a continuous intravenous

TABLE VII

Comparative Effectiveness of the Adrenal Steroids as Anti-Inflammatory Agents in Man (16)

Hormonal Agent	Anti-Inflam- matory Activity	Average Initial Daily Oral Dose (mg)	Average Daily Oral Mainte- nance Dose (mg.)
Cortisone.....	1	200-300	50-100
Cortisol.....	1-1.25	200-300	50-100
Prednisone.....	3-5	40-60	10-25
Prednisolone.....	3-5	40-60	10-25
6-Methylprednisolone.....	3-5	32-48	8-24
3-Methylcortisol.....	4-5	30-50	5-20
Desoxycorticosterone acetate.....	0	—	—
Aldosterone.....	0-?	—	—
9 α -Fluorocortisol.....	10-15	8-12	4-6
9 α -Fluoro-16-hydroxyprednisolone.....	3- 5	32-48	8-24

infusion of five per cent glucose over an eight hour period daily; (c) zinc corticotropin, twenty to forty units twice a day intramuscularly. Of these measures the intramuscular zinc corticotropin and the intravenously administered corticotropin are perhaps most promptly effective. When the acute manifestations of the disease have been brought under control, both zinc and gel corticotropin may be used for maintenance purposes, the former in a dosage of ten to forty units daily, the latter in somewhat larger amounts.

With the introduction of atabrine in the treatment of discoid lupus (13) the value of the antimalarial agents were explored in the management of systemic lupus erythematosus (14, 15). In a recent report, Dubois describes equally good results with both atabrine and chloroquin (15). Twelve of fourteen patients in this group were benefited. Our experience with chloroquin has been less satisfactory in terms of control of the toxic manifestations of the disease. The latter often respond poorly, and in the presence of severe manifestations generally not at all. On the other hand, the rash, when present, subsides within several days after beginning chloroquin therapy. The use of these agents is not without hazard, since leukopenia, exfoliative dermatitis, and gastrointestinal disturbances have followed upon their administration (15). The dosage of chloroquin generally employed varies from 250 to 500 mg. daily. The use of chloroquin as an adjuvant to treatment with steroids has failed in our experience to demonstrate any overt advantages over the use of the steroids alone.

Although the glucogenic corticoids are effective in the suppression of many of the manifestations of systemic lupus erythematosus, the development of certain side effects consequent to their use must be borne in mind. Perhaps the term "side effects" is a misnomer, since such effects may represent specific metabolic actions of these agents. In any event, the efforts of the organic chemist are now being extensively directed to the synthetic preparation of fractions with maintained or increased anti-inflammatory activity but devoid of those effects which we may consider undesirable for our purposes.

Our experience with the various glucogenic steroids which we have thus far employed in the treatment of this disease would indicate that, with the exception of their various effects on electrolyte and fluid metabolism, the other effects occur with approximately equal frequency. Prolonged administration of corticotropin or the adrenal fractions will result in the development of many of the manifestations of Cushing's syndrome. The severity of these manifestations will, of course, depend upon the amounts of hormone used and the duration of treatment. Edema is less likely to occur with prednisone, prednisolone or Medrol® than with other agents. These last three agents are generally not salt-retaining. However, this complication can be almost entirely eliminated when corticotropin, cortisol, or cortisone is used, provided the daily sodium intake is restricted. With control of this complication, congestive heart failure, previously so prone to occur in the hormonally treated patient with systemic lupus erythematosus, rarely develops. The incidence of hypertension as a complication of hormone treatment in patients with this illness is similarly lowered with reduction in the daily salt intake.

Hyperglycemia and glycosuria are occasionally encountered. This complication, however, has greater clinical significance in the diabetic than in the normal individual. This is a reversible complication in the non-diabetic when the dosage of hormone is reduced or eliminated, and the insulin requirement in the diabetic patient becomes lowered under the same circumstances. Osteoporosis can be a more distressing hazard, but is of greater moment in the older age group. In the patient with post-menopausal or senile osteoporosis, prolonged administration of the hormonal agents may result in collapse of the vertebrae and readily induced rib fractures. The severity of this complication may to some extent be reduced by the concomitant administration of androgen to the male patient, and combined androgen and estrogen to the female.

Psychotic manifestations, the development of peptic ulcer, perforation of a duodenal or gastric ulcer already present, and the activation and dissemination of a semi-quiescent tuberculosis are not uncommon complications. Dissemination of a fungus infection is, fortunately, less common. It is interesting to observe, however, that when the patient with systemic lupus erythematosus develops a peptic ulcer while receiving steroid therapy, the continued administration of the hormone may not interfere with the normal healing process of the ulcer when he is placed upon a proper ulcer regimen. I am not sure, however, that the development of a peptic ulcer can be prevented by the prophylactic institution of an ulcer regimen. The problem as to whether a patient with an ulcer history should be treated with steroids depends essentially upon the nature and severity of the underlying disease for which the use of the steroid is planned. In the instance of active systemic lupus erythematosus, the hazard of this illness is so considerable and its response to hormone therapy so gratifying, that even in the face of an existing peptic ulcer we have no choice but to submit the patient to whatever dangers are involved in the use of the steroids as being the lesser of the two evils. I would assume that the same philosophy must apply in the presence of tuberculosis. Here the problem is perhaps less acute in that the

available treatment for tuberculosis is effective and can prophylactically prevent either the activation or dissemination of a latent or quiescent form of the disease.

A most important complication following prolonged use of corticotropin and the adrenal steroids is the development of a hypochloremic, hypokalemic alkalosis with its attendant cardiac arrhythmias and sudden cardiac accidents. This development is often a subtle one and not necessarily heralded by the prior advent of electrocardiographic changes or overt but innocent cardiac arrhythmias. Hypotassemia occurs as a result of the potassium diuresis which follows administration of corticotropin, cortisol, and cortisone. Prednisone, prednisolone, and medrol® induce very little urinary potassium loss, and therefore this complication is much less likely to occur with these latter agents. To avoid this serious complication, it is desirable that all patients receiving corticotropin or the usual currently available adrenal glucogenic steroids for periods longer than ten days should routinely be given two to three grams of potassium chloride daily by mouth.

There are two additional complications following the use of steroids to be considered particularly in the management of this disease: (a) convulsive episodes; and (b) development of muscular dystrophy involving the thigh and girdle muscles. Convulsions may occur either as a result of inadequate therapy or due to excessive therapy with unrestricted salt intake. Where such episodes occur early in the course of treatment and are not associated with other evidence of fluid retention, the probabilities are that they are due to the cerebral involvement of the disease process and call for more vigorous steroid therapy. It is interesting to note, however, that when we learned of the importance of restriction of salt intake when corticotropin, cortisol, or cortisone is used (9), or when we substituted the newer adrenal steroid analogues, the incidence of this complication fell appreciably.

Three of our fifty-five patients developed marked weakness of the thigh and hip muscles. In each of the three instances this complication occurred after more than one year of continuous treatment with cortisol or cortisone. The first evidence of this disability was the difficulty that the patient had in rising from a sitting position without help, and was associated with the appearance of ribose in the urine in one instance. This affliction was slow in development, but progressive and unresponsive to administration of androgens. Where treatment with steroids could be discontinued for adequate periods of time, some improvement followed. But when therapy was once more instituted, the disability almost always promptly reappeared.

In attempting to evaluate the overall results of therapy, it becomes evident that systemic lupus erythematosus is not cured with corticotropin or the currently available steroids. There are several manifestations of the illness which are not at all, or only minimally, affected by these measures. Most prominent of these, of course, is the lack of any appreciable influence on the development and progression of renal disease once it has occurred. This is unfortunate, since most of the deaths in this disease today occur as a result of progressive renal failure. On the other hand, many of the acute and chronic manifestations of

the illness are promptly brought under control and a significant percentage of the patients are satisfactorily rehabilitated, and with continuous or intermittent therapy are maintained in a reasonably good state of health. The complications directly related to treatment are indeed disconcerting. Their incidence, however, can be appreciably reduced by careful use of the hormonal agents and a constant awareness of the possibility of their occurrence. These agents, nevertheless, constitute a very significant advance and represent the most effective measures currently available for the management of this illness.

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Radiological Notes

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FABELLA ARTHRITIC CHANGES

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The fabella is a sesamoid bone, 0.5 to 2 cm. in diameter, found posteriorly to the knee on the anterior gliding surface of the lateral head of the gastrocnemius. It occurs in 16 per cent of adults, bilaterally in 85 per cent of these. It usually ossifies at about age 17. It is located 0.5 to 1.5 inches above the proximal tip of the fibula when the knee is flexed at an angle of 150 to 160 degrees. It is composed of cancellous bone with its free surface covered by cartilage and articulates with the lateral condyle of the femur. The remaining portion possesses no periosteum and is invested by the fibrous tissue of the gastrocnemius (1).

Changes in the fabella associated with osteoarthritis of the knee are frequent. Sutro, Pomeranz and Simon (2) studied 193 patients with osteoarthritis of the knee. Thirty eight of these patients had fabellae. In seven of these, irregularities of the fabella suggesting arthritis were noted.

Kohler (3) states that in degenerative arthritis of the knee, the fabella increases in size and becomes deformed. He does not, however, illustrate this sequence of events. The following case had films before and after the development of osteoarthritis. It thus illustrates the development of arthritic changes in the fabella. Comparison is afforded, at the same time, with the other knee which developed only minimal arthritic changes.



Fig. 1A. Left knee in 1949. The fabella on this side is smaller than on the right.



Fig. 1B. Right knee in 1949. Small fabella is evident



Fig. 2A. Left knee in 1958. Fabella is markedly increased in size with spurs at the articular margins. The enlargement of the bone is due to the increase in its trabeculated substance. The cortex is thin except superficially where the surface of the bone is slightly knobby. The width of the joint space between the patella and the lateral condyle is diminished.



Fig. 2B. Right knee in 1958. Fabella may be slightly larger but arthritic changes are minimal.

The patient was first seen in The Mount Sinai Hospital Out-Patient Department in 1949 at the age of 55. She stated that four years previously she had had a mild left-sided hemiplegia with slight residual weakness. A few months prior to observation, she developed pain in the left buttock radiating down the left leg and pain in the left knee. Roentgen examination of the lumbosacral spine and the lower extremities showed no abnormalities. It was noted that both knee joints showed fabellae which were normal in appearance (Fig. 1A, 1B). The patient was treated with a corset and physiotherapy.

In 1953, she fractured the medial malleolus of the left ankle. Healing was uneventful. In 1957, she fell down a flight of stairs, injuring her left knee. No films were taken at that time. Since then, she complained of a left-sided limp associated with pain and intermittent swelling of the left knee. She was seen again in the Out-Patient Department in 1958 with the above complaints. Examination showed $\frac{3}{4}$ of an inch quadriceps atrophy on the left. There was minimal swelling of the left knee with crepitation on motion.

Roentgen examination of the left knee at this time (Fig. 2A) showed slight narrowing of the joint space and spur formation at the margins of the articular surface consistent with degenerative or hypertrophic osteoarthritis. It was also noted that, in comparison with the examination of 1949, the fabella had more than doubled in size. The increase in size was not the result of spur formation but rather an overall increase with an enlargement of the trabeculated substance of the bone. The cortical covering was not thickened except on its superficial

surface. The fabella was also deformed and showed spur formation at its articular margins. The space between it and the lateral femoral condyle was diminished. Films of the asymptomatic right knee showed only minimal spur formation. There was no significant change in the size or appearance of the fabella on this side in comparison with the examination of 1949.

SUMMARY

A case is presented illustrating the development of enlargement and deformity of the fabella associated with osteoarthritis of the knee.

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CASE NO. 75

This was the first admission of a 38 year old male who entered with the chief complaint of abdominal pain. Six months prior to admission, gastrointestinal x-ray studies were done because of epigastric distress. This examination was negative. Symptoms responded well to an ulcer regimen. Six days before admission, the patient complained of dull epigastric pain which, though intermittent at the onset, became almost continuous and radiated to both lower quadrants. There was moderate anorexia but no nausea or vomiting, diarrhea or constipation. On admission, the positive physical findings were confined to the abdomen. There was guarding in the right upper quadrant and deep and rebound tenderness in the right lower quadrant. Temperature, blood pressure, pulse and respiratory rates were normal. White blood count was 7,000 with a normal differential count. Roentgen examination of the abdomen, oral cholecystography, and barium enema examination were done. These were reported as negative although, as noted below, in retrospect, significant findings were present on the barium enema. After observation for ten days during which time symptoms persisted and tenderness became localized to the right lower quadrant, laparotomy was done with the probable diagnosis of appendicitis. The cecum, ascending

Case 75, Fig. 1. Barium enema examination shows the cecum and ascending colon incompletely distended with barium. In the wall of the colon, there is a continuous column of gas (arrow). The gas pattern parallels the barium. The interhaustral septa are indicated by soft tissue strands extending toward the lumen between the barium in the haustra. The outer aspect of the bowel wall is evident by contrast with the peritoneal fat.

Case 75, Fig. 2A. Examination of the abdomen the day after the barium enema shows a small amount of residual barium in the cecum and ascending colon. The intertwining scroll pattern of barium, gas and soft tissue is exquisitely demonstrated.

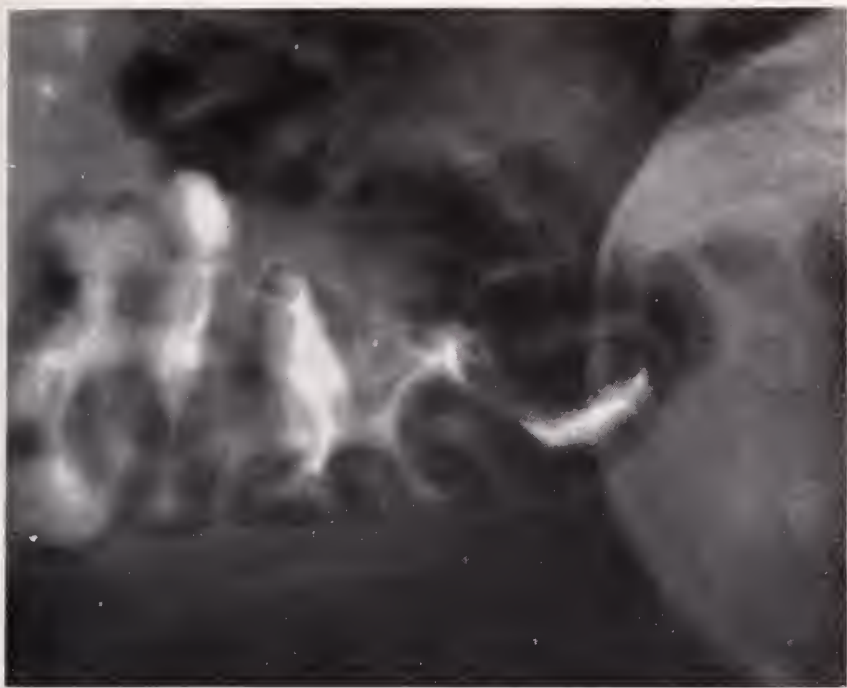
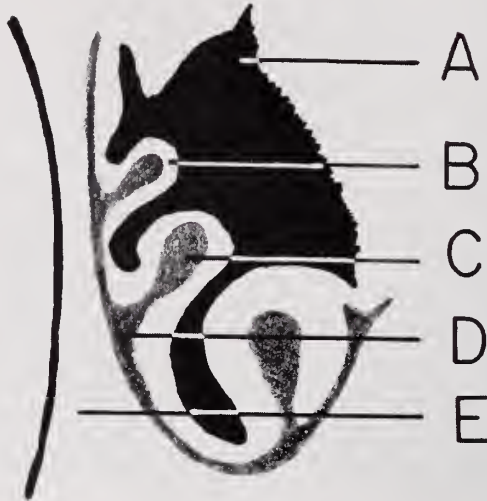


Fig. 2A



Fig. 1



Case 75, Fig. 2B. Diagram of the lateral portion of the cecum in figure 2A; A, represents residual barium in the lumen, B, gas in the wall, C and D, the soft tissue of the wall of the colon, and the interhaustral septa and E, properitoneal fat. A similar pattern may be seen on a simple film of the abdomen with or without fecal material in the lumen.

colon and proximal transverse colon showed innumerable, small gas-containing cysts beneath the serosa, with thickening of the bowel wall particularly in the ascending colon. The largest of the serosal cysts measured about a centimeter in diameter. An ileocolic resection was performed. On opening the specimen, the mucosa of the cecum was markedly edematous and the mucosal folds for about six inches distal to the cecum were markedly thickened. On palpation the mucosa was crepitant. There were numerous areas of shallow ulceration, the largest of which measured about 7 mm. in diameter. On microscopic examination, the findings were typical of pneumatosis cystoides intestinalis. The ileum was free of disease. The appendix showed focal fibrous obliteration and chronic non-specific inflammation. The significant findings evident on roentgen examination are illustrated in figures 1 and 2.

Final Diagnosis: PNEUMATOSIS CYSTOIDES OF THE RIGHT SIDE OF THE COLON.

CASE NO. 76

This was the first admission of a 56 year old white female with the chief complaint of tarry stools of five days duration and right lower quadrant pain of two to three days duration. A barium meal examination had been done five weeks prior to admission because of the complaints of nausea, heartburn and black stools. A barium meal examination done at this time was said to have shown no ulcer. On an ulcer regime, the patient improved. Two to three days prior to admission, the patient again noted black stools associated with marked weakness, dizziness and severe nausea. On this occasion, however, the pain was located in the right lower quadrant. Examination on admission showed an obese, pale female, perspiring profusely. The abdomen was somewhat distended and there was tenderness in both the right upper and right lower quadrants. Rebound tenderness was present in the right upper quadrant. The liver edge was palpable 4 fingerbreadths below the costal margin. The temperature was 101°F., pulse 105, white blood count 22,000 with 70 per cent segmented polys and 18 per cent nonsegmented. Hemoglobin was 9 grams. A Rehfuess test meal showed a



Case 76, Fig. 1. Barium enema examination shows markedly irregular and incomplete filling of the caput coli with multiple scalloped contour defects. In addition, in the inferior and medial wall of the caput coli (lower arrow) and extending into the wall of the ileum (upper arrow) there are numerous gas bubbles forming a lucent band which parallels the course of the intraluminal barium. The appendix is filled, extends medially and does not appear to be involved.

free acid of 35 units and a total of 55 units. Electrocardiogram showed changes compatible with myocardial insufficiency.

Barium enema examination showed markedly irregular, bizarre filling of the caput coli with evidence of interstitial emphysema (Fig. 1). The impression was that of a carcinoma of the caput coli. It was thought that the gas in the bowel wall could be explained on the basis of perforation although a fistula could not be demonstrated. Since carcinoma of the cecum was also the clinical diagnosis, exploratory laparotomy was performed five days after admission. On the anterior and lateral wall of the cecum just opposite the ileocecal valve, a sharply circumscribed area covered by fibrinous exudate about 1 inch in diameter was found. When an attempt was made to pull off the fibrinous material, however, it was evident that the entire thickness of the bowel wall was involved in a necrotizing or gangrenous process. This necrotic portion of the wall of the cecum was excised along with the appendix and the cecum was closed without compromising the ileocecal valve. Bubbles of gas were noted in the serosa and the mucosa. Cholecystectomy was simultaneously done because of the presence of multiple biliary calculi and thickening of the gall bladder wall. On microscopic examination, there was evidence of gangrene and subacute inflammation of the excised portion of the cecum. The gangrenous areas showed vascular occlusions, arteriolarsclerosis and areas of necrosis. The appendix was not remarkable. The pathologist suggested that the necrosis was probably on a vascular basis. In the absence of evidence of gas infection, it was assumed that the gas entered the bowel wall through the gangrenous area. As is usual in cases of pneumatosis, the exact site of entrance could not be determined.

Final Diagnosis: ISOLATED GANGRENE OF THE WALL OF THE CECUM WITH PNEUMATOSIS INTESTINALIS.

CASE NO. 77

This was the first admission of a 68 year old male whose past history was non-contributory. For the past four or five weeks, he complained of dysphagia, regurgitation and weight loss of 14 pounds. A barium swallow (Fig. 1A, 1B) demonstrated a bilobulated filling defect at the junction of the middle and distal thirds of the esophagus which was sharply demarcated and filled the lumen almost completely. It appeared to be attached to the posterior and right wall. Despite the obturation of the lumen, there was no obstruction to the flow of fluid barium through the esophagus and no evidence of unusual distensibility of the esophagus proximal to the site of the lesion. Extensive calcification of the mediastinal pleura was also noted.

Through a left thoracotomy incision, the esophagus was mobilized from the diaphragm to the aortic arch. There was considerable difficulty in doing this because of marked pleural thickening. The external aspect of the esophagus did not appear to be remarkable but on palpation a lobulated mass could be felt within the lumen of the esophagus at the junction of the middle and lower thirds. During this maneuver, the tumor mass suddenly became loose and mobile within the lumen of the esophagus. Esophagoscopy was then done and with the assist-



Fig. 1A



Fig. 1B

Case 77, Fig. 1A. Barium swallow shows a sharply demarcated, lobulated filling defect which fills the lumen of the esophagus almost completely at the junction of its middle and distal thirds. Posteriorly (arrow) a short profile defect is present and, in retrospect, an angulated lucent band which may represent a pedicle. There was no obstruction to the flow of fluid barium through the esophagus and no unusual distensibility of the esophagus proximal to the site of the lesion.

Case 77, Fig. 1B. In the PA projection, the right wall of the esophagus is bulged laterally by the intraluminal mass (upper arrow). The external contour of the esophagus at this site as outlined against the adjacent lung is sharply demarcated and smooth. There is extensive calcification of the mediastinal pleura extending to the base of the right lung (lower arrow).

ance of the surgeon, the tumor mass removed by the esophagoscopist. The esophagus was not opened and the thoractomy wound was closed. The tumor was about 4 cm. in diameter, lobulated and showed a short pedicle about $\frac{3}{8}$ inch in length which was hemorrhagic and which apparently had become twisted and torn off from its point of attachment to the esophagus. Microscopic examination showed a squamous cell with nests of cells resembling an adamantinoma.

The patient was lost to follow-up for about six months after which time he returned complaining of dysphagia. Barium swallow showed an obvious recurrence in the esophagus. With radiotherapy, he obtained some relief within about six months but went on to develop complete obstruction of the esophagus as well as metastatic nodules in the skin of the back of the neck. One of these nodules

was excised and reported as squamous cell carcinoma with histology identical to that of the original lesion. An attempt to insert a Mackler tube through the neoplasm was unsuccessful and the patient died soon after this.

Final Diagnosis: PEDUNCULATED SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS.

This case is presented through the courtesy of Dr. Leon Ginzburg and Dr. Seelig Freund.

CASE NO. 78

This was the first admission of a 67 year old white male with the chief complaint of hematemesis. For several months prior to admission, he complained of fatigue. During this interval, he gained about 20 pounds. Six days prior to admission, he experienced a massive hematemesis and was admitted to another hospital. Hemoglobin was 8 grams with a red blood count of about 3 million. After several transfusions he was referred to this hospital. Physical examination on admission was noncontributory.

Barium meal examination (Fig. 1A, 1B) showed a multilobulated, discrete filling defect in the body of the stomach attached to the anterior wall. The individual lobules in the periphery appeared to be quite large and sharply demarcated but there were also scattered small lobulations which were irregular.



Case 78, Fig. 1A. Barium meal examination shows a sharply demarcated, multilobulated filling defect in the body of the stomach. Many of the lobules appear to be quite large but there are also several smaller irregular ones particularly towards the center. The barium filling the channels between the lobules creates a radiating pattern, in the center of which there is a somewhat triangular collection of barium indicative of ulceration. There was no remarkable limitation of distensibility of the stomach at the site of the lesion.



Case 78, Fig. 1B. A lateral projection of the filled stomach demonstrates the flat contour defect on the anterior wall (arrow) with multiple nodular projections protruding into the lumen.

The barium filling the crevices between the lobules appeared to radiate towards the center where there was a smudge of barium suggesting ulceration. The roentgen diagnosis was that of a polypoid carcinoma but the possibility of a large adenomatous polyp was not entirely excluded. Subtotal gastrectomy was done. Metastases were noted in the omentum and in the mesenteric nodes. On opening the specimen, a cauliflower, polypoid neoplasm about 6 by 4 cm. in diameter was found with an indurated base. Cutting through the center of the tumor demonstrated that its mid-portion was firm, hard and gray while the peripheral part was soft and brownish. On microscopic examination, it was evident that the central portion which comprised the bulk of the neoplasm was adenocarcinoma but that around the center there was still a considerable amount of benign adenomatous tissue. The appearance was highly suggestive of malignant transformation of an originally benign adenoma. No other polyps were found in the removed specimen.

Final Diagnosis: POLYPOID ADENOCARCINOMA OF THE STOMACH ARISING IN A BENIGN ADENOMA.

CASE NO. 79

This was the third admission of a 75 year old white male with the chief complaint of angina. Previous admissions were for prostatic hypertrophy and five years previously for homologous serum hepatitis. During this last admission, the icterus cleared rapidly within a period of two weeks. Hemoglobin at that time was 13 grams. Two years prior to the current admission, the patient was informed of hypertension and heart trouble. For six weeks prior to admission, angina

occurred frequently and on minimum exertion. For about six months, he noted occasional dizziness when arising from bed. The past history indicated that 38 years previously, the patient had undergone a gastroenterostomy for an ulcer. The exact site of this ulcer was not known.

Examination on admission showed a thin elderly male in no acute distress. The chest was emphysematous. The heart appeared to be slightly enlarged. Blood pressure was 145/80. Hemoglobin on admission was 5 grams which increased to 11 grams after two units of packed red blood cells were administered. On admission, the stool was guaiac 4 plus and subsequent stool examinations were reported as guaiac 1 plus and guaiac trace. On sigmoidoscopy, a small adenomatous polyp was seen and removed without incident. A Rehfuess test meal showed absent free hydrochloric acid and a maximum total acidity of 50 units.

Barium meal examination showed no abnormality in the esophagus. The barium left the stomach promptly through a large gastro-enteric stoma rather high on the greater curvature aspect of the stomach. There was no evidence of marginal ulceration. No significant amount of barium left the stomach through



Case 79, Fig. 1. Left oblique view of the stomach during barium meal examination. The portion of the stomach beyond the stoma (arrow) is distinctly narrowed and shows an elongated tubular configuration. The stoma is wide and barium entered the jejunum promptly. The mucosal pattern in the proximal portion of the stomach consists of a few large normally tortuous folds. The fold pattern of the excluded antrum is somewhat thickened. (The white streak above the arrow is an artefact.)



Case 79, Fig. 2. Lateral view of the stomach with patient lying on his left side after insufflation with air through a Levine tube and administration of a small amount of barium confirms the limited distensibility of the distal part of the stomach (arrow).

the pylorus. The mucosal folds in the stomach appeared to be quite large but rather flat and were not rigid. There was no evidence of ulceration or filling defect within the stomach. However, a striking finding was remarkable limitation of distensibility of the distal portion of the stomach beyond the site of the gastro-enteric stoma (Fig. 1). While not appearing completely rigid, this area never distended and showed no peristaltic activity. The lack of distensibility was confirmed (Fig. 2) by blowing up the stomach with air through a Levine tube and positioning the patient so that air filled the distal part of the stomach. Barium enema examination was also done and showed only scattered diverticula in the sigmoid.

The interpretation of the changes in the distal part of the stomach was difficult. The possibility that a scirrhus carcinoma was present in this area could not be completely excluded. However, this appeared unlikely since the narrowed portion was not completely rigid and appeared to be abruptly delimited by the stoma. It was therefore suspected that the narrowed antrum was the result of the fact that a gastro-enterostomy had been present for almost 4 decades and that the distal portion of the stomach had been excluded over this long period of time from the main stream of passage of food and fluid. Findings similar to these have

been seen in previous cases of long-standing gastro-enterostomy with excluded antrum and, in at least one instance, operative intervention had not demonstrated any abnormality. The findings on the roentgen examination were confirmed by gastroscopy. The stoma was easily entered and the jejunum over a distance of 4 cm. revealed normal mucosa. The mucosa of the antrum appeared smooth and normal in color without evidence of ulceration or friability. However, the stomach proximal to the site of the stoma although normally distensible showed a smooth pale mucosa with atrophic areas and friable mucosa as indicated by fresh bleeding during the course of the examination. The impression of the gastroscopist was that an atrophic gastritis was present. Repeat gastric analysis confirmed the lack of free acid after histamine.

This patient has been followed in the Out-Patient Department for about three years. Anemia has persisted but the course of the patient has not indicated any



Case 80, Fig. 1A. Barium enema examination shows limited distensibility involving the entire left side of the colon from the splenic flexure down to the proximal sigmoid. The distal sigmoid and the rectum are normally distensible. The haustra in the descending colon are shallow and blunted with intervening gray areas indicative of thickening of the mucosa. The adjacent loops of small bowel medially are distended with gas. The space between these loops and the barium-filled colon is wider than is ordinarily seen indicative of thickening of the wall of the colon.

rapid deterioration. It is suspected that in addition to the atrophic gastritis, the patient suffers from an iron deficiency anemia because he has avoided the eating of meat for many years. A repeat barium meal examination two years after the original observations showed no change in the appearance of the stomach or the gastroenterostomy.

Final Diagnosis: "SPASM" OF THE EXCLUDED ANTRUM 40 YEARS POST-GASTROENTEROSTOMY SIMULATING SCIRRHOUS CARCINOMA.

CASE NO. 80

This was the second admission of a 58 year old white female. The first admission nine years previously revealed a duodenal ulcer. In the interval, there have been multiple episodes of abdominal pain which responded to an ulcer regime. For many years, she had been markedly constipated. Three days prior to the current admission, while straining at stool for two hours, she suddenly felt faint and broke out into a cold sweat. Finally a normal stool ensued. The next day, however, she experienced a watery, light-red, bloody stool which escaped in two gushes after severe cramping sensations. After a short interval, there was a similar occurrence.



Case 80, Fig. 1B. After evacuation of most of the barium, a markedly coarsened mucosal pattern consisting of elongated islands of thick folds is evident throughout the descending colon and proximal sigmoid.



Case 80, Fig. 1C. With injection of air, the irregular peculiar distensibility particularly of the proximal portion of the descending colon is again evident. Lack of involvement of the distal sigmoid and rectum is clearly demonstrated.

Physical examination on admission was not contributory. The abdominal findings were difficult to elicit because of extreme obesity. Temperature was between 100° and 101° F.; white blood count was 22,000. Sigmoidoscopy on admission showed frank red blood coming from above the end of the sigmoidoscope. During the next two days, the temperature remained slightly elevated and the patient passed small amounts of pinkish fluid material. Three days after admission, a barium enema examination was done (Fig. 1A, 1B, 1C) and showed peculiar, irregular, limited distensibility of the descending colon with thickening of the mucosal pattern. The changes appeared to begin in the distal limb of the splenic flexure and to extend into the proximal sigmoid but the distal sigmoid and rectum were completely normal. Barium meal examination showed a deformed bulb but no evidence of active ulceration. Repeat sigmoidoscopy showed the mucosa of the sigmoid to be deeply hemorrhagic and congested.

With conservative therapy, the patient improved and twelve days after admission the stool was of normal color. The patient was discharged five days later without complaints.

The roentgen findings in this patient at first sight may not appear striking. Close observation, however, indicates that the changes are quite remarkable. The first impression was that of an ulcerative colitis of the left side of the colon sparing the distal sigmoid and rectum. This did not seem to be an entirely satisfactory explanation since, while irregular distensibility and thickened mucosal folds were evident, the contours of the filled colon did not show any spiculation suggestive of ulceration. When the clinical story was obtained, it was clear that the changes in the colon were consistent with vascular compromise as a result of occlusion or interference with the blood supply through the inferior mesenteric vessels. Findings such as those seen in this case have been previously reported in occlusion of the inferior mesenteric artery and/or vein and this alternative diagnosis was suspected prior to obtaining the clinical story. In the large majority of such instances, because of the liberal collateral circulation, infarction does not occur but there is sufficient stasis to lead to marked mucosal congestion and bleeding. The involvement of the left side of the colon with sparing of the recto-sigmoid and the rectum is typical. The prognosis is good.

Final Diagnosis: INFERIOR MESENTERIC OCCLUSION.

Clinico-Pathological Conference

SEVERE DYSPNEA FOR 15 YEARS

Edited by

FENTON SCHAFFNER, M.D.

A 64 year old white married male banker was admitted to The Mount Sinai Hospital complaining of shortness of breath for 15 years.

He had frequent colds usually associated with cough in early childhood and adult life. He had hemoptysis 28 years prior to admission and was told that he had pulmonary tuberculosis. He was put to bed for three months and, as far as he knew, had no further treatment or difficulty from pulmonary tuberculosis. No studies of his sputum were performed.

In 1942 the patient began to develop dyspnea on exertion which gradually became worse. In 1953 he became ill with dyspnea, fever and cough which responded to antibiotics. In 1954 he developed a similar episode which required three months of therapy with antibiotics. In 1956 he developed a third episode of what was called pneumonitis associated with night sweats, fever, cough productive of three to four ounces of white sputum daily. At this time he retired from business and spent most of his time at home. Shortly thereafter he developed edema of his ankles which responded to Diamox® and Mereuhydrin®. He smoked six to seven cigars daily throughout his adult life. No exposure to toxic dusts was recorded.

Because of increasing dyspnea, he was admitted to another hospital two months before the present admission. At that time his respiratory rate was 40/min., pulse 108/min., blood pressure 96/80. His temperature fluctuated between 99 and 100.8° F. The head, eyes, ears, nose, throat, heart and abdomen were normal. In the lungs diffuse inspiratory and expiratory rhonchi were heard. Edema of both ankles was present. The skin color was good.

The urine was acid with a specific gravity of 1.010 and contained no albumin, a trace of glucose, and an occasional WBC and RBC per high power field. Hemoglobin was 15.5 Gm. % with 5,120,000 RBC per cu. mm., 10,050 WBC per cu. mm. with 90 % segmented neutrophils, 9 % lymphocytes and 1 % eosinophiles. Serum CO₂ was 50 vol. % and chlorides 105 mEq./l. An electrocardiogram revealed a PR interval of 0.24 sec., QRS interval of 0.10 sec., a sinus tachycardia with atrial and ventricular rates of 102 per min. (Fig. 1). A large P wave was present in leads 1 and 2, while aVR showed a large R wave. A tall R wave was present in leads 3 and V1 and V2. A deep S was present in leads 1 and V4, V5 and V6. A chest x-ray showed the trachea deviated to the right, and cardiomegaly. The lung fields contained a diffused interstitial infiltration which was particularly marked in the inner half (Fig. 2). There was a fibrocalcific lesion in the right upper lobe.

The patient was treated with oxygen, digitalis, Diamox®, a salt-free diet and

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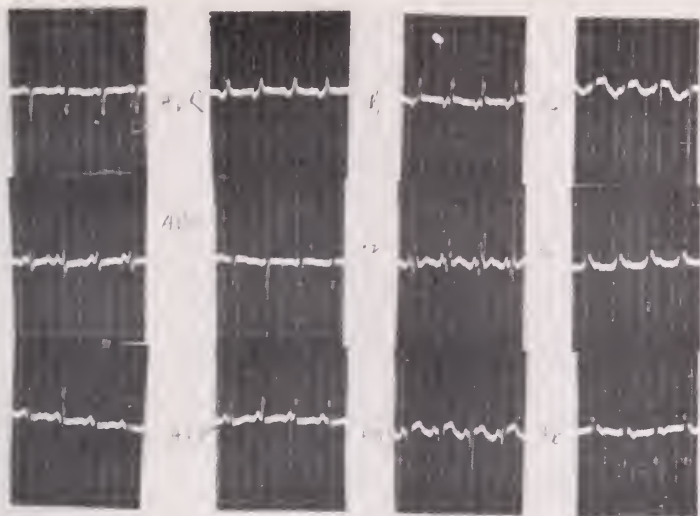


FIG. 1. Electrocardiogram showing right heart strain



FIG. 2. Chest x-ray taken two months before death showing diffuse infiltration of the lungs and cardiomegaly.

tetracycline. He showed some improvement and was discharged after three weeks. His condition at home gradually worsened despite therapy with steroids and broad spectrum antibiotics. A sputum culture grew out 600,000 colonies of *C. albicans* per cubic centimeter.

Six weeks later he was admitted to The Mount Sinai Hospital. He was a thin white male who appeared acutely ill and in respiratory distress. His pulse was 120/min., respirations 40/min., blood pressure 105/70 and temperature 100.4° F. Three irregular white lesions were seen on the pharynx. There was no lymphadenopathy. The chest showed marked retractions of the supraclavicular area. Coarse inspiratory and expiratory rales were heard over both lung fields. A soft apical grade II murmur was heard with a gallop rhythm. The PMI was felt outside the midclavicular line. The liver was felt one fingerbreadth below the costal margin but the spleen was not felt.

The urine was acid with a specific gravity of 1.010, a faint trace of albumin, 8 to 10 WBC per high power field (occasionally clumped), and an occasional hyaline cast. Hematocrit was 53%. Blood urea nitrogen was 22 mg.%, fasting blood sugar 90 mg.%, serum sodium 135 mEq./l., potassium 3.8 mEq./l., carbon dioxide 35 mEq./l., chlorides 92 mEq./l. Total serum protein was 7.2 Gm.% with a serum albumin of 3.5 Gm.% and a serum globulin of 3.7 Gm.%. The electrocardiogram and chest x-ray were unchanged from the findings at the previous hospital. PPD #1, coccidioidin, blastomycin, histoplasmin and torulin skin tests were all negative.

The patient was treated with bed rest, a low salt diet, digitalis, Mercurhydrin®, aminophylline, penicillin, tetracycline and Prednisone®. Amphotericin B was administered as an aerosol, 5 mg. four times daily, and intravenously, 50 mg. daily for three days.

Despite the above measures the patient's condition steadily grew worse. His temperature varied between 98.6 and 101.4° F. On the fourth hospital day his respiratory difficulty increased and his blood pressure fell to shock levels. Despite Levophed® the blood pressure continued to fall and he quietly expired.

*Dr. Coleman B. Rabin**. The case this afternoon concerns itself with a 64 year old man who had increasing dyspnea and cough for 15 years, diffuse infiltrations in the lungs, and a peculiarly enlarged heart with evidence of right heart strain. He had tuberculosis many years ago but had recovered, and he got along fairly well until about 1953 when he had a few bouts of fever with acute bronchial infections responding partially to antibiotics and treatment of his heart disease. He finally became disabled about a year before he died. Before he died, additional findings developed. He had a mild systolic murmur at the apex. The heart seemed to be displaced further to the left than previously. He had a gallop rhythm, and the liver, which had not been palpable before, was one fingerbreadth below the costal margin.

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Dr. Daek, how would you interpret the change in the findings in the electrocardiograms and on the physical examination?

*Dr. Simon Daek**: The first electrocardiogram showed a tachycardia of about 130 per min. It was not an ordinary tachycardia because the P-R interval was somewhat on the short side. This may occur in pulmonary disease but it also suggests an ectopic atrial or nodal focus. The most striking thing was the very marked right axis deviation and, in aVR and V1 and V2, a tall R pattern that was very characteristic of right ventricular hypertrophy as seen in chronic lung disease.

Dr. Rabin: Dr. Daek, could you tell us whether there were any electrocardiographic changes that could be ascribed to acute cor pulmonale, in contradistinction to chronic cor pulmonale?

Dr. Daek: This was not what we would ordinarily see in acute cor pulmonale due to pulmonary embolism or acute asthmatic attacks or acute pulmonary insufficiency of any kind. There you would see a characteristic picture of a deep S1 and Q3, and the T wave would be inverted in V1 and V2.

Dr. Rabin: If this patient who had chronic cor pulmonale were to have developed acute cor pulmonale in addition—in other words, if this patient who had a strained right heart were to have developed failure of the right heart—would you expect any changes?

Dr. Daek: T waves would have been more deeply inverted, especially on the right side of the precordium.

Dr. Rabin: I asked this because the electrocardiographic findings before he died were unchanged in comparison to the original electrocardiogram which was made a few months before that.

Dr. Daek: I would suspect that the changes had been present over a long period of time.

Dr. Rabin: And so Dr. Daek feels that the electrocardiographic changes can be explained entirely on the basis of the resistance to the lesser circulation through the lungs. There was no evidence that the right heart had failed. We had these changes even though the right heart was able to push the blood through the lung satisfactorily.

Dr. Daek: However, clinically, there was no doubt that he developed acute right heart failure secondary to the pulmonary hypertension.

Dr. Rabin: So you would say that, despite the absence of any indication in the electrocardiogram, the clinical evidence pointed to acute right heart failure and this, in part at least, was the cause of the death?

Dr. Daek: Yes, I would.

Dr. Rabin: And that the main disease was not heart disease originally, but disease in the lungs?

Dr. Daek: This is the picture of chronic pulmonary hypertension secondary to restrictive disease of the circulation of the lung.

Dr. Rabin: Secondary to restrictive disease of the lung primarily, or of the pulmonary blood vessels primarily, the picture developed itself as a disease in

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which the circulation was obstructed in the lungs with the eventual development of right heart failure. I am told that the heart was too large. We shall look at the x-ray picture of the heart and lungs and see if we can shed any light on this objection, that the heart was too big for a patient whose heart disease was secondary to disease of the lungs. Dr. Brahms will discuss the films.

*Dr. Sigmund Brahms**: The first film was made in 1954. Some calcification and some linear infiltrations were found in the infraclavicular region on the right side and this was consistent with a history of tuberculosis twenty-eight years ago. In addition, fine interstitial infiltrations were seen diffusely throughout both lungs with no localized agglutinations. Even then it was very difficult to identify blood vessels in these lungs; the vessels were evidently quite small and obscured by the diffuse infiltrations.

The heart had a peculiar configuration for this pulmonary appearance: it appeared somewhat wide towards the left but in the region of the waist it was narrow. This is the so-called boot-shaped heart. However, the displacement of the region of the apex, apparently laterally and somewhat downward, suggested left ventricular enlargement rather than right ventricular enlargement.

Dr. Rabin: Before you go any further, Dr. Brahms, you would say, then, that the left ventricle seemed to be enlarged rather than the right, and you are surprised at the fact that the pulmonary arteries themselves were not wider? Could the smallness of the pulmonary arteries in this case, in a patient who did show evidence of right ventricular hypertrophy, conceivably have been due to pulmonary stenosis?

Dr. Bhrams: If the assumption is correct that this appearance favored left ventricular enlargement, this is against the diagnosis of pulmonic stenosis which is associated with significant enlargement of the right ventricle. We would expect to see some prominence attributable to post-stenotic dilatation although the absence of such is not a valid argument against the presence of pulmonary valve or infundibular stenosis.

Two months before death, the films showed the same appearance seen three years earlier, except that the interstitial infiltrations were more prominent. No other changes in the appearance of the lungs were demonstrated. The heart, however, looked quite different. The enlargement toward the left was again seen but, whereas in the first film the region of the waist was narrowed, here there seemed to have been some filling out. This was not confined to the segment immediately below the aortic knob, where we expected to see the prominence of the pulmonary artery, but it involved the entire supraventricular segment. I do not know what this means but it is very disturbing to see such a heart in a patient who had such a picture in his lungs. The appearance of the lungs was nonspecific. Many things could be listed which might be associated with such an appearance.

Dr. Rabin: And so you found the appearance of the shape and size of the heart, particularly the shape, a little disturbing? In the original film, did you not say that it looked as if the patient had hypertrophy of the left ventricle?

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Dr. Brahms: This would have been typical for a hypertensive heart.

Dr. Rabin: And then the picture changed entirely. You noted widening of the waist rather than narrowing, and a change of the contour of the heart which might now represent *right* ventricular hypertrophy in this patient who previously had left ventricular hypertrophy. Could this be the explanation?

Dr. Brahms: It is possible.

Dr. Rabin: I will read off a list of conditions that were suggested by the x-ray picture of the lungs: lymphangitic carcinoma, miliary tuberculosis, fungus disease, periarteritis nodosa, eosinophilic granuloma of the lungs, silicosis, histoplasmosis, tuberosclerosis, mucoviscidosis, sarcoidosis, scleroderma, Rich-Hamman syndrome, reticuloendotheliosis, and von Wegener's syndrome.

When we look at the x-ray films of the chest, we are impressed by the fact that the diaphragms are neither depressed nor deformed. Furthermore, the patient had inspiratory retraction of the chest, which indicates that the lungs were reduced in volume rather than increased and that part of his difficulty was due to the fact that he could not stretch his lungs well.

Interstitial infiltration was present, indicating some difficulty in gaseous diffusion in his lungs. The electrocardiographic changes indicate obstruction of the pulmonary circulation. There is no evidence of disease of the heart that can be responsible for this. Therefore, the basis of his disease must have been in the lungs. Whether it was in the blood vessels primarily or whether the blood vessel narrowing was secondary to the condition of the pulmonary parenchyma is the next question.

As we analyze the case, we can eliminate many diseases from consideration. There was no history of exposure to silica but we know little about this man's youth. However, the patient with silicosis who gets into respiratory difficulties always has emphysema, but no extensive emphysema was found. The same is true in sarcoidosis and mucoviscidosis and many of the other conditions listed. Certainly, conditions like scleroderma can be excluded. As far as fungus infections are concerned, we shall turn to Dr. Littman.

Dr. Maxwell L. Littman:* The diagnosis of pulmonary moniliasis is rather difficult at the present time because of inadequacies in the laboratory diagnosis. We do not have a simple complement fixation test nor do we have an adequate skin test. The only thing we base our diagnosis on, at present, is the finding of large numbers of *C. albicans* in the sputum, plus a suggestive chest x-ray, plus the exclusion of other diseases which may be responsible for the particular pulmonary infiltration.

The average normal individual has between 5,000 to 10,000 *C. albicans* per cubic centimeter of sputum. This is determined by shaking the sputum with glass beads on a shaker for a half-hour, and then performing a plate count. A pathological count usually runs in the millions and patients with pulmonary moniliasis usually have from 500,000 to several million *C. albicans* per cubic centimeter of sputum. This patient had 600,000 organisms per cubic centi-

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meter and had been treated with broad spectrum antibiotics and corticosteroids, which in themselves could have caused this increase in the fungus count.

The first impression was that this was not a case of moniliasis. However, in an elderly individual with pulmonary distress, a high *C. albicans* count and a suggestive chest x-ray, we were obliged to consider his case one of pulmonary moniliasis, and in the absence of another diagnosis, to treat him with a new antifungal antibiotic, amphotericin B, both by aerosol and intravenously. Amphotericin B can promptly clear the bloodstream and pulmonary tissue of *C. albicans* since it is extremely active on this organism. The minimal inhibitory concentration of *C. albicans* is about 0.09 $\mu\text{g/ml}$. We are able to achieve a blood level of approximately 2 $\mu\text{g/ml}$. by intravenous administration.

Dr. Rabin: Dr. Littman, therefore, is of the opinion that simply the presence of large numbers of *C. albicans* does not mean that the pulmonary process is necessarily due to a fungus infection. I feel inclined to rule out fungus infection in a case of this sort because the infiltrations are streaklike and very fine. When a patient dies of fungus infection, resistance is gone. Whereas originally there may have been a miliary or a fibrotic form of the disease which involves the lungs in the form of fine infiltrations, terminally there is more exudation and more fluffy shadows are seen in the chest.

Reticuloendotheliosis is a disease that involves the lung diffusely. On this x-ray film the upper part of the right lung is not much involved. Similarly many of the other diseases in which the lungs are involved diffusely and more or less homogeneously can be eliminated. Dr. Brahms has said he did not see the vessels so well on the right side of the chest but on the left side he saw the vessels better. This means that there was more emphysema on the right side, and on the left side there was more contraction. This may explain why the heart was situated so far to the left.

One must think, in a case like this, of a form of bronchial disease of spotty distribution and probably associated with some form of bronchial infection and little emphysema. I would pick at this point a condition which was not on the list, namely, bronchiolectasis.

Viewing the films at much closer range, one sees between the infiltrations small areas of honeycombing throughout the diseased areas. In any patient with fine infiltration of the lung, some emphysema is present between the infiltrations, suggesting little cystic cavities. But I think this is more marked in this case, and I think these films show small cyst-like cavities throughout the lungs. Small cystic areas can be seen in sarcoidosis, in reticuloendotheliosis and in other forms of fine fibrosis, but here I think we had a condition that was purely of bronchial origin and involved particularly the tiniest bronchi. These had been distended and there was an associated diffuse fibrosis of the lungs. Emphysema was not outspoken but was a minor, secondary phenomenon, not sufficient to distend the lungs even to their normal volume. In general, the lungs were shrunken and there was interstitial fibrosis and infiltration with enlargement of the bronchioles.

What the cause is, I do not know, but I think it was related to infection. The primary condition was bronchiolectasis with obstruction of pulmonary circula-

tion in the small vessels of the lungs. There was secondary marked right ventricular hypertrophy. The clinical picture was due not only to right heart failure with dilatation of the right ventricle, but to pulmonary insufficiency as well.

*Dr. Hans Popper**: To give you the background of the pathologic findings, I will first describe the organs other than the lungs. In the thyroid, two small nodules were found which were seen on microscopic examination to be single follicular adenomas associated with the diffuse nodularity, probably a long-term stress phenomenon in this patient who has been suffering for fifteen years. In addition to this response, nodular hypoplasia was present in both adrenals.

The kidneys were of enormous size, each weighing 230 grams. A few small cysts were seen in them as well as borderline granularity of the surface, but no more than we would have expected in a patient of this age. There was only a little nephrosclerosis but perhaps enough to explain the hypertension. Benign nodular hyperplasia of the prostate was found with a markedly distended bladder.

The spleen weighed 120 grams and was not significantly enlarged but on microscopic examination there was great cellularity with many basophilic cells, probably plasma cells. A splenic tumor was not present but we had evidence of a splenic reaction or splenitis. We looked at the bones to exclude the possibility of granulomatosis which we had not seen in the spleen. No evidence of any bony trabecular changes was encountered.

In the colon small colonic ulcers with loss of epithelium were present. This typically is a shock manifestation which developed while the patient was dying and the blood pressure was very low. The pancreas appeared normal. The liver was not enlarged. It showed surprisingly little passive congestion. No granulomatosis was found and the only evidence of a possible diabetes was the large glycogen-containing nuclei in the parenchymal cells on the lobular periphery. There was a little nodule in the capsule of the liver but under the microscope it was an unimportant developmental anomaly.

After this background with evidence of infection but no granulomatosis or blood dyscrasia, we turned to the chest organs.

The heart was enlarged, weighing 570 grams. In the left ventricle, no rheumatic changes nor significant hypertrophy were found. The papillary muscle was not hypertrophic but the left ventricle was dilated. The atrium was only slightly dilated. Microscopically, no acute myocardial changes were seen but just a little hypertrophy and edema. The right ventricle was tremendously hypertrophic and dilated and the right atrium was also dilated. The trabeculi carni and papillary muscle were heavily molded and the tricuspid cusps were thickened. Some fibroclastosis was present from increased pressure on the endocardial lining of the ventricle (Fig. 3). The thickening of the tricuspid leaflets was probably a pressure effect which we quite frequently see, and it was not associated with rheumatic fever or any developmental deformity. Pericellular and intracellular edema probable related to the terminal events was seen microscopically. The pulmonary

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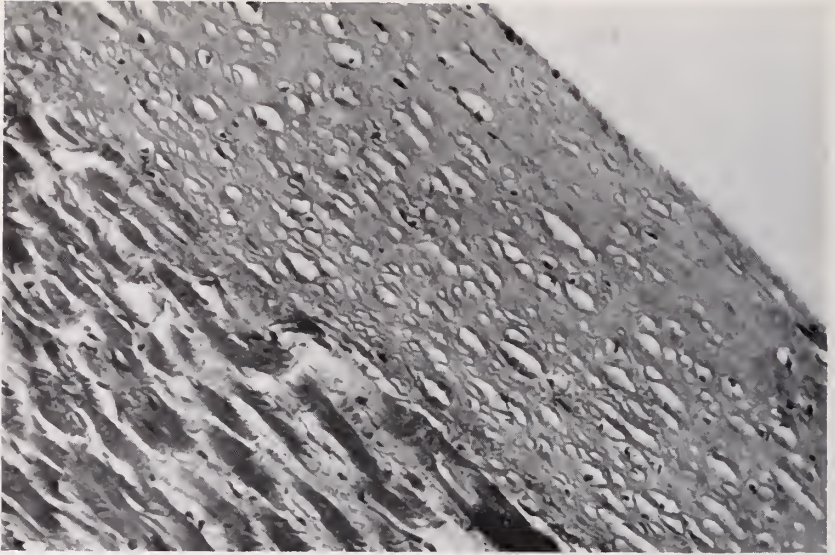


FIG. 3. Endocardial lining of right ventricle showing fibroelastosis (Elastica $\times 63$)

artery was not significantly altered; neither valvular changes nor arteriosclerosis were present. Comparing the right and left ventricles, we saw that the right ventricle was almost as thick as the left, and, therefore, it was a *cor pulmonale*, just as postulated by the clinicians who discussed the case, with added dilatation of the left ventricle.

The lungs were not very large. The left one weighed about 800 grams, the right one about 1100 grams. There were a few adhesions over the right upper lobe. Otherwise, the appearance was uniform, the pleural cavity was dry, and the surface had an almost nodular appearance (Fig. 4). The pulmonary arteries showed no arteriosclerosis. At sixty-four years of age, the patient should have had a little bit, and he had less than we would have expected. There was some enlargement of peribronchial lymph nodes but no significant distortion of the architecture. Microscopically, hyperplasia of the lymphatic as well as of the reticulo-endothelial elements was seen but this was just a nonspecific irritation, even less than chronic lung disease would have led us to anticipate. We looked again at the surface of the lung and saw an irregular nodular appearance and we found that the lungs were very firm. They were very resistant and did not collapse. The cut surface presented a rather homogeneous picture. They were not large but of normal size or even smaller and very firm, almost like a liver. The cut surface on close inspection showed many small cysts, as Dr. Rabin predicted (Fig. 5). Microscopically, it looked a little different from what we would have expected. The alveoli were wide and there were extensively thickened pulmonary septa with inflammation and fibrosis (Fig. 6).

Hamman-Rich disease would be the first diagnosis, except that we saw muscle fiber in the thickened septa. The gross picture was not that of Hamman-Rich



FIG. 4. Hobnail appearance of surface of lung

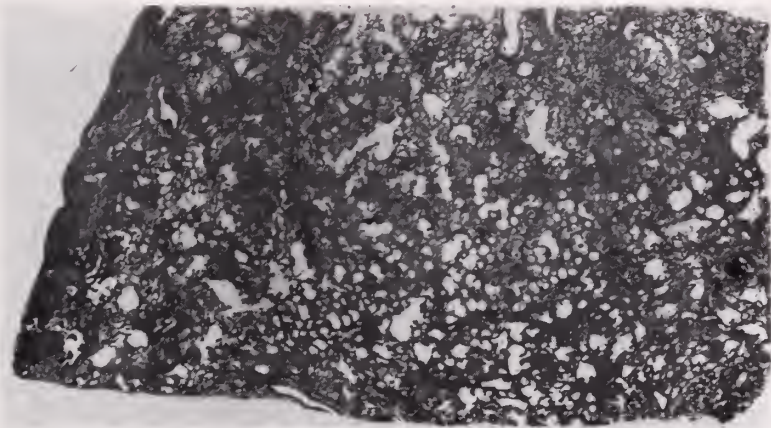


FIG. 5. Fine microcystic appearance of section of lung after fixation (Mallory chroma-trope aniline blue $\times 4$).

disease, and furthermore no epithelial changes whatever were present. The fibrosis was almost too marked to do for this diagnosis, especially when we saw that the muscle fibers had become fibrotic. The bronchi were dilated, with ridges coming out in the smaller bronchi (Fig. 7). Tubular bronchiectasis was found without much inflammation but with a large amount of muscles, and these muscles created the rigidity which we have described. In some areas we had fibrosis and in other areas we had bronchiectasis and in some circumscribed areas consolidation. Now, Dr. Rabin told us we will see fibrosis. It was a diffuse, fine fibrosis with very thick areas and dilated spaces between them. The dilated spaces

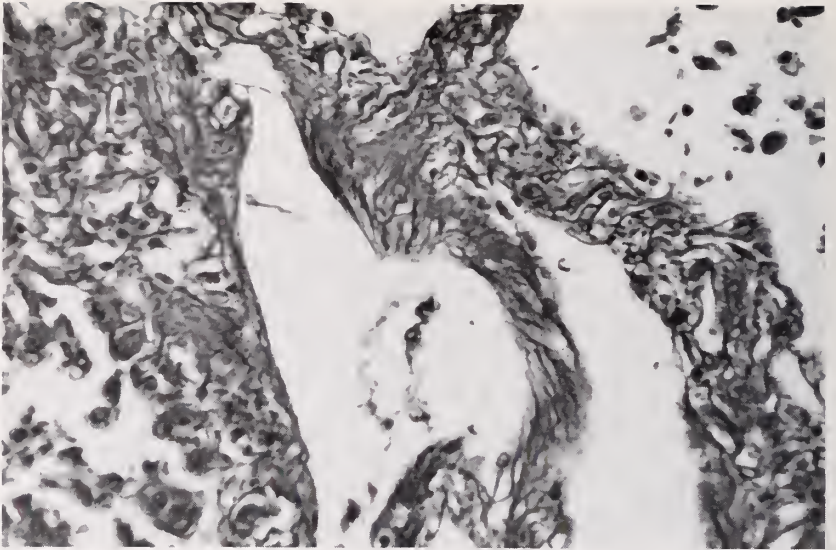


FIG. 6. Thickening of alveolar septa with increased fiber formation (silver impregnation $\times 240$).

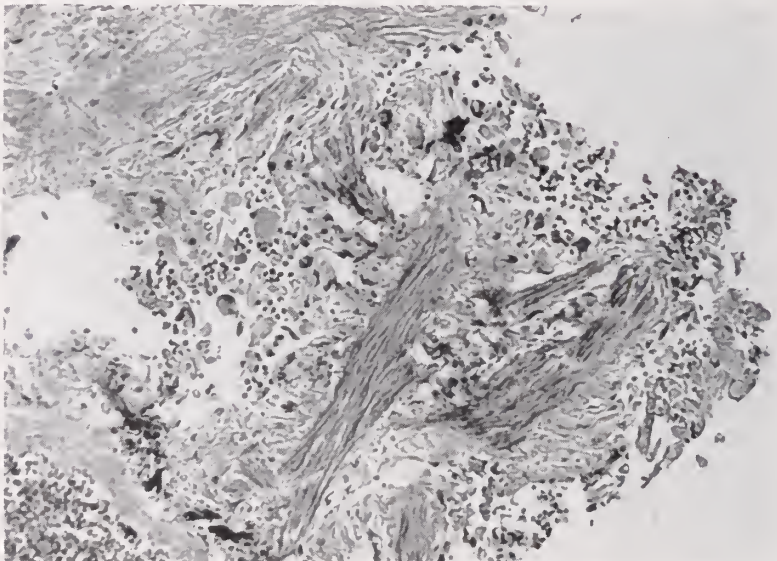


FIG. 7. Ridges containing muscle in dilated bronchi (Trichrome $\times 63$)

were almost ruptured in some areas. There were emphysematous blebs dilated and surrounded by an inflammatory zone. Some were ruptured and had no epithelial lining at all. They were alveolar ducts that became dilated and then underwent marked fibrotic changes associated with breaks of elastica and scar formation with a little muscle developing (Fig. 8). This emphysematous change in the alveolar ducts was accompanied by a lot of mucus (Fig. 9). We start to under-

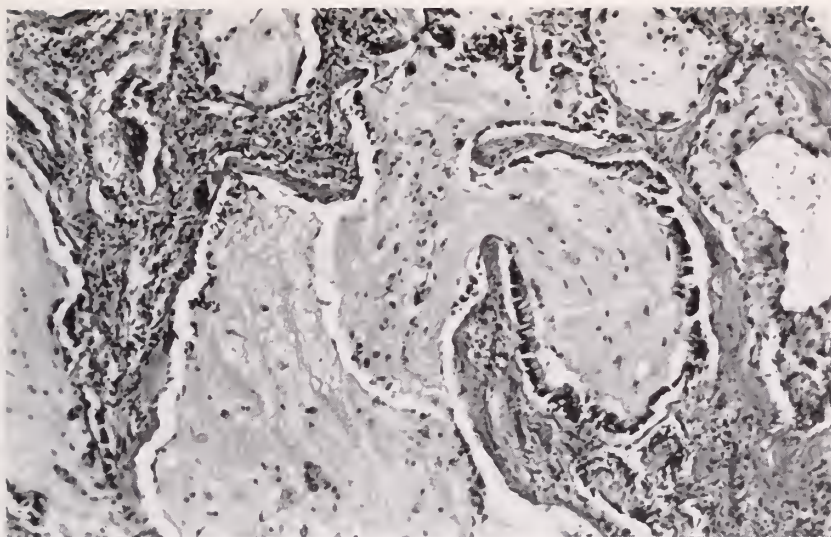


FIG. 8. Mucus derived from epithelial cells living alveolar ducts filling air spaces (H & E $\times 63$)

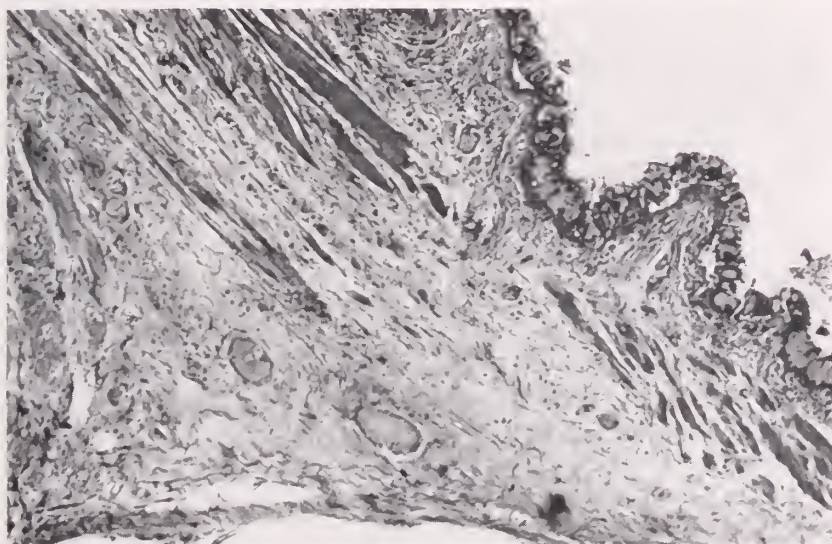


FIG. 9. Muscle bundles in wall of bronchioles (Mallory chromotrope aniline blue $\times 63$)

stand why this lung was so firm. There was a lot of muscle and this muscle contracted and prevented dilatation, probably all during life producing a spastic effect. Some white mucus had been expectorated but there was a large amount of mucus left. The bronchial epithelium was crowded with cells that committed suicide by producing so much mucus. Here again inflammation was seen around bronchiolar cells.

So we had to add, then, to our diagnosis emphysematous blebs, bronchio-

lectasis with mucus stagnation and bronchiectasis with inflammation. In some areas with a large amount of mucus, an excessive overgrowth of the bronchial epithelium occurred which led eventually to something which has been designated as bronchiolar adenoma. There is argument whether this is really neoplasia. It was surely not malignant; but it was an incidental finding. Far more important were the big scars in which we could recognize chronic pneumonitis, interstitial inflammation consisting of lymphocytes and plasma cells. Some fat-containing macrophages were also present. In addition to this pneumonitis, we saw a large amount of muscle fibers. Blood vessels were present in the inflammatory areas which were not pulmonary arterioles, but were branches of bronchial arteries. The pulmonary circulation had been amputated and bronchial circulation was replacing it. In addition, lymph stasis was noted. The muscles were regularly arranged, some of which were already undergoing fibrosis. Some of the muscles came from blood vessels, the bronchial arterial branches, some came from the lymphatics; some came from the bronchioles themselves (Fig. 9), and some apparently developed as a result of stress in the fibrotic tissue (1). In addition we saw a large amount of collagenous tissue which was irregularly distributed, always developing under stress and constantly being destroyed. There was evidence of pulmonary arterial hypertension. Pulmonary artery branches were greatly thickened. The pleura was thick and had a hobnailed appearance. The hobnailed appearance was explained by muscle fiber contraction, and this lesion, because of its hobnailed appearance, has been designated as muscular cirrhosis of the lung. What we really had before was progressive patchy pulmonary fibrosis. The Germans called it muscular pulmonary cirrhosis and a recent American paper used the term bronchiolar emphysema, and this difference of names reflected the difference of opinion as to its pathogenesis (2). The actual lesion is a defect of alveolar sacs, congenital hypoplasia of the alveoli leading to changes in the bronchioles (3). The old explanation which most have accepted is that the lesion is an inflammatory one with subsequent obstruction of the bronchioles. It may be the result of chronic pneumonitis, rheumatic pneumonitis, or syphilitic pneumonitis, although we have no evidence for any of these. The lesion definitely had nothing to do with congenital cysts. It is obviously not a diffuse pulmonary fibrosis, pneumonitis, tuberculosis, pneumoconiosis, or granulomycosis. A small focus of healed tuberculosis was found in the right upper lobe.

In trying to analyze what the patient had, we found obstruction of the bronchioles and disappearance of alveoli leading to dyspnea. Whether it was congenital or inflammatory, we did not know. Primary or secondary bronchiolitis was present with lipid pneumonia. All this was reflected in the episodes of fever, cough, and rhonchi, and this led to bronchiectasis and bronchiolectasis. It was also associated with focal scarring with excess muscle from blood or lymph vessels of the respiratory tree and from proliferation and breakdown of elastica. Also there were changes in the epithelium which led to adenoma formation (Fig. 10) and was associated with dilatation of respiratory bronchioles and alveolar ducts, obstructive emphysema and bleb formation. Bronchial arterial compensatory collateral hyperemia developed as a result of which an increased strain was placed

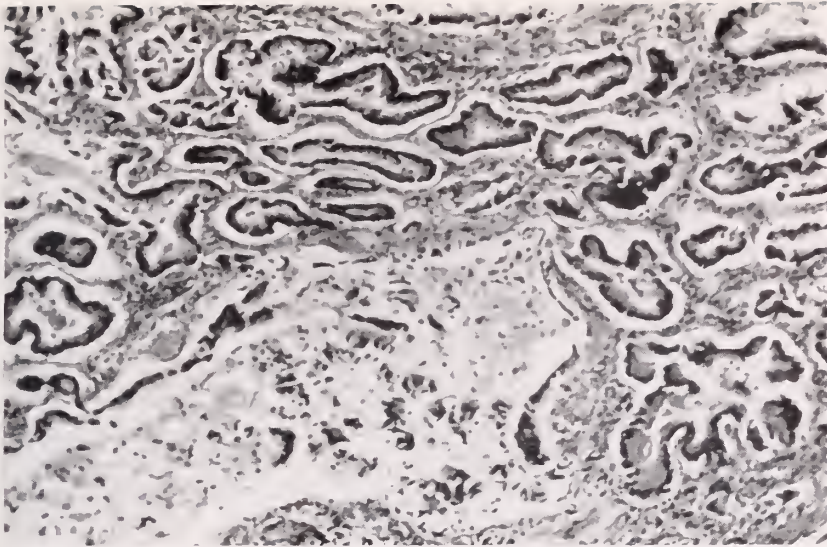


FIG. 10. Severe adenomatous hyperplasia of bronchial epithelium (H & E $\times 63$)

on the left ventricle resulting in left ventricular failure and dilatation. Independently, an old tuberculosis focus of 28 years ago was found.

In closing then, this is a case which I have described as pulmonary muscular cirrhosis or bronchiolar emphysema, which is basically a progressive patchy fibrosis of the lung.

Dr. Rabin: This same condition has been described in the literature as bronchiolectasis, which is the name that I chose to use for this condition. None of the terms that have been used—muscular cirrhosis, bronchiolectasis, or bronchiolar emphysema—seem really to give us the picture of what this disease is. Had I had more time at my disposal, I would have explained a little bit further what I meant by bronchiolectasis, but I would have had to admit that the final pathological picture, while it is one of dilatation of the bronchioli and alveolar ducts, is still not explained. The initial cause of the dilatation of the bronchiolar ducts is not explained by the use of this term. Certainly it is not explained by the use of the term muscular cirrhosis. This is probably the poorest designation because it tells you only that there is excess muscle tissue and that there is cirrhosis of the lung. All of the terms are simply descriptive. I'm afraid that when we speak of bronchiolectasis, we are also not telling you what the nature of the disease is. The theory that we may be dealing with alveolar agenesis might explain the entire picture on the basis of distention of the remaining lung tissue to take the place of lung which cannot distend where no alveoli are present. Thus, the bronchiolar ducts may distend. But this is still not a good explanation because then the emphysema should be more marked. Presumably the lung can stretch easier than the bronchioles, so if, in many places throughout the lung, alveoli never developed, the space should have been taken up by emphysematous lung rather than by dilatation of the bronchiolar ducts. Therefore, we cannot say that

the bronchiolar ducts were distended as a part of a compensatory mechanism alone. There was something in addition, and it may be in the nature of another type of congenital abnormality.

Why the bronchiolectasis developed, I do not know. We see patients who have patchy fibrosis of the lungs from inflammation and we do not see the picture of bronchiolectasis as outspoken as we see it here. If it were simply secondary to a chronic inflammatory infectious disease of the lung, we should see it more often. As a matter of fact, this is an extremely rare disease. I saw one case many years ago and recently I saw a series of x-ray films of a patient in whom I understand the pathological picture was one of cystic formation in the lung. She may have had the same condition. I know of one other case in the thirty-five years or so since I am at this institution. The reports in the literature are few. The term bronchiolectasis, as I mentioned before, is purely a descriptive term.

One of the things that made me think of a bronchiolar disease was the fact that the patient was expectorating three or four ounces of mucoid sputum per day for a period of time. This, plus the distribution of the lesions—not diffuse, but more toward the lower part of the lungs—to me suggest that the disease is of bronchiolar origin. The little spaces between the infiltrations which I did not think were entirely due to compensatory emphysema between the fibrotic areas, but rather to represent dilated bronchioles, indicated to me the pathological picture which has been described.

Final Diagnosis: Bronchiolar emphysema (pulmonary muscular cirrhosis of the lungs).

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MEDICAL EDUCATION IN THE UNITED STATES 1910-1956

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This essay has for its allotted scope the development of medical education in the United States from 1910 to 1956. Strict constructionists may question the use of the term "medical education" for the subject matter at hand, since *education* denotes the development of the powers of the mind, whereas the narrower term *instruction* is limited to the transmission of knowledge or techniques. Rightly considered, the schooling of the physician must attempt more than the inoculation of knowledge, and the wisest observers have understood that the physician who is endowed with nothing more than medical knowledge and medical skill is an incomplete product, like an aborted fetus.

In the following discussion, principal emphasis has been given to the education and instruction of the undergraduate medical student. This draws with it by logical necessity a consideration of premedical education also. Graduate and postgraduate medical education are treated in somewhat less detail. Special cults such as homeopathy and osteopathy are accorded no mention, largely because the primary data are less abundant, less accessible, and less reliable than is the case with orthodox medical education, and good secondary sources are virtually nonexistent.

Since medical education, like all other components of medicine, functions in a complex social environment and reflects or refracts the influences thence derived, the author has at all times endeavored to point out both the influences and their reflection wherever such could be discerned. This is intended to imply no commitment to a doctrine of economic determinism in history, since medical developments reflect not only their external environment but also their own specific antecedents.

MEDICAL EDUCATION 1910 TO 1920

It is often said that the Flexner Report (1) caused a widespread reform in American medical education. The truth is that the Report added force and direction to a movement that had existed for four decades. Those important decades compassed the following achievements: Charles Eliot's reforms in the Harvard Medical School (1870 et seq.); the opening of the first American university hospital, at the University of Michigan (1869, reorganized 1876); the establishment of Delafield's laboratory at Columbia University and Welch's laboratory at Bellevue, in 1878; the establishment of state boards of medical examination and licensure; the reports on medical education by John H. Rauch of the Illinois State Board of Health (1877-1891); the opening of The Johns Hopkins University in 1876 and of its medical school in 1893; the formation of the Association of American Medical Colleges in 1890; the reconstruction of the

Manuscript completed March 1, 1957.

American Medical Association in 1901 on a plan which facilitated effective action; the establishment by that association of the Council on Medical Education (1904), later called the Council on Medical Education and Hospitals (1920); the completion by the Council in 1907 of a first tour of inspection of the medical schools; and the publication of educational standards (1906, 1909). Of great importance also were the establishment of the Rockefeller Institute in 1901, of the General Education Board in 1902, and of the Carnegie Foundation for the Advancement of Teaching in 1905. In 1907, William Welch remarked that in the better schools laboratory teaching had advanced from the weakest to the strongest position in the curriculum, and that improvement in opportunities and methods of clinical teaching was a more urgent problem than the teaching of the laboratory subjects (2).

Although the reform movement was gaining strength during this period, it was as yet too feeble and unorganized to halt the proliferation of medical schools. Statistics gathered by the American Medical Association show that there were 100 medical colleges in the United States in 1880. Between 1900 and 1906 the total fluctuated between 160 and 162. Thereafter a diminution set in (3).*

As has been stated above, the Council of Medical Education, under the chairmanship of Dr. Arthur D. Bevan, conducted a tour and evaluation of all American medical schools in 1906-07. An important part of the work was done by Dr. N. P. Colwell, secretary of the Council. The results of the survey were communicated to the individual schools and to the American Medical Association but were not published.

In the autumn of 1908, after collaboration with the American Medical Association had been arranged, Dr. Henry S. Pritchett, president of the Carnegie Foundation for the Advancement of Teaching, requested Mr. Abraham Flexner to undertake a survey of the medical schools of the United States and Canada. During a period of about 18 months, Mr. Flexner, often accompanied by Dr. Colwell, visited every one of the medical schools then extant in the two countries. His report *Medical Education in the United States and Canada* speedily attained the rank of a classic in its field.

Flexner found that the United States was grossly oversupplied with medical practitioners. He calculated that the country had one physician for every 568 persons; Germany, which very significantly he chose as a standard of comparison, had only one physician per 2000. He found that the United States had 148 medical schools, of which 116 were "regular", while 15 were homeopathic, eight eclectic, one physiomedical, and eight osteopathic. Of the 116 "regular" schools, 16 required two or more years of college work as prerequisite to admission. Six other schools were about to increase their requirement from one year to two years. Three additional schools were about to increase their requirement from a

* Abraham Flexner (1) in 1910 reported the existence of 148 medical schools in the U. S. The A.M.A. statistics for 1910 report 131 schools. The difference appears to consist mainly of eight chiropractic schools and eight osteopathic schools, not included in the A.M.A. computations.

high school course to two years of college. This made an elite group of 25 schools which required or were about to require two years of college work as prerequisite to admission. A second group, almost 50 in number, required high school graduation or an evasive "equivalent." The remaining schools, numbering about 40, had still lower entrance requirements, i.e. virtually none.

The equipment of the schools showed a similar range of variation, and the reader can spend a profitable hour in reading the details so frankly given in Flexner's report. The deficiencies included not only the lack of test tubes, cadavers, and microscopes, but also the lack of access to clinical facilities of proper quality and quantity.

The chaotic if not carcinomatous proliferation of medical schools reflected certain peculiarities of American government. The Constitution of the United States had established no provision for the control of professional education, hence this field of activity became by implication a function of state governments. In general, state governments had failed to fill the void effectively. Hence medical schools could multiply without restraint, legalizing their existence by the simple act of obtaining a charter. It was no wonder, then, that the country contained about as many medical schools as the rest of the world combined.

In part the defects of American medical education were ascribable to the system of proprietary medical schools, a system not wholly devoid of virtue, whereby a group of practitioners constituted itself as a medical faculty, bought or rented a building, gave a medical course consisting mainly of lectures, and awarded doctoral degrees. The fees were divided among the professors and instructors. Expenses were minimal and profits might be large. Moreover the professorial titles were likely to attract consultations.

The proprietary schools were not entirely bad; moreover the deficiencies of medical education at this time were not limited to them. In the first place, aside from the fact that a few schools which had formal affiliation with universities were in actual fact autonomous proprietary establishments, even the schools which had genuine university affiliation often had serious deficiencies in equipment. Moreover, even those schools which were integral parts of a university and which might therefore receive financial and intellectual sustenance thereby, had in most instances no control of the clinical facilities which they used. Hence the medical student might visit the wards or dispensaries of a nearby hospital as a tolerated guest, on sufferance and not by right. Even in the better schools the clinical training of the student might depend on the precarious pleasure of hospital trustees or superintendents.

Flexner recommended that the number of four-year medical schools in the United States be reduced drastically to 31. These schools would produce on the average 70 graduates each year, or a total of about 2000. With few exceptions the schools would be departments of universities; not more than one would be located in any one city. The schools selected for survival would be distributed according to the major sections of the country. This plan would secure for the American people an adequate number of physicians thoroughly trained in modern medicine and wisely dispersed throughout the country.

The Flexner Report was a thorough systematic and frank *exposé*. The reaction is thus described in Flexner's autobiography, *I Remember*:

"The medical profession and the faculties of the medical schools, as well as the state boards of examiners, were absolutely flabbergasted by the pitiless exposure. We were threatened with lawsuits, and in one instance actually sued for libel for \$150,000.* I received anonymous letters warning me that I should be shot if I showed myself in Chicago. . . . Schools collapsed to the right and left, usually without a murmur. A number of them pooled their resources. . . . The fifteen schools in Chicago, which I had called "the plague spot of the country in respect to medical education," were shortly consolidated into three" (3).

In order to form a just estimate of the changes which occurred in the decade that followed the Flexner Report, we must consider certain components of the social climate. A prominent feature was the zeal for reform. As the nineteenth century gave place to the twentieth, nineteenth century reform movements, such as collectivism, the early temperance agitation, and populism, gave place to the single-tax movement led by Henry George, the painful revelations of Jacob Riis and Upton Sinclair, the beginnings of the medical social service movement (4) the progressivism and "trust-busting" of Theodore Roosevelt, the pure-food and drug laws associated with the name of Harvey Wiley, and the meliorism of Woodrow Wilson. It was part of American tradition that the reform of evils which pained the public conscience should be accomplished by free citizens freely associated. Thus the reforms conducted by the American Medical Association and the Association of American Medical Colleges were in accord with national custom. Governmental participation occurred mainly at the level of the individual states and took the form of development of state universities and improvement in the regulation of licensure. In 1910 the Council on Medical Education (5) complained of the inconsistency of state legislatures, which, after adopting strong medical practice acts that provided for fair educational standards, would then proceed to limit the power of the state licensing boards by granting special legislation for various medical sects which had low educational standards. Instead of a single licensing board for each state and territory the 49 jurisdictions had 82 boards, including sectarian boards.

As might have been expected, the educational affairs of the country were influenced by economic conditions. Since the Civil War, American industry had passed through a period of vigorous expansion, which successfully overcame the frequent financial panics and which as yet suffered no effective restraint by government. During the three decades from 1860 to 1890 a logarithmic growth had doubled the nation's population, its population density, and its per capita

* According to information obtained from Hon. Phelim O'Toole, Clerk of the Circuit Court, Eighth Judicial Circuit of Missouri (letter, July 16, 1956) the St. Louis College of Physicians and Surgeons sued Messrs. A. Flexner, H. S. Pritchett and George H. Simmons. The case was never tried but was dismissed for want of prosecution on Feb. 20, 1911. Flexner's entertaining description of this school ("one of the worst in the country") is on page 256 of his Report.

wealth. An important by-product was the creation of a small number of multi-millionaires, some of whom developed into practical philanthropists. At about the same time the application of newer scientific methods to medicine began to yield the definite promise of effective prophylaxis and treatment of disease. Thus medical science and medical education stood to reap the golden harvest which in earlier periods would have gone to theology.

Another element of the American scene was the presence of men who had been influenced by European, especially German, medical science. The most notable and most influential were Welch, Mall, and Flexner. These men and others of similar outlook provided much of the strategy of the campaign. Welch was a pathologist and hygienist. Mall was an anatomist. Flexner was an educator who enjoyed the confidence of philanthropists. It is significant that neither Welch nor Mall had practiced medicine; Flexner, indeed, was not a physician.

Much of the educational development which is to be described in these pages can be regarded as part of the general transition of American society from an indifferently organized *laissez-faire* structure to a more mature, more concentrated, and more highly organized mechanism. In the field of medical education results appeared promptly. The educational standard proposed in 1905 and published in 1906 as "ideal" became the essential requirement for the session of 1914-15.

The change was accomplished by the continuous systematic collection of data and by continuous publicity. In 1907, as has been stated, the Council on Medical Education of the American Medical Association completed its first survey of American medical schools; the results were communicated to the individual schools but were not published. The results of the second tour were presented in the *Journal of the American Medical Association* in 1910 in the annual number which the *Journal*, since 1901, has devoted to medical education. Thus the details, which included the embarrassing division of the medical schools into classes A, B, and C, were placed publicly on record. This was not the first time that the American people had employed publicity as an engine of reform.

Inevitably the question of standardization arose. In part this resulted from a merely verbal confusion, since the word 'standardization' could signify either the creation of standards or the enforcement of uniformity. Welch, for example, stated in 1910 (6). "The tendency in late years has been to attempt to standardize the medical curriculum, but I would not consider that synonymous with fixing standards. Standardizing a curriculum designates what subjects shall be contained in it and how many hours or periods shall be devoted to each subject. There is great danger in such efforts. We are not in a position today to thus standardize our curriculum. If we attempt to do it, we imply that we have reached results more or less final in methods of education. We ought to recognize that we are at present only in a transitional stage of medical education."

From the viewpoint of traditional Americanism, with its historical background in a nation built from thirteen separate colonies, uniformity superimposed by a central authority presented an odious threat. This threat did not lose its strength during later decades which saw a steady advance in the centralization and "uni-

formization" of American life (7). Yet subsequent experience was to show that, long after a high level of instruction had become universally prevalent, significant numbers of medical schools continued to experiment with new organizational methods and new educational techniques. Thus the earlier fear of sterile uniformity was disproved in the event.

Other opposition to the changes in American medical education took the guise of a defense of democracy and equality. The following example is offered for the delectation of logicians and acrobats:

"We have been trying to establish as a requirement for the study of medicine a thing which is not demanded of a man to qualify him for the presidency of the United States, a chief justice, a legislator or any other high office. A man can hold any of our public offices without having seen the inside of a college, and yet we are demanding that before he is even qualified to study medicine he shall have a bachelor of science degree! If a man has not had an opportunity for just the prescribed education, but he has some sense and is capable of acquiring the necessary qualifications he should be permitted to study medicine. To say to a man that because he has not had certain specified training 'you shall not be permitted to study medicine' is distinctly un-American and undemocratic and should not be tolerated" (8).

Another step in the development of standards was the establishment of the National Board of Medical Examiners, which occurred in 1915. Significantly, the new organization first sought and obtained the approval of the American Medical Association, then began to hold examinations. Soon the Board was recognized by the Armed Forces. In 1920 its diploma was endorsed by British authorities and by the American College of Surgeons. In 1922 the three-part examination was introduced.

Number of Medical Schools and Students

For the academic year ending in 1910 the American Medical Association* reported that there were in the United States 131 medical schools with 21,526 students and 4440 new graduates. The 66 Class A schools had 12,530 students (58.2 per cent of the total number) and 3165 graduates. The 43 Class B schools had 6944 students and 854 graduates. The 22 Class C schools had 2052 students and 421 graduates. Continuing a trend which had begun earlier, the weakest schools perished, while schools in the higher categories amalgamated or improved. The number of medical schools was 85 in 1919, and continued to decrease for ten years thereafter. The year 1919 witnessed the minimum registration; 12,930 students, of whom 87.9 per cent were enrolled in Class A schools. Never in the preceding thirty years had the country had so few medical students or so high a proportion who were well trained.

* Statistics not specifically credited to other sources have been drawn from the Journal of the American Medical Association, usually from the annual issue devoted to medical education. Statistics referring to any given year and published in the J.A.M.A. have sometimes undergone slight correction in later years. For the most convenient retrospective tables see J.A.M.A., 153: 119, 1953; 156: 148, 1954; 159: 582, 1955; 161: 1653, 1956.

While the advent of World War I caused the temporary withdrawal of large numbers of instructors from the medical schools and imposed added pedagogic burdens on the remainder, it produced no comparable interruption in the careers of most students. Although the Selective Service Act of 1917 did not specifically exempt medical students, an adequate solution was found in the National Defense Act of 1915, which provided for a Medical Officers' Reserve Corps and also for an Enlisted Medical Reserve Corps in which medical students could be retained until completion of medical schooling and internship. Similarly the Students' Army Training Corps provided a means of retaining premedical students at their work (9).

At this juncture it is convenient to notice very briefly a few additional effects of World War I on American medicine. In addition to providing impetus to purely technical advances in medical practice, such as the treatment of infections and wounds, the sudden demands of military service revealed that the prevalence of physical and mental defects in the American population was far greater than had been suspected. Moreover there was an appalling scarcity of truly qualified experts in all branches of laboratory and clinical medicine. Both of these revelations suggested that the nation had a large educational task before it, even if uninterrupted peace was to prevail.

The war also provided the occasion for an inventory of psychic resources. Intelligence tests were widely done and, though the results were later contested, showed or appeared to show the relative intelligence of men from different parts of the country, different racial strains, and different occupational groups. According to one unflattering survey, U. S. Army medical officers ranked low in intelligence, although those who had been trained in schools which demanded high qualifications at entrance ranked above those who came from less exacting schools (10). Intelligence testing thus advanced to prominence during the war and was soon to make its entry into the field of medical education.

The decline in the number of medical schools in the decade under consideration was accompanied by a steady change in their character. Almost every school became part of a university, and some affiliations previously nominal were now fortified in reality. This transformation was bound to have an important and complex influence on the character of medical instruction and on the characteristics of the newer physicians.

The laboratory studies which commence the medical novitiate were increased in length, value, and impressiveness, partly with the intent that scientific habits of thought should abide with the student through the latter clinical part of the curriculum and indeed through his career as physician. At the same time, those who taught the preclinical scientific subjects, usually doctors of philosophy and not doctors of medicine, tended to acquire increasing influence in the affairs of the medical schools, especially with respect to curriculum. These men worked on a full-time schedule, exactly like their counterparts in the undergraduate colleges. Their increasing power was not unnoticed or unopposed (11).

Although almost every medical school became part of a university and tended to adopt the standards and attitudes thereof, the influence of the universities

upon the medical schools was predominantly confined to science and technology. Humanistic influences were transmitted little if at all. The reasons for this important failure will be discussed in later paragraphs.

Improvement in preclinical instruction was common among the better medical schools before 1910. The provision of proper facilities for clinical instruction was slower to develop; its progress was no doubt accelerated by the progress of union between medical schools and universities, since a medical school which had come under the aegis of a university would have improved its chances to obtain or construct a teaching hospital.

Prerequisites for Admission to Medical Schools

It was in the matter of standards of admission that the medical schools most convincingly demonstrated their improvement. In 1905 the Council on Medical Education adopted as an ideal standard the prerequisite of one year of premedical study devoted to physics, chemistry and biology (12, 13). Since the sudden imposition of these "ideal requirements" might cause excessive difficulty, in part because of the scarcity of four-year high schools, especially in the South and the West, and might even provoke a destructive counter-reaction, the Council also devised a temporary standard prerequisite, viz. four years of work in high school. The prerequisites actually enforced in 1909 were reported by Flexner in his survey and have been summarized in an earlier paragraph of this essay; the conditions which Flexner observed were clearly transitional. By the academic year 1914-15 the ideal standard had become the essential requirement. In 1920 Colwell (14) found that all but five of the 85 extant medical schools required for admission two or more years of study in courses regularly leading to the baccalaureate degree in approved colleges of arts and sciences.

Since the enforcement of these prerequisites made a deep imprint on American medical education, they have a just claim on our attention. For the vast majority of candidates the requirement of a year of scientific study on the college level represented an *accretion* over the high school course which would otherwise have constituted their entire preparation. The new prerequisites were not aimed at a body of humanistically educated men who might be deficient in knowledge of the natural sciences; they were aimed predominantly at a body of men who had had no adult education, either broadly humanistic or narrowly scientific, and who must be compelled to acquire at least the rudiments of natural science. Such men were now to have one or two years in which they must cope with chemistry, physics, and zoology. Each of these subjects required many hours of work in the laboratory in addition to hours in the lecture hall. Any time remaining might be devoted to such afterthoughts as literature and languages.

As a consequence of these educational changes, the high school graduate who had one or two years to devote to premedical studies spent all or nearly all his premedical time in the natural sciences; among these sciences, chemistry took the lion's share of available hours. Students who could afford to spend four years in undergraduate colleges now usually found it easier and more congenial to take advanced courses in the sciences, especially chemistry, rather than risk new

adventures in such impractical and unnecessary luxuries as the classics or philosophy. Hence even the fortunate elite who had baccalaureate degrees at the time of entering medical school were often men who had spent their undergraduate years mainly in the laboratory, especially the chemical laboratory, and had paid no more than a minimal and perfunctory obeisance to anything in the field of the liberal arts. Moreover several universities permitted a curious transaction whereby the first year of the regular medical course counted toward both the baccalaureate degree and the medical degree.* This disgraceful subterfuge deviated numbers of students away from the liberalizing influences of a senior year at college. Thus the predominant effect of the new prerequisites on the overwhelming majority of students was to force them into the natural sciences and away from the liberal arts. The system was one which might produce mechanists, materialists, and competent technicians but was unlikely to create educated men.

Among the scientific subjects demanded as prerequisites the dominant position was held by chemistry. Usually the candidate for admission to the medical school presented at least two courses in chemistry, one in physics and one in zoology. Thus chemistry constituted half of the customary minimum preprerequisite. No doubt this is a reflection of the condition of medical thought in 1905, when chemistry promised to be the basis of important advances in medicine, while physics may have seemed remote and not extensively applicable. In 1905, moreover, psychology and anthropology were little developed in the United States; in anthropology, for example, there were only three full-fledged academic departments in the whole country. Thus at this time chemistry achieved the primacy which it never relinquished, although the subsequent fifty years were to witness great advances in other sciences which might equally deserve the attention of the candidate for admission to medical school.

Curricula of Medical Schools

Consideration of prerequisites has seemed worthy of extensive discussion because the attitudes and limitations imprinted on the future doctor during his premedical studies usually remained with him through his years as a medical student and ever afterward. The strengthening of prerequisites was accompanied by an equally impressive reform of the medical curriculum. The academic year was lengthened. The course was graded and was increased to four years. Good laboratory instruction in the preclinical sciences became nearly universal.

Among the preclinical subjects anatomy long held dominance, which it was to lose gradually in later decades. At the same time this subject, as a result of the influence of Mall, was escaping from its thralldom to surgery and was developing as an independent scientific discipline; this change had potentialities of good and evil for the education of the physician. The osteological part of the anatomy course was often taught by lectures or demonstrations. Gradually this method

* A combined course constructed somewhat along these lines and apparently the first in the country was instituted at the University of Michigan in 1892. See *The Univ. of Mich. an Encyclopedic Survey*, Ann Arbor, 1951, part V, 1.783.

was replaced by the use of collections of bones loaned to the individual students. Much of the student's time was wasted in the fruitless effort to memorize a huge textbook, such as Gray's Anatomy, which might have been used more intelligently as a work of reference. These were the shackles of tradition.

Instruction in bacteriology was often given in association with or subordination to that in pathology or hygiene, just as in an earlier era professorships of pathology were often combined with those of medicine or therapeutics. With the development of graded curricula, instruction in bacteriology was usually designed to precede that in pathology, whether the two subjects were taught by separate or by conjoined departments.

Since the end of the nineteenth century the instruction in physiology given in the better schools included a laboratory course in which the students, singly or in groups, carried out all but the most difficult of the experiments. This method gradually became universal but did not entirely supplant lectures and professorial demonstrations.

Biological chemistry is generally believed to have been the best taught of all the preclinical sciences, perhaps because a good tradition had been established by teachers like Chittenden or because the students had been heavily preconditioned toward chemistry by the predominantly chemical orientation of their premedical studies, or perhaps because the inherent simplicity of the subject, presented without its philosophical and social implications, did not overstrain the reason.

The teaching of pharmacology was inadequate in not a few schools and absent in others. Where the subject was taught by biochemists and treated as a specialized variety of biochemistry, the correlation with clinical medicine was apt to be feeble. Pharmacognosy suffered decline, then banishment; thereby was severed the last link in the traditional botanical training of the physician. Pharmaceutical elements were likewise gradually extruded from the curricula.

Instruction in psychiatry was weak and consisted mainly of visits to state hospitals and their hopeless cases of advanced mental disease. Although Freud had lectured in America, psychiatry had not yet become a significant force in American culture or in American medical education. There were, however, a few evidences of progress. In 1906 the University of Michigan opened the first psychiatric hospital in the United States to be affiliated with a medical school and arranged a clinical course integrated with the rest of the curriculum. Analogous institutes were created at Harvard in 1912 and Johns Hopkins in 1913. The subsequent decade saw further developments along the same line.

General clinical teaching began to improve as universities started to acquire dispensaries and hospitals suitable for purposes of instruction, yet much so-called clinical teaching consisted of demonstrations in which a patient was brought before a whole class. This crude method made no provision for history-taking and physical examination by the student.

Symbolic of future progress was the offer made by Mr. Edward S. Harkness (1914), who donated over a million dollars to The Presbyterian Hospital of New York on condition that it become affiliated with Columbia University. Having

developed in separate and different directions, medical schools and hospitals were now starting to converge. In general, the universities were more willing than the hospitals to participate in affiliations.

The extension and improvement of laboratory instruction in the preclinical subjects and the spread and fortification of bedside teaching in the clinical subjects operated alike to cause the decline of the lecture as a didactic tool. Lectures became less numerous, less important and, though this is hard to prove, less meritorious. Thus a useful technique lapsed into undeserved disrepute. It is probably significant that American oratory declined at about the same time.

The improvement and specialization of laboratory teaching entailed the risk of its divorce from clinical medicine. In response to this threat a teacher of physiology, as early as 1914, sought to improve interdepartmental correlation by inviting chemists, anatomists, and internists to participate in his work. This scheme appears not to have been very successful (15).

Full-time Teachers in Medicine

It has been observed in previous paragraphs that before the end of the nineteenth century the development of laboratory teaching in American medical schools began to outstrip the development of clinical teaching. Until the middle of the decade which followed the Flexner report all clinical teaching was conducted by practitioners who also engaged in the private practice of medicine; some of these were men of very great ability and distinction. As Pineoffs has stated:

“Along with its major defects this system had one quality of value. The clinical chairs were held in the better schools by the leading practitioners and consultants of the community. These men brought to their teaching a point of view developed by their experience with disease in the home, the office and the hospital. They were accustomed to take into account the family and the environment. They were also very commonly the leaders in the medical activities of the profession in their community (16).

Before the end of the nineteenth century the establishment of the full-time system in clinical departments was envisaged by a few men such as Welch and Mall. These men apparently derived the idea from Carl Ludwig, who may have acquired it from Hugo von Ziemssen (17, 18). In America another early advocate of full-time was William Rainey Harper of Chicago (19), influenced by Mall. Osler until almost the end of his life stood in opposition (20).*

Definite action did not occur until 1913, when the General Education Board, after two years of discussion and planning, donated to The Johns Hopkins Medical School the sum of \$1,500,000 for the purpose of reorganizing the medical, surgical, and pediatric departments on a full-time plan (3). Similar reforms were

* For the opinions and reactions of other prominent medical teachers, see (a) Chesney, A. M.: *The Coming of Full Time to the Hopkins and Halsted's Attitude Toward the Plan, Surgery* 32: 482, 1952; (b) Finney, J. M. T.: *A Surgeon's Life*, New York, Putnam, 1940, pp. 229; (c) Barker, L.: *Time and the Physician*, New York, Putnam, 1942, pp. 115 and 190. (d) Sabin, F.: *Franklin Paine Mall*, Baltimore, Johns Hopkins Press, 1934, pp. 114.



IT DOES GO A BIT HARD SOMETIMES

FIG. 1. Cartoon in the *Baltimore American*, October 30, 1913. Reproduced by permission

soon instituted at Washington University, Yale, and elsewhere. After this the system continued to spread and continued to arouse both praise and opposition; the contention had not ceased by the middle of the century.

Research

During the decade which we have been considering, the impressive administrative and pedagogic developments of American medical schools were not paralleled by any comparable development of research. It is true that a very few advanced schools, notably Johns Hopkins (21), continued their investigative activity, but most of the other schools as yet had accomplished little. Since one important research center, the Rockefeller Institute for Medical Research, was entirely independent of universities, it is at least theoretically possible that medical research in America might have developed preponderantly through the creation of independent research institutes, separate from universities and segregated from the lives of professors, practitioners and patients. It may be deemed fortunate that history took a different course.

Since the beginning of the century small research grants were made by various agencies of the American Medical Association (22). An example of specialized benefaction was the Crocker Research Fund, given to Columbia University in

1911 for research on cancer. One of the most famous developments was the establishment of The Johns Hopkins School of Hygiene and Public Health (1916), which added to the volume of medical research by universities. But the great period was yet to come.

Graduate Education

The memorable achievements in the development of undergraduate medical education which occurred during the second decade of the century were accompanied or followed by important but less conspicuous advances in graduate medical education. In 1912 the Council on Medical Education made an initial survey of hospital internships; this was the forerunner of a regular series of published reports. At about the same time the American College of Surgeons (1913) and the American College of Physicians (1915) were founded. These organizations exerted a prompt and favorable effect on the educational standards (and also on the administrative and physical standards) of hospitals. Especially noteworthy were the hospital surveys conducted in 1918 and subsequent years by the American College of Surgeons (23). In 1918 the Council on Medical Education prepared a schedule of standards for the training of interns. In the following year the first edition of "Essentials of a Hospital Approved for Internship" was published. In 1919-20 a complete survey of hospitals was made, and in 1920 the duties of the Council on Medical Education "were enlarged to include all the hospital activities of the American Medical Association" (24).

In 1914 the University of Minnesota Graduate School of Medicine was organized, to which in 1915 the resources of the Mayo Foundation were added. The first complete inspection of all graduate and postgraduate medical schools was made by the American Medical Association in 1916; a second inspection was made three years later. Another significant development occurred in 1916, with the establishment of the American Board of Ophthalmology (incorporated in 1917), the first of a series of voluntary organizations devoted to the examination and accreditation of specialists. It was historically appropriate that this movement should begin with one of the oldest specialties known to medical annals. Despite these and other developments it was recognized that important problems in graduate and postgraduate medical education remained for later decades to confront.

Finances of Medical Education

The changes which have been summarized thus far in the present chapter necessarily had financial and economic implications, which can be given no more than brief mention here. The period under consideration was one of a general rise in prices, which was to continue, with more exacerbations than remissions, into the second half of the century. At the same time the advance in medical knowledge implied that a greater and more diverse body of theoretical and factual matter must be presented to the student. The steadily increasing absolute expensiveness of this transmission soon forced the proprietary schools to close their doors, since the costs of medical education could now no longer be borne by students' fees.

Indeed it speedily became apparent that monies derived from students could pay only about one third or one fourth of the cost of education. This was true despite the fact that tuition fees rose steadily. According to the American Medical Association, from 1910 to 1915 most schools charged \$150 or less per year. From 1916 to 1922 the majority charged more than \$150 (25). Even greater increases were in prospect.

Since Americans had not yet learned to look to the federal government for manna, the necessary financial sustenance could only come from university funds, from individual donors, or foundations. The latter were slowly increasing in size and number. But most private persons, including the wealthiest, had not yet come to regard medical education as the citizen's responsibility. Most medical schools were insecurely financed; most medical professors were penurious unless they could supplement their income from practice or from other sources.

Education for Other Professions

The reform in medical education which occurred in the years immediately preceding and immediately following the Flexner Report exerted an influence beyond the bounds of medicine (26). In 1913 the Committee on Education of the American Bar Association thus addressed the president of the Carnegie Foundation:

"The Committee was greatly impressed by the investigation, made a few years ago under your direction by the Carnegie Foundation, into the conditions under which medical education is carried on in the United States. That the medical profession and the entire country was placed under lasting obligation to your organization because of the service that was then rendered is acknowledged by all who know the facts.

The Committee of the Bar Association is most anxious to have a similar investigation made by the Carnegie Foundation into the conditions under which the work of legal education is carried on in this country . . ." (27).

The Carnegie Foundation acceded to this request and devoted eight years to a study of legal education (27, 28). That no reform resulted comparable to the reform which followed the Flexner Report may be attributed in part to the lack of a powerful professional organization among lawyers, in part to legal traditionalism, and in part to other causes. It is significant that the Reed report on law schools contains innumerable references to medical education. In analogous fashion the Carnegie Foundation undertook studies of education in dentistry (29) and engineering (30). The Mann Report on education in engineering later exerted a reciprocal effect on medical education, evidenced in a correlated scheme of theoretic and practical training instituted at the College of Medical Evangelists (31) and fashioned after a plan used at the Cincinnati Engineering College.

MEDICAL EDUCATION 1921 TO 1941

The preceding section of this essay compassed the great decade (1910-1920) which followed the Flexner Report. We must now consider the eventful period of twenty years (1921-1941) which led the American people, after a brief preliminary depression, through cheerful prosperity, catastrophic economic collapse,

artificial economic restitution, and hasty preparation for war. Each phase exerted direct or indirect influence on medicine and on medical education.

The period of prosperity witnessed a steady increase in American productive power, the economy shifting its emphasis from agriculture to industry and from country to city. Industry became steadily more mechanized; agriculture also adopted the use of machines, but less rapidly and less completely. The populace moved from farm to city and from city to suburbs. Urbanization and industrialization provided a substrate on which the beginnings of industrial medicine were establishing themselves (32). Charitable foundations increased in size and number; medicine became a favored but not exclusive beneficiary. The federal income tax, negligible at its inception in 1913, soon burst out of its infancy. Providing generous exemptions on behalf of charitable benefactions, it encouraged many donors to contribute to educational institutions.

The Great Depression, beginning in 1929, brought unemployment, starvation, and despair to large numbers of people. The effects of depression were aggravated by the agricultural calamities of the 1930's, which caused large numbers of people to migrate westward from the "dust bowl". Widespread depletion or destruction of individual financial resources must have deprived the medical profession of many promising students, yet enough applicants usually remained to fill the rolls. The finances of charitable and educational institutions were weakened, and medical education suffered unmistakable damage, as will be noted in later paragraphs.

Against the economic havoc of the 1930's the American people deployed the forces of government, despite traditional fears of overgrown central authority. For good or ill, the participation of the government in all phases of American life did not diminish in later decades, yet its influence in medical education, restrained by alert and articulate critics, was predominantly beneficial.

In the political sphere American thinking remained isolationist after World War I, despite the fact that the nation had had commitments overseas since 1898. Although the Rockefeller Foundation extended aid to medical institutions and medical scientists in many countries, and the medical missionaries continued their obscure labors, there is no evidence that the American medical profession generally was interested in international public health, tropical medicine, or parasitology. The American physician was as much an isolationist as his patients. Yet the world wide influence of the country was growing and became inescapably obvious as World War II approached.

Within its own confines the United States continued to be a mosaic of individual states observant of differing bodies of statute and custom. Thus the adventurous might still seek out loopholes in the medical practice act of one or another state and gain the diploma which merit would deny. Such opportunities became fewer in the course of time.

American life continued to change in many important ways. The population increased, longevity increased, and, except during depression, per capita wealth increased also. The birth rate decreased steadily from 1924 to 1933, then remained almost constant till 1940. More people could afford schooling than ever

before and more people received it. Class distinction had never been absolute and social mobility was great; hence anyone could at least aspire to have his son or daughter enter the ranks of the professions.

Changes impended also in the composition of the American population. Immigration was sharply and selectively reduced by a series of Immigration Acts beginning in 1921. The proportion of foreign-born whites in the population declined as the proportion of native-born whites increased. The new laws were based on the belief that immigrants from eastern and southern Europe were less desirable than those from northwestern Europe.

The restriction of immigration was accompanied and in part caused by revived anti-foreignism and nativism, which also found expression in such movements as the Ku Klux Klan and others that were even worse. As will be shown later, the feelings which these movements embodied were not without influence on American medical education.

Among other changes which occurred in American life we may single out one special consequence of industrialization, namely the development of vastly improved transportation. The increase in facilities for rapid convenient travel signified a greater range of effectiveness for the individual physician and gave some ground to the contention that an increased number of practitioners and specialists might not be necessary. The precise measurement of the need always remained difficult, however.

Industrialization and its child, mechanization, affected not only the activities of the American but also penetrated his thinking. More and more the American became what he himself loved to call "a gadgeteer", relying on mechanical devices to save labor or even for their own sake. Just as the layman preferred the lathe to the chisel, younger physicians now preferred fluoroscopy to physical diagnosis, and laboratory tests increased in favor while the old fashioned clinical history and physical examination suffered an undeserved and dangerous decline in esteem. Although the older techniques continued to be taught and will always continue to be taught, the long-term effectiveness of their instruction probably was weakened.

The American continued to be preoccupied with his health, his anxiety being stimulated by the press and the mercenary radio. Medical journalism for the layman increased first in quantity, and later in quality. Thus the layman came to have increased awareness of his diseases and his doctors, with little real understanding of either. The ordinary layman's interest in the problems of medical education did not develop to significant intensity until a later period. There was much criticism of physicians in the public press, and this must have impinged upon aspirants and medical students as well as upon practitioners.

Among literary intellectuals in the period between the two world wars the predominant mood was one of disillusion, which often gave rise to expressions of social criticism. Expatriation became fashionable. Although the Scopes trial made superficial diagnosticians regard us as a nation of cretins, careful observers also recognized elements of intellectual vitality in the proceedings. That the forces of humanism were alive was evident from the writings of Irving Babbitt and a

host of others. The influence of Freud and Marx increased strongly among literateurs; medical men, less immediately and less consciously responsive to general intellectual influences, became increasingly oriented toward Freudian psychiatry but remained indifferent or hostile to Marxist economics.

The American continued to be a technician or an organizer rather than a thinker, a Roman rather than a Greek*. This trait revealed itself in many ways in American medical education, especially in the narrow "practical" structure of premedical and medical training, and equally in the efficient voluntary organization of American medicine which was the main engine of the educational reform described in a previous section.

In the world of science the 1920's and 1930's continued to register steady advances, most conspicuously in physics but also in many other fields such as biology, genetics, earth sciences, and mathematics. The influence of developments in psychology was felt chiefly in the application of psychometric tests to premedical students. Anthropology made important advances but, with the possible exception of anthropometry, remained largely outside the pale of medical and premedical education.

In the two decades which we are now examining, American secondary education continued to cope with ever increasing numbers of students, only a minority of whom would go on to collegiate and graduate studies. The educational labor was hindered by the Great Depression and other economic difficulties, and was aided by generous but insufficient governmental subventions. The emphasis of secondary education shifted increasingly from precollegiate to "practical" and vocational. The basic direction for these reorientations came from John Dewey, the influential advocate of a pragmatic and instrumentalist doctrine applied to education in the alleged interests of democracy. Whether or not Dewey and J. H. Kilpatrick are to be held responsible for a dilution of educational content and a deterioration of educational standards and performance is not relevant to this discussion. The present writer is of the opinion that such dilution and deterioration did occur† and that the estimation of the resultant damage to premedical and medical education will be worthy of careful study by historians. At all events the uncontested reorientation of secondary education *away* from studies preparatory to college would have damaged precisely the group whose education forms the subject of the present treatise.

Number of Medical Schools and Students

For the year 1921 the American Medical Association listed 83 medical colleges in the United States, of which 74 were classed as nonsectarian. Corrected statistics for the same year showed that there were 14,466 medical students of all types,

*"The spirit of the Americans is averse to general ideas; it does not seek theoretical discoveries". Alexis de Tocqueville, *Democracy in America*, (1835). New York, Knopf, 1945, vol. 1, p. 315. See also vol. 2, pp. 41.

† For various opinions see (a) Dewey, J.: *Problems of Men*. New York Philosophical Library, 1946; (b) Bestor, A.: *The Restoration of Learning*, New York, Knopf, 1955, pp. 101; (c) Curti, M.: *American Paradox*. New Brunswick, Rutgers Univ. Press, 1956, pp. 62.

of whom no less than 90.5 per cent were in grade A schools, and 3,186 graduates. The number of enrolled students, having reached a minimum in 1919, rose steadily and has continued to the rise until the present. The total number of medical schools decreased from 83 in 1921 to 76 in 1929 and remained virtually constant until 1949, when a gradual increase began. After 1929 the division into classes A, B, and C was no longer necessary and was abandoned.

Almost every medical school in the United States was now part of a university, but great differences prevailed in the amount of administrative, financial, and intellectual autonomy which these medical schools retained. These variations are in part attributable to differences in the historical origins of the individual medical schools, in part to geographical separation of some schools from their parent university, and in part to financial and other causes. The resultant polychromatic picture furnished a good example of the diversity and individualism which the most perceptive foreigners have recognized in so many departments of American life and which the less diligent observers have sometimes overlooked entirely.

Similar variations obtained in the internal administrative structure of the various medical schools, especially in the power of the dean and of the faculty (33).

By 1921, every medical school had affiliation with a hospital, which often it either owned or controlled. These affiliations increased in value as hospitals and the schools improved in physical facilities, administration, and technique. The provision of adequate and adequately diversified clinical material for educational purposes continued to be a problem which required constant thought and planning.

Requirements for Admission to Medical Schools

By 1921, of the 83 medical schools there were 76 that required two or more years of college as prerequisite for admission. Many students exceeded the official minima. In 1938 the American Medical Association recommended that at least three years of college work be required of all candidates for admission. It would be easy to assume that this increase in premedical schooling necessarily signified an increased educational attainment. But, as has been stated earlier, narrowness of scope imposed upon young minds limitations which in most cases were never transcended. We may notice, for example, that in 1932 the Council on Medical Education and Hospitals discarded the former requirement of a modern language. Since generations succeed one another rapidly in the academic life cycle, it was not long before the schools were filled with teachers who had grown up without a good general education and who now had rostra and improved laboratories from which they could disseminate their own narrow ideas.

In 1924 a distinguished educator complained that the whole system was pedagogically unsound (34). Premedical training, as then given, was merely professional training extended downward. It had failed to produce a higher degree of general education or mental maturity or to broaden the interests of the student, nor had it made men able to attack the first year medical course in a manner satisfactory to medical faculties. Educators had let premedical and medical education be taken from them.

Another penetrating critic (35) complained that the physician required, and was not receiving, broad general education, which should include the study of history, sociology, economics and philosophy. "It would appear to be a fair assumption from the results of our present policy that we do not in fact believe that broad educational requirements are important in the training of a physician."

In addition to the technical prerequisites which the medical schools exacted formally in terms of courses and credits there were other important requirements, usually not overt, with respect to sex, race, and religion.

Since the beginning of the present century women usually formed between 4.0 and 5.5 per cent of the student body. The number of schools which refused all female applicants dwindled slowly. One school accepted women only. In 1945 and subsequent years a wartime shortage of male applicants caused the restrictions to be relaxed, and the percentage of women rose, the maximum of 9.5 per cent being attained in 1948. Later the old custom returned and the percentage declined once more. The high cost of educating each student made some authorities reluctant to invest their money in the training of women since marriage and childbirth might cause them to abandon medicine; so went the common official reason or rationalization.

The plight of the Negro in American medicine at this time is implied in the faithful annual tabulations of the American Medical Association. We may select as an example the single academic year 1935 to 1936. Of the 23,777 medical students in the United States, 361 or 1.5 per cent were Negroes, whereas Negroes formed about ten per cent of the American population. Of the 361 Negroes, 183 were enrolled at Meharry and 133 at Howard. The remaining 45 students were enrolled in 20 schools. Meharry and Howard graduated 65 Negro students, all other schools graduated eight.

The extent and complexity of the problem are not fully exposed in these statistics. Even where a liberal dean and faculty might be disposed to admit Negroes in larger numbers there would still remain the problem of finding sufficient numbers of qualified candidates and the problem of bringing Negro medical students into contact with white patients and nurses who might be prejudiced against them. Yet the principal obstacle was neither educational nor economic. The obstacle lay in the American dilemma whereby those who professed an egalitarian creed were still unable to live up to its full implications.

Equally disgraceful to America was the discrimination against Jews and Roman Catholics. The national conscience being somewhat tender on this subject, reliable statistics and genuinely unprejudiced discussions are hard to come by. One may search through volume after volume of official publications and surveys by medical societies and universities without detecting a hint that the problem even exists. In the scarcity of objective data, a definitive historical review cannot be given at this time, especially for the period between the two world wars. The reader is therefore warned that the following presentation is tentative. Discrimination against Jews and Roman Catholics in medical education, although differing in historical origin, presents great similarity in practice

and hence will be considered jointly in the present essay. The naiveté of some comments on this subject, including one statement that will be quoted later, obliges us to recall the elementary fact that not all discrimination is bad. One must discriminate between vice and virtue, between truth and falsehood, and between a better student and a worse. But discrimination based on race, creed, or color violates a basic tenet of American belief.

After the close of World War I the United States was swept by an anti-Red scare and by nativistic movements such as Ku Klux Klan which had for their target any group that appeared to possess distinctive characteristics and that could be deemed to have foreign roots, especially if these were recent. These criteria were fulfilled by Jews and by Roman Catholics of Italian and Irish background. One conspicuous exponent of the trend was Henry Ford, who initiated his racialist publications in 1920 (and recanted them publicly in 1927). At the other extreme of the intellectual scale was President Lowell of Harvard University, who in 1922 "proposed what amounted to a *numerus clausus* for Jewish students at the institution" (36-38). A faculty committee rejected this suggestion and voted that "in the administration of rules for admission Harvard College maintains its traditional policy of freedom from discrimination on grounds of race or religion".

Although the amount and intensity of antisemitism declined during the prosperity of 1924 to 1928, it revived with the advent of the Depression. A distinguished European scholar remarked, "It is the writer's present impression that antisemitism, as he observed it in America during the last years before World War II, probably was somewhat stronger than in Germany before the Nazi regime" (39).

It must be admitted that the evidence of discriminatory admissions practices by medical schools during the period 1921 to 1941 is not of the precision or concreteness which the historian requires. Definite evidence and especially statistical evidence did not become available until more recent decades. Yet the indirect evidence was of sufficiently compelling character to convince leading historians.

First there was the simple observation that most medical schools and hospitals had a pattern, almost constant over any short period of years, of admitting either many Jews or Catholics, or few, or none. Constancy implied policy and policy proved intent.

More definite was the fact that many if not most schools used application blanks which demanded information about race or color or religion or parental origin (40). Such data would identify each applicant with a subgroup of the population. Applicants often were obliged to submit photographs.

A third hint is derived from the increased use of geographical criteria, which could be employed as a device for racial and religious discrimination. Some schools were supported by state governments and were required by statute to admit or prefer in-state applicants. Such schools could and sometimes did wield the map discriminatively against out-of-staters. Among other schools there grew up the sincere but dubious conviction that geographical diversity

was an asset, i.e. that a school situated in Barataria should admit Mr. A. from far-off Idaho in preference to the equally or better qualified Mr. B. from nearby East Barataria. Still other schools simply used geographical criteria as a subterfuge for increasing the proportion of white Protestants. Thus American civil rights were impaled against a curve of distribution.

Analogous in method and illogic was the practice of apportioning applicants according to the composition of the population. An admissions committee might feel sincerely that the presence of 80,000,000 Catholics in a total population of 160,000,000 would determine a proportion of 50 per cent Roman Catholics for the entering class of a medical school. Yet an anti-Catholic dean, discovering that the proportion of Catholics in the state was only 15 per cent, might select the statistics most comforting to his prejudices.

Of more direct evidential value were occasional published statements which involuntarily or implicitly disclosed the existence of discrimination. Thus a responsible and revered medical educator wrote:

"There should be, of course, no blanket discrimination as regards sex, creed, or race; on the other hand, it is equally unfair to have an unbalanced distribution as regards these categories, for this involves discrimination also in that it excludes individuals who would otherwise be acceptable. It is safe to say that a proper proportion within the student body should within wide limits correlate with that of the country as a whole. *The policy followed by the school in the past seems a sound one.*" (Italics not in the original text) (41).

By this method a deserving Persian might be obliged to yield to a less qualified Mede if the quota of Persians were filled, although our American tradition specifically bars consideration of race, creed or color.

One dean of a well-known medical school in New York City admitted the existence of a quota for Jewish applicants based on population (42).

While, as stated previously, almost all the evidence of improper discrimination from 1921 to 1941 is of indirect type, it was convincing to some historians. Thus Professor O. Handlin of Harvard, a leading student of immigration, has stated:

"Although the professions were still relatively open until 1914, they already showed signs of the influence of ethnic preferences. . . . An ugly complex of discriminatory practices had taken form by the mid-thirties; it limited the number of Jews admitted to professional schools, excluded them from favored positions, and by gentlemen's agreements barred them from desirable residential quarters. . . ." (43).

"The most serious forms of exclusion developed in the medical profession. . . . Before the first decade of the century was over the restrictive policies had spread to medical education as well. The number of medical schools and the number of graduates fell steadily, and everywhere the first to be excluded were the Jews" (44).

Statements such as these exemplify the candor of the historian and contrast it with the tactful silence of medical educators.

In 1931 it was recognized that large numbers of Americans were studying

medicine abroad. Statistics believed to be incomplete showed that the number amounted to 921 in 1931 and increased thereafter to an estimate exceeding 2,000 in 1936. After this the number decreased. The movement virtually ceased with the outbreak of war in Europe. Many of these students had failed to gain admittance to American schools, sometimes because of poor scholastic standing but often because of racial or religious prejudice. The low cost of living abroad may have proved an attraction. These Americans often gained entry to extramural schools in the British Isles or to schools in Switzerland, Germany, Italy, or Austria. The majority planned to enter medical practice in the United States but many failed in state board examinations. The American Medical Association felt that the United States already had the highest proportion of physicians in the world and probably did not need the graduates of foreign schools. Yet at the same time there were many unfilled internships. Official statements by organized medicine concerning Americans studying abroad disclose no tincture of sympathy for these men, whose only offense was their desire to become physicians.

Curricula of Medical Schools

In 1923 the Curriculum Committee of the Association of American Medical Colleges laid down maximum and minimum standards describing the amounts of time which should be devoted to various subjects. Thus for anatomy the figures were 560 hours and 740 hours respectively. A survey conducted during 1924 and 1925 showed that 17 schools corresponded with the suggested standard for anatomy, while 43 were above and only six were below. The greatest deficiency with respect to the standard was found in hygiene and sanitation (45).

To judge by the number of complaints in the literature, problems of curriculum were more important to the medical educator than the more general considerations of the type discussed in a previous paragraph. It was asserted that the curriculum was overcrowded, that lecturing was still too frequent, that anatomy still took up too much time and demanded too much memorization of detail, that preclinical teaching was poorly correlated with clinical, and that various specialties received excessive emphasis. Weaknesses were especially obvious in the teaching of therapeutics, psychiatry, hygiene, and obstetrics. Medical history, medical jurisprudence, medical economics, and physiotherapy were omitted entirely from many curricula.

The criticisms were numerous and proved salutary. More up-to-date curricula began to appear. In a few schools the program of required studies was curtailed to allow room for electives, for research, or simply for unencumbered review and reflection. Comprehensive examinations, a stimulant to correlation, were used either at the midpoint of the entire course or at its end. Elementary clinical teaching was introduced into the preclinical course. The first modern preceptorships made their appearance. In a significant number of schools the clinical facilities were inadequate and efforts were made to expand them. Some schools, better favored with instructors and patients, undertook bedside instruction in small groups. A few schools, notably Duke, permitted the student to take part of his clinical study at other institutions in America or abroad.

The result of these and other changes was a degree of diversification which was to increase during the postwar period and which already provided an answer to those who feared that the establishment of educational standards would result in undesirable uniformity.

Graduate and Postgraduate Medical Education

In this sphere American medicine underwent a series of developments which closely resembled those that had taken place earlier in undergraduate medical education. The pattern consisted of (a) the recognition of a need (b) the execution of surveys and their publication (c) the establishment of standards (d) progressive technical improvement.

The earliest surveys of postgraduate medical schools were conducted by actual tours of visit in 1916 and 1919. In 1922-3 a third tour was made, a list of approved schools, fifteen in number, was prepared, and a body of essential criteria was formulated. A list of approved postgraduate courses in medical schools was also compiled, as well as a list of hospitals having approved residencies in specialties. Only general hospitals received approval for internships. In February 1925 the American Medical Association began to require inspection of hospitals as a preliminary to approval. In 1928 criteria for approval of residencies and fellowships were set up. Other developments in postgraduate education can only be given brief mention. By 1939 the J.A.M.A. was able to list no fewer than 109 opportunities for practicing physicians to engage in continuation study in 43 states and the District of Columbia. Of these, 50 courses were itinerant. The offerings were extensive but were far from exhausting the abilities or the needs of the profession.

The internship was growing in importance and indeed was made a requisite for graduation by a few medical schools; the latter trend however was waning in the 1930's and was to become extinct later. It soon became evident that many hospitals and hospital services, especially those which were not closely affiliated with medical schools, would have to reorganize in the interests of medical education. After the middle 1920's the number of internships exceeded the number of new graduates; thus in 1931 there were 6154 internships and 4735 graduates. To some extent this gap was filled by increasing the length of the internship. Some hospitals did not scruple to exploit their interns for technical and clerical labor. In a survey conducted by the Commission on Graduate Education under a resolution of the Advisory Board for Medical Specialties (46) it was recommended that hospitals which could not develop programs of true educational content "might properly appoint as salaried house officers men who have completed an internship. These men should receive an income commensurate with the value of their service."

The 1920's and subsequent decades saw important developments in specialization. The earliest specialty board, that in ophthalmology, had been established in 1916. Otolaryngology followed in 1924. In 1934 the House of Delegates of the American Medical Association approved a body of criteria "Essentials for Examining Boards in Specialties". At about the same time (1933-4) the Advisory Board for Medical Specialties was created. By 1940 fifteen boards had been

established. These boards surveyed the qualifications of the applicant carefully and efficiently. They usually gave both written and practical examinations and judged the applicant far more carefully than state examiners ordinarily could. The only objection which can be charged against them is that specialists in order to gain approval were usually required to abjure practice outside the specialty. This regulation would tend to inculcate an undesirable narrowness of outlook. In practice it was not infrequently disregarded by the diplomate.

Finances of Medical Education

Despite the vicissitudes of American economic fortunes, the medical schools continued their work of instruction, research, and improvement. Some schools were poor even when the nation was rich; all felt the cold winds of the Great Depression.

There was much construction and reconstruction of school buildings and hospitals but the problem of overcrowding was not solved and faculty salaries were usually inadequate. Endowments increased. Student fees rose from about \$200 in 1921 to \$386 in 1941 but continued to supply only a fraction of the cost of schooling; in the best schools about 25 per cent of the cost was paid by students. Were it not for the presence of large numbers of unremunerated volunteer teachers, the financial problems would have been immeasurably greater and many schools would have been forced to close. The problem tended to become worse with the spread of the full-time system. In a few instances the foolish question was raised whether an expensive and heavily endowed institution like a medical school was justified in limiting its instruction to a comparatively small number of students.

As might be expected, the economic depression of the 1930's caused severe damage to the medical schools. Gifts diminished, income from investments decreased, plans for reconstruction or expansion were suspended, salaries were reduced, and some faculty appointments were terminated. Some schools were inclined to increase their enrollment in order to increase the income from student fees; usually there was no concomitant increase in plant or staff. Several state governments began to wonder why professional education should be supported by the public treasury. The total result of the Depression was a deterioration in medical education. To this we must add the fact that many men were obliged to abandon hopes of advanced training and continue as general practitioners (47).

In view of these and other circumstances the American Medical Association in 1933 decided to undertake a new survey of medical education, with the co-operation of the Association of American Medical Colleges and the Federation of State Medical Boards. During a period of two academic years all approved schools were visited (48). Several schools were found to have lapsed from their previous status and were warned, others were disapproved; some of the details are considered in a later paragraph. Follow-up studies later revealed a notable improvement. For example in the matter of finance alone, by 1939 twenty eight medical schools were able to report a total budgetary increase of \$1,132,599. At the time this looked like a big improvement. Yet the finances of many medical schools, like the heroine of a melodrama, were constantly in danger of ruin.

Special Problems in Medical Education

During 1921 to 1941 American medicine was the subject of repeated survey, resurvey, criticism, and, except during the depression, improvement. In addition to the so-called Weiskotten survey (48), there were the report of the Commission on Medical Education (49), the report of the Commission on Graduate Medical Education (50), a series of valuable special studies by the Rockefeller Foundation (51), and the annual reports, really a continuous survey, by the American Medical Association. These were supplemented by innumerable discussions in the *Journal of Medical Education* and other periodicals. We must now consider a few of the salient problems.

Many of the complaints centered about *teaching*. While the fundamental basis of instruction had improved through the replacement of lecturing by laboratory practice and bedside instruction, especially clinical clerkship, there was a dearth of skilled teachers and a virtual absence of men formally trained in pedagogy. Few of the critics speculated about the cause of this condition. Probably one cause was the isolation of medical students (who later became teachers) from the liberal arts and from any discipline which would train the powers of self-expression and communication. Medical teaching was divorced from pedagogy. Second, and closer to home, was the fact that academic advancement in medicine was achieved through research and publication, not through teaching. Worse yet, a devotion to teaching and to students tended to use up time which an ambitious instructor might more profitably devote to his experiments. Consequently teaching was a positive detriment to the interests of the academician and he sometimes carried it out grudgingly. Moreover the belief became current that the best research worker is the best teacher, although daily experience showed that this was far from the truth. For these reasons medical pedagogy failed to mature equally with other branches of medicine. As one observer noted, "practically none of the students in the medical colleges have any notion whatever, while students, of becoming instructors in medicine" (52).

In one detail, however, medical teaching kept abreast of contemporary progress. This was in the use of aptitude tests for premedical students. Preliminary trials were made at George Washington Medical School in 1927-8 (53), and gained currency through the work of F. A. Moss. In 1931 the Association of American Medical Colleges recommended their use. In 1933 the tests were given to 9398 students in 546 colleges (54). In the middle 1920's objective and "yes-no" examinations began to be used in medical schools. These techniques satisfied a desire for objectivity and comparability in the judgment of students.

The full-time plan continued to be discussed vigorously. The system spread, despite delays caused by the economic depression. Because the plan was costly, and for other reasons, modifications arose, especially the less restrictive "geographical full-time", whereby a professor was allowed a limited amount of practice, and might, according to different systems, return the fees to the school or accept them to supplement an inadequate salary. Some observers gave the full-time system the main share of credit for the progress which had been made in medical education and research. Others felt that full-time narrowed, isolated,

and dehumanized the clinician and favored the transmission of impractical instruction to the student. The large number of part-time teachers, many of them volunteers, provided a saving grace, both financial and pedagogic. Full-time schemes tended to spread to independent hospitals as these acquired affiliation with medical schools.

Research

During the period 1921 to 1941 research in medicine was supported chiefly by foundations and large private donors (22). Governmental contributions were important chiefly in state universities. Since most medical research was carried on in universities and since research is held to be of great pedagogic importance, the subject is relevant here. Between 1902 and 1934 nine foundations granted \$154,000,000 to universities for medical work, or almost half of the \$340,000,000 which these foundations spent for all purposes. Some universities had their own research funds, supported from the general university treasury or by specially earmarked donations. The total sum spent for medical research was only a small fraction of that spent during the same period for industrial research.

An interesting picture of the condition of research by medical schools in various subjects can be found in the different chapters of the Weiskotten report (48). In anatomy nearly 30 of the medical school departments showed no evidence of active research. This was especially serious because anatomy departments usually form the student's main initial impression of medical studies. Biochemistry departments proved to be the most active and productive of all preclinical departments in the matter of research. In the other preclinical departments research was active in almost all the best schools and dormant or dead in the worst. A similar situation prevailed in the clinical branches, especially medicine, surgery, and pediatrics. The clinical specialties mostly made an undistinguished showing. Such was the situation from 1934 to 1939.

MEDICAL EDUCATION 1942 TO 1956

At the end of 1941 Americans found themselves suddenly thrust into war. Although events in Europe and Asia had long foreboded our entry, the immediate precipitating cause was sudden. The conflict at its full development caused the formation of military forces greater and more terrible than any the world had ever seen. Large groups of men were exposed to every conceivable climate and to the full diapason of tropical and arctic disease. New inventions brought new traumata and new traumatology. The climax was the atomic bomb. After these events the bitter sufferings of the Korean War could rank only as a minor epilogue.

At the conclusion of these hostilities the United States and the USSR emerged as the only first class powers in the world. This fulfilled the prediction made by de Tocqueville more than a century before. One residual of war was peacetime military conscription. This new feature of American life added new complexities and hazards to plans for medical education.

Despite the formation of the United Nations and despite new and wide foreign

commitments, the American people did not readily relinquish traditional attitudes of isolationism and remained constantly suspicious of foreign entanglements; thus the adult nation retained its childhood fears.

In the realm of national affairs the chief trend was an increase in the power and pervasiveness of the federal government, which now concerned itself to an unprecedented degree with the personal affairs of the citizen, especially his health and welfare. As a corollary, the government manifested a growing interest in medical research and a growing inclination to support it financially.

The close of World War II was followed by a huge expansion of industry. This continued, despite one minor recession, into the boom and inflation of the middle 1950's. The industrial development was based on an improved technology that included electronics and automation and would soon compass atomic energy. Industry not only grew larger and wealthier; it increased in centralization, in power, and in its influence on the daily lives of the people. The salaries paid were large enough to attract the housewife away from the kitchen and the nurse from the hospital ward. Indeed industry was able to seduce into engineering and electronics appreciable numbers of men who might otherwise have gone into medicine. While large corporations expanded, the small businessman, especially the independent grocer and butcher, was tending to disappear, i.e. to become an employee. Indeed, a British historian of America referred to the small businessman as an anachronism (55). Some feared that an analogous fate might be in store for the individual practitioner of medicine.

Advertising, supertypically American in its boldness, energy, and perhaps mendacity, expanded to new dimensions. The drug industry had long been a favorite of the advertiser, and advertising costs were higher in that field than in any other. The techniques of advertising could not fail to extend to the realm of medical care and medical practice. At least one health insurance plan advertised conspicuously in newspapers and the American Medical Association employed skilled public relations consultants. The net result of such occurrences was an increase in the layman's awareness of his health and of his health problems.

The era witnessed also a rise in the standard of living, despite the decline in the value of the dollar, as well as a decrease in the length of the work week, with all that this implied in the increase of vacations, travel, sport, and trauma.

Steadily rising income taxes and corporation taxes continued to provide exemption for funds contributed to educational and charitable institutions. Such institutions thus received what was in effect an indirect government subsidy.

Many interesting developments occurred in the social scene. The population increased steadily, the graph of its augmentation resembling a hyperbola. Although the birth rate, reckoned in births per thousand of population, became stabilized in the 1950's at about the rate observed in 1925, the absolute number of births rose steadily (56). Longevity, life expectancy, and the mean age of the population likewise increased, and geriatrics assumed growing importance. As the standard of living rose, the public demanded the higher levels of nutrition,

sanitation, and comfort which alert industry was only too willing to produce. Labor attained new political and financial power and was groping toward maturity; the labor movement became interested in health insurance and in industrial medicine. The public lost the old habit of frugality. Instead of saving and budgeting for the expenses of illness or the luxuries of his daily life, the citizen now bought life insurance and health insurance and obtained refrigerators and television equipment on the installment plan. There was a rapid spread of health insurance schemes and of new or allegedly new systems such as group practice.

Simultaneous with an overpowering increase in the demand for education there was much dispute as to the quality of instruction. While some spoke bitterly of "educational wastelands" and denounced the teachers' colleges, others championed the concepts of "life adjustment education" and advocated the so-called progressive systems. The latter appeared to be moderating their worst eccentricities. Education was cursed with narrow vocationalism.

In higher levels of the educational world the protagonists of humanism showed new vigor with which to combat the predominantly anti-intellectual tendency of the era. The famous Harvard Report, "General Education in a Free Society" (57), analyzed the situation as follows: "The problem is how to save general education and its values within a system where specialism is necessary. . . . Our conclusion, then, is that the aim of education should be to prepare an individual to become an expert both in some particular vocation and art and in the general art of the free man and the citizen. . . . The body of science includes not only special knowledge and skills but conceptual interrelations, a world-view, and a view of the nature of man and knowledge. . . . These aspects of the sciences are frequently almost entirely neglected in the college teaching of science. . . ."

To this statement and others there was added the authority of Flexner, who complained that the humanities were neglected and urged that their study be endowed by foundations (58).

Humanistic influences were reaching out toward professional fields. In 1956, after a three year survey, the American Society for Engineering Education reaffirmed the importance of studies in the humanities and social sciences in the training of professional engineers. A majority of engineering schools were found to be below a desirable standard in this respect (59, 60). An analogous conclusion concerning prelegal education was expressed by leaders of the bar (61).

The world of the natural sciences continued to produce endless wonders, such as atomic energy, electronics, television, plastics, artificial genetic mutations, and radiocarbon dating, and amateur philosophers speculated incessantly on the absence of comparable improvement in man's behavior. In the eminently practical atmosphere of American life, the theoretic advances were often rapidly transformed into useful innovations in transportation, communication, agriculture, and nutrition. These developments not only enriched the great corporations but further convinced them that research was a necessity. This conviction they carried with them into their attitudes toward research in medicine.

Medical Education During World War II

Even before the United States became directly involved in World War II, ultimate participation was obvious to many. When outlying bases were obtained in exchange for destroyers, American medical officers were charged with the rapid preparation of sanitary surveys and the establishment of hygienic facilities. The American Medical Association in June 1940 established a Committee on Medical Preparedness (62) and high officials of the armed forces took preliminary steps to arrange cooperation with the civilian medical profession (63).

As early as 1941, in the spring which preceded the attack on Pearl Harbor, 44 medical schools increased their entering classes by 329 students. During the war many schools lowered by a year or more the college training required for admission. The accelerated curriculum, by which an extra 7214 graduates were run through the pedagogic mill from 1942 to '47 is described below (see *Curriculum*).

The constant changes in the military situation and in governmental policy produced constant turmoil among medical educators and students. This is sufficiently illustrated by the occurrences of 1944 (64). In January of that year an arrangement was in effect whereby 55 per cent of the places in each entering class were allocated for the training of enlisted men under the Army Specialized Training Program (A.S.T.P.), an additional 25 per cent being assigned to the Navy under the V-12 program, and the remaining 20 per cent for civilians. In February 1944 the Army curtailed the A.S.T.P., then renegotiated its contracts with medical schools to provide 28 per cent instead of 55 per cent of the 1945 entering classes. This sudden change increased to 47 per cent the proportion of new students which medical schools must obtain from civilian sources. In April 1944 the Selective Service System abolished further occupational deferments of premedical and medical students not enrolled in medical schools by July 1, 1944. To meet this deadline, the J.A.M.A. reported, fifty six schools admitted 1,675 civilian students to the freshman class earlier than the normal admission date. To complicate matters still further, Congress in June 1944 passed an appropriation bill which made it impossible to assign new students to the A.S.T.P. program. Consequently the schools were now faced with the problem of finding 75 per cent of their 1946 freshmen from the civilian population.

The war caused a decline in the quality of undergraduate and graduate medical instruction, vacancies in teaching staffs, a transient reduction, followed by a great increase, in board candidates, and a spurt of activity in such fields as tropical medicine, traumatology, public health, and psychiatry. Some of these aspects are discussed in subsequent sections of this history.

Number of Medical Schools and Students

For the academic year 1941-42 the Journal of the American Medical Association listed 77 approved schools (including ten two-year schools of the basic medical sciences).* Enrolled in these were 22,031 students, of whom 5.3 per cent

* One school (Rush), which offered clinical courses only, terminated undergraduate study with the class of 1942.

were women. There were 5163 graduates. The number of schools remained nearly constant until the early 1950's, when a few new schools began to appear and schools of the basic medical sciences showed a tendency to convert into four-year schools. The number of students rose sharply thereafter. The effects of the war on medical education have been treated collectively in the preceding section. After 1949 there was a rapid increase in enrollment, which will probably continue, but with decreasing acceleration. For the year 1955-56 the J.A.M.A. reported 82 schools, 28,639 students, and 6,845 graduates. The inclusion of one school which was developing a new program that had not yet been approved would give a corrected total of 83 schools, 28,748 students, and 6,845 graduates.

Except during the wartime shortage, there was frequent debate as to the number of physicians actually needed. On the one hand it was obvious that the improvement in transportation and communications had lengthened the arm of the practitioner, just as the invention of more effective drugs had increased his power. Such arguments were especially welcome to those who feared that any marked increase in the number of medical students might lower those standards of medical education which the profession had so long struggled to uphold and advance. On the other hand it was equally evident that increased longevity was filling the country with aged persons, many of whom were chronically ill. To this must be added the facts that (a) the demand for medical care was increasing as popular knowledge of medicine became disseminated and as various health insurance schemes gained popularity (b) the demand for specialists was increasing (c) there was an increasing demand for highly trained research workers (d) medical faculties were assuming larger and larger responsibilities for the instruction of students in fields allied to medicine, such as nursing, dentistry, public health, social welfare (e) the government services were drawing heavily on medical manpower (f) the shortage of interns and residents was great, and could not be filled even by the admission of foreign physicians, sometimes inadequately trained (g) there was no conclusive evidence of destitution among physicians in the prime of life. The rise in the number of schools and students appeared to be a response to these pressures.

By the late 1930's the university pattern of medical school affiliation was almost universal in the United States but the actual depth of penetration of the university into the medical school varied widely. Although the steady advance of the natural sciences into the domain of medicine made for a closer integration of the medical school into the university, most medical schools preserved a large measure of autonomy in administration, finance, and attitude. Hospital affiliation, now no longer a novelty, was not yet fully developed. As late as 1953, Deitrick and Berson (65) reported that medical schools controlled the professional staff appointments in less than half of their teaching hospitals, and that approximately half of the schools studied had inadequate control of other factors in their teaching hospitals.

The late 1920's and 1930's had witnessed the construction of huge medical centers, which were arranged around a medical school and hospital, but which also included schools of public health, dentistry, and nursing, clinics, health

centers, community welfare establishments, and research institutes. These vast colossi were the architectural expression of the greatly increased role which the medical school and the hospital were now expected to fill in American life. To the medical school these new developments represented a great deal more than mere proximity. Medical faculties, especially in the preclinical departments, were now expected to provide instruction for large numbers of persons who were being trained for careers in paramedical fields. It was not unusual for medical students to constitute as little as one fourth of the number of students on the premises. Often there was no proportionate increase in the size of the teaching faculties. Moreover the superadded burdens consisted not only of instruction but included a very large amount of medical service rendered on wards, in clinics, in health districts and even in homes. All of these complex enterprises must come under the cognizance of the overworked administrative staff, and the accountants must watch the pennies. Thus the medical schools and the hospitals, like almost everything else on the American scene, must expand or perish.

In the 1950's medical educators noted with alarm a continuous decline in the number of applicants to the medical schools. Whereas in 1949-50 there were 3.47 applicants for each opening, by 1955 the proportion had fallen to about 2.2. In 1956 this trend appeared to have halted. No fewer than 1386 Americans were studying medicine abroad in 1955; doubtless the majority of these were men who had failed of admission to American schools. Foreign schools, fearful that the inundation of the 1930's would be repeated, applied restrictions. At the same time there was a distinct decline in the quality of those students whom the American schools admitted. Thus in 1950-51, 40 per cent of the students admitted were A students; by 1955-56, according to the J.A.M.A., the proportion had fallen to 15.8 per cent. These statistics are confirmed by numerous casual observations. Doubtless large numbers of the best students were attracted by the higher wages and easier lives which industry offered. Educators remembered with despair the psychometric studies of 1918, which showed that medical officers had no better brains than quartermasters (66).

Prerequisites for Admission to Medical Schools

By the second third of the century the total requirement of premedical study had been increased almost to the probable quantitative limit. The Council on Medical Education and Hospitals of the American Medical Association required three years of college work but recommended a full four-year college course. Most medical freshmen (70 per cent in 1955-56) had the baccalaureate degree; others would acquire it at the end of the first year in medical school.

The principal battleground was the composition of the premedical course, although some also objected to its length. Medical writers, medical editors, and many medical and non-medical teachers (67) complained that medical students and practitioners had been narrowly trained, were vocationally oriented, lacked the wide-ranging cultural interests which are expected in educated men, and were consequently incompetent to fill their proper roles in American society.

Medical school catalogues began to advise prospective applicants that premedical studies should not be overbalanced with courses in the natural sciences to the exclusion of courses in the humanities. Available evidence indicates that the students did not believe these sound and virtuous admonitions but continued to concentrate on the natural sciences, especially chemistry, in the belief that this practice increased their chances of admission to medical school. Of 13,407 applicants who took the Professional Aptitude Test of the Association of American Medical Colleges in the autumn of 1947, only 3.8 per cent had concentrated in the humanities or the social sciences (68). While the injunctions of the school catalogues (69) must be accepted as sincere, it has been established that, in some instances at least, the admissions officers of medical schools gave preponderant attention to the grades which applicants had received in the sciences (65). This discrepancy is either an example of the gap between creed and deed so often observed in human life, or it may merely betoken the lack of an agreed and unified policy in the faculties of some medical schools. It cannot be doubted that a written entrance examination in the humanities would establish the sincerity of official pronouncements in a manner unmistakable by applicants. One observer wisely suggested that a premedical student should have two advisors, one trained in science and one devoted to the liberal arts (67).

Among the social studies deemed desirable for premedical and medical students, anthropology made belated entry. A noted psychiatrist advocated field work in social anthropology as valuable preliminary training (67). Duke University announced the creation of a joint course in psychiatry and anthropology to be given to the first-year class.

During the wartime scarcity of applicants, women briefly enjoyed the esteem of admissions committees. From a customary average of 4 to 5.5 per cent the proportion of female students rose to a maximum of 9.5 per cent in 1948, then fell to a steady post-war level of about 5.5 per cent. In 1956 the J.A.M.A. reported that 1,573 women were enrolled in all schools and that there were 340 graduates. The limitation in the number of female applicants to medical schools had long been customary; probably few except women any longer regarded this as a form of discrimination.

Opportunities for Negroes to enter medical schools increased appreciably after World War II. In 1947-48 there were 588 enrolled. In 1955-56 the number was 731, an increase of about one-fourth. In 1955 the number of Negro graduates was less than 200, an accession inadequate to meet the demand or to repair the losses caused by death and retirement. The number of medical schools which enrolled Negro students increased from 29 in 1947-48 to approximately 48 in 1951-52; of the remainder only about 16 were thought to maintain a policy of exclusion (70, 71). In 1948 the University of Arkansas became the first of the medical schools of the South to admit a Negro student. Most of the others rapidly followed. Part of the progress is directly attributable to decisions of the United States Supreme Court and to anti-discrimination laws, and part may represent a genuine expression of the feeling that traditional maltreatment of the Negro is America's greatest disgrace. One persistent obstacle, which time

will surely remove, is the difficulty in obtaining adequate numbers of highly qualified Negro candidates for admission to medical schools and hospital residencies. Even in the North the integration of the Negro physician into American life is still far from complete.

In a previous section of this essay it was asserted that the existence of discrimination against Jewish and Roman Catholic students by medical schools during 1921 to 1941 could be strongly surmised. After World War II a new spirit of aggressiveness arose among minority groups, invigorated by new judicial decisions and new statutes which formally forbade discriminatory practices and which in some instances required the collection of exact information on the subject.

In 1946, after appropriate proposals had been made by Gov. Thomas E. Dewey, the New York State Legislature passed an act creating a Temporary Commission on the Need for a State University. A report prepared for this commission described the presence of geographic discrimination within New York State, operating to the disadvantage of applicants from New York City, but drew no clear conclusion as to racial discrimination (72, 73).

In 1948 the New York legislature passed the Educational Practices Act, which stated that "... the American ideal of equality of opportunity requires that students, otherwise qualified, be admitted to educational institutions without regard to race, color, religion, creed, or national origin. . . ." A study made for the State of New York in 1950 but not published (74, 75) revealed that at one medical school there were differentials running as high as eight to one between acceptances of Protestant and Jewish candidates of equal grades. For three other medical schools in New York State the ratios were seven to one, five to one, and four to one. In 1953 the Regents of the University of the State of New York sponsored a study of discriminative practices in medical education within the state (76). This survey revealed that "... in both the 1950 and 1952 group applicants, Jewish students had the highest median score, Protestant students next, and Catholic students next. This order does not conform to the order of admission. Top-ranking Protestant and Catholic students are more certain to be admitted than are top-ranking Jewish students". Italian Catholics appeared to carry a heavier load of discrimination than Irish Catholics. There was some evidence that recency of identification with American life might be a partial explanation of what appeared to be discrimination against applicants on the basis of Jewish identification.

Latterly it has become evident that discriminative barriers are being lowered. Whether this is due to a wave of liberalism or to the scarcity of suitable candidates may become clearer in the next few years, if the medical schools are again inundated by applicants.

It is noteworthy that little or none of the recent progress in liberalization can be conclusively attributed to the medical profession or its official leaders, so far as the written record shows. The credit apparently must go to the aroused consciences of laymen and to pressure groups organized among minorities.

The practice of geographical discrimination continued to prevail in the post-

war period and to be the subject of repeated complaint in the J.A.M.A. In some schools it resulted from unwise legal enactment. In others it may have expressed a merely parochial outlook. In still others it was unquestionably a cloak for the concealment of racial and religious discrimination. There can be no doubt that geographical quotas, like all other quotas, resulted in the acceptance of numbers of candidates who would have been rejected on grounds of mediocre or poor scholastic record.

States which lacked medical schools were special victims of geographical discrimination and were led thereby to look with favor on the development of new schools of their own or to contribute to existing schools.

All in all, the task of admissions committees was unenviable. Obligated to contend with large numbers of applications, many of which came from men who preferred some other institution, deluged with academic records based on differing standards of excellence and supplemented by unreliable testimonial letters, mistrustful of academic grades as a criterion of excellence, and doubtfully aided by newer devices such as the Medical College Admission Test, they must often have speculated on the justice of their own decisions.

Medical School Curricula

As was to be expected, World War II left a deep but largely temporary imprint on the curricula of medical schools. The luxurious summer vacations customary during peacetime were suppressed. The academic course was compressed into a series of four nine-month sessions separated by the briefest respite. New classes were entered at intervals of nine months, and graduations occurred irregularly, somewhat to the confusion of orderly statistical tables. It was estimated that the accelerated system produced an extra 7214 medical graduates between 1942 and 1947. This result was made possible by the enrollment of medical students either under the Army Specialized Training Program or the Navy V-12 program, which permitted exemption from regular military duty during the years of study.

The accelerated program was a nightmare to all concerned. Students were exhausted, even more so than in peacetime; instructors were continuously occupied in teaching, and many had excessive loads because colleagues were in the armed forces; in some instances the quality of instruction deteriorated. There was a temporary boom in tropical medicine, parasitology, military medicine, first aid, and traumatic surgery. Instruction in atomic medicine became understandably popular. When the Korean War brought the possibility of a new world-wide conflagration, medical educators were disinclined to reinstitute the dreadful accelerated curriculum of World War II.

By the close of the war the J.A.M.A. declared the need for curricular reform. Some suggested changes were reduction in scheduled hours, especially lectures; provision of free time for students for reading, research, and special interests; reduction in the great mass of detail required of students; closer integration of the basic sciences with one another; development of interdepartmental instruction; correlation of basic sciences with clinical work; more complete depend-

ence on the case method of clinical instruction; the development of research, seminars, discussions and courses in the social and economic aspects of medicine and in the distribution of medical care (77). These suggestions are quoted almost verbatim since they are an excellent statement of the needs of the time and also an astonishingly good outline of the changes which actually occurred in the post-war decade.

One critic (78) expressed the opinion that medical education was partly responsible for the failure of the medical profession to exhibit insight and aggressive leadership in molding public opinion toward solution of the problem of medical care. "The reason is that medical education of the past, which trained the current leaders of the organized profession, concentrated almost exclusively on the science, technology, and art of medicine. . . . Adequate attention was not given to the social implications of medical practice and the social responsibility of the physician". Another educator felt that medical teaching was far behind the times (79). Curriculum committees, he asserted, were composed of technicians uninterested in educational science and unfamiliar with it. There was no premium on pedagogic skill comparable to the rewards given for research. Medical teachers had unrealistic concepts of motivation, were preoccupied with eliciting psittacine responses from students, and lacked familiarity with the principles of learning.

One group of twelve faculty members undertook its own investigative analysis of fundamental educational principles. Some 20 hours of discussion were held. With the help of the Commonwealth Fund this project will now develop into an annual series of seminars and workshops (80).

Another evidence of serious interest in improved medical teaching was the conference on psychiatric education held in 1951 under the sponsorship of the Association of American Medical Colleges, and followed in 1952 by one on preventive medicine. These conferences were supported by philanthropic foundations. The next year, 1953, witnessed the start of a series of annual teaching institutes conducted by the Association of American Medical Colleges. Subjects covered in past or future institutes are: physiology, biochemistry, and pharmacology; pathology, microbiology, immunology, and genetics; anatomy and anthropology; medical ecology; clinical teaching and specialty training.

In 1956 the J.A.M.A. reported that ten medical schools had received from the Commonwealth Fund appropriations totalling \$7,150,000 to initiate or maintain creative programs in medical education. The Ford Foundation in December 1955 devoted \$90,000,000 to the endowment of privately owned medical schools to aid them in strengthening instruction. This colossal benefaction was increased three months later by an appropriation of \$10,000,000 for a five-to-ten year program of matching grants to the National Fund for Medical Education.

The material aid provided by these and many other donors allowed the realization of a host of new curricular reforms. Many of these innovations represented humanistic impulses, and some demonstrated the leadership of psychiatry and preventive medicine in building a new world of medical education.

The general tendency was to see the patient as a whole human being, not merely an assemblage of tissues embedded in fluids of constant pH, but a rational and emotional creature who lived in a family and a social order. Correspondingly the attempt was made to liberate medical instruction from the rod of the grammar school teacher and to develop self-reliant well rounded physicians who should be able to cope with man in all his complexity.

Only a few individual projects can be noticed here. In 1941-2 New York University commenced the teaching of environmental medicine and the study medico-social problems. At about the same time the Association of American Medical Colleges formed a subcommittee charged with the exploration of the same subject (81). Social and environmental medicine were taught at Vanderbilt. Family medicine was introduced at Pennsylvania, Louisville, and Albany. An important correlative multidisciplinary method was created at Western Reserve in 1952-3 (82) and supplemented by intramural clinical preceptorships. A few schools emphasized preparation for general practice (83). Others introduced clinical teaching at the start of the medical course. The tendency to introduce clinical instruction into the pre-clinical years produced difficulties for the two-year schools, which lacked clinical material. Still other schools extended the teaching of psychiatry through the length of the curriculum. New York Medical College introduced clinical clerkships as a regular feature occupying the entire fourth year of the course (84). In one school a well-designed short course in the history of medicine was given as an orientation course to introduce the student to medicine (85).

The study of the history of medicine was slowly gaining favor. In 1955 the subject was presented as either a required or an elective study at no less than 71 schools (86). The courses were conducted by departments of medical history, cultural medicine, social and environmental medicine, or by long-established departments of the older type, viz., anatomy, medicine, surgery, etc. The special institute at Johns Hopkins continued to be a leader. Especially noteworthy also was the instruction at the University of Kansas; here the teaching of the history of medicine was well integrated into teaching of other subjects.

Minor curricular alterations, too numerous to be noted here, continued to occupy the attention of medical faculties. Often the condition of the curriculum at a school reflected the aggressiveness or power of some one determined faculty member. In the pre-clinical branches there was probably a weakening of the earlier tendency to teach such subjects as anatomy, physiology, and bio-chemistry as entities by and for themselves. The increasing trend toward correlation now compelled pre-clinical teachers to keep steadily in mind the fact that they were teaching future physicians and not specialists in this or that science.

Another old weakness had been the separation of the professor from the student. It was perfectly possible for a man to complete the medical course without being personally known to the dean or the major professors. Since the chief educative force is apt to be personal as much as curricular, the defect was regrettable. The popularity of the new preceptorships tended to insure that each student would be individually guided, helped, and influenced. This far transcended curricular details in importance.

The clinico-pathological conference, characteristic of American teaching, continued to enjoy favor, despite attacks on the value of the autopsy and occasional unjust depreciation of morbid anatomy (87-94).

The clinical clerkship remained the main instrument of clinical instruction in most schools. It was especially popular in some 60 medical schools which maintained effective connection with 54 Veterans Administration Hospitals because most of these hospitals maintain residency programs without parallel internship programs. Consequently there could be no competition between student and intern.

In some hospitals instruction on the public wards was weakened by the new proliferation of health insurance plans, which deflected many ward patients into semi-private and private departments. Accordingly an effort was made to utilize such departments for clinical teaching. By 1956 this attempt had attained incomplete success.

A weakness remained in the use of out-patient clinics for teaching. Although out-patient practice was closest in character to the office practice of the future physician, the problems encountered in this department usually seemed less interesting and stimulating to student and instructor than the graver problems encountered in hospital wards.

A new and forward-looking tendency was the use of television in teaching. Black and white television was used at the University of Kansas in 1950; regular surgical teaching by means of color television was adopted there in 1951.

Graduate and Postgraduate Medical Education

During World War II the quality of the internship tended to decline, quite understandably. Instructional staffs were depleted and overworked, hospital facilities were often inadequate, and some of the interns were men who had had part of their schooling under unfavorable wartime conditions. After the war an effort was made to improve the teaching of interns. This was especially necessary in hospitals which had no effective connection with medical schools. As an experiment, part-time instructors were installed in a few hospitals. In the state of Michigan a statewide pooling of hospital teaching resources was devised (67).

Gradually the opinion spread that the internship was less valuable than it had been, partly because of the general development of student clerkships and partly because of the increase in the number of residencies. Medical schools abandoned the requirement of a year of internship as a prerequisite for graduation.

Many internships remained unfilled. For example, in 1954 it was reported (95) that 856 approved hospitals had offered 11,006 internships, of which about 6000 were filled by American students and 1800 by foreign graduates. Thus about 3000 or more internships remained vacant. An effort to cope with this difficulty produced the so-called Matching Plan, in which an attempt was made to list and reconcile the preferences of hospitals and internship applicants (96).

By the middle 1950's there was a marked preference for rotating internships. In 1956 the J.A.M.A. reported that so-called straight internships, i.e., intern-

ships in a single branch of medicine, represented only ten per cent of all approved internships.

Residencies blossomed and multiplied after the War. Army doctors had ample opportunity to observe the high rank and esteem which were accorded to both military and civilian specialists. Hence a great many physicians who left the armed forces after the war immediately sought residencies, while medical officers of the permanent army and navy likewise felt the desire for specialized training and for the advancement which this might bring.

Whereas in 1941 there had been 5256 physicians in approved assistant residencies, residencies, and fellowships in 610 hospitals, by 1946 the J.A.M.A. reported 8930 approved residency positions in 887 hospitals. This rapid expansion was accomplished by organized medicine in collaboration with large and small hospitals; some of the smaller institutions procured affiliation, temporary or otherwise, with larger hospitals and with medical schools. The number of residencies continued to increase after the immediate postwar period. In 1955-56 there were 26,516 approved residency positions in 1,202 hospitals (97). Despite the expansion and the widespread increase in affiliation with medical schools, it was noted that a few city and county hospitals resisted connection with schools.

The increase in the demand for residencies acceptable to specialty boards had many consequences. Since the boards wisely required that training for the residency include study of the basic medical sciences, a huge burden was thrown upon the medical schools. Thus in 1947 the basic science departments of no less than 58 medical schools offered organized training of this type for residents. This added to the strain on the physical, pedagogic, and financial resources of the medical schools.

Despite these difficulties a magnificent accomplishment was achieved in the technical training of specialists in almost all fields. After the war new specialty boards were created in such fields as preventive medicine, proctology, and thoracic surgery.

Much was accomplished also in the realm of postgraduate medical education. Large numbers of physicians engaged in active practice felt the need for refresher courses, continuation courses, and special training of many kinds. A wide variety of facilities sprang up in response to this need. The chaotic situation was studied by Vollan over a period of two and one half years; his observations are reported in a series of eight articles, to which the reader is referred for full details (98-105). Some of Vollan's conclusions were as follows: There was gross maldistribution of postgraduate opportunities, the South Atlantic states and Plains states having least. There was a dearth of postgraduate opportunities designed specially for general practitioners. Young graduates needed special subsidies in order to take courses. There was great need for refresher courses designed to bring the practitioner up-to-date. "Didactic" methods were more useful in postgraduate than in undergraduate medical education; television promised to be a useful adjuvant. There was need of a larger teaching force, which would have to be recruited from medical schools and large hospitals.

Postgraduate medical education, Vollan found, lacked clearly defined purposes and needed a permanent national advisory council. He observed also that the system was variously sponsored and insecurely financed.

In 1956 the Council on Medical Education and Hospitals of the American Medical Association announced the creation of an Advisory Commission on Postgraduate Medical Education. Thus postgraduate medical education showed evidence of pursuing the developmental cycle followed earlier by undergraduate and graduate medical education.

Finances of Medical Education

During the decade which came after World War II, medical schools continued to be afflicted by financial problems. These were not solved by the end of 1956, although impressive progress had been made. Much of the statistical information in this section has been taken from the Journal of the American Medical Education and from the comprehensive survey by Deitrick and Berson (65).

As medical instruction developed from the simplicity of the late nineteenth century into the big complex business which arose in the twentieth century, the need for detailed accounting practices became unavoidable. Especially necessary was a system which should separate routine instructional and administrative funds from funds designated for special research and teaching projects. It was also useful to segregate the cost of teaching medical students, who often constituted one-third or less of the total educational clientele, from the cost of instruction given to nurses, dentists, social workers, and others, and to separate the expense of teaching from the expense of services rendered to hospital and clinic patients.

In its most recent issues devoted to medical education the J.A.M.A. has used the term *basic medical school operating budget*, which is defined as "funds utilized for the operating activities of the school exclusive of appropriations for hospital and for clinic operation and maintenance or grants-in-aid from outside sources for research or teaching" (106). The basic operating budget is separated from (a) research grants received from outside sources and (b) teaching grants from outside sources. Because of local variations in accounting practices and because of the modernization of accounting practices in many schools, figures obtained from different schools are not always comparable. For the same reason figures reported in different years are also not always comparable.

In the post-war period there was a marked rise in the total basic operating budgets of all schools taken together. The figure for 1947-8 was in excess of \$43,000,000.* The total budget for 1956-7, exclusive of funds for construction and operation of major clinical facilities, was \$178,650,460. It is interesting to observe that of the basic operating budget for 1956-7, government appropriation at all levels provided 47.5 per cent, endowment 11.5 per cent, tuition income 18.2 per cent, general university funds 6.7 per cent, and gifts, grants and other sources 16.1 per cent. For a slightly earlier period Deitrick and Berson (65) reported that for 37 privately supported medical schools the proportion of income

* Estimate for 1956-57 was \$11,167,673.

derived from taxes federal and other, rose from 2.6 per cent in 1940-41 to 30.5 per cent in 1950-51. This increase in the proportion derived from the government amounted to almost a forty-fold increase in terms of dollars, and pointed to one of the salient characteristics of medical school finance of the postwar period. It strikingly exemplifies the tendency, which we have previously noticed, for the spread of the government into areas earlier regarded as the concern of the private citizen.

Another important development has been the increase in support from corporations and foundations. Sporadic efforts in this field were concentrated (in true American style) in 1951, when leaders in industry, labor, agriculture and other fields joined with organized medicine in sponsoring the National Fund for Medical Education to raise money from voluntary sources in support of medical schools. In the same year the American Medical Association sponsored the establishment of the American Medical Education Foundation as a mechanism through which physicians and medical societies could contribute to the same important cause; the monies would be distributed through the National Fund. Between 1951 and 1955 the Fund distributed more than 9.5 million dollars to medical schools. In December 1955 the Ford Foundation contributed ninety million dollars for instruction at privately supported medical schools. In March 1956 the same foundation allocated an additional ten million dollars for "matching grants" to the National Fund for Medical Education.

The dean of a leading medical school estimated that in 1954 the corporate contributions to all private educational institutions represented eight per cent of the money expended by those universities and colleges. This sum, amounting to about a hundred million dollars, was only 0.25 per cent of net corporate profits before taxes. He further estimated that .025 per cent of those net profits would underwrite the deficits of all the medical schools in the United States (107).

Despite help from industry and government the finances of American medical schools were beset with difficulties. The layman usually failed to understand that even with their huge incomes the medical schools could not function without large gifts in the form of highly skilled unpaid labor contributed by volunteer teachers. Thus in 1948 the J.A.M.A. reported that in many schools teachers who serve without pay are responsible for a major part of the instruction in clinical departments.

The students, too, had their financial problems. In the immediate post-war period many were veterans, and as such received subventions under the so-called G.I. Bill of Rights. Moreover the old-fashioned idea that a man should not marry until he could support a wife yielded to the newer imprudence of early marriage. In 1950 no less than 40 per cent of students, disregarding Bacon's essay, had taken wives*.

In 1954 it was found that the average student spent \$1500 a year in addition to tuition and other fees. His total annual expense averaged \$2300 a year, or

* "... for they are impediments to great enterprises, either of virtue or mischief". Bacon, *Of Marriage and Single Life*.

\$9200 in four years. Approximately three-fourths of the students received either a gift or a loan, averaging more than \$1000 a year, usually without interest, from their parents. Approximately two-thirds of the wives of students were employed and supported their husbands (108). About one-fourth of the students, despite heavy scholastic schedules, held some kind of job during the school year (109).

Full-time Teachers

A major difficulty, having both financial and pedagogic aspects, was the problem of full-time. The German origin and American evolution of this system have been described in earlier sections of this history. By the middle of the twentieth century the full-time method was firmly entrenched in preclinical departments. The clinical departments remained an arena of combat. The most usual method was to have a nucleus of full-time professors and other ranks in the major clinical branches. These men had academic careers, titles, and power. Supplementing the oligarchy was a group of "geographic full-time" men of various ranks (106) who concentrated their main interest at the medical school and practiced there, retaining either all or part of the fees. Still others practiced in their own offices and taught at the medical school, receiving stipends or not as the case might be. Its protagonists credited the full-time system with a major share in the notable efflorescence of American medical education in the twentieth century. The system, with all its virtues and defects, was a costly one, even though professors were chronically underpaid. Hence many full-time men were obliged to resort to practice in order to supplement their incomes. Practitioners, sensitive to any real or imagined economic threat, feared that competition from academic rivals was being added to competition from prepaid health plans; they complained vigorously in public and sulphurously in private. The difficulties are too important to remain unresolved. Increasing diversion of full-time men into practice would be a regression to conditions of 1910. It was generally agreed that the solution lay in increasing the income of the medical schools, but it was not easy to see how this could be brought about.

Research

An additional financial peculiarity of the postwar period concerned research. As we have previously seen, part of the massive expansion of American industry was directly attributable to aggressive programs of applied research. The tangible financial success of such efforts made it easy for industrialists to become enthusiastic about research in medicine. This attitude coopted well with the old American idea that a man's fate is basically the result of his own willingness to work, and that mundane problems are inherently soluble. Added to this was the fact that research had been glamorized in novels, plays, and radio broadcasts, whereas teaching was usually ignored as uninteresting or spinsterish. For these and perhaps other reasons medical research rapidly became the favorite child of philanthropy. By 1953 Deitrick and Berson (65) reported that while funds obtained for the general operating expenses of 59 schools had risen by almost

140 per cent in the years between 1940-41 and 1950-51, funds restricted to research had increased almost 800 per cent in the same period of time. Funds of the latter type were unequally distributed; privately supported medical schools expended much more for research than did tax-supported schools and made a much greater contribution to research. In 1955 the J.A.M.A. reported further marked increases in funds contributed by outside agencies in support of research by medical schools. It was anticipated that 54.4 million dollars would be received in 1955-6 in this way, an increase of 9.1 million over the previous year. At the same time teaching grants would amount to seven million dollars, an increase of only \$161,494 in one year.

The admirable system of fellowships and grants awarded by the National Institutes of Health expanded rapidly. The system came to include five categories of research fellowship corresponding to five grades of advancement and knowledge. To these were added training awards and research grants. In the fiscal year 1945, according to the J.A.M.A. (106) the National Institutes of Health appropriated \$28,000 for research fellowships, \$29,000 for training awards, and \$85,030 for research grants in the fiscal year 1945. For fiscal 1957 the respective figures were \$5,397,000, \$28,057,000, and \$89,697,000.

These considerations are relevant to our theme because of the marked influence which medical research has had as a stimulant to medical teaching and medical teachers. At the same time the aureate hyperplasia of research has had certain unfavorable effects on teaching. As has been stated previously, academic advancement in medicine depended and still depends on achievement and publication in research. It was not to be wondered, therefore, that the allocation of huge sums of money to research, an expression of public approval, should cause further relegation of teaching to a low rank on the scale of the ambitious academician. To this must be added the fact that sums of money donated for research often included inadequate provision for the overhead costs, which thus represented a drain on the administrative purse and consequently impoverished the instructional funds. It is greatly to the credit of the National Institutes of Health that its projects have been administered in a liberal spirit, and not in a spirit of bureaucratic control. Future developments are likely to be along the line of "block grants" for uncommitted investigators, instead of "project grants" (110).

FUTURE DEVELOPMENTS IN MEDICAL EDUCATION

Many historians feel that prediction has no proper place in historical writing. Yet the reader who has had the hardihood to follow the text up to this point may wish for at least a brief suggestion of probable future developments in the field of medical education.

It is safe to predict that the number of medical schools and students will continue to increase slowly. Although the number of college graduates will increase sharply, this does not automatically imply a corresponding increase in the number of applicants to medical schools, since the competition from industry can be expected to strengthen. We have no justification for expecting an improvement in the calibre of applicants in the next decade, since high schools

will be overwhelmed by a huge increase in their enrollment and no adequate measures are announced for improving the quality of secondary school education. College education shows a slight and apparently authentic shift away from vocationalism but it cannot yet be asserted that this will affect any significant number of students. It is uncertain whether the recent decline in discriminatory patterns of admission to medical schools will persist. The curricula of medical schools and their equipment will continue to improve but there will be a serious shortage of competent instructors and medical research workers. The fate of the internship is precarious but its total extinction is improbable. Residencies will be supervised even more strictly than heretofore and will improve, especially if suitable arrangements can be made for the use of private patients for teaching. Some small hospitals will probably pool their clinical resources and will perhaps appoint coordinators of medical education. Postgraduate education will improve greatly. The entire educational structure would crumble if government aid should be withdrawn, but this is improbable. The present economic inflation, with its threat of future economic depression, implies a fundamental instability in the finances of medical schools.

The future American medical graduate will be well grounded in clinical medicine, psychiatry, and public health. If he is lucky, he will be an educated man in addition.

Acknowledgments

The author wishes to express appreciation to the following persons and agencies for information, permissions and other assistance generously given during the preparation of this study:

Mr. Julius S. Loewenthal, New York; Mr. Lawrence Bloomgarden, New York; Mr. Thomas E. Regan, Baltimore News-Post and Sunday American; Dr. Myron M. Weaver, Schenectady; Mr. L. Gottlieb, New York; Hon. Phelim O'Toole, St. Louis; American Medical Association and the J.A.M.A.; Carnegie Foundation for the Advancement of Teaching; Enoch Pratt Library, Baltimore.

Statistics not specifically credited in the text are mostly from the J.A.M.A.

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Clinico-Pathological Conference

ABDOMINAL PAIN WITH FEVER, COUGH AND CACHEXIA

Edited By

FENTON SCHAFFNER, M.D.

A 66 year old Hungarian gardener was admitted to The Mount Sinai Hospital complaining of severe mid-abdominal pain of six weeks duration. He had been followed intermittently in the Outpatient Department for 12 years because of abdominal distress. Gastrointestinal x-rays were reported negative 12 and 8 years prior to admission. The abdominal discomfort came two to three hours after meals, lasted an hour, and was sometimes relieved by milk. Six weeks before admission the pain became severe and constant and was not relieved by anything the patient would do. His appetite fell markedly and he lost 45 pounds during the three months prior to admission. He occasionally vomited small amounts of whitish material with no blood. His bowel movements had been normal with no change in habit. He also developed a cough productive of small amounts of white mucus with no blood. He had been feeling weak and dizzy for six months and on the day of admission he collapsed but did not lose consciousness. He smoked ten cigarettes a day and had been taking no drugs. Two sisters had hypertension, one of whom died of it.

He appeared emaciated, dehydrated, and acutely and chronically ill. His temperature was 100.5° F., pulse 88 min., respirations 20/min., and blood pressure 144/60. Eyes, ears, nose and throat were normal. No enlarged lymph nodes were felt. A few rales which cleared on coughing were heard in the right upper lung field. The heart tones were poor, but no enlargement, arrhythmia or murmurs were present. The abdomen was scaphoid and tender even to light palpation in the umbilical region and in the right upper quadrant. No rebound tenderness was elicited and no organs were felt. Bowel sounds were loud. A 3 × 5 cm. mass was felt in the right lower quadrant. No other abnormalities were found in the remainder of the examination.

Urinalysis was negative. Hemoglobin was 11.5 Gm.%, white blood count 5,200/cu. mm. with 70% segmented cells, 15% band forms and 15% lymphocytes. Sedimentation rate was 10 mm./hr., blood urea nitrogen 9 mg.%, blood glucose 83 mg.%, CO₂ 25.2 mEq./l., chlorides 103 mEq./l., albumin 2.7 Gm.%, globulin 2.5 Gm.%, calcium 9.8 mg.%, phosphorus 2.2 mg.%, sodium 140 mEq. l., potassium 4.5 mEq./l., cholesterol 90 mg.%, alkaline phosphatase 7.7 KA units, acid phosphatase 0.8 KA units, cephalin flocculation 1+ and serum amylase 56 units. The bone marrow was hypocellular but nondiagnostic. Mucoproteins were 130.0 mg.%, acid precipitable globulins 1.7 units and zinc sulfate turbidity was 3.0 units. Free acid was present in the stomach. Stools were guaiac negative. Tuberculin test with PPD #1 was positive. Sputum and gastric smears were negative for tubercle bacilli. Chest x-ray showed infiltrations involving the right upper and middle lobes. No cavities nor calcifications were seen except in

the basal pleura on the right. A small infiltration was seen in the left infra-clavicular region. Tomograms revealed small irregular lucencies but no discrete cavities. Barium enema showed a narrowed and irregularly shaped cecum and some rigidity of the terminal ileum with a cobblestone appearance. Barium meal showed some small bowel dilatation. The distal three feet of ileum showed extrinsic pressure effects and the terminal six inches showed effacement of the mucosa with slight serration in its edges.

The patient was treated with fluids, penicillin and tetracycline, but despite this his temperature rose to 102° F. and he became unresponsive and hypotensive. He expired on the 16th hospital day.

*Dr. Bernard Wolf**: This is a very simple story, at least from a historical point of view, but the history is not actually very helpful diagnostically.

A 66 year old Hungarian male had been seen like many patients off and on in the Outpatient Department apparently for many years. Because of the abdominal distress, it would appear that he should have had a duodenal ulcer or benign peptic ulcer of the stomach. However, barium meal examination on two different occasions during this interval was negative for any abnormality in the esophagus, stomach or duodenum. As a matter of fact, the barium meal examination during his stay in the hospital also showed no abnormality in the stomach or duodenum. About six months prior to his admission to the hospital, he became weak and dizzy. In the interval of three months prior to admission, he lost about 45 pounds in weight.

This was associated with some anorexia which, however, did not appear to explain the total weight loss. About six weeks prior to admission, he began to complain of constant abdominal pain which was not relieved by anything he could do. Apparently shortly before admission, he began to cough but this was not a prominent feature and it was productive of only a small amount of white mucus.

His bowel movements, surprisingly, in view of the fact that there is considerable disease in the intestinal tract, were always normal and had not changed in the period prior to admission.

He was a desperately ill male, dehydrated, emaciated, acutely and chronically ill. His temperature was 100.5° F. There were some rales heard over the right upper lobe which disappeared after coughing. The most prominent physical findings, however, were in the abdomen.

The abdomen was scaphoid, and this is of interest because there was evidence on the simple film of the abdomen of considerable distention of small bowel. The abdomen was tender to very light touch in the umbilical region and right upper quadrant and in the right lower quadrant a mass was palpated.

He had a moderate anemia but no leukocytosis, although there was some shift to the left. The sedimentation rate was only 10 mm./hr. Blood urea nitrogen, glucose and electrolytes were well within normal limits. Albumin was somewhat low, the A/G ratio approaching one.

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At this point I would like to call on Dr. Schaffner for a little help in interpreting some of the laboratory results with rather specific questions as to whether any information is presented which permits a differential diagnosis between a neoplastic and an inflammatory process, for example, whether there is any evidence of tumor metastases to the liver.

•*Dr. Fenton Schaffner**: In some instances, laboratory tests are a clue to the diagnosis. In others, they only confirm what is obvious clinically. The latter was the case here. We can see evidence of emaciation in the low serum albumin and the low cholesterol, reflecting the three months of semistarvation. Further, we have been told that the man was sick. This is also suggested by the serum mucoprotein elevation. This patient had some inflammatory disease or neoplastic disease occurring elsewhere but in the liver. No evidence of metastatic tumor or involvement of the liver in the inflammatory process was present.

Dr. Wolf: This is somewhat helpful because, on examination of the abdomen, and also clinically, his liver was not apparently enlarged.

That the stool guaiac was negative is not very helpful. A tuberculin test was positive but sputum smears and gastric smears were negative for tubercle bacilli.

I do not have available the conventional chest film. But as the history stated, there were infiltrations not only on the right side but another infiltration on the left side in the infraclavicular region.

The sectional radiographs or tomographs of the chest showed very extensive disease which apparently involved the right upper lobe and possibly also the right middle lobe (Fig. 1). This consisted of infiltrations of a linear character, for the most part, but also of areas where the consolidation or the infiltrations appeared to be conglomerate. In addition, particularly in the right upper lobe, there were several lucent areas, none of which, however, appeared to have a complete ring and were not visualized as a single tuberculous cavity. These irregular lucencies were the kind seen in old fibrotic healed tuberculosis. On the other hand, some of the infiltrations looked somewhat soft and the possibility, certainly roentgenologically, existed that there may still have been active disease or caseation in several foci.

There was calcification in the pleura at the base of the right lung but no evidence of primary infection or Ghon tubercle. In the abdomen on the left side of the spine rather low, a calcified node was evident.

A supine film of the abdomen taken shortly after admission showed that multiple loops of small bowel in the mid-abdomen and extending into the pelvis were considerably dilated, giving the appearance of a mechanical intestinal obstruction. On closer inspection, however, it was evident that there was gas in the colon, particularly the transverse colon, so it certainly could not be a complete intestinal obstruction. The gray stripe between the dilated loops of small bowel was unusually wide. This can result only from two things, either considerable thickening of the bowel wall or peritoneal exudate intervening between these

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FIG. 1. Tomograph of right upper lung field showing multiple radiolucencies.

loops of small bowel. It is of significance since our problem is one of a differential diagnosis between carcinomatosis, and tuberculosis of the bowel and peritoneal cavity. This finding was somewhat in favor of tuberculous peritonitis in contrast to carcinomatosis since in carcinomatosis we usually see a considerable amount of ascites. This has a somewhat different appearance, i.e. a small amount of exudate between individual loops. In the right lower quadrant, peculiar air and soft tissue shadows were seen, confirming the clinical suspicion that something special was going on in the right lower quadrant.

Prior to the barium meal examination, a barium enema examination was done. This was apparently not a happy one. The patient was quite uncomfortable, had difficulty retaining the barium and was particularly uncomfortable when the barium reached the right side of the colon.

There was evidence of some obstruction in the ascending colon to the retrograde flow of barium, but some did go by and outlined a very irregular lumen.

The barium meal examination showed some very remarkable features. It confirmed the fact that the proximal loops of bowel were considerably dilated, but there was no unusual delay in the transit of barium through these loops. As a matter of fact, the barium in approaching the terminal ileum filled this channel without any delay.

The terminal ileum showed marked rigidity, multiple indentations with no sharp demarcation proximally and almost complete obliteration of the ileocecal valve distally (Fig. 2). An amorphous collection of barium with a bizarre stellate configuration was noted in the caput coli. This suggested the "destroyed mucosa" that we associate with malignant infiltration. At any rate, the homogenous ap-



FIG. 2. X-ray of barium outlined terminal ileum and cecum with deformity of caput coli, straightening and narrowing of terminal ileum, and irregular distension and mucosal destruction of more proximal area.

pearance of the barium was evidence of ulceration in the caput coli extending for a short distance into the ascending colon.

The terminal ileum appeared to be rigidly fixed. This is usually associated with malignant infiltration or an inflammatory process such as granulomatous ileocolitis or tuberculosis. In ileocolitis, spasm is usually present with change in caliber in successive films. This ileum never changed in configuration. Certain features are against or at least make us uncomfortable in making the diagnosis of carcinomatosis, and one is the configuration of the terminal ileum. Ordinarily with a carcinoma in this area, there is such severe rigidity that the bowel is straightened at the site of the tumor. This unfortunately is not conclusive because if there is much extrinsic growth of a tumor, often with a perforation, the appearance of a so-called bent carcinoma can be produced.

It is not common for a carcinoma of this area to involve both a considerable portion of the ileum and a considerable portion of the colon. I say it is not common, but unfortunately this afternoon a case was resected that showed, apparently, a carcinoma in this area with considerable involvement of the ileum. This does happen, here perhaps two or three times a year. The possibility that this was lymphosarcoma certainly must be considered because lymphosarcoma in the terminal ileum is more common than carcinoma, but this lesion does not have the appearance of lymphosarcoma. Lymphosarcoma has two classical forms, a pseudopolypoid or nodular one, and the other is aneurysmal with marked dilatation at the site of the tumor. If this were a tumor, it would have had to be a carcinoma.

The segment of ileum immediately proximal to the terminal ileum also showed several interesting features. The mucosal pattern appeared to be intact. We saw a short segment of narrowing and then an area where the folds again appeared to be intact, although thickened. One short segment was angulated and narrowed with a normal mucosal pattern, and another segment started with a convoluted outpouching.

The next segment had a peculiar hammock-like configuration. The antimesenteric side seemed to bulge, while the mesenteric side was considerably shortened, and the fold pattern appeared to radiate toward the shortened mesenteric side of this particular loop of the small bowel. The impression was, again, that there probably was a mass in the mesentery and that it involved the adjacent portion of the small bowel, but the mucosal pattern was intact.

In favor of an inflammatory process was the fact that this segment appeared to be contracted or retracted as if by a fibrotic inflammatory process rather than a mass.

As we progressed further in retrograde fashion into the ileum, we saw a so-called skip lesion, a lesion which seemed to be discrete and had a minimal lack of distensibility and a somewhat nodular profile. As a matter of fact, these nodules could also be seen in the barium column at a lower level. This may be the most important lesion from a diagnostic point of view since presumably it represents the earliest stage. This lesion did not seem to be associated with any mass in or outside the bowel and it looked like an ulcerative process associated with multiple small nodularities of rather localized character, in fact, a discrete lesion very characteristic of tuberculosis starting in a Peyer's patch.

These, then, were the roentgenological findings in this particular patient. Without going over them in detail or attempting to summarize them, the features are most consistent with tuberculosis which involved the ileum, the colon, the peritoneum and the lungs.

*Dr. Burrill B. Crohn**: There are several features about this case which are inconsistent with the facts. The first impression is one of involvement of the small intestine and the ascending colon which suggests an inflammatory lesion of a combined ileocolitis, a rather common disease. On the other hand, this is not consistent with the pulmonary findings.

Also, the ileitis that accompanies a combined ileocolitis does not usually show a skip-lesion above. It could give the symptoms of the mass and of the intestinal obstruction, but this is a very marked and unusual deforming lesion for a simple benign inflammatory ileocolitis.

With the pulmonary lesion and the involvement of the terminal ileum and cecum, all the data are at hand for a diagnosis of hypertrophic ileocecal tuberculosis. We do not encounter hypertrophic ileocecal tuberculosis very often because we are not a tuberculosis institution and because this intestinal manifestation is the end stage of a phthisis. It occurs only in cases with open cavitation in the lungs.

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Dr. Wolf, did you say there was an open lesion in the lung?

Dr. Wolf: We did not see a cavity, Dr. Crohn, but most people who looked at this suspected there might be activity.

Dr. Crohn: Tubercle bacilli were looked for in the sputum and not found. Hypertrophic ileocecal tuberculosis, which is a very rare disease in this institution, would be a consistent diagnosis with a lung lesion, but in those cases, tubercle bacilli should have been found either in the sputum or gastric contents.

What do we always take into consideration in the differential diagnosis of a right lower quadrant lesion? We have a regular list of diseases we look for. I have been fooled by Hodgkin's disease in the ileum, but without involvement of the cecum. Hodgkin's disease here is rather rare.

Lymphosarcoma is not unusual in this region, and sometimes the diagnosis is unclear until an inguinal node appears. Lymphosarcoma and Hodgkin's disease are the two diseases which most commonly have to be taken into consideration in differential diagnosis.

Endometriosis is another disease which can give inflammation in this region, but this patient, being a male, rules that out.

Sarcoidosis in the small intestine is rather unusual, but cases have been described, and it enters into the differential diagnosis, particularly with a pulmonary lesion. I am not a radiologist but I think Dr. Wolf would agree with me that this is not the pulmonary lesion of sarcoid.

Dr. Wolf: I assumed that most of the left lung was free of disease, Dr. Crohn. This would be very unusual for sarcoid. Also, the hilum and mediastinum are not involved.

Dr. Crohn: That leaves only one final consideration I can think of; namely, a carcinoid lesion involving the terminal ileum or appendix and the ascending colon. Since we now know that carcinoid is no longer a benign disease and does go on to malignant phases and does give multiple metastasis, one must think of the bare possibility that this might be a carcinoid of the small intestine with involvement of the cecum and distant metastases in the lung.

Leitis cases do not usually die. Patients with lymphosarcoma and Hodgkin's disease do die and of course hypertrophic ileocecal tuberculosis is an end stage.

Dr. Hans Popper:* Thank you very much, Dr. Crohn. We will now present the pathologic findings.

The heart was of normal size, weighing 275 grams, and except for a moderate degree of anemia, no significant changes could be seen in the myocardium or the pericardium. On high power microscopic examination of the myocardium, pigmentation was noted around the nuclei. This was lipofuscin pigment, confirming the gross impression of brown atrophy of the heart.

In the right lung, in which most of the lesions were found radiologically, we saw, in confirmation of the x-ray findings, lesions involving primarily the upper lobe and extending into the lower lobe. The lesions were of somewhat variegated

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appearance with fibrosis as well as with a gray-white discoloration and some cavity formation. In the extensive scar tissue in the lung, we saw relatively small cavities, in which debris was surrounded by the scar tissue, the vessels, and somewhat contracted wall of the cavities. These were older pulmonary scar tissues with bronchogenic cavities in the walls of which was caseation. Away from these many large caseated foci were present with daughter tubercles around them, representing lymphogenous spread into the surrounding tissue. We had to assume that activation of old fibrotic scar tissue took place. Smears performed at the autopsy showed these areas to be full of tubercle bacilli. This was, therefore, tuberculosis, with old scarring, activation of, apparently, an old bronchogenic cavity, and lymphogenous spread. These were already older lesions because we saw in an artery an old reactive end-arteritis. But from the bronchogenic cavity, apparently more recently, a spread had taken place into smaller bronchi by aspiration (Fig. 3). This bronchial tuberculosis was a channel-like spread with development of large distant foci. Apparently multiple such foci aggregated in various areas especially in the base of the right upper lobe; a process we call acinose-nodose dissemination (Fig. 4). In addition, fresh caseous pneumonia was seen and part of this lesion was from fresh lymphogenous dissemination. Some areas did not fit this description in that in the interstitial spaces of the lung a conglomeration of tuberculous lesions was present. Also in the left lung, we saw some scarring plus recent small foci of conglomerate tuberculosis. This was a more recent, apparently hematogenous, miliary spread of tuberculous lesion. We

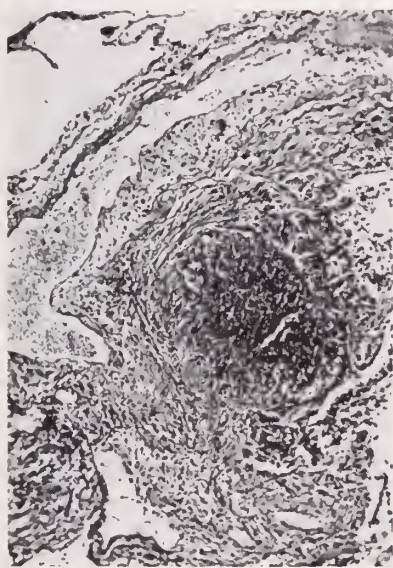


FIG. 3.

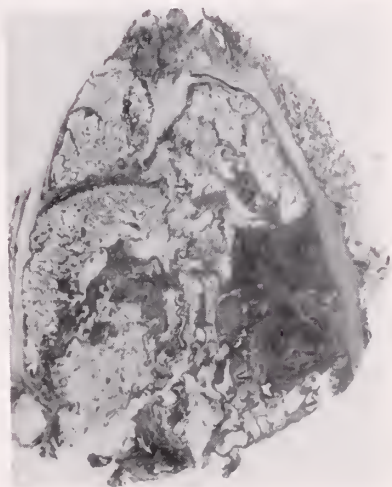


FIG. 4.

FIG. 3. Bronchial and peribronchial caseous tuberculosis. (Trichrome $\times 63$).

FIG. 4. Acinose-nodose focus of tuberculosis near scarred and obliterated interlobar fissure. (Mallory aniline blue $\times 4$).

tried to identify the original lesion (the primary complex) but were unable to do so. Therefore what we had before us was the stage of reactivation and apparently recent hematogenous dissemination.

In keeping with that, many slightly enlarged lymph nodes were found full of little tuberculous foci with beginning fiber formation, calcification and caseation. The only very old lesion which could be found anywhere was in one mesenteric lymph node.

Turning to the other organs, there were irregular rings of the mucosa in the



FIG. 5. Fixed gross specimen of ileocecal region showing destruction of ileocecal valve



FIG. 6.

FIG. 6. Perforating ulcerative lesion of ileum with some undermining of mucosa. (Mallory aniline blue $\times 4$).

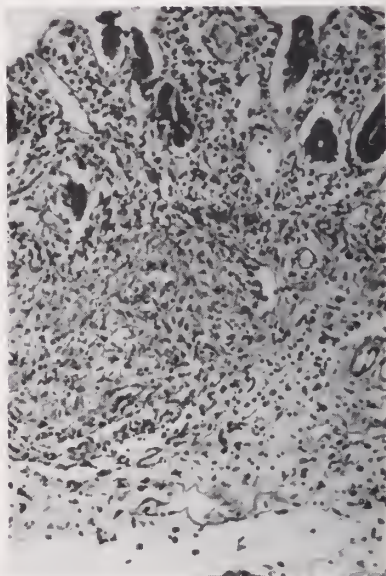


FIG. 7.

FIG. 7. Early tuberculous lesion below the mucosa of the ileum but above the muscularis. (H & E $\times 120$).

epiglottis as well as in the bronchi. Some small ulcers were seen but neither tubercle bacilli nor tuberculous granulation tissue was present. This process was healing, with some squamous metaplasia of the epithelium developing but without any evidence of a tuberculous lesion.

The liver was of normal size and crowded with small, apparently centrally caseated foci. The foci were filled with central giant cells. They were not very recent because they already had connective tissue rings around the multiple, diffusely spread tubercles. The same lipofuscin pigment as in the heart indicated brown atrophy of the liver as a result of a reduced metabolic rate.

The spleen was full of tubercles as was the bone marrow, again with the characteristic giant cells. The kidney on the fixed gross specimen failed to reveal any significant abnormality but here again some tubercles were present microscopically.

In the terminal ileum there was a distinct stenosis, a thickening of the wall extending from the terminal ileum through the destroyed ileocecal valve into the proximal portion of the cecum (Fig. 5). In this area, the mucosa appeared destroyed. It was ulcerated and small projections were noted. The ileum behind this was somewhat dilated. The ulcerations found were not in the longitudinal axis but in the transverse axis and appeared as long slits. In some areas of the ileum, there was severe irregular thickening of the mucosa. In others the mucosa was normal while in still others, in addition to thickening of the mucosa, the muscularis was destroyed. In the areas of mucosal involvement, considerable thickening of the serosal portion was also present. A section taken through the slit-like area proximal to the stenosis showed intact but hypertrophic muscularis. A deep defect was seen in the mucosa with destruction of the mucosa and the muscularis, and a breakthrough into the mesentery (Fig. 6). Here there was marked cellular infiltration, thickening and edema of the serosa. The lesion was an ulcer with virtually no attempt at re-epithelialization. This was an ulcerative form of what appeared to be a caseating lesion, caseation associated with the characteristic Langhans types of giant cells. In acid-fast stained sections of this particular area, a large number of tubercle bacilli were demonstrated. This was an ulcerative form of ileal tuberculosis with multiple little ulcers and only relatively little attempt of hyperplasia.

How did the process develop? The earliest lesion away from the areas of necrosis showed an intact mucosa (Fig. 7). Between mucosa and muscularis mucosa, possibly where a lymph follicle once was, we found a type of early tubercle which some (1, 2) have considered the result of hematogenous spread, but which the majority (3-5) assumes results from tubercle bacilli coming from the intestinal lumen. They readily pass through the intact muscularis, setting up first exudative lesions in the submucosal layer, expanding from this mucosal layer to a larger focus with final breakdown of the area and breakthrough to the surface. This forms the characteristic undermining ulcer with relatively little participation of the mucosa in this earlier stage (6).

There was hardly any regenerative attempt of this epithelium. Then severe caseation followed with extension to the serosa (Fig. 8). In this case no tubercu-

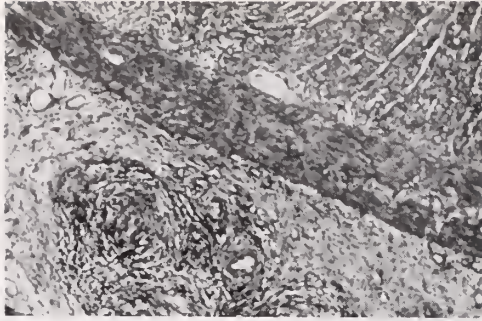


FIG. 8. Tubercles on the thickened subserosal layer. (Mallory aniline blue $\times 63$).

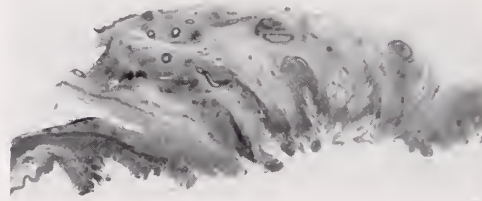


FIG. 9. Beginning hyperplastic tuberculosis produced by tuberculous infiltration of the mesentery after destruction of the muscularis and mucosa. (Mallory aniline blue $\times 4$).

lous peritonitis was present but only serosal involvement over the affected area. In one area a formidable mass was formed, the same mass which probably had been felt. It consisted of tuberculous granulation tissue, partly of the intestinal wall and to a greater extent of the peri-ileal structures, starting to produce the hyperplastic type of tuberculosis with little fibrosis (Fig. 9). The appendix and peri-appendiceal tissue were also involved. The appendiceal mucosa was destroyed and all of us have seen occasional cases where the clinical manifestations were those of appendicitis and the surgeon had removed the lesion. The colon was involved to the same degree except the same type lesion broke through, producing more extensive undermining. In the ileum also, we found considerable vascular involvement.

One type of vascular involvement was endarteritis. There was, in addition, involvement of the veins, especially the subserosal veins, with the development of the classical intima tubercle extending into the wall (Fig. 10). In some areas it destroyed the wall which accounted for the extensive miliary spread.

There was also the involvement of the lymphatics. It is not remarkable that the bronchial lymph nodes and mesenteric lymph nodes showed severe caseation with the recent tuberculosis and with also somewhat older beginning fibrosis. However, the oldest tuberculosis which could be seen anywhere was a small little nodule in the mesentery which was really the only calcified lesion which was found in the entire body and probably long antedated the recent episode.

In summary, the patient had an old pulmonary tuberculosis and apparently

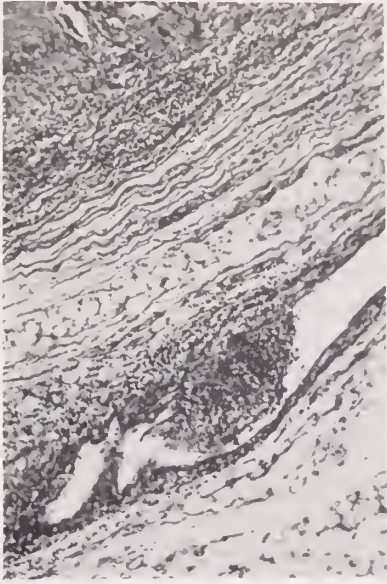


FIG. 10. Tubercle in the intima of a vein. (Mallory aniline blue $\times 63$).

very early dissemination must have taken place by the hematogenous route to the intestine to account for the calcified mesenteric node. I do not think that the latter represented a Ghon tubercle, the primary lesion, as would have been present with bovine tuberculosis (3). These are so rare that notwithstanding the fact that we could not find a primary complex in the lung, I still think this was a secondary lesion (2,4). Anyway, there was a fibrosing pulmonary tuberculosis with bronchogenic cavities. From there, a lymphogenous spread occurred as well as spread into the mediastinal nodes. Bronchogenic spread also took place with caseous pneumonia and acinose-nodose dissemination. Six months before death, he developed a cough and then emaciation, reflected in brown atrophy of heart and liver. From the bronchogenic spread, laryngeal tuberculosis which was healing as well as ileocecal ulceration with beginning hyperplasia developed. This probably took place three months before death. The patient then had persistent abdominal pain, weight loss, anorexia, vomiting, right lower quadrant pain and a low total protein. The disease spread to the lymphatics and to the venous intima and then generalized dissemination followed with terminal severe fever.

Dr. Wolf: Those of us from general hospitals are so unacquainted with tuberculosis of the bowel that we miss this diagnosis regularly. It is not true that we do not see tuberculosis of the bowel, particularly of the ileocecal region, at this hospital. I think if we went through the records, we would find we have had two or three cases each year. I think the X-ray Department is responsible to a considerable extent for missing these cases. I should like, therefore, to suggest that we lean over backwards and think of this diagnosis because rather specific therapy is available.

Dr. Crohn: You should really differentiate primary tuberculosis and secondary tuberculosis. The question of primary intestinal tuberculosis came up some years ago. Primary intestinal tuberculosis occurs practically only in the colon as far as we know; we reviewed the records of The Mount Sinai Hospital, and in the course of 25 years we found just four cases of primary bovine-type intestinal tuberculosis. We have not seen much secondary hypertrophic ileocecal tuberculosis in this hospital but we have seen it on occasions.

In discussing it before, I seem to have completely overlooked the fact that there was a possibility of primary cecal carcinoma in this case. A primary carcinoma of the ileum involving the colon or carcinoma of the colon with this appearance in the ileum was so remote that I gave it no consideration. Since sarcoidosis and other conditions were mainly ruled out, hypertrophic ileocecal tuberculosis was the most logical diagnosis.

Final diagnosis: Tuberculosis of terminal ileum, appendix, ascending colon and lungs, with generalized miliary spread.

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Radiological Notes

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CASE NO. 81

This was the first admission of an 11 year old male child. At the age of six weeks, a pyloromyotomy (Rammstedt operation) was performed for hypertrophic pyloric stenosis. However, vomiting persisted after this procedure and a posterior gastroenterostomy was performed at the age of three months. At the age of seven years, he began to complain of intermittent epigastric pain not associated with vomiting, nausea or diarrhea. A barium meal (Figs. 1A, 1B) examination three years prior to admission showed the status post-gastroenterostomy. The anastomosis was located high on the greater curvature of the stomach and most of the barium appeared to leave the stomach through the anastomosis although a small amount did outline the duodenal bulb and descending duodenum. There was no evidence of marginal ulceration or dilatation of either the afferent or



Case 81, Fig. 1A. Barium meal examination shows the anastomosis located rather high on the greater curvature aspect of the stomach (arrow along greater curvature). Most of the barium left the stomach through the gastrojejunal stoma. There was no evidence of ulceration in this area. There is limited distensibility of the antrum, particularly on its lesser curvature aspect (right arrow). Rather thick longitudinal folds are seen in the antrum.



Case 81, Fig. 1B. The common appearance of the antrum during the course of the examination was persistent narrowing, presumably the result of spasm. The bulb is partially filled. No ulceration is evident in the antrum or the bulb.

effluent loops. However, there was persistent narrowing of the antrum which showed limited distensibility particularly on its lesser curvature. The gastric fold pattern in the antrum was somewhat thickened but maintained a normal longitudinal appearance. An ulcer crater could not be demonstrated in this area. The visualized duodenal bulb appeared to be small but not remarkably deformed. Emptying time of the stomach did not appear to be abnormal. The child was treated by regulation of diet and antispasmodics but intermittent epigastric pain persisted. Three weeks prior to admission, he vomited a large amount of bright red blood followed by passage of black stools. Hemoglobin fell to 5 grams per cent. He was hospitalized for one week elsewhere during which time he was transfused and bleeding gradually stopped. A barium meal examination at this time showed the same findings as seen three years previously. On admission to this hospital, the child appeared to be well developed and not acutely ill. There were no pertinent physical findings. Hemoglobin was 10 grams per cent, white blood count 12,650 per cu. mm. with a normal differential. Gastric analysis showed a free hydrochloric acid of 28 units and a total of 54 units. The gastric contents showed 2 plus guaiac reaction.

The child underwent laparotomy. There were numerous adhesions between the distal portion of the stomach and the edge of the right lobe of the liver. On external palpation, it was evident that there was rather marked thickening

of the wall of the stomach in the region of the pylorus and the adjacent portion of the antrum but an ulcer crater was not felt. A partial gastrectomy was performed with the upper level of resection immediately distal to the gastrojejunal stoma. The mucosa of the antrum was hemorrhagic and showed several erosions up to 3 mm. in diameter. Along the lesser curvature aspect, about 1½ to 2 cm. from the pylorus, there was a small stellate scar about 6 mm. in diameter which had the appearance of a healed chronic erosion of the stomach. Microscopic examination confirmed muscular hypertrophy of the pylorus.

This patient is of interest because of the fact that a gastroenterostomy was performed so early in life. The development of bleeding presumably the result of antral erosions appears to be a complication of this type of operation which may occur many years later. The original operative procedure for hypertrophic pyloric stenosis was a gastroenterostomy but this has been long abandoned.

Final Diagnosis: MULTIPLE ANTRAL EROSIONS WITH MASSIVE BLEEDING 11 YEARS AFTER GASTROENTEROSTOMY FOR HYPERTROPHIC PYLORIC STENOSIS OF THE NEWBORN.

Acknowledgment

This case was presented through the courtesy of Dr. Ernest Arnheim.



Case 82, Fig. 1A. Barium meal shows the patulous gastro-jejunal stoma (arrow on greater curvature) through which the barium passed promptly. Little barium left the stomach through the pylorus. No evidence of marginal ulceration is present. The folds in the fundus are thickened. The distal portion of the stomach (arrow) beyond the stoma is markedly narrowed with normal appearing longitudinal rugae. The bulb is not deformed.

CASE NO. 82

A 75 year old white female was admitted with the chief complaints of dizziness, weakness and nausea of three months duration. Twenty-six years previously, because of a peptic ulcer, a gastroenterostomy had been performed elsewhere. Six years after this operation, an incisional hernia required repair. One year prior to admission, the patient was admitted to the Orthopedic Service for treatment of a bursitis and a hemoglobin of 8.8 grams per cent was discovered at that time. For three months prior to admission, in addition to weakness, she complained of sour eructations and occasional mid-epigastric burning pain not related to food and relieved only slightly by alkalis. Appetite was good and bowels moved regularly. There was a weight loss of about five pounds, apparently of recent origin. Examination on admission showed an elderly female appearing chronically ill. Blood pressure was 170/100. The heart did not appear to be enlarged. The abdomen was obese, and non-tender, with a low midline abdominal scar. Hemoglobin was 7.5 grams per cent, red blood count 3.9 million per cu. mm., hematocrit 29 per cent. Serum iron was 96 micrograms per cent. White count was 6,100 per cu. mm. with a normal differential count. Stool guaiac showed a trace on one occasion but was negative on five subsequent examinations. Gastric analysis showed no free acid. Barium meal examination (Fig. 1A, 1B) showed a patulous gastrojejunal stoma on the greater curvature aspect. The fold pattern in the proximal portion of the stomach was thickened. The most



Case 82, Fig. 1B. This film demonstrates the maximum degree of distensibility of the antrum (arrow) achieved during the examination.

striking feature was a marked lack of distensibility of the portion of the stomach beginning a short distance distal to the anastomosis. Barium also outlined the duodenal bulb and a part of the duodenal sweep which did not appear to be remarkable. The impression of the roentgenologist was that the findings were most likely due to a scirrhus carcinoma of the distal portion of the stomach.

Exploratory laparotomy was performed. On examining the stomach, it was evident that the antrum was markedly narrowed but pliable and that no discrete mass was palpable. No abnormality was noted in the region of the gastroenteric stoma. The entire small bowel and the colon were examined carefully and showed no evidence of an intrinsic lesion. A gastrotomy was then done. The inner aspect of the stoma was normal as was the first inch of jejunum. The mucosa of the stomach appeared to be normal. The index finger could barely be inserted into the antral portion of the stomach but no mass or ulceration was palpable. A biopsy of the gastric mucosa was taken and, incidentally, a small neurofibroma about 5 mm. in diameter enucleated from the anterior wall of the stomach. The pathological report of the biopsy of the stomach was "severe acute and chronic gastritis with cystic dilatation of the glands".

The patient did well post-operatively but has continued to complain of a variety of upper abdominal symptoms. Re-examination two years after the exploratory laparotomy again showed marked narrowing of the antrum. In general, however, the patient has not deteriorated or shown evidence of malignant disease.

Final Diagnosis: CONTRACTED ANTRUM 26 YEARS POST-GASTROENTEROSTOMY SIMULATING SCIRRHUS CARCINOMA.

CASE NO. 83

This was the first admission of a 39 year old male who began to complain six months prior to admission of right lower quadrant pain and over this period of time lost 15 pounds in weight. For three weeks before admission, he noted the presence of tarry stools associated with some increase in the severity of the right lower quadrant pain. For about three weeks, he had been constipated but, five days prior to admission, he began to have loose watery bowel movements which appeared to be black. Shortly prior to admission, he began to vomit. The past history was not contributory except for an appendectomy done at an unknown time previously.

Physical examination on admission showed a tender mass about the size of a tangerine on the right side at the level of the umbilicus. It appeared to be soft and round and easily movable. The borders of this mass were easily defined by palpation.

Hemoglobin was 6 grams per cent, white blood count 11,200 per cu. mm. with a normal differential count. Stools showed 4+ guaiac on several occasions. With multiple transfusions, the patient's hemoglobin was elevated to 12 grams per cent.

Barium enema examination showed no abnormality in the colon but no barium



Case 83, Fig. 1. The terminal ileum shows an irregularly multinodular filling defect sharply demarcated proximally (medial arrow) where the appearance suggests overhanging edges. Distally the segment immediately proximal to the ileocecal valve is markedly narrowed but the valve itself (upper lateral arrow) appears as a sharply demarcated globular filling defect. The caput coli (lower lateral arrow) is small. The loops of bowel proximal to the terminal ileum are not dilated and there was no delay to the passage of barium through these loops or through the terminal ileum into the ascending colon.

entered the terminal ileum. Barium meal examination with serial films of the small bowel demonstrated a markedly irregular terminal ileum over a distance of about three inches (Fig. 1). The caput coli appeared to be quite small and irritable. The ileocecal valve was prominent and, immediately proximal to the ileocecal valve, the mucosal pattern was completely absent and numerous nodular intraluminal projections were present. The proximal margin of this segment appeared to be sharply demarcated with overhanging edges. There was no remarkable delay to the passage of the barium through the small bowel at this time and the barium passed through the lesion in the terminal ileum into the ascending colon without difficulty.

Because of the location of the lesion in the terminal ileum and the relative

lack of narrowing associated with an extensive neoplasm, the diagnosis of lymphosarcoma of the terminal ileum was made.

The patient was explored, a mass found in the ileocecal region and an ileocelectomy performed. The specimen consisted of a segment of colon 34 cm. in length and a segment of ileum of approximately the same length with attached mesentery. One centimeter proximal to the ileocecal valve and extending proximally for a distance of 5 cm., there was a flat ulcerated mass of very firm grayish white tissue which replaced all the layers of the intestinal wall and extended into the surrounding fat tissue. Two very large firm lymph nodes measuring up to 2 cm. in diameter were found in the surrounding fat. The mucosa in the ileum proximal to the lesion was not remarkable. The strip of ileum 1 cm. in length between the distal margin of the tumor and the ileocecal valve was irregularly but superficially ulcerated. The ileocecal valve was not remarkable and the colonic mucosa was smooth and free of abnormalities. The caput coli was small but uninvolved. The appendix was absent. On histological examination, the tumor turned out to be an infiltrating adenocarcinoma of the ileum. The ileocecal valve was not involved. There were three involved lymph nodes in the mesentery of the ileum.

A carcinoma of the terminal ileum is a rare lesion. In the experience at this hospital, most of the neoplasms seen in this area have been in the lymphoma or myosarcoma groups.

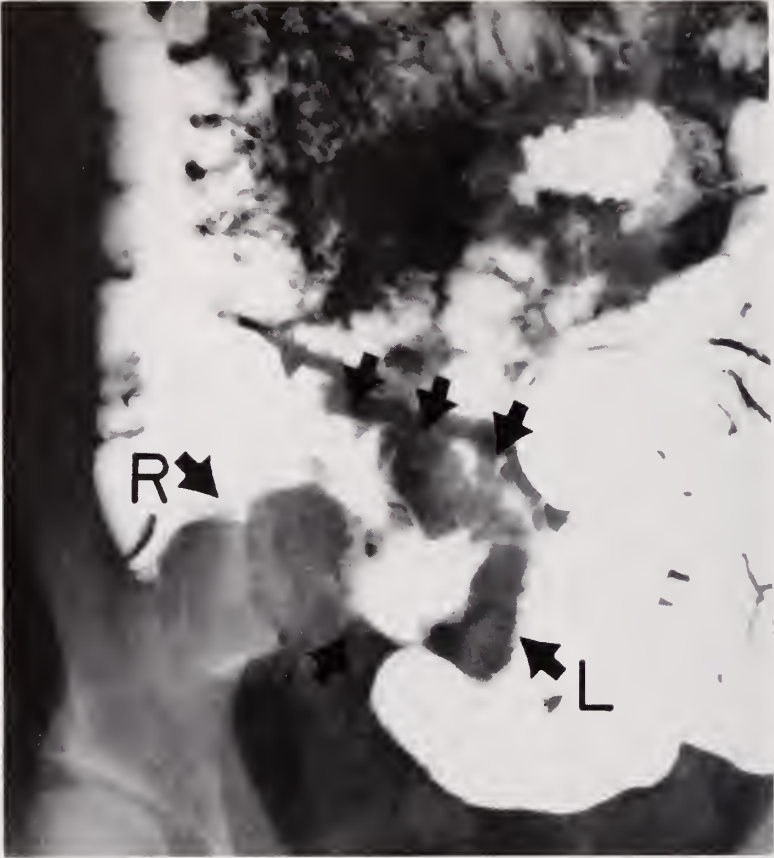
Final Diagnosis: PRIMARY ADENOCARCINOMA OF THE TERMINAL ILEUM.

CASE NO. 84

This was a 39 year old male who was originally seen with a history of two days of right lower quadrant pain, fever and leucocytosis. A diagnosis of acute appendicitis was made and the patient was explored. On exploration, however, a large abscess was discovered in the right lower quadrant with markedly adherent loops of small bowel that appeared to be thickened. The surgeon felt that he was dealing with terminal ileitis, made no attempt to expose the appendix and closed without intervention. The patient thereafter was treated conservatively with antibiotics and supportive therapy but despite this, the right lower quadrant mass increased in size and the patient was obviously going downhill. A small bowel series done elsewhere was said to have confirmed the diagnosis of terminal ileitis. The patient developed a draining sinus in the anterior abdominal wall and also gross hematuria. Barium meal examination (Fig. 1) including small bowel series was then repeated and demonstrated a large mass in the ileocecal region with central excavation. On cystoscopy, a mass was noted in the bladder which was biopsied. This was reported as adenocarcinoma.

The patient continued to bleed profusely from the bladder. The right lower quadrant mass enlarged progressively and he died approximately eight months after the onset of symptoms. At autopsy, a large carcinoma of the cecum extending into the terminal ileum was present.

Final Diagnosis: CARCINOMA OF THE CAPUT COLI WITH DIRECT EXTENSION INTO THE TERMINAL ILEUM.



Case 84, Fig. 1. Film from the small bowel series shows a large mass in the right lower quadrant involving the caput coli and the terminal ileum. The right border of this mass (R, arrow) occupies the caput and is sharply demarcated and somewhat lobulated. The medial or left margin of this mass (L, arrow) is indicated by the indentation and compression of adjacent small bowel. Within the center of this mass (lower arrow), there is an irregular collection of barium indicative of central ulceration and excavation. Only the superior margin of the terminal loop of ileum (upper 3 arrows) shows a normal fold pattern. Most of the lumen of the terminal ileum is occupied by mass which communicates through several fistulous communications with the central ulceration. This appearance may be mistaken for ileitis if it is assumed that the large ulceration represents the lumen of the ileum. To avoid this error, it is necessary to realize that the superior wall of the terminal ileum, at least in places, is intact and that a mass defect is present which involves the caput coli and extends into the ileum from below.

CASE NO. 85

This was the first admission of an eight month old male infant. Eight hours prior to admission, the foster mother of the child, while carrying the infant in her arms, accidentally fell and was unconscious for an unknown period of time. She awoke to find the child crying and noted apparently for the first time a swelling at the lower end of the left humerus of the infant. At birth, the child had been placed in a Home and at the age of four months was placed in a foster home. The child was backward physically and, up to the time of admission, had not sat, cut teeth or supported himself in the prone position. After the discovery of the swelling by the foster mother, she took the child to the Emergency Room and, after x-ray examination, the child was admitted. X-ray examination of the skeleton (Figs. 1A, 1B, 1C) showed rather remarkable changes. Both humeri showed multiple layers of periosteal thickening extending the full length of the shaft with markedly irregular bone formation and calcification in both metaphyseal regions extending into the soft tissues. The cortices of the shafts were thickened. There were also epiphyseal and metaphyseal plate irregularities at the medial ends of the clavicles and acromion processes and infractions at the medial margins of the metaphyseal plates of the distal end of the left femur and left tibia.



Case 85, Fig. 1A. Right humerus shows multilayered periosteal new bone formation along the shaft. At both ends, particularly marked proximally, there is irregular new bone or calcified osteoid extending into the soft tissues. The metaphyseal plate is completely disorganized and fragmented.



Case 85, Fig. 1B. Left humerus showing similar changes, most marked distally. The metaphyseal ends of the clavicle and acromion are also severely fragmented.



Case 85, Fig. 1C. Left leg. Metaphyseal infractions (arrows) through the medial ends of the distal femur and distal tibia are evident. These represent areas of minimal trauma as compared with the upper extremities.

On admission, the significant positive findings were swelling of both humeri most marked on the postero-superior aspect of the left elbow. There was limitation of motion at both elbow joints particularly of extension and pain in full motion of the shoulder joints. Temperature and vital signs were within normal limits. The patient weighed about 14 lbs., and the head measured 17 inches in circumference. Neurological examination was negative and the child appeared to respond normally to pinprick. Hemoglobin was 13 grams per cent, red blood count 4.2 million per cu. mm., white blood count 7,100 per cu. mm. with 93 per cent lymphocytes. Total protein was 6.4 grams per cent, albumin 4.3 grams per cent, globulin 2.1 grams per cent, blood calcium 9.2 mgm. per cent, phosphorus 4.8 mgm. per cent, alkaline phosphatase 20 K-A units and on another occasion 6 K-A units. Wasserman test was negative.

From a clinical point of view, luetic periostitis, Caffey's syndrome, hypervitaminosis A, trauma, and scurvy were considered. There was no clinical or laboratory evidence to substantiate any specific diagnosis. Moreover, the x-ray findings were typical of the syndrome of multiple overlooked fractures and/or epiphyseal dislocations in infants. At this age, the periosteum is loosely attached to the shaft and fractures through the epiphyseal cartilage lead to massive subperiosteal hemorrhage. It has been suggested that unusual metaphyseal fragility may be a predisposing factor but it is likely that the changes are due to neglect after a variety of trauma. The child was treated on this basis with rapid improvement. Reexamination six months after discharge (Figs. 2A, 2B) con-



A



B

Case 85, Fig. 2A. Right humerus. Re-examination six months later shows reconstitution of normal epiphyseal-metaphyseal relationships and disappearance of periosteal new bone. The shaft is moderately thickened.

Case 85, Fig. 2B. Left humerus six months later shows similar improvement.

firmed remarkable regression with disappearance of periosteal new bone and normal appearances at the ends of the bones.

Final Diagnosis: MULTIPLE NEGLECTED INFANTILE FRACTURES.

CASE NO. 86

A five month old female child was admitted for the second time to this hospital because of persistent jaundice and dark urine, progressive abdominal swelling



Case 86, Fig. 1. Examination of the extremities shows irregularity of all of the zones of provisional calcification with rather diffuse demineralization of both shafts and the epiphyses.

and edema of the lower extremities. Previous admission was at the age of ten weeks because of jaundice said to have been present since birth and clay colored stools. On the first admission, the possibility of biliary atresia was considered

and exploratory laparotomy planned until it was noted that the blood bilirubin, both direct and indirect, fluctuated. Despite the fact that the clinical determinations in blood, urine and stool seemed to indicate obstructive jaundice, it was felt that a neonatal hepatitis was more likely. Physical examination on this admission showed an icteric infant with markedly distended abdomen and shifting dullness. The liver edge was felt three fingers below the costal margin. The spleen was felt $1\frac{1}{2}$ fingerbreadths below the left costal margin. There was sacral edema extending up to the lower thoracic vertebrae and three plus pitting edema up to the knees. Hemoglobin was 7.8 grams per cent, urine showed 4+ bilirubin, Wasserman test was negative.

The child was treated supportively, including paracentesis. Extensive work-up appeared to be consistent with cirrhosis of the liver. Alkaline phosphatase was 25 K-A units, calcium 9.8 mg. per cent, phosphorus 2.2 mg. per cent. The patient went downhill despite active therapy and died about two weeks after admission. Post mortem examination confirmed the diagnosis of cirrhosis.

Of interest from the roentgen point of view was the examination of the bones (Fig. 1) which showed changes similar to those seen in a mild degree of rickets. In long standing jaundice in infants whether due to biliary atresia or, as in this patient, cirrhosis, these changes are common presumably resulting from failure to absorb vitamin D and other nutritional disturbances. In this particular child, the evidence of ascites on the examination of the abdomen plus the bone changes suggest the correct diagnosis.

Final Diagnosis: RACHITIC BONE CHANGES IN PROLONGED INFANTILE JAUNDICE.

CASE NO. 87

A 34 year old woman was delivered of a male infant after induction of labor by rupture of the membranes at the 38th week. Because of recurrence of hyperthyroidism, the patient was treated with propylthiouracil during the last four months of pregnancy. The original dose was 300 mgm. a day which was diminished to 250 mgm. a day after a month. Lugol solution, 30 drops a day, were also given. The newborn infant had palpable thickening in the region of the isthmus of the thyroid and on both sides of the neck somewhat more marked on the left, with minimal stridor during crying episodes. The skin of the face and the eyelids appeared to be somewhat puffy.

Roentgen examination of the neck in the lateral projection (Fig. 1A) showed widening of the soft tissues around the trachea, particularly anteriorly, where there was a smooth indentation on the anterior aspect of the air canal. Examination of the bones showed no epiphyses of the long bones. The child was treated for hypothyroidism and improved rapidly.

The induction of hypothyroidism in the fetus as a result of administration of antithyroid drugs to the mother is well known but this combination of circumstances is relatively uncommon. The roentgen findings are typical.

Final Diagnosis: CONGENITAL GOITRE DUE TO ADMINISTRATION OF PROPYLTHIOURACIL DURING PREGNANCY.



Case 87, Fig. 1. Lateral view of the neck shows no remarkable narrowing of the air canal but the soft tissues on each side of the trachea are widened, particularly anteriorly where there is a smooth indentation of the tracheal wall.



Case 87, Fig. 1B. No evidence of epiphyseal calcification was present in either knee.

GASTRIC EMPTYING IN THE TRENDELENBURG POSITION

Considerable attention has been paid to the sphincteric mechanism which prevents reflux of gastric contents into the esophagus when the patient assumes the inverted or Trendelenburg position. A large amount of information is also available on motor activity of the stomach. Under ordinary circumstances, it is accepted that peristaltic activity is responsible for gastric emptying. It is not clear, however, how peristaltic activity can be effective if the individual is maintained in the inverted position since the gastric air bubble rises to the pyloric region and acts as an air trap. On a clinical basis, however, it is evident that patients maintained in the Trendelenburg position over a considerable period of time, e.g. in traction, do not develop remarkable gastric retention or difficulty in maintaining nutrition. It was decided to illustrate this fact by

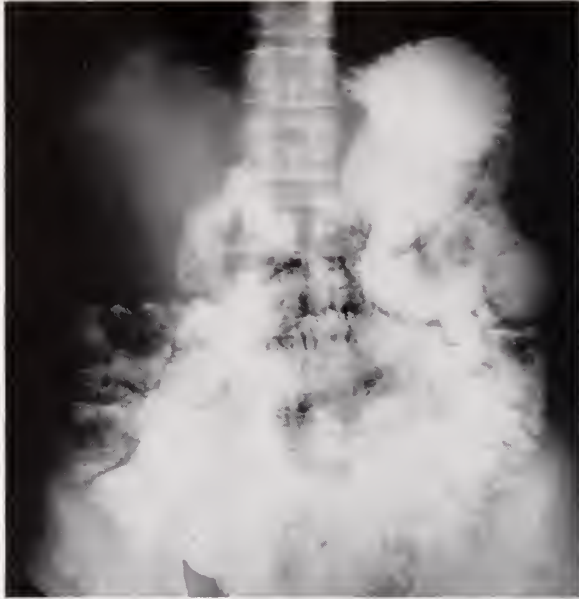


Fig. 1. Film taken 30 minutes after administration of barium with patient maintained in the Trendelenburg position shows filling of small bowel and colon. However, the barium was given with the patient erect.



Fig. 2A. Repeat examination the next day. Barium given to patient after he assumed the inverted position. Residual barium is present in the colon but all the barium given is in the distal esophagus and fundus of the stomach. A large quantity of air is present in the body and the antrum.



Fig. 2B. One hour after Fig. 2A with the patient still in Trendelenburg position. Re-examination shows practically complete emptying of the stomach which is moderately distended with air. Most of the barium is in the ileum and ascending colon.

roentgen methods by administering barium to a patient otherwise well but maintaining him in a markedly Trendelenburg position. On the first occasion, unfortunately, the barium presumably was administered with the patient not in Trendelenburg position although he assumed this position immediately thereafter. Therefore the fact that examination of the abdomen 30 minutes later (Fig. 1) showed extensive filling of the small bowel was not considered to be unequivocal evidence of emptying with the patient inverted. The experiment was then repeated with careful administration of a fluid barium mixture to the patient after he was placed in the inverted or markedly Trendelenburg position and the patient was maintained in this position for about an hour. The film taken immediately after administration of the barium in the Trendelenburg position showed a considerable amount of air in the distal stomach as well as the barium in the fundus (Fig. 2A). An hour later, re-examination of the patient still in the same position showed practically complete emptying of the barium from the stomach and extensive filling of the small bowel loops (Fig. 2B). A small amount of barium had entered the right side of the colon as well. Further observations will be required to clarify the mechanism of gastric emptying under these conditions.

Daniel Stats Memorial Prize

The Dr. Daniel Stats Memorial Committee is pleased to announce the first annual award. By terms of the Fund, the award is granted to a member of the House Staff who during the current academic year has published or has accepted for publication, the most meritorious paper on a subject with hemologic orientation. Several excellent papers were submitted for consideration. The Committee unanimously chose:

“A Study of Haptoglobin”

by

Dr. Harvey J. Weiss

Dr. Weiss received his A.B. and M.D. degrees from Harvard University. He interned at Bellevue Hospital and took his medical residency at The New York Veterans Hospital. During the course of this residency, he served for three months as a Fellow in Hematology at The Mount Sinai Hospital. He returned here July 1, 1958 as a Research Fellow in Hematology and on July 1, 1959 left to do a two year tour of duty in the army. Dr. Weiss plans to return to the New York area where he will practice hematology and internal medicine.

It is the hope of the Committee that subsequent awards will equal the high quality of this year's selection.

Alan F. Guttmacher, M.D., Chairman

Alexander B. Guttman, M.D.

Lester R. Tuchman, M.D.

Louis R. Wasserman, M.D.

In Memoriam

BERNARD SUTRO OPPENHEIMER

1876-1958

Dr. Bernard Sutro Oppenheimer was born in 1876 and died June 10, 1958 at the age of 82 years. He received his baccalaureate degree from Harvard College in 1897, and his medical doctorate in 1901 from Columbia University, College of Physicians and Surgeons where he later held a professorship.

From 1901 until shortly before his death, when physical disability made an active life no longer possible, he was a devoted laborer in the vineyards of medicine.

In 1901 he was a candidate for an internship at The Mount Sinai Hospital, under the fiercely competitive system then in vogue. In that year among those chosen were Ben Oppenheimer, Alfred Fabian Hess and Sigismund Goldwater. Others that met this test at about the same time were Emanuel Libman, Edwin Beer, Israel Strauss, Charles Elsberg, Robert T. Frank, Eli Mosechowitz and I. C. Rubin, to mention but a few. He remained on the house staff from 1901 to 1904 and, following the pattern of his time, went to Central Europe to continue his post-graduate studies. He developed an early interest in cardiology and the infant science of electrocardiography, and maintained a close and personal relationship with the world leaders in those fields. He was among the first to use the electrocardiograph as a clinical instrument in this country.

In 1916 he became Cardiographer to The Mount Sinai Hospital, a post which he held until 1929 when he became Attending Physician, after having served from 1921 to 1928 as Associate Attending Physician. He remained as Attending Physician to the First Medical Service until his retirement in 1939 when he was appointed Consulting Physician to the Hospital, a worthy follower of Janeway, Brill, Libman and others.

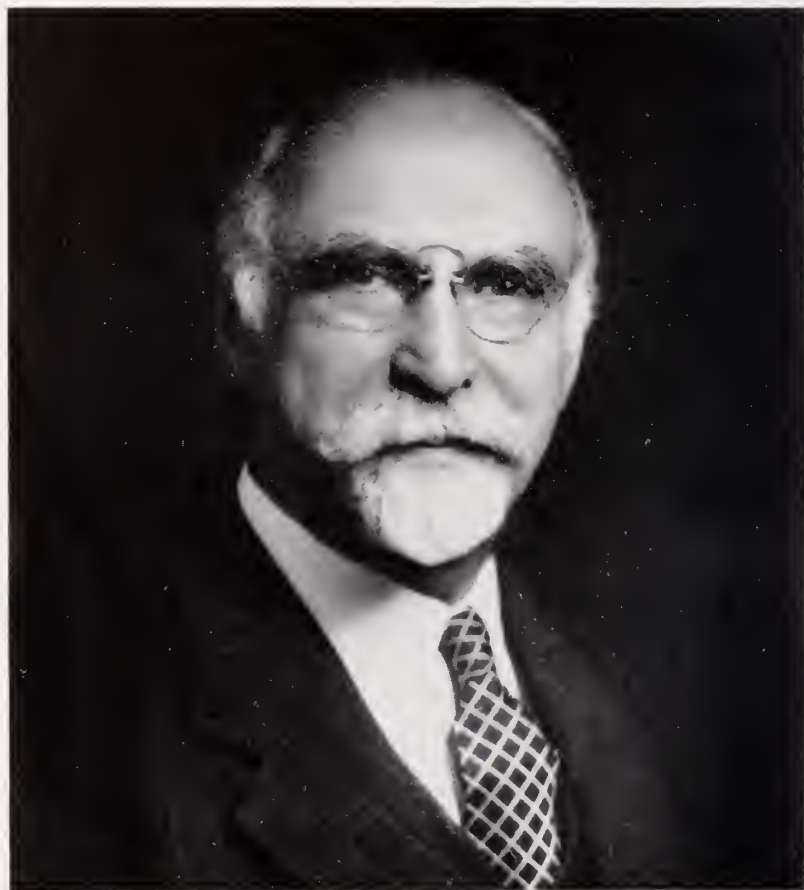
During those years he was an active and successful practitioner and teacher.

He was of such an energetic temperament and his interest in clinical medicine was so great, that one large hospital service and all its duties could not satisfy his needs. He became Chief of the Medical Service at the Montefiore Hospital where he rendered devoted service.

Every house physician of the late 20's and 30's remembers him as the tall, erect bearded gentleman who made rounds from 3:00 to 6:00 P.M. every day, including Saturdays, and then personally made the ward consultations on the surgical side. They did not know that he had already done a full day's work at his office and had usually seen a patient at home in consultation before he had arrived at the hospital. He attended every hospital conference, although they were not as numerous as at present.

To most, an active practice and two major hospitals would have been suffi-

Delivered at a memorial meeting held at The Mount Sinai Hospital on November 17, 1958.



DR. BERNARD SUTRO OPPENHEIMER
1876-1958

cient, but not to Ben Oppenheimer! He worked in the physiology laboratories at Columbia University with Dr. Williams and was a leader in the educational program at the New York Academy of Medicine and at this hospital. It is in this field of postgraduate medical education that he was a pioneer. For many years he was chairman of the Committee on Medical Education of The Mount Sinai Hospital during which period the educational functions of the hospital were widely expanded. He realized that the physician who had been given the opportunity to acquire special knowledge also had the obligation to make that knowledge available to his colleagues who were less favorably situated. Ben Oppenheimer took that duty seriously and fulfilled it magnificently.

Many of his summers were spent in Europe where he visited more hospitals and laboratories than museums. These medical contacts were always at the disposal of younger men, many of whom had their postgraduate work in Europe made pleasant and profitable because of a note from Dr. Oppenheimer to a European friend.

Before the United States entered World War I Ben Oppenheimer went to the British Heart Station at Colchester and with Sir Thomas Lewis and Marcus A. Rothschild made notable contributions to, and named, the syndrome now known as neurocirculatory asthenia. He later joined The Medical Corps of the U. S. Army, reaching the rank of full colonel in the Medical Reserve Corps after the war.

The English experience was not entirely professional. It was there that he met his future wife, Enid, who was teaching physiology in London. Dr. Oppenheimer was the most fortunate of men, having been blessed with a devoted and understanding wife who added her own talents of intellect and sympathy. Their home was a meeting place for many medical greats, both native and foreign, where young interns were often asked to dinner and an unforgettable experience.

In 1942, on the occasion of the celebration of his retirement from the Ward Service, his friends and colleagues published a Festschrift volume of over 850 pages, the contributors being a veritable who's who of world medicine. One would suspect that this crowning honor would have left Ben Oppenheimer in quiet repose. But that was not in his character. He had made the fortuitous observation, in some studies on experimental hypertension in the rat, that kidneys wrapped in cellophane gave rise to malignant sarcomas in the peri-renal tissue. This observation was made at a time of his life when most men were looking for the well-earned ease of retirement. To him it was a new challenge and there started an intensive study of experimental transplantable sarcoma induced by foreign bodies. His close collaborator in this work was his wife, Enid, and they were both honored this very year by an invitation to the International Cancer Congress in London to present their work. Ben's death in June prevented his personal presence in London, an honor to which he had looked forward in spite of his physical handicaps at the time.

On the occasion of his 80th birthday, his friends and patients established the Bernard Sutro Oppenheimer Lectureship at the New York Academy of Medicine, with funds sufficient to invite a lecturer of international distinction each year.

This was no physician of limited scope and vision—true, his major interest was in cardiovascular disease but a mere list of the titles of some of his publications will show you the breadth of his interest.

The Problems Involved in a Case of Typhoid Fever in Pregnancy. 1910

The Pathological Findings in the Parathyroids in a case of Infantile Tetany. 1911

Ochronosis. 1922

Syphilis of the Stomach. 1926

Lipemia and the Reticulo-endothelial Apparatus. 1925

Hypertensive Encephalopathy. 1927

(Note: This was the first description of this syndrome.)

Gaucher's Splenomegaly. 1929

Vascular Occlusion in Polycythemia Vera. 1929

Transplantation of the Adrenal Cortex for Addison's Disease. 1934

Werner's Syndrome. Report of First Necropsy. 1941

This, in part, is the picture of the man. This was the hospital that was closest to his heart. From the many whom he trained, loved and helped,

Hail and farewell!

SOLOMON SILVER, M.D.
for the
Editorial Board

In Memoriam

REUBEN OTTENBERG

1882-1959

Reuben Ottenberg, associated with The Mount Sinai Hospital for half a century, passed away in April 1959 after almost a decade of incapacitating illness. His was a remarkable career in that he was an investigator of the first rank, contributing to the advancement of medicine fundamental discoveries and at the same time practicing medicine as a "beloved physician." He was born in New York City in 1882, received his B.A. degree from Columbia University in 1902 and his M.D. degree from the College of Physicians and Surgeons in 1905. He interned at the Lenox Hill Hospital and thereafter did research work at Columbia University with Hans Zinsser and at the laboratories of The Mount Sinai Hospital, where he was appointed Adjunct Physician in 1921 and Associate Physician in 1931, a position he held for fifteen years. He was Assistant Professor of Medicine at Columbia University.

Reuben Ottenberg had an unusually fine character and an exceptionally original mind. In spite of this he was a very modest person, so much so, that he never would see newspaper reporters when they came to interview him about his work. He was a quiet, kind, sympathetic person, always glad to talk over his work with other physicians and research workers, but always doing so with a certain self-effacement.

He published numerous papers on a wide variety of clinical subjects, among them Differential blood cultures in sinus thrombosis; The rate and location of removal of bacteria from the blood in human disease; Explanation for the cyanosis in sulfanilamide therapy; The etiology of eclampsia: historical and clinical notes; and many papers on jaundice and diseases of the liver. However his main contribution was in the field of blood groups and transfusion of blood where he was truly a pioneer.

Not until September 1954, more than forty years after his earliest publication, did he receive public recognition for this work when he was honored by receiving the Karl Landsteiner award of the American Society of Blood Banks and given an illuminated scroll with the following inscription:

"For distinguished pioneering contributions to blood banking and hemotherapy. In 1907 he performed the first blood transfusion in which the donor was selected by tests for compatibility. In 1908 he suggested (together with A. A. Epstein) that blood groups were inherited according to Mendel's law. In 1911 he established the principle that hemolytic transfusion reactions occurred when the plasma of the recipient contained antibodies for the red cells of the donor. In the same year he demonstrated blood groups in dogs. Every one of these were milestones in the growth of our knowledge of blood groups and formed the basis for the subsequent development of blood transfusions."

In an interesting article entitled "Reminiscences of the history of blood trans-



REUBEN OTTENBERG

1882-1959

fusion" (*Jour. Mount Sinai Hosp.*, 4: 264, 1937), Ottenberg reveals his modesty in the following quotation: "I did not realize that I had been the first to apply Landsteiner's discovery for determination of compatibility in an actual transfusion, and when, in 1908, I published an article on the arterial anastomoses and the blood transfusions, I merely mentioned that such tests had been done on my patients, and ventured the prophesy that they would be important for the future of blood transfusion. It took about five years of campaigning, experimenting and a few accidents to convince the medical public that blood tests before transfusion were essential."

It was quite characteristic of Reuben Ottenberg that, being himself the victim of an unusual disease, he should have kept careful notes on his symptoms, and have published an excellent case report of his illness under the title "Occlusion of the internal carotid artery: clinical diagnosis and therapy" (*Jour. Mount Sinai Hosp.*, 22: 99, 1955).

He was survived by his wife, a brother and a son who teaches anthropology in a Western university.

MURRAY H. BASS, M.D.
for the
Editorial Board

PATTERNS OF BONE CHANGE IN THE SICKLE CELL STATES

JOHN E. MOSELEY, M.D.

New York, N. Y.

The individual skeletal manifestations of sickle cell disease mimic the changes seen in other conditions and frequently require a high index of suspicion for undelayed diagnosis. But while no one of the findings may be considered specific for sickle cell disease, the combination of several features, in many instances, forms a pattern which is strongly suggestive, if not diagnostic, of the condition. In other instances the occurrence of a single feature in the presence of certain non-specific clinical findings constitutes a fairly firm basis for a sound opinion.

Many patients with sickle cell disease fail to show any skeletal changes whatever and we have been unable to correlate the extent of bony change, when it occurs, with the severity of the disease. Several skeletal features, however, do have some relation to the age of the patient and others appear to be more common in the genetic variants of the disease.

The osseous lesions in sickle cell disease are considered to be due to hyperplasia of the erythroblastic elements of the bone marrow and to thromboses and infarctions. This explanation of the findings appears to be taken for granted by most authors although it must be noted that the pathologic evidence for thromboses has not been demonstrated to the satisfaction of all observers. Kimmelsteil (1), for instance, reported a case of sickle cell disease in which there was ischemic necrosis in several organs but no evidence of vascular thrombosis. He suggested that sickling of red cells and diminution in oxygen carrying capacity results in reflex vasospasm, engorgement of capillaries with packed sickled red cells, local ischemia and infarction. The viscosity of the blood, due to sickled red cells, is increased at lower oxygen tensions and results in slowing down of the circulation with capillary stasis which aggravates tissue anoxia. Thus the circulation may be reduced without true thrombosis. More recently, Cohen, Sung and Robins (2) described a fatal case of sickle cell disease in which autopsy revealed ischemic necrosis in the spleen, liver, lungs, and the anterior lobe of the pituitary, but in which no evidence of vascular thrombosis could be demonstrated. Clarification of the disturbed physiology involved in these changes awaits further investigation.

Erythroblastic hyperplasia, a response to hemolysis and anemia, results in widening of the medullary spaces, thinning of the cortices and coarsening of the trabeculae. The radiographic shadow of the bone shows a diminution in density. The vertebral bodies, in addition to showing demineralization and trabecular coarsening, may become eupped (biconcave) from the pressure of the nucleus pulposus on the weakened bony structure. The diploic space between the tables of the skull may be widened by the proliferating marrow. The outer table is

From the Departments of Radiology, The Mount Sinai and Sydenham Hospitals, New York, N. Y.

thinned by this pressure and there may be radial striation of the diploic trabeculae.

Thromboses or vasospasm and stasis result in areas of ischemic necrosis or infarction. Usually beginning in late childhood or in young adulthood there may occur a characteristic laying down of new bone along the inner aspects of the cortices of the long bones with resultant narrowing of the medullary spaces. This process, which we have found to be much more common than the literature indicates, appears to be related to the change over from red to yellow marrow in long bones but the exact mechanism of this phenomenon has not been established. It is usually described as a thrombotic phenomenon.

In infants the bone changes, on occasion, may be confined to the small tubular bones of the hands and/or feet. Attention is first called to the condition by soft tissue swelling. The swollen parts are usually tender but may not be so. It must be emphasized that radiography of the hands or feet may, at first, reveal no abnormalities of the bones. There is apt to be a delay of from 10 to 20 days between the appearance of clinical signs and radiographically demonstrable osseous changes. However, some cases may never show any bony change despite meticulous follow-up study. The course of events is analogous to that occurring in traumatic periostitis in young children and to the development of cephalhematomas in infants where there is a time lag between injury and bone change. We suspect that many cases of this type are overlooked because roentgen changes happen not to be present at the time of examination. Swelling of the hands or feet occurs sufficiently often in infants with sickle cell disease to warrant an immediate suspicion of this dyscrasia in any Negro infant in whom there is no readily apparent cause for the swelling. When bone changes become manifest, they take the form of areas of bone destruction and repair of varying extent and of periosteal reaction. In some cases the changes do not progress beyond a periostitis (Fig. 1). These bone manifestations may be accompanied, on occasion, by changes in the lungs due to infarctions or pneumonitis or there may be evidences of infarction in other bones unaccompanied by any clinical findings. The bone change involves the phalanges, metacarpals or metatarsals. It simulates the appearance of osteomyelitis, syphilis or tuberculosis and may or may not be accompanied by periostitis. Healing, which is complete, may be rapid or slow and varies between one and eight months. It is likely that periosteal reactions are seen more commonly in infants and children because at this age the periosteum is more vascular and more loosely attached to the cortex than in older children and adults. A few cases of this type have been reported (3-6) but it is likely that they do not reflect the true incidence of this manifestation of sickle cell disease.

The osseous changes in the long bones, considered to result from thromboses or vasospasm and infarction, apparently vary with the extent of the vascular involvement and that portion of the bone affected. When the changes are minimal and affect only the periosteum the radiologic diagnosis can only be suggested. In older infants and young children, the ages at which periosteal reaction is more commonly seen, such cases may have to be distinguished from benign infantile cortical hyperostosis (Caffey), hypervitaminosis A and trauma. It may be more



FIG. 1. Hand of 5½ months old male with homozygous S sickle cell anemia. The soft tissue about the proximal phalanges is swollen. There is periosteal reaction along the shafts of the second and fifth metacarpals. The bone change did not progress beyond a periostitis.

helpful to suggest that in a Negro infant sickle cell disease should be included in the differential diagnosis of simple periosteal elevation since some of these patients present only a swollen extremity and other evidence of crisis may not be readily appreciated. In some instances, however, there may be tell-tale areas of infarction at the ends of the shafts. Such a case is shown in figure 2.

Vascular phenomena may be extensive enough to cause massive infarction of a long bone. The radiographic appearance, then, is practically indistinguishable from diffuse osteomyelitis. We have seen this type of bone change only in children and suspect that vascular anatomy at that age predisposes to lesions of such extent and degree. While such lesions are not common in sickle cell disease there have been recent reports (6, 7) which suggest an increasing awareness of this pattern of bone change. The roentgen appearance is that of extensive bone destruction and sclerosis with the development of involucrum identical to that seen in osteomyelitis (Fig. 3). In these cases, however, the clinical and laboratory evidences of osteomyelitis are not convincing. Blood cultures are negative, white counts and temperature drop after the subsidence of the crisis and maintain no positive relationship to antibiotic therapy. No sinus tracts develop and the clinician is faced with a paucity of findings to accompany such an extensive lesion.

There have been recent reports calling attention to an unusual frequency of salmonella osteomyelitis in patients with sickle cell disease (8, 9). It is considered that there is an increased frequency of osteomyelitis in sickle cell disease related to the assumption that avascular zones in bone would be appropriate foci for



FIG. 2. A 10 month old female with homozygous S sickle cell anemia who developed a swollen tender left thigh while recovering from a hemolytic crisis. Film made 12 days after onset of swelling shows frank periosteal reaction along shaft of left femur and very minimal periosteal elevation along shaft of right femur. There are irregular areas of osteosclerosis at the distal femoral metaphyses representing areas of bone infarction.



FIG. 3. Diffuse destruction of the humeral shaft with reactive sclerosis, involucrum formation and pathological fracture at proximal end. The patient was a 4 year old male with homozygous S sickle cell anemia. This appearance of massive infarction of a long bone cannot be differentiated radiographically from a diffuse osteomyelitis.



FIG. 4. Femur of patient with sickle cell-hemoglobin C disease. Irregular areas of sclerosis and lucency in head. There is thickening of the trabeculae in the neck and upper shaft. The medullary cavity is considerably narrowed by thickening of the inner aspect of the cortex.

the settling of organisms during a bacteremia. But the lesion described here as massive infarction of a long bone is not an osteomyelitis, despite its radiographic appearance. When such bony lesions are opened, no exudate is found and cultures are sterile (10).

The lesions described above as resulting from vascular occlusion or stasis are essentially lesions of infancy and early childhood. When bone infarction occurs in late childhood and in the adult it tends to involve the ends of the long bones or to present as a localized area of infarction in the medulla. In our experience the femoral and humeral heads are the most common sites of bone infarction in adults. The changes which result are quite varied in appearance. One or more good-sized areas of necrotic bone may be removed by osteoclasts leaving the head mottled with lucent areas, or this appearance may be mixed with areas of osteoblastic reaction so that the head shows a combination of bone destruction and production (Fig. 4). In the weight bearing hip joints, particularly, but also at the shoulders, the infarcted heads may collapse and lose their normal contour. In time, secondary hypertrophic arthritic changes may involve the joint (Fig. 5).

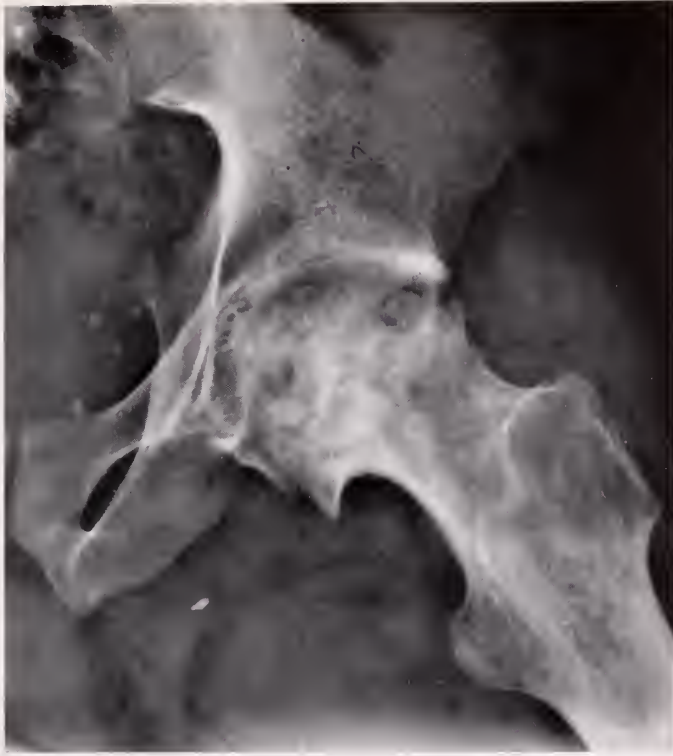


FIG. 5. Advanced destructive and productive changes in mal-shaped femoral head with secondary degenerative arthritic changes. Some trabecular thickening can be seen in the neck and upper femoral shaft. Patient was a 45 year old man with S-C disease.



FIG. 6. Sequestration of subchondral necrotic bone producing the appearance of osteochondritis dissecans in a young adult with S-C disease.

On occasion, a single lytic area may be walled off by reactive sclerosis or a ring of calcification. A sub-articular fragment of necrotic bone may sequestrate and produce the appearance of osteochondritis dissecans (Fig. 6). Such areas of aseptic necrosis are not difficult to recognize but there is another more limited form of necrosis which is often overlooked and which is almost as common as the



FIG. 7. Minimal sclerotic changes in head and neck of femur. Close inspection reveals thickening of the trabeculae in the neck and head, a portion of which is overlapped by the acetabular rim. Patient had S-C disease with mild joint pain.

more obviously destructive lesion. In this type there is a minimal to moderate diffuse increase in the density of the bone. Close inspection will show that the fine trabeculae are thickened. While a large area of the head may be so affected, in some cases only the proximal half may show sclerosis. This portion of the head may be overlapped by the acetabulum at the hip or by the acromion at the shoulder and this slight increase in density may be mistaken for double shadow of head and acetabulum or acromion. Careful study, however, will often show normal trabeculae in the acetabular bone and thickening of the femoral trabeculae (Fig. 7). Films made in positions of rotation will throw the involved area free from overlying structures.

When infarction occurs in the medulla it results in a localized lytic area surrounded by reactive sclerosis or with calcification at its border or there may be calcified debris within it (Fig. 8). Occasionally the infarct may result in an irregular area of trabecular sclerosis.

A common finding in the long bones of adults is diffuse thickening of the inner aspect of the cortices with resultant narrowing of the medullary spaces. The sclerotic bone may be separated from the cortex by a thin lucent area and present what has been described as a 'bone within bone' appearance (Fig. 9). It can be seen in areas to consist of thickened lamellated layers of new bone. In some instances, however, the appearance is that of smooth thickening of the cortex in a single compact layer (Fig. 10). We consider this pattern of bone change to be very strongly suggestive of sickle cell disease. It is seldom seen as more than a purely local process in other conditions and it is of immeasurable aid in diagnosis when it occurs in conjunction with aseptic necrosis at the end of a long bone. The two findings occur frequently together and in all cases of aseptic necrosis at the hips



FIG. 8. Large area of infarction at distal end of femur filled with calcified debris. Lesion has sclerotic border as does smaller irregular infarct at upper end of tibia.

or shoulders one should carefully inspect the upper ends of the femora or humeri for such changes (Fig. 4). There is nothing radiographically characteristic about aseptic necrosis of the femoral or humeral heads as it occurs in sickle cell disease. In adults it cannot be differentiated, for instance, from the aseptic necrosis occurring in caisson disease, necrosis following interruption of the circulation in fractures of the femoral neck and dislocations of the femoral head, nor from necrotic changes presumed to be due to arteriosclerosis. In children it may resemble the necrosis of Legg-Perthes disease or that due to Gaucher's disease. However, if there is an associated thickening of the inner aspect of the cortex of the shaft the probability of sickle cell disease is increased.

The skeletal appearances which result from hyperplasia of the erythroblastic elements of the bone marrow are confined more or less to infants and children. One important exception, however, is the change seen in the spine. As a result of marrow proliferation the cortices are thinned from internal resorption, widening the medullary spaces. The normal trabecular markings are diminished due to atrophy. Those remaining are more prominent and appear coarsened. The general appearance is that of osteoporosis. All of the bones may be affected but we have not found these changes to be as frequent as the literature would suggest.



FIG. 9



FIG. 10

FIG. 9. Layering of new bone along the inner aspect of the cortex with resultant narrowing of the medullary space in a patient with S-C disease. The clear zone between the layers of cortex creates a "bone within bone" appearance.

FIG. 10. Narrowing of medullary spaces as a result of relatively smooth thickening of cortices of shafts of radius and ulna in patient with homozygous-S sickle cell anemia.

In infancy and early childhood such changes may occasionally be seen in the phalanges, metacarpals and metatarsals. In the long and short tubular bones the changes may be similar to those seen in Cooley's anemia and in the proliferative reticuloses but are usually much milder than those seen in erythroblastic anemia. In the skull the diploic space may be widened and the coarsened trabeculae tend to assume a perpendicular striation. The outer table is thinned (Fig. 11). This appearance is similar to that seen in Cooley's anemia and in familial hemolytic anemia. More rarely it may also be seen in iron deficiency anemia and in cyanotic heart disease. These skull changes are among the least often found manifestations of sickle cell disease. They resolve with time leaving a normal appearing skull or one with slight thickening in the affected areas. In the long bones, osteoporosis, with widened medullary spaces and thinned cortices, is an uncommon finding. The vertebrae show a generalized demineralization with coarsening of the trabeculae. They are apt to show biconcave compression defects due to the pressure of the nuclei pulposi on the weakened bodies (Fig. 12).

Osteoporosis of the spine may occur in early childhood or may not become apparent until late childhood or early adult life. Unlike the porosis involving the

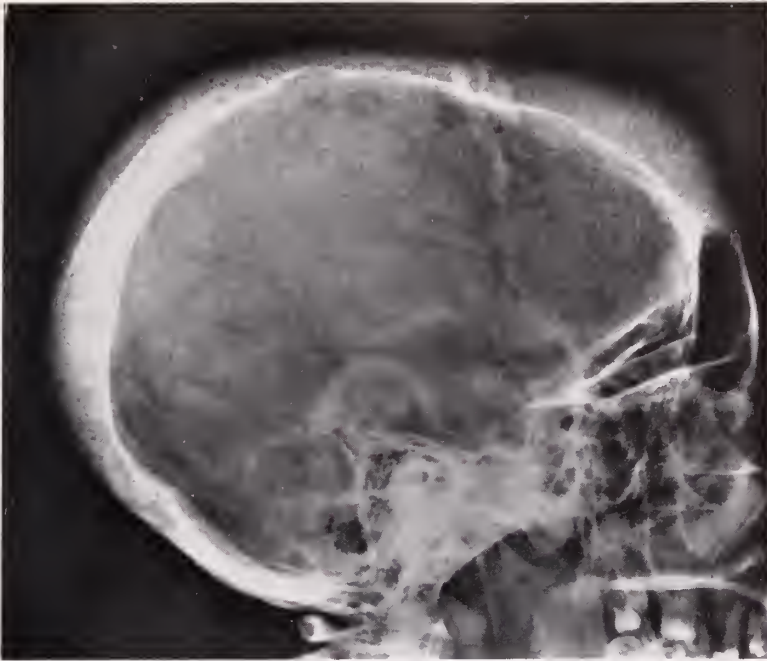


FIG. 11. Skull of boy showing widening of diploic space and thinning of outer table. There is tendency to radial striation of diploic trabeculae. Patient died at age of 15 from homozygous S sickle cell anemia.

peripheral portions of the skeleton which tends to disappear during adolescence, the changes in the spine persist into adult life. This is presumably related to the conversion of red marrow to yellow marrow in the extremities and the persistence of red marrow in the central skeletal segments throughout life. Osteoporosis of the spine is probably the most important skeletal change in sickle cell disease. It is frequently present when no other changes can be demonstrated and when it is seen in combination with any of the infarctive changes it is practically diagnostic. There are very few conditions which cause generalized demineralization of the spine alone in young adults. Osteoporosis of the spine is frequent enough to warrant examination for it in all cases of bone infarction. It may be considered that bone infarction alone suggests the possibility of sickle cell disease. Infarction associated with medullary sclerosis, thickening the inner aspects of the cortices of long bones, makes the diagnosis probable. If either of these two processes or both are associated with osteoporosis of the spine the diagnosis is practically certain.

The development of hemoglobin analysis by electrophoresis by Pauling and his associates (11) in 1948 and the genetic analysis of families with the sickling phenomenon reported by Neel (12) in the same year, heralded the beginning of a period of rapid progress in the elucidation of the sickle cell diseases. Since that time a series of observations of fundamental importance have been made with a rapidity which has few parallels in the history of medicine. Pauling and his



FIG. 12. Generalized demineralization of the spine with early cupping of the vertebrae in patient with homozygous S sickle cell anemia.

associates introduced the concept of molecular disease. Such disease is the result of genetically determined abnormalities of protein synthesis. Following the description of sickle cell hemoglobin as molecularly distinct from normal hemoglobin, an ever-increasing number of other abnormal hemoglobins have been described and their inheritance studied. Sickle cell trait, the result of inheritance of the sickling character from only one parent does not, except in rare instances, produce any clinical manifestations. Instances of splenic infarction during aerial flight have been reported in individuals with sickle cell trait (electrophoretically determined) (13), and at least two cases of recurrent gross hematuria have been encountered in individuals shown to have only the sickling trait (14). The hemoglobin in the red cells of such persons is a combination of normal and sickle cell hemoglobin. Sickle cell anemia, on the other hand, occurs in persons homozygous for the sickling character. The red cells possess only sickle hemoglobin. These patients suffer from a congenital, chronic hemolytic anemia. The combination of

sickle cell hemoglobin with other newly discovered abnormal hemoglobins produces diseases which are similar to and may be mistaken for sickle cell anemia. Of the abnormal hemoglobins so far found in combination with sickle cell hemoglobin, hemoglobin C is by far the most common. Hemoglobin D and G combinations are extremely rare.

In addition to inherited abnormalities of hemoglobin there are inherited abnormalities of red blood cells not reflected in the electrophoretic mobility of their hemoglobins. Among these are hereditary leptocytosis (thalassemia), hereditary spherocytosis and ovalocytosis. Inheritance of a gene for sickling from one parent and a gene for one of these abnormalities of red blood cells from another parent may occur but is rare.

The genetic variants of sickle cell disease in which bone changes have been found are sickle cell-hemoglobin C disease and sickle cell-thalassemia. Experience with other sickle cell variants is so limited at present that the possibilities of skeletal changes in them cannot now be entirely excluded. Smith and Conley (14) in an interesting report on the clinical features of the genetic variants of sickle cell disease were unable to find instances of aseptic necrosis of the femoral or humeral heads in sickle cell anemia but did observe such findings in 6 of 27 patients with sickle cell-hemoglobin C disease and in 3 of 11 patients with sickle cell-thalassemia. They suggested that these lesions might be confined to the variant groups. Since that report, however, these authors have encountered cases of aseptic necrosis of the femoral and humeral heads in patients with sickle cell anemia (homozygous S) (15). Tanaka, Clifford and Axelrod (16) have recently studied 38 cases of electrophoretically proven sickle cell anemia. Six of the thirty-eight patients showed aseptic necrosis of the femoral head. More recently Cookshott (17), reporting from Nigeria, was unable to find any instances of aseptic necrosis of the femoral heads in 120 cases of electrophoretically determined sickle cell anemia. Review of several of our patients with sickle cell anemia, proven by electrophoretic studies, has revealed instances of femoral and/or humeral head necrosis (Fig. 13), and we have not been able to use this finding as an item in differentiating between sickle cell anemia and the sickle cell variants. Experience with electrophoretically analyzed cases is now beginning to accumulate and it may well be that aseptic necrosis at the hips and shoulders is far more common in the variants but it does occur in sickle cell anemia and we doubt that it is by any means a rare finding. Experience with sickle cell-thalassemia is limited and perhaps does not warrant any conclusive impression, but there do not appear to be any significant differences in the nature of the bone changes seen in sickle cell anemia and those found in sickle cell-hemoglobin C disease. Differentiation between the two, however, can frequently be made when the age and history of the patient are known. When aspects of the hematologic study and physical examination are also known the differentiation between sickle cell anemia and sickle cell-hemoglobin C disease can be made in the majority of cases. It is important to make this differentiation because of the difference in prognosis in the two conditions.

Most patients with sickle cell anemia die by the age of 30 and almost all by the



FIG. 13. Patient with homozygous S sickle cell anemia showing osteoporosis of the sacrum, aseptic necrosis of the femoral heads and narrowing of the medullary spaces of femora by thickening of inner aspects of the corticalis.

age of 40. Any patient with skeletal changes and sickling, therefore, over the age of 40 is likely to be suffering from sickle cell-hemoglobin C disease or, rarely, one of the other variants. Patients with sickle cell-hemoglobin C disease may live to old age and we have seen numerous patients in their fifties and sixties and one in his seventies with this variant of sickle cell disease in whom there were unequivocal bone changes.

Actually, with some slight overlapping, the clinical courses of the two conditions differ in such a way as to suggest one or the other from the history alone. In sickle cell anemia the course of the disease is more severe and its manifestations tend to appear at an earlier age. The history is usually that of an unremitting, fairly severe hemolytic anemia with frequent bone and joint or abdominal crises. These patients tend to be asthenic in body build with disproportionately long legs. After the age of 9 or 10 the spleen is never palpable. Target cells in the blood smear may vary between 5 and 25 per cent, practically never any higher. The clinical course of patients in the variant groups, on the other



FIG. 14. Portion of film made as part of a pelvimetry showing biconcave cupping of the lumbar vertebrae and minimal sclerotic changes in the heads and necks of the femora. Diagnosis of sickle cell disease was suggested to clinicians who found patient to have S-C disease. Patient died suddenly on third post-partum day, presumably from an embolus.

hand, is usually mild. There are infrequent crises or none at all. A large number of patients with sickle cell-hemoglobin C disease have enlarged palpable spleens and splenic size may increase or decrease with changes in symptomatology. Splenic enlargement also may be found in patients with S-thalassemia. Target cells in the blood smears of patients with S-C disease are likely to run between 30 and 85 per cent. While not usually as high as in S-C disease the percentage of target cells in S-thalassemia tends to be much higher than that in sickle cell anemia and is usually around 30 to 50 per cent. Many patients with sickle cell-hemoglobin C disease have been found in arthritic or orthopedic clinics where they have gone for joint pain and it is often impossible to elicit any history of previous crises or debility of any kind. Three of our sickle cell-hemoglobin C patients were first seen because of hematuria. All of them had been classified as "idiopathic" or "essential" hematuria. In two of the cases aseptic necrosis of the femoral heads was detected on the intravenous pyelography films and the attention of the urologist called to the probability of sickle cell disease. The occurrence of hematuria in sickle cell disease has been well established. Goodwin et al., (18) reported four cases in 1950. Ryan and Fuller (19) in 1951 reported one case and Harrison and Harrison (20) reported nine cases in 1952 with pathological examination of the kidney specimens in four of them. These specimens showed areas of local ischemic necrosis of tissue and vessel walls and multiple hemorrhages.

Hematuria is more common in sickle cell-hemoglobin C disease than in sickle cell anemia and, as indicated above, may occur in sickle cell trait.

Another of our cases was discovered when necrotic changes were observed in the femoral heads on films made for pelvimetry (Fig. 14). This patient bled considerably at delivery and died suddenly on the third postpartum day. It is significant, although at present not explained, that patients with sickle cell-hemoglobin C disease tend to do poorly in pregnancy. This does not appear to be the case in patients with the more severe condition of sickle cell anemia. While patients with sickle cell anemia may show some increase in their anemia during pregnancy, acute exacerbation of their condition is not common. In sickle cell-hemoglobin C disease, on the other hand, there is apt to be a marked increase in the degree of hemolytic anemia and crises often occur during the last trimester of pregnancy or in the early postpartum period. Smith and Conley (14) have reported that of five sickle cell-hemoglobin C patients they observed, all of whom had one or more pregnancies, in every instance there was a marked increase in anemia often associated with other manifestations of crises. Eastman (21) has reported that of six pregnant women seen in The Johns Hopkins Hospital Obstetric Clinic since 1952 with S-C disease, three died in the course of pregnancy or labor. Two died of post-partum hemorrhage and one of pulmonary emboli composed of necrotic bone marrow.

It is of considerable value, therefore, if bone changes can be detected in patients unsuspected of having sickle cell disease. Because of the mild course of S-C disease there may be no history to suggest its possible existence to the clinician. This is particularly so in hospitals in which there is a small Negro census, and search for sickling is not done routinely. It should also be remembered that most S-thalassemia patients are caucasians and the finding of suggestive bone changes in these patients may be the first clue to the underlying sickle cell disease.

The visceral manifestations of sickle cell disease which may be radiographically demonstrated have been described by several authors, most recently by Middlemiss (22). These changes include splenic infarction, lung changes, cardiomegaly and cholelithiasis. With the exception of cardiomegaly in sickle cell anemia, however, bone changes are the most common radiographic manifestation of sickle cell disease and the findings most likely to suggest the diagnosis. Because the variants of this disease frequently present no suggestive history of the condition and at times not even an anemia, the clue to the diagnosis may come from the radiologist familiar with the various patterns of bone change which occur in these conditions.

SUMMARY

1. The bone changes which may be found in cases of sickle cell disease have been described. Attention is called to three patterns of bone change occurring in the early months or years of life which have received only scant notice in the literature.

2. Demineralization of the spine is considered the most frequent and most important skeletal alteration. When this feature is seen in combination with

aseptic necrosis at the ends of long bones or with medullary sclerosis along the inner aspects of the cortices, the diagnosis of sickle cell disease is most likely.

3. Aseptic necrosis of the humeral or femoral heads has been seen much more commonly in S-C disease but may be found in sickle cell anemia as well. In the latter instances, however, the diagnosis has usually been made on the basis of clinical manifestations while in S-C disease the individual may show aseptic necrosis in the face of an otherwise uneventful history. In this circumstance the radiologist is in a position to suggest the hematologic diagnosis.

4. Some of the important clinical manifestations of sickle cell anemia and the most common variant, S-C disease, are discussed. It is considered that with this information the radiologist can offer a more specific diagnostic impression.

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DYSKINESIAS FOLLOWING THERAPY WITH PHENOTHIAZINE DERIVATIVES

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Since the introduction of chlorpromazine* other drugs of the phenothiazine type have been developed and extensively used in all fields of medicine. For each new drug its maker claims distinctive properties. In general, the newer phenothiazines are more potent and produce fewer side-effects than does chlorpromazine; thus drugs are now available which produce less drowsiness, hypotension, jaundice, and dermatitis. However, not all the properties of the newer drugs are desirable. The incidence of extrapyramidal symptoms is much greater with most newer compounds than it is with chlorpromazine.

The extrapyramidal symptoms following therapy with phenothiazine derivatives have been divided into three categories. The most common type resembles the usual picture of Parkinsons disease, with tremor, rigidity and increased salivation. Generalized feelings of restlessness, often accompanied by an inability to sit still form another group, known as turbulence, or akathisia. It is the purpose of this report to call attention to the third group, called dystonias or dyskinesias, which are characterized by spastic contractions and involuntary movements that may involve any part of the musculature, and that often produces bizarre appearing attitudes in the patients. These dyskinesias will occur more frequently now that the newer phenothiazines are being used extensively. When this condition is recognized, the management becomes simple and effective, but until the diagnosis is made, the symptoms, because of their variable and dramatic nature, can be a cause of anxiety for all concerned. The following five cases, which were seen by the Psychiatry Service during the past six months, illustrate some of these points.

CASE REPORTS

The first patient, a 35 year old man, came to the emergency room complaining of difficulty in breathing. He was a drug addict who had been taking large doses of heroin intravenously. Three days before coming to the hospital he stopped the drug and, because of withdrawal symptoms, received chlorpromazine from his physician. He took 200 mgm. a day for three days, and three hours before the onset of symptoms he had an additional dose of 200 mgm. because his withdrawal symptoms were increasing. He had taken a total of 650 mgm. of chlorpromazine in 60 hours. While the patient was being examined in the emergency room his tongue started to protrude and he was unable to return it to his mouth except by pushing it in with his hands. His speech became unintelligible,

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Presented at the monthly staff conference, Department of Psychiatry, March 3, 1959.

* Available as Thorazine[®], Smith Kline & French.

more so than could be accounted for by the malfunctioning tongue. Irregular contractions of the muscles of the angle of the jaw and neck were noted. There was sweating and hyperpnea and the patient appeared in acute distress. His sensorium was clear and he communicated readily through signs and writing. The neurological examination was negative except for a flattening of the left nasolabial fold. No diagnosis could be made by the medical, neurology, or psychiatry resident. It was not recognized at the time that the syndrome of forced protrusion of the tongue, accompanied by spastic contractions of the muscles of the floor of the mouth and neck had been described as an effect of phenothiazine medication (1). Because the tongue appeared swollen, the possibility of an allergic reaction was considered and the patient received 50 mgm. of diphenhydramine hydrochloride* intramuscularly. After twenty minutes the symptoms had completely disappeared. The tongue was returned to the mouth and was of normal size, there was no longer flattening of the nasolabial fold, the speech was easily intelligible, and the patient appeared relaxed and calm.

The second patient is a 26 year old woman who was admitted to the Psychosomatic Service following a serious suicide attempt. This occurred in the course of a post-partum depression, for which she had had some weeks of private psychotherapy. She was extremely agitated and because of this, two days after admission, she was placed on prochlorperazine.† Forty-eight hours after the drug was started, when she had received a total of 150 mgm., there was a sudden onset of contractions of the muscles in her neck, forcing her head towards the right shoulder with the face turned upwards and to the left. The eyes were also fixed, looking upwards and to the left. This was accompanied by slow, halting speech, motions of swallowing, and a mild hyperpnea. The symptoms were only momentarily reversible on effort. The initial impression was that of a catatonic state. After the condition was recognized as due to the medication, 5 mgm. of trihexyphenidyl‡ were given. The symptoms disappeared completely within twenty minutes. The patient was then able to relate the overwhelming feelings of panic she had experienced on finding herself unable to control the motions of her head and eyes. She had thought that this indicated a complete psychological collapse, proof that she would never get better. She did not think of the possibility of an organic explanation for her symptoms. For the next two weeks the patient continued on 80 mgm. of prochlorperazine and 5 mgm. of trihexyphenidyl per day. The trihexyphenidyl was then discontinued and for four days she received 30 mgm. of prochlorperazine a day, after which all drugs were discontinued. There was no recurrence of extrapyramidal symptoms.

The third patient is a 29 year old man who was admitted to the hospital after a suicide attempt with barbiturates which was serious enough to require a tracheotomy. After his medical condition had improved he was transferred to the psychosomatic ward. Because of increasingly paranoid ideas he was started on prochlorperazine. He had received 50 mgm. over a twenty-four hour period

* Available as Benadryl[®], Parke Davis.

† Available as Compazine[®], Smith Kline & French.

‡ Available as Artane[®], Lederle.

when he complained of the sudden onset of difficulty in swallowing. His tongue felt out of control though it did not protrude. He had difficulty in opening his jaw and his facial muscles contracted involuntarily. He complained of a feeling of tightness in his throat and expressed fears that he would require another tracheotomy. He had difficulty with phonation and his speech was hard to understand. This episode occurred six hours after the patient learned of the symptoms of the previous case. He was reassured by references made to the recovery of the previous patient. He received 5 mgm. of trihexyphenidyl which he swallowed with difficulty, and the symptoms disappeared after 30 minutes. The prochlorperazine was discontinued and he was placed on promazine,* 75 mgm. a day, later raised to 300 mgm. a day on which he remained for one month without showing any extrapyramidal symptoms and requiring no further trihexyphenidyl.

The fourth patient is a 20 year old student, who while at college in the Spring of 1958 had an acute psychotic reaction for which he was hospitalized in another city. Among his symptoms then was manneristic behavior, including frequent falling to the ground. He received no drugs during that time. In the Summer of 1958 he returned to his home in New York and began psychotherapy. In December, 1958, the patient became quite agitated so that his therapist referred him to the Psychosomatic Service for admission. He also placed him on prochlorperazine 30 mgm. twice daily. Five days after he had begun drug therapy he was interviewed in the hospital prior to admission to the ward. On the previous day he had taken an additional 100 mgm. of prochlorperazine. He had thus had 350 mgm. of prochlorperazine in a five day period. On the morning of the fifth day he was restless and increasingly verbose and after several hours noted the involuntary elevation of his right arm. There was rotation of the upper part of the trunk which was controlled when the patient bent at the waist. Two hours later while being interviewed, both arms moved in irregular and bizarre patterns, while there was a spasm of the back resulting in stiffening of the entire vertebral column. All these movements could be controlled with effort, though only momentarily. There was some grimacing but no involvement of speech. During these contortions the patient stated that he had been in bad shape before but now was really gone. He felt that the stooped position he had assumed meant that he wished to return to the womb. He told the interviewing doctor that she need not fear his flailing arms, that he would not attack her like he had attacked his previous female therapist. The patient was told to lie down, with relief of symptoms, and was given 5 mgm. of trihexyphenidyl which he had difficulty swallowing. Twenty minutes later he was symptom free and when told that his symptoms were due to the drug, he burst into tears and said, "You mean its not me. I thought I was gone completely." Since then he has been maintained on 60 mgm. of prochlorperazine and 2½ mgm. of trihexyphenidyl per day without recurrence of symptoms.

The last patient is a 23 year old single man with a long history of poor social adjustments, who became overtly delusional at the age of 16 and has been receiving supportive psychotherapy since then. Several months ago the delusional

* Available as Sparine[®], Wyeth.

content became more intense and the patient was hospitalized at another hospital for eight weeks. Prior to transfer to The Mount Sinai Hospital, he became agitated and received 300 mgm. of chlorpromazine over a three day period which was discontinued on his arrival here. On admission to the psychosomatic ward he appeared acutely disturbed. He thought that he was in a concentration camp, that he had concluded a pact with the devil, and that he had been turned into a robot. After a two week period of observation he was started on prochlorperazine. After receiving 100 mgm. over a twenty-four hour period he noted difficulty in opening his mouth. His upper lip was pulled to the left and the lower lip and jaw were pulled to the right. The speech was slurred though there was no impaired movement of the tongue. He did not mention his condition to anyone for two hours because he thought it would go away. When he did speak to the staff he appeared quite anxious. He was reassured and given 5 mgm. of trihexyphenidyl with improvement of symptoms within twenty minutes and disappearance of symptoms within an hour. Since then he has been maintained on 80 mgm. of prochlorperazine and 5 mgm. of trihexyphenidyl per day without recurrence of symptoms.

DISCUSSION

The extent of the dyskinesias can vary from a transient increase in the tonus of an isolated muscle group to involvement of the entire musculature producing the picture of advanced tetanus. The head and neck, including speech and swallowing mechanisms, are most frequently involved. The shoulder girdle and back are less often affected and it is uncommon for the legs and forearms to be involved. Though more frequently unilateral, bilateral symptomatology occurs. Oculogyric spasms, trismus, torticollus, opisthotonus, carpopedal spasm, and tremors resembling Jacksonian seizures are all seen as a result of phenothiazine medication. Hyperpnea, sweating, pallor, and occasionally fever may accompany the motor disturbances. This condition has been mistaken for tetanus, tetany, hysteria, catatonia, encephalitis, meningitis, and brain tumor. The symptoms usually have a sudden onset. During a single episode the symptomatology may be quite changeable. Milder attacks are often self-limited, lasting from a few minutes to several hours, and the symptoms may be under some voluntary control. The symptoms often disappear while the patient is recumbent, only to recur whenever he arises. In severe attacks the patient has no control over his movements and the symptoms may last for days unless treated. In all cases the symptoms eventually stop and no lasting consequences of this reaction have been reported (2). The dyskinesias differ from the Parkinsonian syndrome not only by the type and fluctuance of the symptoms, but also by the time of onset. A great majority of the dyskinesias occur within three days after treatment has begun and it is rare after the first week unless there has been an increase in dosage, while most Parkinsonism occurs between the second and fourth week (3).

The incidence of dyskinesias is related to the specific drug that is used. The phenothiazines can be divided into two main chemical groups. The dimethyl

derivatives of phenothiazine include chlorpromazine, promazine, and trifluorpromazine,* while the piperazine derivatives include prochlorperazine, trifluoperazine,† perphenazine‡ and thiopropazate§. The second group is the more potent in that a smaller weight of the drug is needed for a therapeutic effect and in general, this group produces the most extrapyramidal symptoms. Thus dyskinesias with chlorpromazine and promazine are quite rare, though more cases are reported with trifluorpromazine; while in well observed series there is a 10 per cent incidence of dyskinesias with prochlorperazine and a 20 per cent incidence with trifluoperazine and perphenazine (3, 4). It is claimed that these symptoms are a function of dosage but dyskinesias occur frequently at low dosages. Thus our third case had only 50 mgm. of prochlorperazine, while cases after 3 mgm. of trifluoperazine are common (4). On the other hand our first and fourth case became symptomatic after they had taken additional doses of medication.

There is a question whether the personality of the patient influences the incidence of dyskinesias. It is the impression of the author of a series from a Surgical Service where prochlorperazine was used to control vomiting that the patients who developed dyskinesias were chronic complainers who were hyperreactive to pain before they received the medication (5). The possibility of suggestion is indicated in a report of three adolescents, all taking chlorpromazine, who shared a room and who all developed dyskinesias within two weeks, though each patient showed different symptoms (6). Two of our cases on the ward occurred even closer temporally. It appears that the incidence of dyskinesias may be higher in the younger age groups and among males. However, there is no real evidence as to what individual factors contribute to the development of dyskinesias. For the most part, the reaction seems to be due to the action of the drug itself, as was shown in a study where symptoms were reproduced by disguised medication but not by placebos in a patient who had shown dyskinesias previously (7).

The generally recommended management of the acute attack consists of withholding the drug in mild cases and giving anti-Parkinsonian drugs for the more severe reactions. Our experience with trihexyphenidyl has been good, but others have reported that procyclidine hydrochloride|| and benztropine methanesulfonate¶ are more effective (4, 8). There have been dramatic responses with intravenous caffeine sodium benzoate (1). Good results have also followed the intramuscular or intravenous use of barbiturates, often to the point of sleep, though large doses are required and the symptoms sometimes have recurred after the patient has awakened. Our first case showed a good response after dephenhydramine hydrochloride; this may have been due to the anti-Parkinsonian action which this drug has or it may have been coincidental. If

* Available as Vesperin[®], E. R. Squibb.

† Available as Stelazine[®], Smith Kline & French.

‡ Available as Trilafon[®], Schering.

§ Available as Dartal[®], G. D. Searle.

|| Available as Kemadrin[®], Burroughs Wellcome.

¶ Available as Cogentin[®], Merck Sharp & Dohme.

the symptoms were mild, once the acute attack has passed the previous dosage of phenothiazine medication may often be resumed without causing symptoms again. However, recurrent attacks are not rare and may occur whenever the drug is reintroduced at a later date (9). Lowering the dosage frequently prevents recurrences. After a more severe attack, or if symptoms recur, the patient can be changed to a phenothiazine which has a lower incidence of dyskinesias or be maintained indefinitely on anti-Parkinsonian drugs.

Reports from state hospitals and non-psychiatric services have stressed the lack of anxiety that patients display despite severe symptomatology. We have not found this to be true. Particularly in our second and fourth case, both of whom had received psychotherapy before they took medication, anxiety was a prominent feature. Both these patients felt that the loss of muscular control they experienced indicated a grave psychological condition. Our third patient tried to give the dynamic meanings of his contortions. This type of reaction is to be anticipated in a patient in active psychotherapy and may also be seen in the non-psychiatric patient. The sudden onset of strange movements over which he has no control and which remind him of no known physical condition will produce a great disturbance if the patient is at all given to psychological contemplation. The prompt recognition and reassurance by the physician that drugs and not an aberration of the patient's psyche are responsible can be a tremendous relief to a patient who believes he is losing his mind because of his symptoms. It may be advisable to mention the possibility of dyskinesias at the time the drug is introduced. When the physician is not at all times available, as in a clinic setting, or when it is anticipated that factors in the patient will make him hesitate to call his doctor promptly if symptoms should occur, as with our last case, the patient should be warned ahead of time in order to spare him the anxiety he will feel until he contacts his physician. Some institutions now routinely add an anti-Parkinsonian drug whenever a phenothiazine is given, but in view of the benign nature of the dyskinesias this does not seem indicated.

In conclusion, one can expect to see many more of these reactions, with their bizarre and confusing manifestations as newer and more potent drugs are introduced and used. If the dyskinesias are kept in mind and anticipated they should present no real problems to either the patient or his physician.

SUMMARY

Five cases of dyskinesia following therapy with phenothiazine derivatives are presented.

The syndrome is described and attention is called to the prompt response to anti-Parkinsonian medication and the importance of reassuring the patient when symptoms occur.

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INVERTED DUODENUM WITH DUODENAL ULCER: CASE PRESENTATION

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On the very active radiological service at The Mount Sinai Hospital, the finding of an inverted duodenum is so unusual that a single occurrence warrants special mention. When this anatomical variant is complicated by the presence of a duodenal ulcer and hypertrophied mucosal folds, the resultant roentgenograms are frequently so bizarre that their interpretation may be quite difficult.

CASE PRESENTATION

K. B. (*117467) was a 55 year old white male cabinet maker, who entered the hospital with a six month history of non-radiating epigastric pain occurring between meals and especially at night. At the onset of the illness, the pain was relieved by the ingestion of food and antacids, but later became resistant to these simple measures, and relief could be obtained only with narcotics. Two weeks prior to admission, the patient began to vomit after each meal. There was no melena or weight loss. Physical examination was completely negative.

Gastric analysis revealed a fasting level of 18° total acid and 0° free acid which rose after histamine to 108° total acid and 84° free acid. The hemoglobin was 13.0 grams %, white blood cell count 6,550 per cu. mm with a normal differential count. The urinalysis was likewise within normal limits.

The roentgenographic findings are depicted in Figure 1. It will be noted that in the first portion of the duodenum there is a filling defect and a pseudodiverticulum. The second and third portions of the duodenum then turn superiorly, rather than inferiorly, and swing to the right, rather than the left, so that the third portion lies superior to the first portion.

At operation a large penetrating ulcer located on the superior border of the first portion of the duodenum was demonstrated*. Dense inflammatory adhesions bound together into a conglomerate mass the ulcer bearing duodenum, the transverse colon, and the third portion of the duodenum. Delineation of the anatomy was difficult and required tedious sharp dissection. The position of the pancreas was inverted but bore normal relationship to the curve of the duodenum. The first portion of the duodenum was so elongated that 8 cm. were measured in the operative specimen. Operation consisted of a partial gastrectomy of the Hofmeister variety with retrocolic gastrojejunal anastomosis, plus an infradiaphragmatic vagotomy. The patient tolerated the procedure well.

The surgical specimen consisted of a partially resected stomach. It measured 22 cm. along the greater curvature, 17 cm. along the lesser, and 8 cm. in diameter along the proximal resected edge. A long segment of duodenum, measuring 8 cm. in length was attached. The serosal surface near the duodenal resected edge showed a large area of marked fibrosis with adhesions and induration. The mucosal surface 1.5 cm. from the duodenal resected edge showed a large punched out ulcer, 1.7 by 1.4 cm. The ulcer edges were elevated and the mucosal folds were arranged in a star-like fashion. The bed of the ulcer was deep and covered with clotted blood. The underlying tissues were fibrosed and markedly indurated. The pylorus was dilated and the remainder of the stomach showed exaggerated rugal pattern. In the lesser omentum there were several enlarged lymph nodes. Final diagnosis: Large chronic peptic ulcer of duodenum (Figure 2).

Post operatively, the patient's course was complicated by a prolonged febrile episode

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*Operation performed by Dr. John Garlock.



FIG. 1. Showing the characteristic findings of inverted duodenum with penetrating ulcer and pseudodiverticulum of first portion.

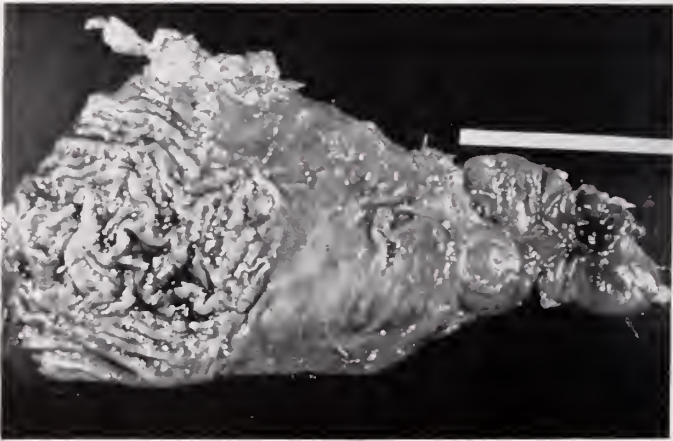


FIG. 2. Photograph of operative specimen indicating the penetrating ulcer at right side of photograph and greatly elongated first portion of duodenum.

accompanied by a discharge of purulent material from the drain site (to the right sub-hepatic area). With penicillin, chloromycetin, and erythromycin, and daily saline irrigations of the drain site, the infection resolved and the leukocytosis and temperature returned to normal limits. At no time was there drainage of duodenal contents. The patient was dis-

charged on the 27th post-operative day. When seen recently, on Jan. 21, 1959, the patient was free of symptoms and the operative wound was solidly healed.

DISCUSSION

Inversion of the duodenum is a congenital anomaly involving the second and third portions of the duodenum. In a review of the available literature, Rozek and Graney (1) found 55 reported cases. Since that time, Haedicke and Gonzalez (2) and Galambos (3) reported two additional cases. The present communication brings the total number of reported cases to approximately 58. Feldman and Morrison (4), in a comprehensive review of the subject, report an incidence of 0.7 per cent in 20,000 gastrointestinal roentgen examinations. The anomaly occurs more frequently in males, approximately 70 per cent, to 30 per cent in females (2).

Feldman and Morrison (4) classify inverted duodenum into four types, depending upon the degree of inversion and malrotation. In the first a complete inversion of the duodenum is observed. The entire duodenal curve is absent and its course and direction are completely changed. In the second type, the inversion takes place in the second portion of the duodenum, and the duodenal curve is similar to the one demonstrated herein. The third type reveals a similar inversion to the second type, and a marked redundancy of the superior duodenum. The last type has inversion of the duodenum in addition to a congenital non-rotation of the intestine. The present case falls into the third type of their classification, that of inversion at the second portion with redundancy of the first portion. The anomaly is believed to be a result of the persistence of the dorsal mesentery with a mobile duodenum (5). Although, clinically, these patients may have symptoms suggestive of ulcer, roentgen evidence of peptic ulceration is not a frequent finding (1, 4). When duodenal ulceration does occur, the response to conservative medical management is usually excellent. Judging from the reports in the literature, it is quite unusual to have an inverted duodenum with ulcer requiring surgical intervention for relief. The reason for this differentiation is not apparent.

SUMMARY

A case is presented of an inverted duodenum with a penetrating ulcer of the first portion and pseudodiverticulum formation. Several unusual features of this anomaly are discussed.

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SEROTONIN AND GASTROINTESTINAL TRACT FUNCTION*

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Since knowledge concerning serotonin and its role in normal and disease states is rapidly expanding, although it is presently quite incomplete, and since what knowledge we do have about this substance implicates it in many areas, it is worthwhile to precede a discussion of serotonin and its action in the gut *per se* by review of a variety of aspects of the substance.

Interest in serotonin started in 1911 during the course of studies searching for the mechanism of arterial hypertension. O'Connor (1, 2), then trying to measure the adrenalin content of blood by studying its effect on the gut, noted in defibrinated blood the presence of another substance which counteracted the effects of adrenalin on the gut, but which disappeared on perfusion of the blood through lung (3), kidney and spleen (4). Adrenalin, he noted, relaxed the gut whereas the unknown substance had just the opposite effect. It was further observed that this substance(s) was dialyzable and heat stable, and also had strong vasoconstrictor properties (5, 6). Even before these observations the presence of vasoconstrictor substances in elotted blood was recognized by Stevens and Lee (7). Subsequently, it was noted that ergotamine reversed the vasoconstrictive action of defibrinated blood (8) and more recently this has been confirmed in the case of serotonin (9). In the years following these initial observations a number of studies were reported further characterizing the properties of this unidentified substance in the blood (10-12).

In 1933 Erspamer and his associates (13) began to report their observations on a substance which they named enteramine (later found to be identical to serotonin) obtained in extracts of rabbit gastric mucosa. This substance, they felt, originated from the enterochromaffin cell system, and they demonstrated that it was quite widespread in nature (14). At that time and subsequently, serotonin has been demonstrated to be present in wasp venom (15), tentacles of sea anemones, the plant cowhage (and is here held responsible, even to a greater degree than histamine, for the itching and pain which result on contact with this plant (16)), nettles (17), scorpion venom (18), tropical toad venom (19), and certain other marine creatures (20-22), and to a considerable extent in the liver fluke, *Fasciola hepatica* (23). In 1953 Lembeck, pursuing further the work of Erspamer which indicated that enteramine (serotonin) originated from argentaffin cells, assayed an argentaffinoma (carcinoid tumor) and did indeed find very large amounts of this substance present (24). Rapport and associates isolated serotonin and demonstrated its structure (25, 26), and soon thereafter Ham-

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* Aided in part by Grants #2A-5126, and #A-3228 from the U.S.P.H.S., National Institute of Arthritis and Metabolic Diseases.

lin and Fisher (27) synthesized it. Thorson and associates then reported a series of cases illustrating the syndrome now recognized and accepted to be caused by functioning carcinoid tumors (28). Various features of such cases had been sporadically reported a number of years before but had never been grouped together and appreciated as a specific entity. Soon after the report of Thorson and associates, Sjoerdsma, Weissbach, and Udenfriend reported additional cases and indicated many details of the metabolic aberration involved (29), and from them, particularly Udenfriend, has since come a steady stream of basic chemical and biological studies pertinent to the indolealkylamines.

Since 1950 study of serotonin has engendered great interest and the subject in all of its aspects was first reviewed by Page in 1954 (30) when he listed 153 references in his comprehensive review. Again in 1958 he reviewed the developments pertinent to serotonin reported since his first paper, and in this latest review he lists 529 references (31). Some of the various roles or actions in which serotonin has been implicated are: anaphylaxis (32), allergy (33), histamine elaboration (34), blood clotting and bleeding (35), control of water retention by the kidneys (antidiuretic action) (36), production of bilateral renal cortical necrosis (37), hypertension (38), myocardial (39) and pulmonary infarctions (40, 41), massive thromboembolic disease (40), bronchial constriction (42), bronchial adenoma (43), pellegra (44), mental disease (45, 46), hepatic coma (102), dysautonomia (47), and finally gut function, both secretory and motor.

In spite of this wide array of conditions and actions in which serotonin has been purported to be involved, it has been shown definitely to play a specific role in body function in a proven and understandable manner in only one condition, the carcinoid syndrome, where it produces most of the signs and symptoms which we associate with this entity (29). There is no question but that it plays a part at least in some way in other pathological conditions involving the gut. This is suggested by the finding of increased urinary excretion of its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in sprue and Whipple's disease during exacerbation, and by the decrease in this substance during remission (48-50). Urinary levels of 5-HIAA have also been found to be markedly diminished after extensive resection of segments of intestine (49). Furthermore, an aberration in serotonin metabolism has been suggested by Donaldson and Gray to occur in cirrhosis of the liver (51). No alterations in blood serotonin or urine 5-HIAA levels, however, have been noted in regional enteritis or ulcerative colitis (48-50). There is no exact knowledge of the place of serotonin in the pathophysiology of these conditions, nor has its role in normal gut function been well-defined. Research in this field is still in the exploratory stage and observations as yet are too few and poorly integrated to present a clear picture.

It has been demonstrated in animals that most (but probably not all) of the serotonin produced in the body originates from the gut, and this appears to hold true for man also. Haverback and Davidson noted an absence of significant amounts of serotonin and 5-HIAA in a patient whose small and large intestine had been almost entirely resected (49). Serotonin is found in many species but not in those whose intestinal tract has no argentaffin cells (52). Erspamer, using

a very sensitive isolated, atropinized, estrous rat uterus assay method made extensive surveys of the serotonin content of stomach, small and large intestine, spleen and serum in a variety of mammals. He found great variation from one species to another and from one part of the gut to another in the same species. In general, it appears that serotonin is present in greatest concentrations in the areas where argentaffin cells are most numerous. Study of the wall of the gut in the dog demonstrated that serotonin was not present in the muscularis but did occur in the mucosa. It was found in the mucosa in amounts between 4 and 10 $\mu\text{g. gm.}$ and it was noted to be in highest concentration in the mucosa of the pylorus and only in traces in the esophagus (53).

Over ninety per cent of body serotonin is in the blood or gut wall (54). Practically all of the serotonin in the blood is carried by the platelets (55). Plasma contains almost no serotonin. In man normal blood values are of the order of 0.1 to 0.3 $\mu\text{g./ml.}$ (29). Extracts of whole blood from the portal vein studied by Toh were found to contain three times as much serotonin as did arterial blood, and it was found that serotonin was released into the perfusate upon perfusing stomach and small bowel (56).

Early studies of some of the properties of serotonin in the gut indicated that, when administered to animals even under deep anesthesia, its most pronounced effects are stimulation of defecation, increased peristalsis, and increased tone of the bladder wall (30). Its action upon guinea pig ileum was noted to be blocked by atropine and partially blocked by nicotine and was felt to be cholinergic. Some studies of the contraction of isolated guinea pig ileum when exposed to serotonin demonstrated a tachyphylactic type of reaction. In spite of the tachyphylactic reaction, the gut remained responsive to histamine, acetylcholine, pilocarpine and nicotine. Serotonin action was not blocked in the guinea pig gut by hexamethonium but was blocked by cocaine. It was then concluded that the action of serotonin was on the post-ganglionic fibers of the intramural nervous system in the gut, acting more peripherally than nicotine (57).

Among a number of interesting observations concerning tryptamine was Reed's report that the intravenous administration of tryptamine (which has actions quite similar to those of serotonin) produced an increase in portal pressure in dogs (58, 59).

Early methods for assay of serotonin were biological and were dependent upon the contraction of smooth muscle of a variety of animals exposed to serotonin. Among many methods particularly useful and popular were those utilizing guinea pig ileum (57), rat uterus (60), rat colon (53), perfused rabbit ear (61), clam heart (62), and sheep carotid artery rings (63). In recent years these methods to a great extent, but not entirely, have been superseded by chemical methods of analysis which have consisted of color reactions with the end point measured by spectrophotofluorometry (64) in the case of serotonin, or by spectrophotometry in the case of the metabolite, 5-HIAA (65). Chromatography has also been utilized with success. By these means both tissues and biological fluids have been assayed (64, 65). In the hands of some workers, however, biological methods of assay have continued to be accurate and useful.

As noted above, plasma contains almost no serotonin; over ninety-nine per cent of the substance is carried by platelets. Exactly how it is carried by platelets has not definitely been shown but the material thus transported is considered to be "bound." There seems to be no unanimity of opinion as to whether the "bound" serotonin in blood or the extremely minute amounts of "free" serotonin in the blood is the physiologically active form (29). Similarly, there are speculations regarding "bound" and "free" serotonin in the tissues. Studies involving measurements of serotonin in blood, serum or plasma are often difficult to interpret, not only because of different methods of analysis and different standards in various laboratories, but also because analyses in some cases are done on platelet free material and in others the presence or absence of platelets is not specified. The chemical tests for quantitation of these substances are extraction processes which, as noted, finally revolve around the development of a color when serotonin or the metabolite is allowed to react with the appropriate reagent. Certain substances lower the amounts of 5-HIAA measurable in the urine both in normal individuals and in patients with the functioning carcinoid syndrome. These substances are: compazine, sparine, phenergan, and chlorpromazine. They appear to lower the measurable amounts of 5-HIAA in the urine not by interfering with the metabolism of serotonin, but rather by interfering with the development of the color reaction, yielding falsely lowered values (66, 67). Bananas, on the other hand, increase the actual amount of 5-HIAA excreted in the urine (68, 69). They do this apparently because they provide fairly large amounts of serotonin, an average banana containing approximately 4 mg. of the substance in its pulp. Normal 24 hour urinary excretion of 5-HIAA ranges approximately between 1 and 8 mg., with slight variations in the values depending upon minor differences in technique in different laboratories (29, 48, 50).

Until recently it was thought that degradation to 5-HIAA was the major final common pathway for serotonin. However, it now appears that conjugation with glucuronide (70) and possibly sulfate (71) also are important metabolic pathways for serotonin degradation, although not as much is transformed to these substances as goes to 5-HIAA. Donaldson and Gray showed that levels of urinary 5-HIAA in cirrhosis of the liver were the same as in normal individuals. However, after giving serotonin precursor, 5-hydroxytryptophan, intravenously to normal individuals, about thirty per cent of the administered substance appeared in the urine as 5-HIAA in the ensuing twenty-four hours as compared to sixty-four per cent in cirrhotic individuals (51). This was taken to suggest that in this situation there was an impaired ability of the liver to conjugate serotonin with glucuronide (and sulfate). This appears to be a correct line of reasoning since the administration to rats of excesses of orthoaminobenzoate, a substance which is conjugated with glucuronide, caused an increased urinary excretion of 5-HIAA (72); apparently glucuronide conjugation was competitive and hence less glucuronide was available for conjugation with serotonin.

Studies of this type which entail calculation of the percentage of administered precursor recoverable in the urine as 5-HIAA must be interpreted with considerable caution because the amount of 5-HIAA excreted in the urine of a test sub-

ject (man and dog) varies from day to day. These fluctuations correlate to a considerable degree with the volume of urine produced.

Further implication of serotonin in liver disease has been provided by the recently published studies of Borges and associates. They observed improvement in the abnormal electroencephalographic tracings of patients in hepatic coma following production of an increase in the levels of serotonin in the cerebral circulation of these individuals. Increasing serotonin in the cerebral blood supply of normal individuals caused no alteration in their electroencephalographic recordings (102).

METABOLIC PATHWAYS IN SEROTONIN SYNTHESIS AND DEGRADATION

Ingested tryptophan is utilized in the synthesis of proteins and indoles. Some is converted via kynurenin to nicotinic acid, a small amount is changed to tryptamine, and, in normal man, one to three per cent is converted to 5-hydroxytryptophan. This latter reaction takes place in the liver, presumably under the influence of an enzyme, hydroxylase, not yet demonstrated in man. In the presence of pyridoxal phosphate and decarboxylase (in gut, liver, brain, and kidney), 5-hydroxytryptophan is decarboxylated to form serotonin (5-hydroxytryptamine, 5-HT). Serotonin then follows at least two pathways, glucuronide and possibly sulfate conjugation in the liver, and oxidative deamination under the influence of monoamine oxidase in many tissues and particularly liver and lung) to form 5-hydroxyindoleacetic acid (5-HIAA) which is excreted in the urine in amounts which usually parallel fairly closely the blood serotonin levels. Tryptamine is

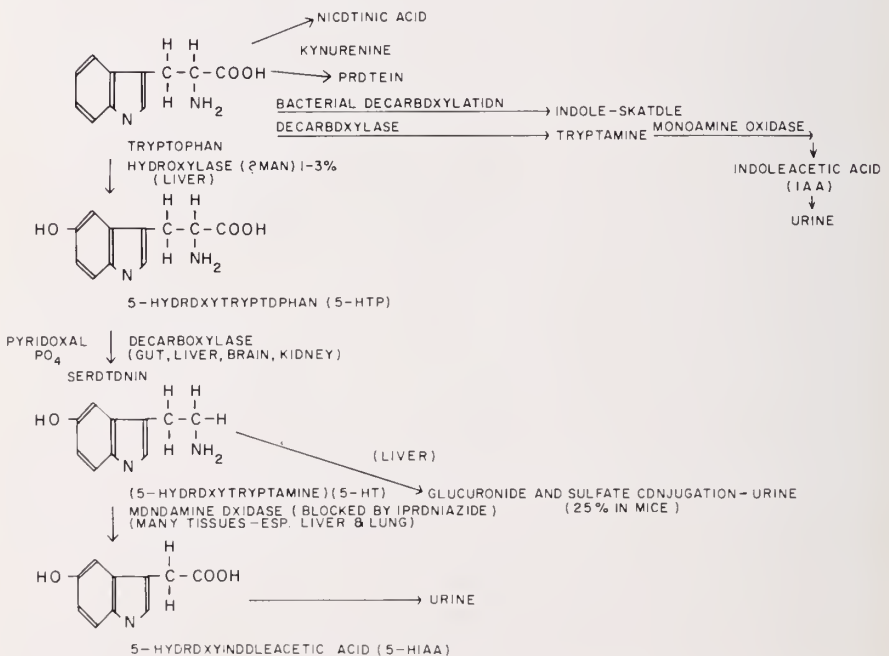


FIG. 1. Pathways involved in serotonin metabolism.

also a substrate for monoamine oxidase. It is converted to indoleacetic acid which is excreted in the urine. The degradation of serotonin to 5-HIAA and of tryptamine to indoleacetic acid (103) may be blocked by monoamine oxidase inhibitors such as iproniazid (29-30, 73-76) (Fig. 1).

RESERPINE AND SEROTONIN

The actions of reserpine are to a very great extent interrelated with or mediated by serotonin. It has been shown in animals that reserpine liberates serotonin from tissues and blood, apparently by blocking the binding of serotonin by the tissues and platelets. In animals during the course of the response to reserpine, decreasing amounts of serotonin can be found upon analysis of gut mucosa studied at intervals following the administration of reserpine. After the administration of reserpine a very transient initial increase in metabolite levels in urine is seen, and then a gradual prolonged decline in levels occurs until a persistent plateau at a low level is reached. This low level represents the metabolic degradation of the small amounts of serotonin which are constantly being formed but not bound, and which are being metabolized and excreted (77-80). The same chain of events appears to occur in humans (50, 81). Langemann and Goerre noted the persistent finding in functioning carcinoid cases of markedly increased 5-HIAA levels in the urine after the administration of reserpine, whereas they did not observe such a response in normal individuals (82).

One wonders if the occasional diarrhea associated with reserpine might be related in part to alteration of the serotonin content of the gut mucosa.

RESPONSE IN MAN TO PARENTERAL ADMINISTRATION OF SEROTONIN

The following manifestations result in man after the intravenous injection of serotonin (30, 83): flushing of the extremity into which the injection has been given, hyperpnea, tachypnea, amphibolic blood pressure response (rise or fall in blood pressure depending upon the degree of neurogenic control present), tingling in extremities, feeling of warmth over the face, nausea, salivation, lacrimation, varying degrees of abdominal cramps, vigorous peristaltic sounds, and the urge to defecate and void. These events occur within 15 to 20 seconds after the rapid intravenous administration of serotonin and subside within approximately a minute. Upon administration of serotonin precursor, many of these features of the response are absent or extremely mild, only the effects on gut motility predominating. These occur within six to forty minutes after the intravenous administration of serotonin precursor and persist for at least 90 minutes (49).

GASTRIC VASCULAR EFFECTS OF SEROTONIN PRECURSOR

Serotonin precursor given intravenously in large amounts (of the order of 300 $\mu\text{g./Kg.}$) in rats produced hemorrhagic gastric ulcerations after a period of approximately three hours. Chlorpromazine protected the animals from this effect, which apparently was the result of ischemia from intense vasoconstriction (84). Gastric or duodenal ulceration has been noted in approximately 38 per cent of functioning carcinoid cases (85) and is presumably on this basis. It is

certainly worthy of note that the gut appears to be the most sensitive site in the body to the action of serotonin or its precursor, and that very small amounts of these substances, insufficient to produce measurable responses on the part of other organs or structures, do evoke a response in the gut (49).

ANIMAL SECRETORY STUDIES

Haverback and associates, upon administering serotonin intravenously in doses up to 10 $\mu\text{g.}/\text{Kg. min.}$ to dogs with Heidenhain pouches, noted no significant effect on gastric acid secretion. However, in larger doses, 40 $\mu\text{g.}/\text{Kg. min.}$, they noted definite inhibition of the output of acid. They also noted that serotonin precursor inhibited spontaneous gastric acid secretion but did not inhibit the gastric acid secretory response to histamine (86). However, Black, Fisher and Smith (87, 88), and others (89), reported that both serotonin and its precursor inhibit histamine-stimulated gastric secretion in animals. They have commented on their observation that recent feeding diminishes the acid secretory response to histamine (90), and in view of the observation of Stacey and Sullivan that feeding increases the serotonin content of the gut wall (91), they suggested that in recently fed animals the diminished acid secretory response to histamine might be due both to changes in serotonin concentration in the gut tissues and to released serotonin.

White and Magee (92) noted that serotonin administered intravenously to dogs in doses of 10 to 30 $\mu\text{g.}/\text{Kg. min.}$ increased gastric production of mucin. They noted that mucin production from dog pyloric pouch preparations was inhibited by 1 mg. of atropine intravenously and was not affected or enhanced by hexamethonium. The effect of serotonin was to increase tone and motility as measured by balloons, in addition to the production of mucin, and only the effect on motility was blocked by both atropine and hexamethonium. To distinguish motility from direct stimulation, studies were repeated on everted antral pouches and the same effect was noted with the exception that atropine did not block it. That is, they found that serotonin, by direct action, increased the pyloric mucosal production of mucin and that hexamethonium inhibited motility stimulated by serotonin but did not inhibit secretion stimulated by serotonin. Study of the denervated pyloric pouch showed the same effect of serotonin but atropine still reduced it. In addition, during the experiments the dogs vomited mucin and it could be seen that mucin production had been stimulated throughout the stomach. White and Magee commented on the observation that serotonin is present in large amounts in the pyloric mucosa in the dog (93), and suggested that its predominance in this location might be related to the acid depressing function said to reside here.

HUMAN SECRETORY STUDIES

Reported studies of the effects on human gastric secretion of serotonin or its precursors have not made their way into the literature in any detail. Haverback has reported an inhibitory effect of serotonin on gastric acid secretion in man just as he had noted in dogs (94). Cali and Cordova, however, reported stimula-

tion of gastric acid production in humans following the intravenous administration of 5 mg. of serotonin (95).

In a small group of humans, Warner, Janowitz and Dreiling (96) observed the effects of serotonin on the volume of secretions and acid production by the stomach, and also the effects of serotonin on the external secretion of the pancreas and on bile pigment flow. In the test subjects the secretory response was determined by studying material continuously aspirated from the stomach and duodenum via a double lumen tube. Aspirates obtained before and during the intravenous administration of serotonin creatinine sulfate for one hour at a rate of 10 $\mu\text{g. Kg./min.}$ were studied. The results indicated that serotonin produced an average increase in gastric secretory volume of 14 per cent, and average decrease in hydrochloric acid of 38 per cent, and an average decrease in total acid of 47 per cent. In regard to the duodenal aspirate, no significant change was noted in volume or in bicarbonate and amylase content, but an average decrease in bile pigment flow of 21 per cent was observed.

ANIMAL MOTILITY STUDIES

Serotonin and its precursor, as previously noted, had been characterized as inducing responses somewhat like cholinergic effects. Pick noted that minute amounts of serotonin potentiated the motor response of guinea pig ileum to cholinergic compounds (97). The motor response of the gut to serotonin, as emphasized before, is probably the most sensitive body response to this substance. Haverback and associates (86) noted that the lower dose which they used in their secretory studies (10 $\mu\text{g./Kg./min.}$), although not effective in influencing gastric secretion, was a potent stimulus to gut motility in the dog, and this response to serotonin was not blocked by atropine, hexamethonium, bilateral cervical vagotomy, or an histamine-like drug, mepyramine. Lysergic acid diethylamide potentiated the intestinal response to serotonin, in contrast to its central antagonism. Interestingly enough, the tachyphylactic type of response to serotonin does not occur following the administration of serotonin precursor (49). Furthermore, Haverback and Davidson report that gut motility stimulated by serotonin precursor was inhibited by atropine. Some investigators have observed inhibition of the intestinal motor response to serotonin after administration of atropine (83).

In an ingenious and elaborate series of experiments, Bülbring and Lin studied peristaltic activity in isolated loops of guinea pig ileum and rabbit jejunum under conditions in which they introduced into the lumen substances which were thus enabled to act on the mucosa (98). Furthermore, these investigators were able to measure intraluminal pressures and fluid transport after the segment of intestine was subjected to substances applied within or without. They found that serotonin introduced into the lumen stimulated peristalsis and increased the volume of fluid transported, whereas serotonin applied to the outside inhibited or stopped peristaltic activity. A correlation was noted between the intraluminal pressure, the release of serotonin, and the volume of fluid transported by the studied segments of intestine. The amount of serotonin released

by the intestine and found in the effluent was increased by raising the intraluminal pressure. Further studies involving 5-hydroxytryptophan, iproniazid, acetylcholine, phenyldiguanide, hexamethonium, and procaine were carried out. They concluded that serotonin, which is formed and stored in the mucosa, is released in amounts proportional to the rise in intestinal intraluminal pressure and acts by sensitizing mucosal pressure receptors which then trigger peristaltic activity.

Woolley has recently theorized and presented initial supporting evidence that serotonin stimulates smooth muscle contraction by transporting calcium ions across the cell membrane into the cell (99). Exactly how this is accomplished has not been demonstrated but he postulates the possibility of the formation of a complex consisting of a cell membrane component (perhaps a phospholipid), serotonin, and calcium ions. This complex would be fat soluble and thus be able to diffuse across the principally lipoidal cell membrane. Appropriate enzyme systems would be located on the exterior and interior of the cell membrane to facilitate both formation of the calcium portering complex and its breakdown with release of calcium ions. He further points out that serotonin in animals has been indicated to be the hormone analogous to indoleacetic acid in plants. He notes that in many respects his concept of the mode of action of serotonin resembles Bennet-Clark's hypothesis for the mode of action of indoleacetic acid in plants (100). The latter substance was proposed by Bennet-Clark as also involved in a metallic ion portering system complex.

HUMAN MOTILITY STUDIES

About a year prior to the publication of the findings of Bülbring and Lin, Hendricks and associates (83) reported their observations of the effects of rapidly injected serotonin on motor function in man, as measured by balloon kymography. They noted that the injection of serotonin produced increased intestinal tone followed by an inactive period of about fifteen minutes (the previously noted tachyphylactic type reaction). During this inactive period the gut was unresponsive to further injections of serotonin. In these studies the gut response to serotonin was potentiated by antihistamines (presumably via monamine oxidase inhibition), was inhibited by BAS, and was inhibited by anticholinergics. It was not altered by ganglion blockade by hexamethonium. They concluded that serotonin appeared to stimulate gut motor activity through cholinergic nerves at a site distal to the ganglionic synapse.

Haverback and Davidson (49) observed in man the effect on intestinal motility and intraluminal pressure of endogenously produced serotonin resulting from intravenously administered 5-hydroxytryptophan. The observed increase in intestinal motility occurred within six to forty minutes after the start of the infusion. This response was inhibited by atropine. However, if an infusion of serotonin instead of the precursor was given as the stimulus for intestinal motility, atropine failed to exert an inhibitory effect. Brom-lysergic acid diethylamide inhibited intestinal motility stimulated by either serotonin or its precursor. These investigators also reported (as had been previously noted by Hendricks

and associates) that neither serotonin nor the precursor when given intraluminally produced any apparent effect on intestinal motility.

COMMENT

Although their roles are not yet completely and precisely defined, it appears that serotonin and precursor(s) are integral parts of the complex biochemical-anatomical mechanisms underlying both intestinal motor activity (particularly the transport of intestinal contents), and certain secretory functions of the gut. Furthermore, as knowledge of serotonin metabolism is continuously expanded by many additional studies it is becoming more apparent that aberrations in serotonin metabolism may be involved in an increasing variety of gastrointestinal tract diseases.

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SYMPTOMATIC HIATUS HERNIA

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INTRODUCTION

A great deal has been written by internists, surgeons and radiologists during the past three decades on the subject of diaphragmatic hernias. This study concerns itself only with esophageal hiatus hernia and was prepared in an effort to answer certain questions: (a). Are small or minimal hernias responsible for symptoms? (b). What are the symptoms associated with these defects? (c). What are the complications of this disorder? Do they occur with small as well as large hernias? (d). Is the radiographic demonstration of gastroesophageal reflux necessary to indict the hiatus hernia as being responsible for symptoms?

MATERIAL

The present report was divided into two parts. The first was a clinical study of 137 patients, all hospitalized at The Mount Sinai Hospital during the 18 months beginning July 1955 and ending December 1956. The basis for inclusion was the mentioning of hiatus hernia in either the primary or secondary discharge diagnosis. In every case the diagnosis was based on x-ray examination of the upper gastrointestinal tract.

The second part was a study of 101 patients attending the Consultation Service of The Mount Sinai Hospital on an outpatient basis. Every patient in whom a hiatus hernia was discovered on a roentgen examination of the esophagus and stomach during the ten months beginning April 1955 was included.

DEFINITIONS

The majority of cases studied have been classified as "sliding." This term is used because a portion of the hernial sac consists of the included viscus, in this situation, the stomach. A sliding hernia is identified when the esophagogastric junction is observed to have prolapsed through the hiatus and located above the diaphragm. Although it may be reducible, it also may be fixed in its abnormal position.

A paraesophageal hernia is not truly a hiatus hernia. The fundus and a portion of greater curvature of the stomach have herniated into a preformed peritoneal sac alongside the esophagus. The esophagogastric junction remains in its normal position and the esophageal hiatus frequently is separated by diaphragmatic muscle fibers from the hernial sac.

A "combined hernia" has both "sliding" and "paraesophageal" components.

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The term "small" is of course a relative one. Included in this category are those hernias described as "small," "minimal," or as 3 cm. or less in greatest diameter. The "large" category consisted of hernias described as "large," "lemon," "orange," "plumsized," or "moderate-sized."

The routine roentgen examination of the upper gastrointestinal tract at The Mount Sinai Hospital includes a fluoroscopic and x-ray examination of the esophagus with the patient drinking barium while in the Trendelenburg position. After the barium has been ingested, the patients are studied for evidence of gastroesophageal reflux in the Trendelenburg position and occasionally in the Johnstone position (the patient bending as far forward as possible with the knees extended).

RESULTS

Part I

Of the 137 hospitalized patients (Table I), hiatus hernia was the primary, or one of the primary diagnoses in 84 cases. The hernia was described as being small in 56 cases, all of the sliding variety. Gastroesophageal reflux was demonstrated by the radiologist in only three of these. Of the 81 cases with large hernias there were 71 sliding, nine combined, and one pure paraesophageal (which at a later examination was considered a combined type). There was roentgen evidence of reflux in three of the patients with combined hernias, and 12 of the sliding. There was no reflux seen on the examinations of the patient with the paraesophageal hernia.

In this group, the women outnumbered the men by 87 to 50. The patients ranged in age from 24 to 82; however, most were in the fifth to the eighth decade at the time of hospitalization. Symptoms described varied from several weeks to 25 years duration.

In any patient with objective evidence of any disease known to cause symptoms that might be ascribed to hiatus hernia, the other disease(s) was considered responsible for the symptoms, and the patient was not included in the following analysis.

Epigastric pain, for which there was no evidence of another cause, was the most frequent symptom, being present in 60 patients. It was the complaint of 24 of the 53 patients with small hernias, each without roentgen evidence of reflux. It was present in 24 of the 59 patients with large sliding hernias without reflux, eight of the twelve large sliding with reflux, all three of the combined hernias with reflux, and one of the six combined hernias without reflux. It was noted in patients with anacidity, normal acidity, as well as hyperacidity (more than 50 mEq/L of free acid). The pain was most frequently located in the midline, but also was found toward the right and left upper quadrants. When described, it was cramping, pressing, burning, steady and severe in that order of frequency. Twenty patients noted a relation to position i.e. pain either developed or was made worse by lying down during the day or going to bed at night. Six noted that it developed in the immediate post-prandial period. Relief was obtained

TABLE I
Symptoms of 137 hospitalized patients

	Small Hernias—56 (All Sliding Hernias)		Large Hernias—81				
	With Demonstrable Reflux—3	Without Demonstrable Reflux—53	With Demonstrable Reflux—15		Without Demonstrable Reflux—66		
			Combined 3	Sliding 12	Combined 6	Paraesophageal 1	Sliding 59
Epigastric pain	0	24	3	8	1	0	24
Heartburn	2	8	1	4	3	0	21
Nausea	1	12	2	4	0	0	13
Substernal or chest pain	0	12	2	5	0	0	10
Bloating	1	8	2	2	1	0	13
Excessive eructation	1	2	0	0	2	0	16
Radiation of pain to back	0	8	0	1	0	0	5
Radiation of pain to shoulder	0	5	0	3	1	0	2
Dysphagia	1	0	0	1	0	0	1
Radiation of pain to axilla or to scapula	0	1	0	0	0	0	1
Pain worse after meals	2	12	3	3	0	0	11
Pain worse after lying down	0	3	0	0	2	0	16
Pain worse after bending or lifting	0	0	0	0	0	0	1
Asymptomatic	0	13	0	1	1	1	2

with antacids in 11, with vomiting in five, and with eructation in three. Thirteen patients noted radiation of the pain through to the back, eight to either or both shoulders, and four around the left flank to the back. Axillary or scapular radiation was only from associated substernal pain when the latter was present.

Heartburn, the second most common symptom, is generally accepted as being an esophageal symptom, a motor phenomenon related to gastroesophageal reflux. In this series, it was noted in two of the three small hernias with evidence of reflux and in eight of the 53 small hernias without radiologic evidence of reflux. Of the large hernias, heartburn was associated with five of the 15 with reflux, and 24 of the 66 without reflux, roentgenographically. It was present in five of the nine patients proven to have esophagitis. It is interesting that gastric analyses (after histamine) revealed heartburn to be a symptom in patients with achlorhydria as well as in normal and hyperchlorhydric subjects.

Nausea, with or without vomiting, is a symptom that may be produced by distension of the lower end of the esophagus or the stomach. It was present in 23 per cent of both the large and small hernias, in 21 per cent of the patients without and 39 per cent of those with x-ray evidence of reflux. It was present in six of the nine cases with esophagitis.

Substernal pain or chest pain was fourth in frequency. It was present in 21 per cent of our entire group, 23 per cent of the small hernia without demonstrable

reflux, 15 per cent of the large hernia without reflux, and 47 per cent of the large hernia with demonstrable reflux. The pain, when described, was usually a pressing type, rarely severe and squeezing, less often a dull steady ache. Most patients noted no radiation of the pain; but when radiation was described, it went to the left or both shoulders and arms, to either scapula or axilla, or straight through to the back. Only 26 per cent of this group noted development or aggravation of the pain at night after lying down or within two hours after eating. Two patients noted aggravation of the pain with lifting or exertion, and one at times with emotional upsets. Five patients noted relief of the pain with antacids, two with vomiting, two with belching, and one with nitroglycerine at times. This type of pain is quite difficult to distinguish from the pain of coronary artery disease. Four of the above patients were admitted to the hospital because of the suspicion of an acute myocardial infarction and one for a possible impending infarction. In these cases, electrocardiographs, including those after exercise revealed no significant abnormalities. There were, however nine other patients in our series with electrocardiographic evidence of coronary artery disease.

Post-prandial bloating was noted in 16 per cent of the small hernias and 22 per cent of the large, in 19 per cent of those with and 21 per cent of those without radiologic evidence of reflux. True dysphagia was relatively uncommon. It was present in but four of the 137 cases, one with a carcinoma in the hiatus and the other three with stricture and esophagitis.

There were nine cases of peptic esophagitis (see Table II) in this series as proven by esophagoscopy, surgery, or unequivocal x-ray evidence. (Only nine patients of the 137 in this group were studied by esophagoscopy and abnormal findings were observed six times.) There was x-ray evidence of esophagitis in six of the nine patients proven to have this complication. The esophagoscopist confirmed the diagnosis of esophagitis in every patient studied with x-ray evidence of this disorder. Of these, five patients complained of epigastric pain, five of hematemesis, two of hiccough, one of chest pain. Six of these patients noted aggravation by lying down. There was no patient with melena or with massive bleeding. In general, the course of these patients was similar to those of the general group mentioned above until esophagitis was observed on x-ray or some further complication arose leading to esophagoscopy or surgery. Only one patient in this group had evidence of a peptic ulcer (duodenal) and one other had hyperacidity on gastric analysis. There was one patient with anacidity on a fasting specimen; however, histamine stimulation was not performed. Analysis of the cases with demonstrable esophagitis showed: two small hernias with demonstrable reflux; two small hernias without demonstrable reflux; two large hernias with demonstrable reflux, and four large hernias without demonstrable reflux.

Perforation occurred in one case. This was an elderly man with a long-standing history of heartburn and two episodes of hematemesis. X-ray revealed a moderate-sized sliding hernia. Reflux was not demonstrated. Esophagoscopy and biopsy revealed esophagitis and gastritis. The heartburn subsided, but anemia developed and persisted. Because of this surgery was performed and at operation, a perforated walled-off ulcer at the esophagogastric junction was observed.

TABLE II
Nine hospitalized patients with objective evidence of esophagitis

Type of Hernia	Symptoms	Evidence of Esophagitis	Additional Information
Small sliding hernia with demonstrable reflux	4 years of postprandial heartburn. Recurrent vomiting and singultus. No anemia	a) Lack of distensibility in distal esophagus on x-ray b) Esophagoscopy revealed narrowing, inflammation and ulceration of distal esophagus c) Biopsy revealed fragment of esophageal mucosa with an acute inflammatory exudate a) No evidence of esophagitis on x-ray b) Esophagoscopy revealed reddened bleeding area in distal esophagus	Patient had chronic lymphatic leukemia 100 units of free hydrochloric acid on gastric analysis Improved on medical therapy
Small sliding hernia without demonstrable reflux	4 months of epigastric pain with occasional vomiting. Admitted because of hematemesis Had a recent cholecystectomy after 15 years of intermittent biliary colic History of epigastric and right upper quadrant pain radiating through to back. Some recent vomiting and singultus Several months of epigastric burning, nausea, and some vomiting	Peptic esophagitis noted on x-ray Peptic esophagitis noted on x-ray	Also had a duodenal ulcer Treated by subtotal gastrectomy, vagotomy and repair of hiatus hernia Responded to medical therapy Also has ureterosigmoidostomy after many years of vesicovaginal fistulae
5 cm. sliding hernia with demonstrable reflux	10 years of epigastric pain and bloating, 4 years of dysphagia and regurgitation due to esophageal stenosis secondary to esophagitis Past history of heartburn plus two episodes of hematemesis	x-ray and esophagoscopy proof of esophagitis a) Narrowing of distal esophagus on x-ray b) Esophagoscopist noted reddened friable areas at distal end of esophagus which on biopsy were fragments of gastric mucosa showing chronic inflammation c) Esophagitis with a walled-off perforation of distal esophagus at surgery a) No esophagitis on x-ray b) Bleeding areas in distal esophagus seen at esophagoscopy	No free HCl on fasting specimen. Histamine test not done. Treated with periodic esophageal dilatations Transthoracic repair of hiatus hernia
Moderate sliding hernia without demonstrable reflux	Long-standing history of heartburn and excessive eructation. Several episodes of melena Many years of heartburn, belching. Recurrent dysphagia	a) No esophagitis on x-ray b) Esophagitis noted on esophagoscopy	No response to left phrenicectomy. Eventual subsidence of symptoms on medical therapy
Moderate sliding hernia without demonstrable reflux	8 years of epigastric and substernal pain plus heartburn. More recent nausea and vomiting	Lower esophagus thickened at time of surgery	Transthoracic repair of hiatus hernia Transthoracic repair of hiatus hernia

TABLE III

"Silent" or asymptomatic bleeding associated with a hiatus hernia; 7 cases—hospitalized group

Type of Hernia	Evidence of Bleeding	Severity of Bleeding
Small, sliding without demonstrable reflux	Hypochromic anemia	Hb—8.6 grams
Large, sliding, without demonstrable reflux	Three episodes of melena	Admitted in shock
Large, sliding, without demonstrable reflux	Hypochromic anemia	Hb—10 grams
Large, sliding with demonstrable reflux	Melena	Had syncopal attack. Hb 8.2 grams
Large, sliding, with demonstrable reflux	Melena	Hb—7.8 grams
Large, sliding, with demonstrable reflux	Hypochromic anemia	Hb—10.4 grams
Large, paraesophageal	Melena for three weeks	Hb—6.0 grams

Objective evidence of bleeding from the gastrointestinal tract (Tables III and IV) was noted by the physician referring the patient to the hospital or by the hospital staff during the period of hospitalization in 30 patients (22 per cent). There were seven cases of silent bleeding including one with a small sliding hernia, five with large sliding hernias, (three with demonstrable reflux), and the paraesophageal hernia. In each of these cases, the bleeding was severe enough to produce some degree of anemia. There was no hematemesis in this group.

Bleeding was associated with a symptomatic hiatus hernia in 23 cases. Included here were four small sliding hernias without demonstrable reflux. Bleeding was identified as coming from the distal end of the esophagus by the endoscopist in one of these. There were 12 moderate to large sliding hernias without reflux. In one of these, the Einhorn string test indicated bleeding within the esophagus. One patient was observed by the esophagoscopist to be bleeding from the distal end of the esophagus. Another had esophagoscopic and operative evidence of esophagitis, and biopsy evidence of gastritis. There was objective evidence of bleeding in five of the nine cases with large combined hernias (four without and one with demonstrable reflux). In this group of 23 cases, there were two in whom hematemesis was the only objective evidence of gastrointestinal bleeding. Neither of these patients had a resultant significant anemia. The lowest hemoglobin value in the bleeding associated with symptomatic hiatus hernia group was 3 grams per cent.

In the overall group of 137 cases, 18 (13 per cent) were asymptomatic as regards the upper gastrointestinal tract. This included 13 small hernias without demonstrable reflux, one of the large hernias with it, one paraesophageal hernia, and one large combined hernia and two large sliding hernias without demonstrable reflux.

The physical examination in these 137 cases was of no value in diagnosing the

TABLE IV

Bleeding associated with symptomatic hiatus hernia; 23 cases—hospitalized group

Type of Hernia	Symptoms Described	Evidence of Bleeding	Severity of Bleeding	Additional Information
Small, sliding without demonstrable reflux	Epigastric pain, heartburn worse lying down	Hematemesis	Lowest Hb. 15.0 grams	Subsequent x-ray showed a large hernia with reflux
Small, sliding, without demonstrable reflux	Epigastric pain	3 episodes of melena	Lowest Hb. 7.0 grams	
Small, sliding, without demonstrable reflux	Heartburn post-prandially	Melena for two weeks	Lowest Hb. 8.0 grams	
Small, sliding, without demonstrable reflux	Epigastric pain and occasional vomiting	Hematemesis and melena	Lowest Hb. 9.0 grams	Bleeding seen on esophagoscopy, from distal end of esophagus
Moderate, sliding, without demonstrable reflux	Post-prandial heartburn, bloating and belching	Melena	Lowest Hb. 13.0 grams	
Moderate, sliding, without demonstrable reflux	Postprandial bloating and belching	Numerous episodes of melena	Lowest Hb. 6.0 grams	String test positive at 25 cm. Gastroscopy and esophagoscopy done during interval between bleeding episodes were unrevealing
Moderate, sliding, without demonstrable reflux	Postprandial heartburn	Melena	Lowest Hb. 11. grams	
Large, sliding, without demonstrable reflux	Postprandial bloating and epigastric pain	Hematemesis	Lowest Hb. 12.4 grams	
Large, sliding, without demonstrable reflux	Chest pain	Hypochromic anemia	Lowest Hb. 3.0 grams	
Large, sliding, without demonstrable reflux	Nausea and belching. Occasional vomiting	Hematemesis and melena	Lowest Hb. 9.0 grams	
Large, sliding, without demonstrable reflux	Heartburn and belching	Hypochromic anemia and guaiac positive stools. Melena on another occasion	Lowest Hb. 9.0 grams	Bleeding from distal end of esophagus seen on esophagoscopy
Moderate, sliding, without demonstrable reflux	Heartburn	Hematemesis, and hypochromic anemia	Lowest Hb. 9.0 grams	Reddened friable area seen on esophagoscopy biopsied and was proven to be chronic gastritis. At operation, evidence of esophagitis and a walled-off esophageal perforation discovered
Large, sliding, without demonstrable reflux	Postprandial heartburn, belching and bloating	Melena, 2 episodes	Lowest Hb. 9.0 grams	
Large, sliding, without demonstrable reflux	Postprandial epigastric pain, preordial pressure & nausea. Worse when recumbent	Melena	No anemia	Esophagoscopy done during period without any melena revealed normal esophageal mucosa
Large, sliding, without demonstrable reflux	Bloating and belching	Melena	Lowest Hb. 5.1 grams	
Moderate, sliding, without demonstrable reflux	Epigastric distress	Occult blood in stool	Lowest Hb. 12.0 grams	
Moderate, sliding with reflux	Heartburn and "indigestion"	Three episodes of melena	Lowest Hb. 12.0 grams	
Large, sliding, with reflux	Chest and epigastric pain	Two episodes of melena	No anemia	Esophagoscopy done 8 days after bout of melena revealed normal mucosa
Large, combined, without demonstrable reflux	Heartburn and epigastric fullness	Melena	No anemia	
Large paraesophageal with a small sliding component. No reflux	Heartburn	Melena	Lowest Hb. 8.0 grams	
Large, combined, without demonstrable reflux	Heartburn and belching	Hematemesis and melena	No anemia	
Large, combined, without demonstrable reflux	Heartburn	Melena	Lowest Hb. 6.0 grams	
Large, combined with reflux	Epigastric pain	Hypochromic anemia	Lowest Hb. 10. grams	Esophagoscopy revealed normal mucosa

hernia. In not one case were borborygmi noted in the anterior or posterior chest.

Other diseases of the gastrointestinal tract found to be present in these patients were as follows: 16 duodenal ulcers, two gastric ulcers, one jejunal ulcer (after a sub-total gastrectomy), and seven patients with cholelithiasis. There were five patients who in the past had had a cholecystectomy for symptoms other than biliary colic. These symptoms, as described above, were not relieved by the cholecystectomy and probably were due to the coexistent hiatus hernia. There were two patients in this series who were proven to have a gastric carcinoma in the hiatus hernia.

Part II

This disease, as seen in the Consultation Service of The Mount Sinai Hospital (Table V) was in general milder than that seen in the hospitalized patients. There were 52 women and 49 men in this phase of the study; and they ranged in age from 27 to 72 years. There were 64 small sliding hernias; and reflux was demonstrable in only six. There were 36 large sliding hernias, seven with demonstrable reflux. No reflux could be demonstrated in the one large combined hernia.

The most common complaint in this group also was epigastric pain, present in 48 patients. It was present in approximately one half of the patients with small

TABLE V
Symptoms of 101 patients attending consultation service

	Small Hernias 64		Large Hernias 37		
	With demonstrable reflux 6	Without demonstrable reflux 58	With demonstrable reflux 7	Without demonstrable reflux 30	
	All sliding hernias		All sliding hernias	Combined 1	Sliding 29
Epigastric pain	3	30	3	0	12
Heartburn	3	25	4	1	11
Bloating	3	17	4	0	16
Excessive eructation	3	17	4	1	3
Nausea	1	14	0	0	2
Substernal or chest pain	0	7	1	0	7
Regurgitation	0	3	0	0	5
Vomiting	0	6	0	0	1
Sensation of food getting stuck in lower esophagus	0	3	1	0	1
Radiation of pain to back	0	3	0	0	2
Radiation of pain to shoulder(s) or left arm	0	2	0	0	3
Radiation of pain to scapula or axilla	0	3	0	0	0
Radiation of pain to neck	0	0	0	0	2
Pain worse after meals	3	17	2	1	9
Pain worse lying down	0	15	2	0	6
Pain worse after bending or lifting	0	1	0	0	3
Asymptomatic	2	15	0	0	7

or large hernias, with or without demonstrable reflux. More than 40 per cent of this group of patients were able to describe the pain only as a feeling of epigastric discomfort. Others described it as a burning pain, cramping pain, growing pain, or a steady ache. More than half the patients noticed the pain developed between 30 minutes and 2 hours post-prandially and approximately one-third noted aggravation in the recumbent position. Radiation of the pain was uncommon; however, when present, it was usually around either side and into or straight through to the back. Some patients obtained relief with eructation, others with antacids, and a few with induced vomiting.

Heartburn, the second most common symptom was present in 44 patients, and it too was fairly evenly divided between the small and large hernias, and those with or without demonstrable reflux. Almost one half of the patients with this complaint noted aggravation with the recumbent position at night or during the day. About the same percentage noted the development or worsening of the symptom in the 30 minutes to 2 hour post-prandial period. A few noted aggravation by bending down. The most frequent modality for obtaining relief cited was the use of antacids or the drinking of milk. At times, the drinking of warm water was noted to provide relief.

Post-prandial bloating, was the symptom next in order of frequency, and it was represented in all the types of hernia considered in this discussion. Excessive eructation also was found in each category. In almost one half of the patients with the latter symptom, it was induced for relief of the flatulence.

Nausea was much more prevalent among the patients with small hernias. Less than half the patients complaining of nausea had associated vomiting.

Substernal or chest pain was present in 15 patients, seven small hernias and seven large hernias without demonstrable reflux, and one large hernia with it. Eight of these patients described the pain as a sensation of pressure or distress, two as a severe pain, two as a squeezing pain, one as a pulling pain, and one as a growing pain. Four of the patients noted aggravation of this symptom by lying down or its awakening them from sleep. In three the symptom developed or was worsened with lifting or bending; and only one in the post-prandial period. Patients noted radiation of the pain to the left arm, back scapular or interseapular area, left shoulder, neck, and jaw. Some patients noted relief with eating, others with antacids, some with induced eructation. One noted occasional relief with nitroglycerine.

There was no dysphagia in this group. Five patients complained that occasionally food got stuck in lower substernal region, but in none of these was there any narrowing or a hold-up of barium. There was no proven ease of esophagitis in this series by x-ray. There were no operations performed nor were any esophagoscopies done. Esophagoscopy was suggested but refused by one patient with rather severe symptoms.

There were eight patients in this group in whom the hiatus hernia might be associated with blood loss (see Table VI). There were two post-menopausal women with iron deficiency anemias of 9.5 and 9.7 grams per cent of hemoglobin respectively. One with a small sliding hiatus hernia without demonstrable reflux

TABLE VI

Patients attending consultation service in whom association of bleeding and hiatus hernia is possibly suggested

Type of Hernia	Symptoms Described	Evidence of Bleeding	Severity of Bleeding	Additional Information
Small sliding hernia with demonstrable reflux	No symptoms referable to gastrointestinal tract	Stool strongly positive reaction for occult blood	Normal hemoglobin	Negative barium enema. Patient has chronic bronchitis
Small sliding hernia without demonstrable reflux	Abdominal discomfort and epigastric bloating worse with spicy foods and lying down	Stool positive on two occasions for occult blood	Normal hemoglobin	
Small sliding hernia without demonstrable reflux	Heartburn, nausea, bloating, excessive eructation	Hypochromic anemia. Stool positive for occult blood	Hb. 9.7 grams	Negative barium enema and small bowel examination
Small sliding hernia without demonstrable reflux	Occasional heartburn	History of hematemesis and melena two years before. History of melena again recently	Normal hemoglobin	
Minimal sliding hernia without demonstrable reflux	Epigastric pain slightly worse in supine position	History of Melena	Normal hemoglobin	
Small sliding hernia without demonstrable reflux	Postprandial abdominal cramps and anterior chest pain on exertion	History of two episodes of melena	Normal hemoglobin	Neurotic patient with possible angina pectoris. Told she had a duodenal ulcer in past, but no crater or deformity demonstrated
Small sliding hernia without demonstrable reflux	Many years of heartburn and epigastric discomfort, worse after meals and lying down. Recently an epigastric pain and some nausea after meals	Two episodes of melena within recent months; by history	Normal hemoglobin	
4 cm. sliding hernia without reflux	Heartburn, on lying down. Also has some right upper quadrant pain	Strongly positive guaiac	Normal hemoglobin	Diabetic. Gallbladder visualized faintly, no stones seen
Large sliding hernia without demonstrable reflux	Postprandial epigastric distress for 8 years	Iron deficiency anemia. Stool guaiac negative	Hb. 9.5 grams	

had a moderately positive stool guaiac reaction. The guaiac test of the patient with a large sliding hernia without demonstrable reflux was negative. Both these patients had symptoms that might be ascribable to the hiatus hernia. There were three patients without any anemia who had moderately or strongly positive guaiac reactions. The patient with the small sliding hernia with demonstrable reflux had no symptoms referable to the gastrointestinal tract, whereas the patients without reflux did have symptoms. There were four patients with small hiatus hernias without demonstrable reflux who gave a history of melena in the past; two of these on two occasions. Three of these four had symptomatic hiatus hernias. The fourth had only occasional heartburn. The latter patient also gave a history of hematemesis in the past.

In 24 of the patients in this group the hiatus hernia was apparently asymptomatic.

matic. This included two of the small hernias with reflux, and 15 small hernias and seven large hernias without demonstrable reflux. Each of the seven large hernias with demonstrable reflux had to be considered as symptomatic.

The diseases of the gastrointestinal tract discovered in these 101 patients were noted. There were six with evidence of a duodenal ulcer, two with a gastric ulcer, six with cholelithiasis. Of four patients status post-cholecystectomy two were suspected of having a "post-cholecystectomy syndrome." Intravenous cholangiography was normal in each case. There was one patient proven to have a common duct stone. Saint's triad (gall stones, colonic diverticula, and hiatus hernia) was found in one instance. There was a patient with scleroderma and this interesting association will be discussed below.

DISCUSSION

Incidence

No one knows what the true incidence of this common condition is; Schatski (1) claimed that hernias could be demonstrated in 70 per cent of patients over the age of 60. Cernock (2) found hiatus hernias in 1.5 per cent of 200 patients over the age of 50 having no gastrointestinal symptoms. It is obvious that we will not be able to determine the incidence of this condition unless a large unselected portion of the population is studied by a standardized technique. This has yet to be done.

Etiology

The congenitally short esophagus associated with hiatus hernia is apparently a rarity, and we have no such case represented in our series. A short-appearing esophagus is not necessarily congenital. In experimental animals, vagal stimulation has led to retraction of the esophagus and herniation of the cardia above the diaphragm. It is certainly conceivable that coexistent lesions in the gastrointestinal and biliary tract may cause persistent vagal stimulation and reflex retraction of the esophagus (3).

Obesity, in association with a hiatus hernia, has been observed by others (4, 5) as well as an improvement in symptoms with weight loss. Eight of Edmunds' (5) patients considered a rapid gain in weight as a precipitating cause for the symptoms attributed to the hernia.

An increase in intra-abdominal pressure may be etiologically related. Rigler (6) drew attention to the high incidence of hiatus hernia in pregnancy (18.1 per cent of 116 multipara, and 5.1 per cent of 79 primipara). In seven of these 25 patients, the hernia could not be demonstrated on reexamination after delivery. More recently, Siegel et al., (7) observed the development of a hiatus hernia in seven of 40 pregnant women. Four of the seven had symptoms suggestive of a hiatus hernia. All seven studies done after delivery revealed the disappearance of the hiatus hernia. We have recently followed a patient who developed severe peptic esophagitis in the latter months of pregnancy. She was found to have a large hiatus hernia which had not changed in size by the end of the third post-

partum month, a gastro-intestinal series done two years prior to the pregnancy revealed no evidence of a hiatus hernia.

An ovarian cyst may have been a precipitating factor in the development of the hiatus hernia in two of Edmunds' (5) patients. The wearing of a tight belt was considered in one, and the moving of furniture in another. We have observed the presence of a large combined hernia in a young man who had received one year of pneumoperitoneum therapy. We have also reviewed the record of a man who had a successful repair of a symptomatic hernia; only to have a sudden recurrence of symptoms three years later when he lifted a heavy object.

The weakening of the hiatus by procedures such as vagotomy should be mentioned. Beal (8), reported a paraesophageal type of hernia discovered ten days after a vagotomy had been performed. Hanlon and Higgins (9) reported herniation of small bowel through the esophageal hiatus five weeks after a vagotomy, and Van Hoek and Musselman (10) reported the development of severe anemia due to a hiatus hernia which developed after a vagotomy. Each of these authors drew attention to the fact that in every case the opening into the mediastinum had not been closed as has been advocated by Dragstedt et al. (11).

The association of hiatal insufficiency and hiatus hernia with scleroderma has been described. In reviewing 220 cases of hiatus hernia of the short esophagus type, Olsen and Harrington (12) observed that nine (4 per cent) were afflicted with scleroderma. In their review of 350 cases of scleroderma, 18 with evidence of esophageal involvement, Olsen, O'Leary and Kirklin (13) noted that nine had x-ray evidence of a hiatus hernia, and four had esophagoscopy evidence of esophagitis. Kemp Harper (14) found a hiatus hernia to be present in two of 14 cases whose roentgenographic findings he discussed. Johnstone (15) stated that it is conceivable that scleroderma may affect the lower end of the esophagus to impair the efficiency of the cardia. Then the sequence of esophagitis, ulceration, and contraction may bring about a hiatus hernia.

Clinical Picture

Epigastric pain, and substernal pain, the most frequently observed symptoms in this series, were also the most frequent complaints in the series of Mobley and Christiansen (16) and of Palmer (17). They were second and third, respectively, in Jones' series (4). Palmer noted that only 13 per cent of his patients were able to describe this pain as an epigastric and substernal burning pain, aggravated by recumbency and relieved by assuming the upright position. He did note, however, that epigastric or substernal pain after meals and complex dyspepsias were relatively common. As noted by Boekus (18) the segmental localization of pain may be significant. He cites the work of Jones with balloon distention experiments. If the distention was not too great in the distal end of the esophagus, the pain could be localized to the level of, or just below the xiphoid. This corresponded to the studies of Hurst correlating location of hernias with localization of pain. It was also noted that pain in organic disease of the stomach is usually experienced in the midline of the epigastrium. In lesions near the cardia, the pain may be near the xiphoid.

Tinsley Harrison (19) has noted that the location, quality, and intensity of pain with esophageal disorders may be indistinguishable from that due to disease of the coronary arteries. In both, the pain may be precipitated by emotional disturbances or by the ingestion of large quantities of food. The following points for differentiation were suggested: (a). Pain arising in the esophagus is not ordinarily related to muscular exertion. (b). Pain precipitated by swallowing or coming on during eating is more likely due to an esophageal disorder. (c). The presence of even a minor degree of dysphagia constitutes strong evidence in favor of esophageal pain. (d). The duration of esophageal pain is more variable (lasting a few seconds to many hours) than is that of angina pectoris which usually lasts for a few minutes. (e). Electrocardiographic, x-ray and esophagoscopy studies are of great value when they yield positive results; but many errors are made by placing undue emphasis on borderline findings. (f). Atropine and similar drugs often produce striking relief in patients with esophageal pain, but do not usually affect anginal pain. Nitroglycerine may relieve esophageal pain, but the effect is rarely as striking as with anginal pain. Boekus (20) commenting that substernal pain of anginal origin may be indistinguishable from pain that may originate from stimuli arising in the esophagus, drew attention to the frequency of evidence of bleeding in hiatus hernia as a diagnostic point. He also stated: "It is my impression that there is considerable proof to the contention that afferent impulses over vagal pathways originating in the lower esophagus and stomach, may, under certain circumstances decrease coronary blood flow." Von Bergmann (21) did demonstrate a fall in coronary blood flow in dogs subjected to balloon distention of the esophagus. Baylis et al. (22), and Balint and Edmunds (23), noted that balloon distention of the esophagus, even in the presence of known coronary artery disease, did not produce electrocardiographic changes.

Harrison (19) also noted that the differentiation of pain arising in the stomach from that of esophageal origin is often impossible from the history alone. He suggested: (a) Pain of a burning quality may arise from either organ, but is more typically of esophageal origin. (b) Localization of discomfort in the epigastrium or behind the ribs on the left is more common when the stomach is at fault. (c). Dysphagia or pain on swallowing points to an esophageal lesion. (d). Belching is usually a means of obtaining relief of pain of gastric origin. (e). When related to meals, esophageal pain is more likely to occur during eating while gastric pain more commonly sets in after eating.

At times, pain of pancreatic origin may be difficult to distinguish. This pain too may be aggravated by lying down, but this pain may be relieved by sitting up and bending forward. With a hiatus hernia, the pain may be worsened by bending forward. When radiation of pain to the back occurs, it may be to the level of D4 with lesions in the distal esophagus, to D8-10 with gastric lesions (24) and to the level of the lower dorsal vertebrae with pancreatic lesions.

Heartburn, nausea, belching and bloating were the other frequently noted symptoms. Jones (24) has reported that in distention experiments on normal subjects irritation of the lower part of the esophagus frequently results in a sensa-

tion indistinguishable from heartburn. Furthermore, acute muscular distention of the distal end of the esophagus by acid, alkaline, neutral, and chemically inert solutions all produce a distinct burning sensation under the lower portion of the sternum. The symptom may occur in the presence of achlorhydria. We have observed it to be present in patients with hiatus hernia and pernicious anemia. Therefore, the chemical nature of the gastric juice cannot constitute the cause of the symptom. This burning sensation is deemed to be a pain variant, related to a localized neuromuscular disturbance in the distal esophagus. We feel that this neuromuscular disturbance is probably initiated by gastroesophageal reflux, the natural barriers to which may be lost with the development of a hiatus hernia.

Belsey (3) has stated that he believes chronic heartburn to be pathognomonic of hiatus hernia. Lawler and McGreath, however, in their study of 56 patients with symptoms attributable to gastroesophageal reflux, 53 of whom showed reflux during roentgenographic examination, noted the presence of a sliding hiatus hernia in only 34.

One of the questions in the introductory paragraph of this paper was: "Is the radiologic demonstration of gastroesophageal reflux necessary for one to indict the hiatus hernia as being responsible for symptoms?" The answer, as demonstrated in this study is: "No." Flood et al., (26) had previously shown this to be so. In comparing intubation technique to x-ray study they noted that of 14 patients, there was evidence of reflux by both techniques in nine, by tube only in three, and by x-ray only in two. There were 11 patients with esophagitis as diagnosed by the esophagoscopist. Flood and his co-authors were able to ascertain evidence of reflux by x-ray or esophageal intubation in only six of these and in only two out of four patients with an active ulcer at the distal end of the esophagus.

The reflections of Johnstone (27) on this subject are of great interest. He stated that: "Most radiologists must be aware of the fickleness of hernia and reflux; for example, both may be demonstrated readily, and yet on subsequent examination, even a few minutes later, the phenomenon may be absent. It is conceivable that the weight of the meal reduces the hernia." He also commented on the possibility that fatigue after physical exertion might permit a hernia (and one may infer . . . reflux) to be more readily demonstrable. Perhaps radiologists should conduct gastrointestinal examinations in the evenings after the patient has completed a days' work.

Bloating, or a sense of distention cannot be classified as a diagnostic symptom. Hoelzel (28), who ate until he felt distended observed that radiologic examination performed at the time when the symptom appeared revealed that the ingested material was in the small intestine and colon and concluded that the sense of fullness arose in these organs and not in the stomach. Hertz (29) produced a sense of fullness by distending the colon of patients with colostomies. A sense of distention may occur in obstructive lesions of the colon or of the biliary tree. Inflation of the stomach was shown by Wolf and Wolff (30) in their fistulous subject to result in a sense of distension. To accomplish this, they had to achieve

a pressure of 20 cm. of water; the volume required depended on the rapidity with which the air was injected, and the sensation passed off after a few seconds as the pressure fell by receptive relaxation of the stomach; it could then be reproduced by further distension. By attaining a pressure of 48 cm. of water by the injection of 1500 ml. of air, distention became extreme and pain and sometimes nausea was produced. The ingestion of food in usual quantities would hardly be expected to give rise to a feeling of fullness comparable to that above, especially when one considers the ability of the stomach to relax in the face of any but the most sudden distention. I would like to suggest the possibility that air is trapped in a hiatus hernia after the ingestion of a meal, particularly a large meal. Because of the confinement of this air to a small loculated sac, aerophagia is particularly liable to produce the symptoms of bloating and perhaps pain or nausea.

The question as to whether small or minimal hiatus hernia may be responsible for symptoms may now be answered. Chester Jones (4) who considered a small hernia to be less than 7 cm. in maximum diameter answered the question with an emphatic "yes." In fact, he noted that the symptoms of substernal pain and heartburn were present in a higher percentage of the patients with small rather than large hernias. Palmer (17) commented that it is common observation that among patients with heart-mimicking syndromes the smaller a hiatus hernia tends to be the more violent its pains are likely to be. In fact, the patient with a hernia which is very large and which for the most part remains in the chest is often aware of no problems. Our data, we believe, as well as the data cited above, leave no doubt that small hernias may be responsible for all the symptoms as well as all the complications of hiatus hernia.

Complications

There are two complications of hiatus hernia that require discussion. The first is esophagitis and the second is hemorrhage.

Peters (31) in a review of 20,000 autopsies found an incidence of severe digestive esophagitis in 0.92 per cent (116 cases). In this group, there was a 20.3 per cent incidence of what he felt was a congenital enlargement of the hiatus and a congenitally short esophagus.

Winkelstein (32) has attempted to classify two distinctive types of esophagitis. Reflux esophagitis, which is associated with sliding hiatus hernias, is a superficial ulcerating lesion localized to a short area adjacent to the cardia. Peptic esophagitis which usually occurs in patients who have experienced a great deal of vomiting or who have been subjected to prolonged intubation, and is associated frequently with duodenal ulcer, is an exudative ulcerating lesion involving a longer tubular stretch, usually one-third to one-half of the esophagus; and is more superficial. The latter type is more responsive to medical therapy while the former, after a course of medical therapy and esophageal dilatations, where indicated, would then be treated with surgical repair of the hiatus hernia to control reflux.

Belsey (3) noted that the incidence of reflux esophagitis in hiatus hernia in England was between 57 per cent and 77 per cent. In the United States the

incidence has been deemed much lower; however, fewer endoscopies are performed here. Chevalier Jackson (33) has been quoted as saying that: "Esophagoscopies are usually performed only when there is an important indication. It is probable that in patients with gastric or duodenal ulcers who have severe heartburn and acid regurgitation, evidence of mild esophagitis would be revealed if esophagoscopy and biopsy were included in the study." In support of this we would like to comment on the esophagoscopic findings of seven consecutive patients presently attending the Gastrointestinal Clinic at The Mount Sinai Hospital. All complained of a mild to moderate degree of postprandial and nocturnal epigastric distress and heartburn. Six of the seven patients showed gross evidence of esophagitis at the distal end of the esophagus. The seventh had biopsy evidence of esophagitis.

As we have attempted to point out in our data, the symptoms associated with a mild to moderate degree of reflux esophagitis are not necessarily distinctive from the hiatus hernia group per se unless, the esophagitis is further complicated by bleeding, esophageal spasm, stricture. In fact, Palmer (17) reported that nine of 43 cases of erosive esophagitis due to reflux were asymptomatic.

If there is no spasm or stricture, there are usually no distinguishing roentgenographic features, therefore, the diagnosis can only be made endoscopically.

When the esophagitis is more severe, the symptoms usually are more severe and persistent. It is in these more severe degrees of esophagitis that esophageal ulceration, lack of distensability, esophagospasm or stricture are usually discovered by the radiologist. In general, the more severe degrees of esophagitis seem to be associated with hyperacidity. Belsey (3) noted that in the Frenchay hospital series, all but two patients with esophagitis had abnormally high acid curves. In the nine cases of esophagitis referred to in the present study, hyperacidity was noted in three, normal acidity in one, while there was no gastric analysis in the other five. The last three cases of severe reflux esophagitis that we have studied on the wards of The Mount Sinai Hospital were all patients with hyperacidity, or peptic ulcer diathesis (i.e., active peptic ulcer or deformity on x-ray due to old ulcer), and sliding hiatus hernia.

One fact that seems to be elucidated in this study is that small hernias may be complicated by esophagitis (three of the nine cases with esophagitis had small hernias). One other fact is that esophagitis occurred without the radiologist being able to demonstrate gastroesophageal reflux in six of our nine cases.

The actual incidence of bleeding as a complication of hiatus hernia remains an enigma. In his review, Belsey (3) noted that in various series the reported incidence of hemorrhage from a hiatus hernia varied from 2.5 per cent to 33 per cent, anemia varied from 3.5 per cent to 66 per cent. Approaching the subject from another viewpoint, it is interesting that of more than 2000 cases hospitalized for upper gastrointestinal tract bleeding, Avery Jones (34) noted that in only 1.8 per cent of the cases was the bleeding due to a hiatus hernia, and in this group there were no deaths. Bleeding of all degrees and severity have been reported in hiatus hernia. Winkelstein (32) mentioned that peptic esophagitis may bleed and stated that he knew of three cases that bled to death. Schwartz

and Blumenthal (35) reported a severe iron deficiency anemia in 20 patients with hiatus hernias. They drew attention to the insidious character of the bleeding and to the paucity of associated symptoms. Murphy and Hay (36) who reported an incidence of anemia in 66 per cent of 72 patients with hiatus hernia, also stated that most often the bleeding is prolonged and gradual; but massive hemorrhage did occur in a few cases. Effer and Ballinger (37) stated that bleeding in all probability is the most common complication of hiatus hernia. Such bleeding had been observed to vary from occult blood loss to massive bleeding without premonitory signs. They stated that hemorrhage did not seem related to the size and shape of the hernia. Fourteen of their patients operated on for hernia manifested evidence of bleeding—seven with hematemesis, nine with melena, 14 with a hemoglobin less than 11 grams, and five with a hemoglobin less than 7 grams per cent. Sahler and Hampton (38) reported a study of 19 patients with a positive history of upper gastrointestinal bleeding associated with hiatus hernia. There was localized gastritis (diagnosed on gastroscopy) in the hernial sac in five patients, a questionable gastritis in one, an esophagitis on endoscopic examination in one, and a healing ulcer in the upper portion of the stomach in one. One patient showed an ulcer in the herniated portion of the stomach at autopsy. In this paper, Benedict (39) was quoted as saying that in the cases of hiatus hernia with bleeding which he has observed gastroscopically and have shown gastritis, he considers the bleeding as due to the gastritis. Ohler and Ritvo (40) also drew attention to bleeding in association with hiatus hernias and reported 12 cases with gross hemorrhage. Four were small hernias, three moderately large, one large, and four unclassified.

As emphasized above, the bleeding in a hiatus hernia may come from the esophagus or the stomach. Erosive esophagitis may be associated with hematemesis and blood loss as well as may be from erosive gastritis or gastric ulcers. The esophagitis, as previously outlined is probably due to reflux of acid gastric juice. Explanation for the erosive gastritis has been based on congestion of the mucosa due to the compression of the stomach wall at the diaphragm producing venous obstruction, stasis, congestion, and erosions. This was actually shown to be the case in the autopsy study of the cases reported by Bock, Dulin and Brooks (41). Harrington (42) has stated that erosions or ulcerations when they occur in a hiatus hernia may also be traumatic, due to the to and fro action of the diaphragm against the gastric wall.

TREATMENT

The medical treatment of hiatus hernia may be succinctly discussed as consisting of attempts to decrease reflux and to neutralize the acid gastric juice. To decrease reflux, patients are advised (a) to lose weight if they are obese, (b) to avoid tight garments, (c) never lie down after meals, and (d) sleep with the head of the bed elevated with one-foot blocks. (Sleeping high on pillows may "jackknife" the body and actually aggravate reflux.) To neutralize the acid gastric juice we advise the use of frequent small feedings and the use of antacids. We have found the use of a mixture of ten parts of calcium carbonate to one part of magnesium oxide as a powder suspended in mineral oil or olive

oil, as recommended by Warthin (43) to be particularly efficacious. As anticholinergics may delay gastric emptying without significantly effecting gastric acid production, they are not routinely recommended; however, they have been found to be quite useful at times in providing symptomatic relief from intractable heartburn.

Repair of the hiatus hernia is resorted to if symptoms persist despite adequate medical therapy, or if complications ensue. Prior to surgical repair of the hiatus hernia, treatment of reflux esophagitis by medical means as outlined above, supplemented in selected cases by an intraesophageal milk drip through a plastic tube is indicated. If a stricture is present, but is not advanced, it frequently will respond to cautious dilatations as well as therapy for the esophagitis, prior to repair of the hiatus hernia. If the stricture is advanced, and scarring is great, resection of this area frequently must be performed.

We do not believe that a hernia should be repaired merely because it is large. Hiatus hernia repair is a major operation and may be fraught with any and all postoperative complications. The only recent death at our hospital associated with a hiatus hernia was in an elderly lady with a large hernia with moderate symptoms who died during the immediate postoperative period after repair of the hiatus hernia. We have recently observed three patients who had a trans-thoracic repair of a hiatus hernia with such a great deal of pain due to intercostal neuralgia, that they preferred their preoperative plight. Dysphagia has also been observed on occasion. This is associated with excessive tightening of the crura. It is a minor complication, usually responding to several esophageal dilatations.

CONCLUSIONS

To assess the significance of hiatus hernia, the histories of 137 hospitalized and 101 ambulatory patients with this diagnosis were analyzed.

The symptoms ascribed to the hernias in 196 cases included: Epigastric pain, substernal pain, heartburn, bloating, nausea, regurgitation, and excessive eructation.

The size of the hernia could not be correlated with the symptom-complex. Furthermore, large hernias as well as small hernias may be asymptomatic; although, in our experience this appears more frequent in the case of the small hernia.

The ability of the radiologist to demonstrate reflux apparently is limited. Heartburn, a symptom ascribable to gastroesophageal reflux, was an outstanding complaint of many patients in whom the phenomenon of reflux could not be demonstrated radiographically. Furthermore, six of the nine patients with reflux esophagitis had no evidence of reflux at the time of roentgen study.

Bleeding and esophagitis are the major complications of hiatus hernia. It appears that the large hernia is more prone to bleeding; and bleeding in association with a large hernia was noted in 27 cases. Hemorrhage may be a complication of a small hernia and this association was noted in 13 cases. The actual source of the hemorrhage in each situation can only be verified by endoscopy or by inspection of the mucosa at surgery performed during the bleeding episode.

Esophagitis, the second important complication, was present in nine patients,

three of whom had small hernias. Despite that fact that the pathogenesis of this complication implies gastroesophageal reflux, the radiologist could demonstrate this phenomenon in but three of these patients.

SUMMARY

Hiatus hernia is a common condition.

Small hernias as well as large hernias may be responsible for any and all of the symptoms and complications of hiatus hernia.

The radiographic demonstration of gastroesophageal reflux is by no means necessary for one to indict the hiatus hernia as being the cause of the patient's symptoms.

The symptoms and the complications of hiatus hernia are discussed.

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CULTURALLY PATTERNED BEHAVIOR REACTIONS
AMONG THE SPANISH-SPEAKING PATIENTS AT
THE MOUNT SINAI HOSPITAL OF NEW YORK CITY

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INTRODUCTION

There is no question that the Puerto Rican society in New York offers most valuable material for psycho-social studies. The static nature of its culture, transplanted into the highly dynamic one of New York, presents fascinating aspects. It is a fast growing political and sociological unit, the impact of which in the whole structure of our community can not be underestimated. The 600,000 Puerto Rican immigrants in the city offer themselves as a crude laboratory for the study of social dynamics, within the frame of their own society, which is obviously in a transitional period.

Psychiatrists must become increasingly aware of the cultural determinants in personality development. For the planner, the social worker, the physician in general, and The Mount Sinai doctor in particular, this cultural point of view is of primary importance, even though it will not increase our therapeutic acumen. The significance of the cultural point of view lies in the field of preventive psychiatry and mental hygiene education.

The only source of data for the present paper has been the clinical interview and the study of case histories; the result of hundreds of contacts with Spanish-speaking patients; approximately 900 at The Mount Sinai Hospital, and nearly 2000 in other centers and in private practice. Most of them were in lower-income groups, with meager education and humble occupations. The majority of our patients were unskilled laborers and housewives.

The material derived from these interviews could not, on the whole, be confirmed by repeated observation, and generalizations made in these studies must be looked upon as suggestive rather than definitively established. However, since there are certain easily recognizable common features in the individual case-histories, it was felt that their analysis was a valuable technique in establishing the most obvious ideological trends of this society of Spanish-speaking people. Any sort of generalization tends to err, but social life is lived by individuals. In each person the prevailing social trends necessarily reflect themselves, and this is what happens in our patients.

Freud's concept that the nuclear family situation is the prototype of social behavior has been followed. It seems in this case to have a cross cultural validity. Though the basic emotional patterns are universal, and there is no single trait or motive that is confined to a single society, the variations of these themes and patterns are manifold. The combination of patterns produce a social character, a society that is always unique.

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ETHNOGRAPHICAL AND HISTORICAL BACKGROUND

The island of Puerto Rico is one of the Greater Antilles between the Atlantic and the Caribbean seas. They are the summits of submerged mountain ranges. The island is very small (35 by 100 miles). It was discovered by Columbus in 1493. The Spanish conquest involved, for the islander, a radically new economic and religious system. Its expressed intent was to mold the aboriginal culture into a form that could be dominated and controlled by the Spaniards. Some features including social and religious concepts were forced upon the two different groups of people, the Arawak and the Carib, found by the discoverers. These inhabitants, unlike their brothers in Mexico, Peru or Guatemala, did not have an advanced culture, (which in any case, was going to be obliterated). The original number of natives is estimated to have been 600,000. In a very short period of time they were exterminated. In 1582 it was officially reported that none was left. Thereafter, the surviving culture was largely concerned with subsistence and utilitarian pursuits, but even these were modified by Spanish influences. In 1898 the Spanish rule ended after 400 years of government. Meanwhile, the continuous influx of Negro slaves and their descendants had a striking effect upon the Spanish-Indian culture. The possible influence of the Negroes upon aboriginal and European inhabitants of the island should not be minimized.

The factual ethnic basis of the existing Puerto Rican population is possible of almost exact determination. Their blood lines can easily be detected from three main sources: Indian (negligible), Negro (actually 25 per cent of the population is Negro) and white Spaniard.

At present the alerted Puerto Rican tends more and more towards the centers of economic activity, and for them the promised land of wealth and comfort seems to be New York City. It is of interest to notice that Puerto Ricans and Negroes comprise 17 per cent of the population of this city.

6 BEHAVIOR REACTIONS CULTURALLY PATTERNED

A sort of official culture or tradition, whose characteristics are not within the scope of this paper, is forced upon the children by the father, the mother, and of course by the society in which they live. In the area of family background certain patterns are transmitted by the parents to their offspring. The parental role in the bringing up of the children is, as expected, very important. The father has unquestioned authority and rules the entire household. Modern developmental concepts of parenthood and childhood are absent. Beating is almost universally accepted. Physical punishment of the child seems to be the approved method of teaching and a valuable educational tool, thus honoring the centuries old Spanish aphorism: "La letra con sangre entra." (To learn must be done through pain, even to the point of having blood come out of your body.)

One of our patients commenting on juvenile delinquency said: "... today's generation is lost . . . Reasons? Children can't be touched by their parents. If you don't hit a child you can't teach him. . ." This parental attitude is found in practically every clinical history.

Another behavior reaction that seems to be culturally patterned is the almost

universal tendency to consider woman as inferior to man. This trend is undoubtedly favored by the Spanish-Catholic tradition which sees man as inherently superior to woman. Culturally, in the case of the man, extra-marital relations are permitted. Common-law marriages are frequent, although the woman, called concubine, has roughly the same social status as a legal wife.

Summarizing, these brief examples indicate that their behavioral practices are different from the society into which they come and, inevitably, conflicts between the two cultures arise. In this work an attempt is made to present some of these patterns of behavior, which are frequently exhibited by the Spanish-speaking group. Two of them, Spiritualism and what we call the demanding attitude, will be analyzed in some detail.

SPIRITUALISM AS A RELIGIOUS PHENOMENON

The claim that religious phenomena can be brought within the orbit of science has not yet been substantiated or even widely conceded. Frazer defines religion as: "A propitiation and conciliation of powers superior to man." Herbert Spencer says: "The beginnings of religion are due to the necessity of propitiating ancestors already dead." Freud's paper on Religious Origins (1919) states that: ". . . if the prehistoric and ethnical material is worked over psychoanalytically, we arrive at unexpectedly precise results: namely, that God-father once walked upon the Earth in bodily form and exercised his sovereignty as chieftain of the primal human horde, until his sons unite to slay him. . ."

Spiritualism as an articulate form of religion owes its name to Andrew Jackson Davis, whose book "Nature's Divine Revelation," published in 1847, has gone through more than 40 editions. His manner of expression was colored by Mesmer's theories in vogue at the time. Davis accepted the tri-partite nature of man. The Spirit was one with the Divine, as a process of it. The Soul, the intermediate substance, linking body and spirit, is animal in origin and may be regarded as a sublimation of the Body, with its limbs and senses. The Body is nothing but the material covering by which the Soul communicates with the rest of the material world. As we grow older, Spirit and Soul gradually withdraw from the fleshly wrapping, and when the process is finished, the Soul quietly and peacefully abandons it. Davis deduced that death is not merely figuratively but literally a birth from lower to higher planes.

The dead pass slowly from sphere to sphere, but as Spirits they are not troubled by distance, and of course not excluded by corporeal bars. The communication between earthly and spiritual spheres is effected through "mediums." They pass messages from the next world. These activities are carried out at seances, where ten or twelve persons gather together, two or three of them being mediums. The others come to the session to learn about their problems, life and future. The three active participants sit around a table. One by one they are "taken" by the spirits. A sort of hysterical convulsion follows, indicating the entrance of the spirit into their bodies. Then they start to talk, questioning each member of the audience about himself. One in the group produces his symptoms or problems; the medium, at that point in a trance, proclaims that an evil hired spirit is re-

lently pursuing the person. The medium calls for a private consultation which takes place after the seance. During the patient-medium conference, the consultant is informed about the character of the pursuing spirit. He is given remedies, often "spirituous" substances, such as spirit of turpentine, etc., or a concoction of herbs to rub the skin with. One or two dollars is the price of the consultation. In New York City there are innumerable practicing mediums.

Spiritualism encircles our Spanish-speaking patients as a religious saturnal ring. Everyone is exposed to its influence. The majority of our patients' religiosity is catalyzed by the spiritualistic phenomenon. Statistical studies have indicated that 12 per cent of the total population of Puerto Rico believes in spiritualism. A rough estimate of its prevalence among our patients, would suggest a figure closer to 98 per cent. Furthermore, those who are not actual believers have, inevitably, been in contact with relatives who actually were practicing spiritualists. This sort of spurious religion plays a very important role in the behavioral practices of a large sector of the Puerto Rican patient population that comes to our clinics and medical services.

CASE HISTORIES

A summary of eleven cases will be presented. However, it is of interest to recount, as a prologue, the following incident.

On February 3rd, 1958, strange things happened in the home of a Catholic middle-class family. Bottles of holy water on the bureau became uncapped, jumbled and tumbled around. The police had to be called. A priest of the Church of Saint William the Abbot, in the town of Seaford, Long Island, came to the house and blessed it. There was some discussion of the Catholic rite of exorcism. Twenty days later an 18-inch statue of the Virgin flew over 12 feet; it was suggested that the disturbances were caused by a poltergeist, the noisy ghost of folklore. Several people have assumed that the family must have some "occult knowledge."

These facts were reported in the March 17th issue of Life Magazine under the title: "House Of Flying Objects—A Ghostly Mystery Plagues A Family." The author was able to telescope in a few pages all the ingredients that made the incident national news. Here, as before in the history of mankind, supernatural forces were invoked to explain a mystery, but the basic elements remain unchanged in spite of time, place and cultural milieu. A religious family possessed by evil forces, probably the devil, the Church considering exorcism, a priest blessing the house and actively fighting the demoniac spirit. Even the scientific world, (Duke University) entered by sending one of its researchers to investigate the case. But the problem remained unsolved and in the minds of millions of readers lives the certainty that uncanny forces of the beyond have been at work.

It is curious to notice that centuries of civilization, progress and scientific achievement were ignored and that man himself started to operate at the same level of primitivism, frightened by what he considered uncontrollable devilish forces, as his less civilized brother did in ancient time or as he still does in other areas of the world, including the world of our Spanish-speaking patients. Long

ago Sigmund Freud said: "The basic emotional patterns are universal," and we may very well add: "they have not changed with time, and do not recognize culture, civilization or other frontiers. . ."

CASE REPORTS

Case 1

A girl of 22, diagnosed as acute anxiety neurosis, told the following: "My mother was a 'medium'—she used to be taken by spirits. When my cousin married, her dead mother communicated with mine and approved of the marriage. I myself have faculties. The spirit of a prostitute, who died with her face jabbed by a knife, wanted to cut my face. She will never allow me to marry. I went to see a 'medium.' He told me that my mother, now dead, will always protect me."

Case 2

A woman of 40 had the spirit within her. It was a spirit hired by a former girl friend of her husband's. The medium recognized certain sexual connotations in the case. He decided that by having sexual intercourse with the possessed woman his supernatural powers would force the spirit of the prostitute to get out by way of the woman's vagina through his penis, and thus break the spell.

Case 3

A young man of 22 told me: "My aunt whose son died a few months ago, talks with him in almost daily sessions. She feels that she has not lost him." The same patient related that a boy friend of his sister's was killed in a brawl. The spirit of the assassinated person took possession of the girl. After that she behaved as a man, walked as a man, talked as a man, and thought as a man. The entire family knew very well what it was.

Case 4

A 44 year old woman, with a college degree in social work, had a fight with a "client" on a Friday. The client cursed her and told her that ". . . she would crawl like a snake. . . ." A month later, thieves robbed her home. She also broke her arm and lost her savings. In the meanwhile, one of her daughters became mentally ill. Several "mediums" and the entire family agreed that she was under the influence of an evil hired spirit.

Case 5

The parents of a young girl came to me for diagnosis. Was their daughter mentally ill or not? Once they were told that she actually was an incipient case of Schizophrenia, they departed very happy. Confidentially they told me: "Look doctor, we know who does it, and why. We will work at it, and the spirits will leave her . . . she does not need your treatment."

Case 6

A married woman was seen psychiatrically. The family came to congratulate me. Their medium had told them that I (the doctor) was doing all right, and that she (the medium) did not object to have the patient seen by me.

Case 7

In the medical wards a man had a coronary thrombosis, his third, and probably his last attack. He said: ". . . nothing is wrong with me, some spirits are doing this. . . if I could only drink some concoction made of herbs I could be cured . . . but doctors here do not understand these things . . . they are good, but ignorant in these matters. . ."

Case 8

A young woman was told that happiness depended on her marrying the reincarnation of one of her ancestors. In a former life, centuries ago, she had been a princess, married to a prince. In pursuit of happiness she married an old Portuguese sailor, who mistreated her and drank too much. This patient came to me in a mild depressive mood. Very soon she announced that I was the reincarnation of the former husband and prince. The "medium" confirmed the theory.

Case 9

A 35 year old compulsive barber was obsessed with the idea of his wife being unfaithful to him. During the course of the treatment the family decided that his case should be brought to the attention of a higher spiritual power in Puerto Rico, since several "mediums" in New York agreed that the man was possessed by a spirit. A "medium" in San Juan (P.R.) sent a silk handkerchief to the patient for him to wear for seven days and seven nights. This was done and the handkerchief was returned to the "medium" by air mail. He "worked" on the handkerchief, and again the piece of cloth was sent to New York. The patient was to throw the handkerchief in a remote street of the Bronx, and then be cured. Unfortunately the obsessional doubts of the patient did not allow him to follow the orders of the "medium." He walked miles and miles, up to the point of exhaustion, to return home day after day with the satanic handkerchief still in his possession. Finally it was decided that he should throw it in the toilet bowl.

Case 10

In the Klingstein Pavilion a young expectant mother vomited continuously. Vomiting started soon after the onset of her pregnancy, and this resulted in her admission to the Maternity Ward. She, of course, believed in spirits, and accordingly her husband organized a few spiritualistic seances at their home. It was elicited that the vomiting was the wrong doing of an evil spirit, and that pregnancy should be discontinued. She openly asked me for interruption of pregnancy.

Case 11

In the Neurological Ward a 36 year old female was diagnosed as hysterical blindness. Raped at a very early age, she had her first child before she was 13. She came directly from Puerto Rico to New York in order to be hospitalized at The Mount Sinai Hospital. She said that before the attacks of blindness, the Virgin Saint Lucy, blind herself, appeared to her and talked. The next morning, and after a violent headache, she would become temporarily blind. There was no question in her mind about the spirits having a great deal to do with her case and the disease. One of her nurses had blue eyes and blond hair, and like the Virgin, she was dressed in blue and white. The patient knew that some benevolent spirit had arranged for her to have a blue-eyed nurse, an alter-ego of the Virgin, to help her in the process of being cured.

INTERPRETATION

In these cases the following elements are present: spirits deciding marriage, prostitution; communication with the dead; determining bad pregnancies and causing diseases such as blindness, coronary thrombosis and mental illness. They may work either with or against the doctor. If these facts are accepted as true, other associated trends such as hallucinations, delusional ideas, ideas of influence by outside forces, interference with thinking, persecutory trends, voices calling their names (mostly the mother's voice), etc., can be present; and they actually are in the majority of our patients. These phenomena do not have a particular pathological significance and they do not necessarily represent a psychotic process. They are merely part of this people's religious structure. Once the strange

spiritualistic nature of the symptoms is appreciated the only possible cure is to outwit or to get rid of the spirits. Thus the power obtained by spiritualism is immense. It gives an undisputed control over the world of the dead and procures for the possessor of this belief a mastery over nature. While it is true that everyone can be exposed to someone else's vengeance, as is the case in most of our patients, each one can also hire a spirit and become omnipotent. This almost religious feeling of omnipotence, as mentioned by Freud in "Civilization and Its Discontents," is what the deprived Puerto Rican man considers so valuable. A dynamic interpretation of the phenomenon of Spiritualism will take us to the paper on "Neurosis of Demoniacal Possession" by S. Freud. He states: "... the problem of motivation here is that one sells oneself to the devil, because the devil in return for the immortal soul has much to offer that is highly treasured of man: health, immunity from dangers, power over mankind and over the forces of nature. . ."

Spiritualism, in our group of patients, has also the meaning of a valiant unorthodox gesture of rebellion against the monolithic power of the church, it quite probably representing a largely unconscious resentment of the clerical grasp of the psyche of the Puerto Rican man. The authority of the priest cannot be argued along terrestrial lines, only along spiritual ones. Engaging into dealings with spirits, commanding them or propitiating them, casting spells, or learning the art of controlling nature, brings defeat to the churchman and victory to the underdog. Using an analytical terminology, Spiritualism as we see it in our patients with its exacerbated mechanisms of rebellion, may be an attempt to solve the otherwise unsolved oedipal situation, but in almost collective terms.

THE DEMANDING ATTITUDE TOWARDS THE DOCTOR

Once a patient said to me: "I don't care who you are, what you do or how you feel. The city pays you, you have to take care of me, this is my right and your duty." This demanding attitude repeats itself again and again. The hospital, with its physical structure that gives shelter to patients when in need, is an incontrovertible reality, but the doctors do not seem to exist as individual entities. It is true that they are powerful persons invested with authority, but they never do what they are supposed to do. Systematically the doctor is wrong, surgery is wrong most of the time and frequently uncalled for. Diagnoses are wrong, and wrong are the treatments. Very seldom do we hear laudatory comments among these patients.

To the layman, this attitude is reprehensible and calls for rejection. Even the doctor or the social worker is prone to be irritated and behave accordingly, developing a sort of ethnological bias. It is clear, however, that we are confronted with a reaction-formation mechanism, directed toward the man-physician invested with so much authority. Its significance as a collective mechanism should be fully understood.

A psycho-social interpretation of this demanding attitude gives us a different view of the situation. It seems that we are dealing with a piece of cultural behavior that must be referred to some historically antecedent pattern of behavior. The majority of our patients come from a fundamentally peasant culture;

their traditional patterns are already so consolidated by this time that they can hardly be uprooted and therefore remain predominant. To them, the law with its implications seems inevitably at the service of the powerful who in turn uses his strength in a very arbitrary way. The ruler, gigantic father figure, during the past 400 years has been embodied with all the powers and helped in his endeavors by a punitive, castrating mother-church. A collective form of resentment could have taken place and crystallized in a definite antagonism toward organized society or the principle of authority. This goes so far as to consider the delinquent as a hero-like figure who fights for righteousness. To be in jail is not infamous but an obvious sign of manhood that is commendable. One of our patients expressed it in a clear-cut fashion: "If someone does something to me I will let him have it, and if I go to jail I don't care, because I know the jails are made for men that are really men. . ."

STATISTICAL SURVEY

The following data indicate the great influx of Spanish-speaking patients at The Mount Sinai Hospital (Tables I-V).

TABLE I
In-patients at The Mount Sinai Hospital 1957

	Number	Percentage
Total patients.....	6338	100.0
Spanish-name patients.....	1932	30.4
Male.....	815	12.8
Female.....	1117	17.6

TABLE II
Percentages of groups within Spanish-name in-patients for 1957

	Number	Percentage
Total Spanish-name in-patients.....	1932	100
Sex		
Male.....	815	42.2
Female.....	1117	57.8
Age (both sexes)		
1-15 years.....	626	32.4
15-30 years.....	506	26.1
30-45 years.....	438	22.6
45-55 years and over.....	361	18.6
Birthplace		
Puerto Rico.....	1292	66.8
United States.....	525	27.1
Elsewhere.....	116	6.0
Borough of residence		
Manhattan.....	1569	81.2
The Bronx.....	275	14.2
Other.....	88	4.0

TABLE III

Percentages of services admissions within Spanish-name in-patients at The Mount Sinai Hospital 1957

Service	Number	Percentage
Surgery	439	22.7
Orthopedic	73	3.7
Pediatric	444	22.9
Gynecology*	370	19.8
E N T	145	7.5
Eye	77	3.9
Dental	11	.5
Neurology	46	2.3
Psychiatric	2	.1
Total	1932	

* In 161 admissions to Gynecology, 34 were for incomplete abortions (21%).

TABLE IV

Percentages of Spanish-name in-patients in total services admissions at The Mount Sinai Hospital 1957

Service	Spanish-name In-patients	Total In-patients	Percentage
Surgery	439	1569	27.8
Orthopedic	73	171	42.6
Pediatric	444	1058	41.9
Medical	325	1809	17.9
Gynecology	370	756	48.9
E N T	145	255	56.8
Dental	11	58	18.9
Eye	77	171	45.0
Neurology	46	363	12.5
Psychiatric	2	128	15.6
Total	1932	6338	

TABLE V

Summary

Out-patient Department			
All new applicants	7000	43% were P.R. (40% were adults, 60% children)	3220
All new applicants to Pre-natal Clinic	800	50% were P.R.	400
In-Services			
Total admissions	6338	30.4% were P.R.	1932
Monthly average of Puerto Rican			150-190

CONCLUSION

It is a basic assumption that societies will maintain their culture through an indefinitely long period of time, at least longer than one life-time. Yet, here in New York we are spectators of a process of absorption and annihilation by assimilation of a newly arrived society, the Puerto Rican group, that is being forced to a drastic and sudden change in its habits and patterns of culture.

Thousands of these people come to us for help and advice, utilizing our clinics and services. It is our obligation to be properly equipped to perform our duties to the best of our abilities, speeding the process of their integration into our ways of life.

To understand them is to help them. In the ultimate analysis, to understand and to help a single man is to understand and to help the entire human race.

SURGICAL CLOSURE OF THE INCOMPETENT CERVICAL OS DURING PREGNANCY

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Surgical closure of the uterine cervix as a method of management of the incompetent cervical os, a proposed cause of second trimester abortion, first came to the attention of obstetricians in 1955. In an attempt to evaluate this therapy and to define the limits of its usefulness, this procedure was performed on a series of patients on the Obstetrical Service of The Mount Sinai Hospital. In a little over a year, while approximately 5000 patients were delivered on this service, only twelve patients were found to be suitable for surgical closure of the cervix although the widest latitude was taken in laying down the criteria for selection. With this broad base, it was hoped that an accurate evaluation of the method, its hazards and benefits, and the type of case for which it was suited, might be more easily achieved.

TECHNIQUE

Our primary concept has been to place a purse-string suture of non-reactive and non-absorbable material sub-mucosally about the cervix, and by constricting this to close the cervical canal for the duration of the pregnancy. From the onset, our intent has been to divide this suture when labor started, and to permit vaginal delivery if possible.

As the series of cases unfolded, several minor problems were clarified:

Suture material: Initial trials were made with strips of preserved ox fascia; these results were disappointing, the suture disintegrating in one instance in 14 days, and in a second instance in five days. All subsequent cases were sutured with polyethylene tubing of 0.065 inches diameter (Becton, Dickinson and Company, #444T). To prevent stretching of this tubing, a wick of #5 braided surgical silk was threaded through its center to form a non-elastic cord. This suture has been observed *in situ* for periods up to 14 weeks without evidence of degeneration or tissue reaction, and is felt to be eminently satisfactory for this procedure.

Anesthesia: The procedure, with the exception of pressure of vaginal retractors and traction applied to the cervix, is relatively painless. Saddle-block anesthesia (Pontocaine, 4 mg.) was used in three cases and then discarded because of the impression that uterine irritability was enhanced with this type of anesthesia. The final agent of choice was pentothal-nitrous oxide-oxygen, which gave

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Presented at a meeting of the Section on Obstetrics and Gynecology of the New York Academy of Medicine, May 27, 1958.

maximum patient comfort with a minimum level of anesthesia. In two cases where the patients had eaten shortly prior to admission to the hospital, it was possible to perform the procedure under heavy sedation alone, i.e., morphine sulfate, 15 mg., and scopolamine hydrobromide, 0.4 mg. intramuscularly, and seobarbital sodium, 200 mg. intravenously.

Vaginal preparation: Initial cases were prepared for surgery by cleansing the vagina thoroughly with tincture of Zephiran®. In view of the open cervix in these cases, frequently with the membranes bulging, the question was raised as to whether a chemical amnionitis or deiduitis might thus be induced and contribute to a bad result. All subsequent cases were simply cleansed externally and the interior of the vagina not disturbed. No cases of infection could be attributed to the procedure *per se*.

The actual technique was as follows: The patient was placed in lithotomy position, catheterized, prepared, and draped as for delivery. The cervix was exposed adequately using several vaginal retractors; two assistants were found to be essential. The rim of cervix was grasped in four quadrants with long Allis forceps and pulled forward. If the membranes were bulging into the vagina, they were replaced gently at this time and controlled with moist, narrow uterine packing. At the junction of rugose vagina and smooth cervix, a vertical nick was made anteriorly at 12 o'clock in the vaginal mucosa to expose the sub-mucosal layer. The cervical suture was passed at this level. In this series, no attempt was made to advance the bladder or to reach the level of the internal os. The polyethylene tubing with braided silk core, threaded on a heavy, large, cutting-edge needle, was then passed sub-mucosally around the entire circumference of the cervix; five or six passes of the needle were necessary to accomplish this. The suture was tied anteriorly as tightly as possible, and the ends clamped with lead shot to prevent slipping. There was usually moderate bleeding during the procedure, but blood loss ceased with tying of the suture. Although the suture was tied very tightly, no cervical ischemia could be demonstrated by the test of blanching to digital pressure and the immediate return to normal color. No vaginal packing was used. All patients received morphine sulfate, 15 mg. intramuscularly every four hours, until the further course of the pregnancy was clarified, and all received a broad spectrum antibiotic prophylactically. No other adjuvant therapy was employed. In all cases, whether successful or unsuccessful, there were no ill effects to the mother from the procedure, nor sufficient blood loss to merit transfusion.

MATERIAL AND RESULTS

Cases were chosen from both the Private and Ward Services of The Mount Sinai Hospital in three categories: poor obstetrical history, premature labor, and patulous cervical os in the absence of contractions. It was hoped that this wide selection would demonstrate rapidly the limits of the procedure. Details of nine cases are presented in Table I.

The remaining three cases presented with a large, tense protrusion of the amniotic sac into the vagina. It was found that these cases were irreversible;

TABLE I
Cases of sutured cervix in pregnancy

Case	Age	Parity	Weeks of Gestation	Reason for Suture	Cervical Dilatation	Duration of Suture	Outcome of Pregnancy
GT	21	0201	24	Patulous os; contr.	2 cm., long	14 weeks	Rupt. of memb. @ 38 wks; IV pit drip after 48 hrs; 2290 gm. male, L & W.
JR	16	1001	32	Premature labor	3 cm., effaced	5 days	Spont. labor recurred; 1930 gm. male, L & W
RK	38	0241	11	Poor obst. history	1 cm., long	8 weeks	Prem. rupture of memb., spont. labor; 530 gm. male, d. 2 hrs n.n.; placenta previa and accreta—hysterectomy.
IB	29	3142	33	Premature labor	4 cm., long	3½ weeks	Spont. labor @ 36½ wks.; amniotomy; 2700 gm. female, L & W.
LM	27	0150	14	Poor obst. history	1 cm., long	12 weeks	Prem. rupt. of memb. @ 24 wks; amnionitis; spont. labor @ 26 wks; 825 gm. female, d. 4 days.
MR	23	0000	30½	Premature labor	2 cm., effaced	14 hours	Temp. 103.2—"flu"; 1680 gm. male, d. 12 hrs. n.n.
CO	22	0401	24	Poor obst. history	1 cm., long	12 weeks	Prem. rupt. of memb. @ 35 wks; labor @ 36 wks; 1700 gm. male, d. 4 hrs. n.n. of atelectasis.
NP	18	0010	25	Patulous os	2 cm., long	12 weeks	Spont. labor @ 37 wks; 3000 gm. male, L & W.
NP	19	1011	24	Premature labor	3 cm., effaced	20 hours	Labor recurred; amniotomy; 875 gm. male, d. 2 hrs. n.n.

one amniotic sac ruptured while preparations for suturing the cervix were under way, a second ruptured during the procedure, and the third a few hours after the cervix was sutured. All three pregnancies terminated rapidly in immature deliveries. Much difficulty was encountered in replacing the tense amniotic sac into the uterine cavity, and it seemed that underlying uterine irritability was the causative factor here rather than passive cervical dilatation.

The behavior of the sutured cervix following the onset of labor was of interest, since this represented an area of possible danger to the mother. Initially, the question of uterine rupture in the neglected case was raised. As it developed, proper sub-mucosal placement of the purse-string suture did not prevent normal cervical effacement and dilatation. With the exception of two cases in which the suture had not been adequately anchored posteriorly and in which it tore through the mucosa at that point once contractions started, the cervical tissue behaved normally since it, *per se*, was not transfixed. The cervix effaced

TABLE II
Summary of cases of cervical suture

Reason for Suture	Number of Cases	Successful Result	Per-cent Success
Poor obst. history.....	3	0	0
Premature labor.....	4	1	25
Bulging membranes.....	3	0	0
Patulous cervical os.....	2	2	100
Overall totals.....	12	3	25

and was drawn up inside the suture. Cervical dilatation then proceeded in normal fashion, but with the para-cervical mucosa being stretched tightly over the purse-string suture. It was evident that this taut mucosa would tear long before the uterus might rupture because of obstructed labor. Once the suture was severed and tension relieved, cervical dilatation jumped at once to 7 to 8 centimeters. Vaginal delivery was uneventful in every case, and post-partum inspection of the cervix revealed only minor lacerations of the cervical mucosa which did not require suturing. No instance of unusual cervical bleeding was encountered.

Reviewing the cases, it becomes evident that suturing the cervix is not a panacea for the ills of gestation. The series is summarized in Table II.

The limitations of the procedure are thus laid bare. Surgical closure of the cervix will not prevent the onset of true labor from whatever cause. It is of no help in the patient with a poor obstetrical history because of germ plasm defects and uterine, placental, or fetal anomalies. It will not inhibit uterine contractions caused by hormonal or constitutional factors. Its successful application seems to be limited to the few cases of *passive* cervical dilatation presumably caused by internal os incompetence; in these cases, prevention of this passive dilatation may inhibit the onset of uterine contractions. Both of the successful cases gave a history of previous similar late abortion or premature labor, and success was possible in both cases because the process was interrupted before true labor could supervene. In the cases where fetal membranes were already bulging under tension, uterine irritability was such that the process had become irreversible.

DISCUSSION

The status of the incompetent internal os as a cause of second trimester abortion has not been clarified. There is little information available about the condition of the cervix in normal pregnancy; there are no figures to indicate how long a cervix may remain patulous without the onset of labor. The only recent study of this problem by repeated vaginal examinations in the third trimester showed that by the beginning of the ninth month the cervix was at least two centimeters dilated in 60 per cent of primipara and 70 per cent of multipara,

and that in most instances this dilatation had occurred since the beginning of the third trimester. It was felt that Braxton-Hicks contractions were responsible for these cervical changes (1). The significance of effacement and dilatation of the cervix in the second trimester is unknown. Further, the patulous status of the cervix in cases of multiple gestation is noted by all. Does then a passive cervical dilatation, *per se*, stimulate uterine contractions, or are these the result of a secondary deciduitis, or of premature rupture of membranes? Is there any such entity as completely passive cervical dilatation? These questions remain open for further investigation, especially via the tokodynamometer.

We may conclude at present that the entity of incompetent internal os does exist, but that this is a rare syndrome. In our own series, only four patients presented the clinical picture as rigidly defined, thus giving an incidence of 1:1250 deliveries. Barter had 19 cases in 35,000 deliveries, an incidence of 1:1850 (2). Eastman also feels that this syndrome plays a relatively minor role in the etiology of late abortion in his experience (3). One must therefore adhere to very rigid criteria in the selection of patients for surgical intervention.

The therapeutic approach to this problem has been along two lines: during pregnancies and between pregnancies. The interval procedure was first proposed in 1950 by Lash and Lash (4). Many questions about this method are still unsettled (3, 5-9). The problem of diagnosis has not been satisfactorily solved, nor have the operative results been uniformly good as regards subsequent fertility of the patients (10). Surgical repair of the incompetent os during pregnancy was first reported in 1955 by Shirodkar (11), and further developed by McDonald (12), and Barter and his co-workers (2, 13) among others. The modifications of the Shirodkar procedure seemed to have many advantages: the pregnancy is already *in situ*; the procedure is innocuous to mother and fetus; it is applicable to any stage of gestation and to patients first seen during pregnancy; and there need be no interference with normal labor and delivery. There would seem to be no good reason to leave the cervical suture in place and deliver the patient by cesarean section, since almost all of these patients have relatively easy labors and simple vaginal deliveries if permitted to do so. The psychological problems attending suturing of the cervix with each pregnancy are more than offset by the trauma and hazards of repeated cesarean section.

The major problem remains the proper selection of patients for this procedure. From our limited experience, it seems that the optimum method of diagnosis is observation of a patient's reproductive performance. With the symptoms of profuse vaginal discharge, pelvic pressure, and "lump" in the vagina, examination will usually reveal the cervix to be already effaced and dilated and the amniotic sac bulging into the vagina. At this stage, the outcome is almost inevitably abortion. Therapy must be instituted before this point is reached, which in McDonald's experience appeared at 20 to 24 weeks gestation (12). The two most important avenues of diagnosis are therefore history and examination. A poor obstetrical history, although suspicious, is not sufficient; many other factors may be responsible for repeated premature labors, and these must be ruled out. Even if the pregnancy may be prolonged, the cases

in which poor germ plasm, placental abnormality, or poor uterine environment are the etiologic factors will terminate with poor fetal results. This was demonstrated by several cases in our series. Even repeated premature rupture of membranes is not sufficient for diagnosis. The typical history is that of cervical dilatation in the second trimester without painful contractions, determined by examination before rupture of membranes or onset of labor. If this has occurred even once with the delivery of a normal fetus, suture of the cervix is indicated with future pregnancies. Given this history, the procedure is best performed prophylactically at the beginning of the second trimester, once the period of early spontaneous abortion has passed. With a suspicious but inconclusive history, repeated and frequent vaginal examinations must be carried out, and the cervix sutured if there is any sign of effacement or dilatation. That this is not the method of choice was shown by one case in our series in which a fully effaced and four centimeter dilated cervix with a tensely bulging sac of membranes was found 48 hours after vaginal examination had revealed a long, closed cervix; there had been no interim symptoms or noticeable contractions. It is our feeling that if any doubt exists, the cervix is better sutured; that there is so little risk inherent in the procedure that it may even be employed as a therapeutic trial with impunity.

Definite contraindications to the procedure do exist. These include active labor, ruptured membranes, fetal anomaly, uterine bleeding, and hydramnios.

CONCLUSIONS

(a). A series of twelve cases of cervical tuture in pregnancy is presented, the method described, and the results discussed.

(b). Suturing of the cervix uteri is a satisfactory method of therapy for the incompetent internal os. Vaginal delivery can be readily accomplished and should be the method of choice.

(c). To achieve the maximum benefits from the procedure, strict criteria must obtain in the selection of patients. The indications and contraindications are listed.

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OBSERVATIONS ON THE HISTOLOGY OF AGING HUMAN CONNECTIVE TISSUES

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The connective tissue system pervades all the structures of the human body. In doing so it takes many structural forms. These may differ considerably, as in the delicate interstices of the arterial wall, the areolar network of the lymphatics, the yellow ligament of the vertebral laminae, the skeleton itself or the dense fibrous fascia of the lateral femoral band. It is among the most stable and resistant of tissues and the most readily reproductive in the form of inelastic scar tissue. In all areas, however, it remains qualitatively similar, differing only in the relative quantities of its several histologic and cytologic components and, in certain specialized sites, by the inclusion of extraneous cells and extracellular material, meandering or deposited in its network.

Within the large body of writings on the connective tissues there is a notable paucity of studies relative to the effect of aging on their structure. That which has appeared deals chiefly with the chemical changes in collagen and elastin in the connective tissue elements of the derma (1-9), or with the elastin of the arterial walls (10, 11). A review of these studies reveals a considerable divergence of views on the extent to which any significant change takes place, and the chemical nature of that change.

One observation on the effect of age in these areas appears with considerable frequency in these reports and refers to changes in the elastic fibers. Chemical interpretations vary somewhat but the general impression is expressed by Banfield. "Elastic fibers of the skin during the process of aging undergo fragmentation, clumping and acquire an affinity for basic stains." If true this fact is highly significant to a number of problems in musculo-skeletal dysfunction in the aged. It has been generally noted, but I know of no specific observational evidence in support of the concept, that while collagen fibers continue to reproduce themselves thruout all ages, elastic fibers once destroyed do not reproduce. But observations which apply to fibrous elements of the skin or blood vessels may or may not be valid in the purer and more compact connective tissues of the locomotor apparatus. Since, of this last, no significant studies on the effect of aging seem to have appeared, the present investigation was undertaken.

Twenty-four specimens were removed from the fascia lata of that many human subjects at the operating table. These patients were undergoing surgical intervention for skeletal lesions not involving systemic disease or disease of the local soft tissues. Therefore the specimens approximated, if they were not identical with, normal human fascia in the living subject. The ages from which specimens were taken ranged from 13 to 89 years. The specimens were prepared in

Read in part at The Mount Sinai Research Society, January 28, 1959.

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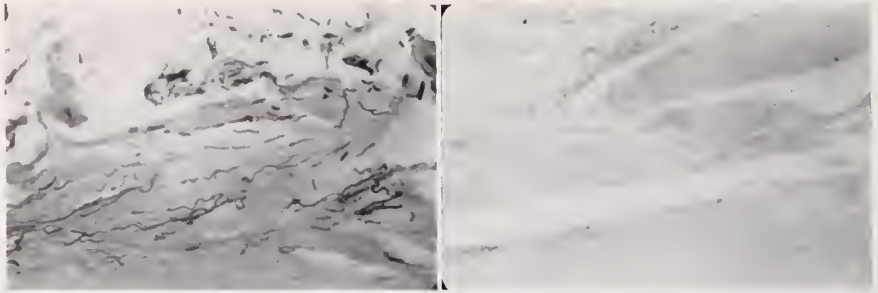


FIG. 1 (*left*). 13 $\frac{1}{2}$ year old male. Elastin stain.
 FIG. 2 (*right*). 76 year old female. Elastin stain.

paraffin, cut in the usual fashion and stained. In most instances each specimen was stained by four methods, haematoxylin-eosin, van Giesen (for collagen), a Mallory modification of the Verhoef elastin stain, and Schiff's stain for periodic acid (12). Three or four sections were available for each stain of each section.

Observations on these twenty-four specimens can be noted very briefly.

a. Specimens stained with haematoxylin-eosin showed no significant perceptible histologic or cytologic variation within the age range of this series.

b. Similar specimens stained for collagen by the van Giesen method disclosed no significant variation in structure of the fibers or in the density or hue of the stain. This observation was not unexpected since present stains used to demarcate collagen do so by a gross chemical reaction of the apparently amorphous substance and do not differentiate the structural elements of the fibers.

c. In similar sections stained for periodic acid (Schiff), no significant variation in the staining reaction could be related to the age of the patient. Here again the Schiff stain grossly demarcates areas of mucopolysaccharides, and in doing so seemingly overlaps structural boundaries of the fibers. The hue and density of the stain varied thruout the series without regard to any recognizable tissue factor. However, much more is to be known of periodic acid as a histochemical technic before histological appearance may be interpreted adequately.

d. In similar sections stained for elastin by a Mallory modification of the Verhoef technic, those in the group from 70 years of age and upward were noteworthy. In the younger age group the elastic fibers within the fibrous areas (as distinguished from the perivascular) appeared for the most part as rather fine wavy lines. When broken by their undulations thru the flat plane of the section the appearance is that of a dotted line not perceptibly thicker than the uncut fibers. No important variation in this pattern in shape, size or density of stain was noted until specimens were studied from patients in the 70's and 80's. In many specimens of this older age group the elastic fibers appear coarser, uneven in thickness, and in some areas curled, clumped and fragmented. In some areas of these specimens, however, the findings still resembled these of younger adults.

Histologic study of the connective tissues of the locomotor apparatus shows them to be remarkably stable in response to aging. Of the four common staining methods only that which demonstrated the elastic fibers is noteworthy. Deterio-

ration in the structure of the elastic fibers appears to occur in aged subjects, although this is not uniform. Apparently the degree of elastic fiber degeneration is as variable as most other manifestations of senility. However, the tendency to coarsening, fragmentation and clumping is easily observable in any group of specimens from aged subjects. No such variation in the aging connective tissues appears in the cytologic elements, the structure or staining qualities of collagen fibers or the so-called Schiff reaction to periodic acid.

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Radiological Notes

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RETROGRADE ESOPHAGEAL PERISTALSIS?

During the course of observations of the swallowing function with a large image intensifier, a sequence was observed which suggests that retrograde peristalsis can be demonstrated in the distal half of the thoracic esophagus. There is considerable controversy in the literature as to whether true retrograde peristalsis occurs in the esophagus of human beings. The opportunity of performing ciné-radiography with an image intensifier large enough to include the entire thoracic esophagus has not been realized until recently. Part of the controversy is related to the definition of peristaltic activity. In the sequence illustrated by tracings from the film (Fig. 1), the emptying of the barium from the distal half of the esophagus *proximally* appears quite comparable to a peristaltic wave. This sequence was from a rather elderly female taken in the right oblique prone

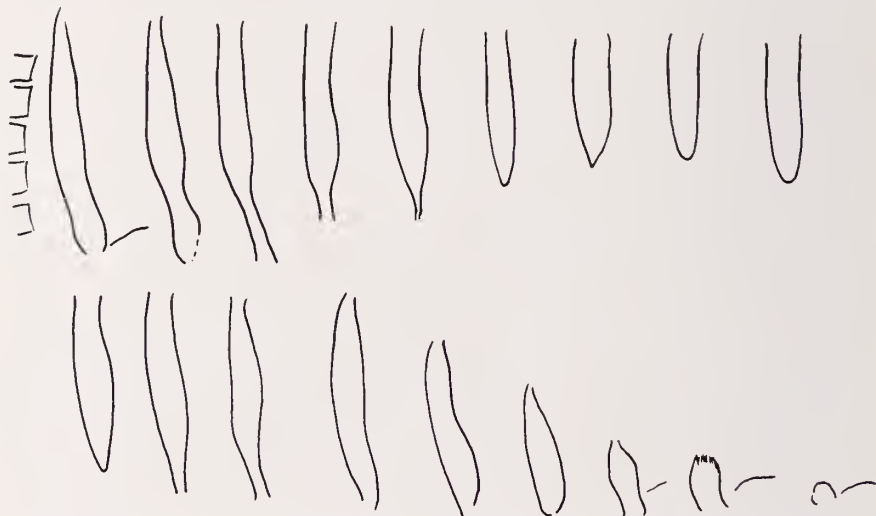


Fig. 1. Tracings from serial frames of a ciné recording made during the course of swallowing shows the distal portion of the esophagus to contract and then to be stripped from below upwards. The distal end of the barium column assumes a blunt appearance during this period. The proximal half of the thoracic esophagus remained filled and the barium rather promptly returned to the distal esophagus followed by the normal stripping peristaltic wave which emptied the esophagus completely in the usual fashion. The diffuse incomplete contraction of the distal esophagus prior to retrograde stripping does not resemble a peristaltic wave. However, the short complete retrograde progression of this contraction more proximally resembles the progress of the normal peristaltic wave seen in the subsequent frames (lower row). Incidentally, this type of progressive retrograde contraction is not uncommon and probably is best seen during belching or production of laryngeal speech.

position while she was drinking the conventional fluid barium water mixture. She complained of no particular symptoms during this recording and there was no evidence of hiatus hernia or other abnormal motor pattern.

CASE NO. 88

This was the second admission of a 41 year old white female who nine years previously had undergone subtotal gastrectomy for a chronic peptic ulcer of the duodenum. The patient had complained of epigastric pain for about five years prior to that operation and had undergone two prior operations for perforated ulcer. Two months before the current admission, the patient noted a tender mass to the right of the umbilicus and at about the same time noted postprandial nausea and occasional vomiting, especially after eating solid food.



Case 88, Fig. 1A. With a small amount of barium, a mass defect (arrow) involving the lateral portion of the stoma and extending into the efferent jejunal loop is evident. Opaque clips adjacent to the medial portion of the anastomosis were applied at the time of subtotal gastrectomy nine years previously.



Case 88, Fig. 1B. With more barium, limited distensibility and irregular contour of the stomach is seen. Sharply demarcated nodular projections (arrow) straddle the stoma. The uninvolved portion of the anastomosis is sufficiently wide so that obstruction is not present. The jejunal involvement may be submucosal to a great extent since the mucosal folds appear to be intact.

The vomitus was not coffee-ground. The patient limited herself to a soft diet which furnished some relief particularly when proprietary antacid preparations were also used. She finally consulted a physician who found, on barium studies of the gastrointestinal tract, no evidence of a lesion. However, stools were persistently guaiac positive. Physical examination on admission was not contributory except for the abdominal scars and the presence of a stony hard mass to the right of the umbilicus, and a second somewhat smaller mass to the left. Barium meal examination (Figs. 1A, & 1B) showed a coarsely serrated pattern of the distal part of the residual portion of the stomach immediately proximal to the anastomosis. At the anastomosis, there were nodular projections which formed a mass extending into the efferent loop of the jejunum. The roentgen

findings were consistent with a neoplasm arising in the residual stomach and extending to and through the anastomosis.

The patient underwent exploratory laparotomy and a hard mass just proximal to the gastrojejunal stoma was noted. There were numerous omental metastases. In an attempt to resect the tumor, large retroperitoneal metastases adherent to the stomach were found which made the lesion inoperable. Biopsy of an omental metastasis was reported as showing infiltrating scirrhous carcinoma.

The diagnosis of carcinoma of the stomach after subtotal resection is being made with increasing frequency as these patients survive for many years. It is unlikely that the incidence is increased after subtotal resection but the diagnostic problem may be greater. The location in the region of the anastomosis extending into the jejunum is of interest.

Final Diagnosis: CARCINOMA OF THE STOMACH 9 YEARS POST SUBTOTAL GASTRECTOMY FOR DUODENAL ULCER.

CASE NO. 89

This was the second admission of a 64 year old white female because of tarry stools of four days duration and weakness. Thirty years prior to admission a gastroenterostomy had been performed for a chronic peptic ulcer because of persistent pain. Pain, however, recurred five years later and has been present intermittently in the entire interval. Eight years prior to the current admission, she was hospitalized because of abdominal pain and x-ray examination was said to have revealed a marginal ulcer. Blood pressure at that time was 238/118. Because of the hypertension, surgical intervention was not performed. She was relatively well on medical therapy until two years prior to the present admission when symptoms recurred. On admission, physical examination showed a well developed, obese, rather pale female. Blood pressure was 180/90. One observer felt a circumscribed, firm, tender mass in the epigastrium just to the left of the mid-line which moved on respiration. Hemoglobin was 10 grams per cent. Stool was guaiac 3+ on one occasion and guaiac negative on two other occasions. Rehfuess test meal showed no free acid and a maximum of 35 units total acid.³ After histamine, free acid increased to about 40 units and total acid to about 70 units.

Barium meal examination (Figs. 1A, & 1B) showed the status post gastroenterostomy. The stoma was located high on the posterior aspect of the greater curvature of the stomach. There were several diverticula in the adjacent jejunal loops (often seen with a long standing gastroenterostomy). Immediately opposite the stoma, on the lesser curvature, there was an elongated crater about 3 cm. in length. The wall of the stomach on both sides of the ulceration showed limited distensibility. This was most prominent distally where the antrum assumed a sickle-shaped configuration. The barium left the stomach quite promptly



Fig. 1 B



Fig. 1 A

For legend see facing page



Case 89, Fig. 2. Late film from barium meal done elsewhere 14 months previously shows an ulcer crater (arrow) as well as retention of barium in the sickle-shaped antrum and in several jejunal diverticula.

and it was difficult to fill the proximal portion of the stomach. No barium appeared to leave through the pylorus. The folds in the proximal portion of the stomach were thickened but normally tortuous.

The roentgen findings were somewhat difficult to interpret because of the inability to satisfactorily distend the stomach. A gastrointestinal series taken

Case 89, Fig. 1A. Barium meal examination shows a well-functioning anastomosis on the greater curvature with rapid emptying of the proximal portion of the stomach. The antrum (lower arrow) has a sickle configuration. On the lesser curvature, an elongated ulcer crater (upper arrow) is evident, partly overlapped by adjacent small bowel.

Case 89, Fig. 1B. In the lateral projection, the stoma (posterior arrow) on the posterior wall is more clearly seen. It is evident that the elongated ulcer (anterior arrow) is not directly related to the anastomosis, but is at a considerable distance from the efferent jejunal loop and therefore is not a marginal ulcer.

one year previously was reviewed (Fig. 2) and showed similar findings. In view of the presence of a gastric ulcer in a patient with a gastroenterostomy, the suggestion was made that this should be of malignant character. A benign gastric ulcer with a functioning gastroenterostomy is extremely unusual.

At exploratory laparotomy, a large tumor mass was found occupying almost the entire lesser curvature of the stomach. There were grossly involved lymph nodes in the perigastric fat as well as involvement of retroperitoneal nodes posteriorly. Palliative resection was undertaken because of the history of bleeding. The specimen revealed a large punched-out ulcerated mass, the ulceration measuring about 3 cm. in diameter and 1 cm. in depth. The stomach wall was markedly thickened. Microscopic finding was that of an infiltrating anaplastic carcinoma with involved lymph nodes.

Final Diagnosis: CARCINOMA OF THE STOMACH 30 YEARS AFTER GASTROENTEROSTOMY.

CASE NO. 90

This was the first admission of a 42 year old white female. Three years prior to admission she had been admitted elsewhere with a story of ulcer-type pain of five years duration, and tarry stools of two or three days duration. Barium meal examination was said to have shown a shallow gastric ulcer high on the lesser curvature of the stomach. Laparotomy was performed and a large indurated chronic ulcer found high on the lesser curvature of the stomach immediately adjacent to the entrance of the esophagus into the stomach. The remainder of the stomach was not remarkable. The small and large intestines, liver, spleen, and pancreas were negative. The uterus and adnexa were normal. A subtotal gastrectomy was performed. Six months prior to admission to this hospital, she began to complain of periodic vomiting up to 25 times daily brought on by eating. By taking small amounts of food, particularly in the recumbent position, she was able to eat. Two months prior to admission, she was admitted to another hospital where two barium meal examinations were said to have been negative.

Examination on admission showed a fairly well developed and nourished female who did not appear to be ill. Physical examination was non-contributory. Hemoglobin was 12 grams per cent, white blood count 8,600 per cu. mm. with a normal differential count. Rehfuss test meal showed no free acid and a maximum total acidity of 37 units. Barium meal examination (Figs. 1A, & 1B) showed the status post subtotal gastrectomy with the anastomosis apparently on the lesser curvature aspect of the stomach. Almost one-half of the stomach was still present. With the first swallow of the barium, the mucosal folds in the distal portion of the stomach appeared to be thickened. As the patient drank additional barium, the stomach distended normally except on its lesser curvature aspect which remained coarsely irregular. Moreover, barium left the stomach slowly through a rather markedly narrowed efferent loop, over a distance of about two inches. The visualized portion of the afferent loop for about the same distance also ap-



Case 90, Fig. 1A. Erect film from barium meal examination shows a coarsely irregular lesser curvature extending from the cardia to the anastomosis. The anastomosis is wide but circumferentially compressed as indicated by its haziness. The afferent and efferent jejunal loops are separated and markedly narrowed. The mucosal pattern of these segments is intact suggesting extrinsic involvement.

peared to be similarly narrowed. The fine mucosal folds in the narrowed portions of jejunum, however, appeared to be intact. The entire region of the lesser curvature of the stomach, the anastomosis and the adjacent portions of the afferent and efferent loops of jejunum appeared to be rigid and fixed in position. The impression was gained of a neoplastic mass involving these areas. Gastroscopy was performed with difficulty. It was not possible to pass the tube beyond the proximal portion of the stomach so that the region of the stoma was not visualized. The mucosa of the stomach was smooth, edematous and somewhat hyperemic. On the posterior wall below the cardia, there was a smooth mass covered with normal appearing mucous membrane. The impression of the



Case 90, Fig. 1B. Film taken with patient supine shows identical findings demonstrated in "double contrast" fashion. The exact duplication, with barium and with air, with the patient erect and supine, proves rigidity and fixation.

gastroscopist was that of extrinsic pressure on the posterior wall of the stomach without evidence of intrinsic disease.

On exploratory laparotomy, the stomach was exposed with considerable difficulty because of the large number of adhesions. Palpation behind the stomach revealed a large retrogastric mass which was rubbery in consistency and which extended down to the ligament of Treitz. There appeared to be so much inflammatory reaction that dissection of the afferent loop was not possible. A piece of dense, rubbery firm tissue was removed and sent for frozen section and reported as scar tissue. There was no evidence of metastatic disease of the liver. It was felt at the operating table that the mass was inflammatory in nature, most likely the result of a leak following the gastrectomy performed three years previously. However, the paraffin section of the piece of tissue removed was reported as showing "fibro-fatty tissue diffusely infiltrated by mucous cell carcinoma."

The origin of the carcinomatous mass involving the lesser curvature aspect of the stomach and extending retroperitoneally is not entirely clear. It would appear likely that the ulceration operated on three years previously, which apparently was not resected, may have been a primary carcinoma of the stomach. If this is so, it is rather remarkable that an ulceration or a large defect was not demonstrable within the stomach at the present time. Nevertheless, the appearance is consistent with a scirrhus carcinoma of the stomach with metastatic retroperitoneal disease.

Final Diagnosis: CARCINOMA OF THE STOMACH THREE YEARS AFTER SUBTOTAL RESECTION WITH EXTRINSIC INVOLVEMENT OF THE ANASTOMOTIC LOOPS.

CASE NO. 91

This was the second admission of a 56 year old white female with the chief complaints of abdominal pain and vomiting of two months duration. On her first admission to the hospital seven years previously, she gave a history of an episode of hematemesis 16 months before. Roentgen examination at the time of the hematemesis revealed a gastric ulcer. She was treated medically with repeat x-ray examination of the stomach every six weeks. She improved, had no complaints and the ulceration was said to have diminished in size. However, three weeks prior to her first admission, she began to complain again of epigastric pain and tarry stools and repeat gastrointestinal series demonstrated that the ulcer had increased in size. Hemoglobin on admission at that time was 7 grams per cent and stool was guaiac positive. The patient was explored and a remarkably extensive ulceration of the lesser curvature aspect of the stomach in its superior third was found which was densely adherent to the underlying pancreas. A subtotal gastrectomy was performed. On the posterior wall of the removed portion of stomach extending on to the lesser curvature, there was a firm indurated mass in the center of which an ulceration 4 cm. in diameter was present. Microscopic examination demonstrated this to be an adenocarcinoma possibly arising in a chronic peptic ulcer of the stomach. No involved lymph nodes were found.

The patient did remarkably well and was asymptomatic for more than seven years. Epigastric pain then recurred particularly after eating and radiated through to the back. Two months prior to her current admission, she began to vomit. The vomitus contained bright red blood and was coffee-ground in appearance. In a period of six weeks, she lost about 30 pounds. Examination on admission showed a moderately obese white female in no acute distress. To the right and somewhat above the umbilicus, a mass was palpable. Hemoglobin was 9 grams per cent. Barium meal examination (Fig. 1) showed evidence of an extensive recurrence involving the lesser curvature aspect of the stomach but extending to the anastomosis and through it into the adjacent limbs of the afferent and efferent loops of the jejunum.

Final Diagnosis: RECURRENT CARCINOMA OF THE STOMACH 7 YEARS AFTER GASTRIC RESECTION.



Case 91, Fig. 1. Barium meal examination shows marked fixed irregularity of the entire lesser curvature of the remaining portion of the stomach. The anastomosis and adjacent portions of the jejunal loops are diffusely ulcerated, fixed, and involved by neoplasm. Obstruction at the stoma is incomplete.

CASE NO. 92

This was the first admission of a 62 year old white male with the chief complaint of tarry stools of five or six days duration. Three years before admission at another hospital, an esophagogastrrectomy had been done for an adenocarcinoma of the stomach. It was said that no liver metastases or involved lymph nodes were found at that time. The patient did very well post-operatively and complained only occasionally of mild left upper quadrant and lower left chest pain ascribed to rib resections. Despite some anorexia, he was able to gain

weight. He could tolerate only small amounts of food at one time since larger quantities would produce a substernal sticking sensation.

Physical examination showed a well developed and well nourished male in no distress. No masses were palpable in the abdomen and the edge of the liver could be felt only on deep inspiration. Hemoglobin was 11 grams per cent, white blood count 7,600 per cu. mm. Stools were persistently guaiac positive. Gastric analysis showed 78 units of free acid 15 minutes after histamine and a total acidity of 90 units. Gastric specimens showed a trace of guaiac. On a clinical basis, it was felt that recurrent tumor was unlikely but that the patient might be bleeding from a regurgitant esophagitis. Esophagoscopy, however, showed no abnormality in the esophagus or at the anastomosis which appeared smooth and widely patent. On entering the stomach, a large quantity, approximately 150 cc., of acid, clear fluid poured out. The gastric rugae appeared in places somewhat enlarged but no mass lesion or ulceration was evident. Biopsy of gastric mucosa showed no significant change.

Barium meal examination (Fig. 1) showed no abnormality in the region of the esophagogastric anastomosis which was located about 1 and one-half inches distal to the level of the arch of the aorta. The intrathoracic portion of the stomach showed retained secretions and a coarse mucosa but appeared to be distensible. At the level of the hiatus there was a rather marked narrowing, and at this site an ulcer crater about 1.5 cm. in diameter was demonstrated. This ulcer crater appeared to be sharply demarcated and the adjacent wall of the stomach somewhat flattened in a smooth fashion. Barium entered the infra-diaphragmatic portion of the stomach and then the duodenum without difficulty. The roentgen findings were interpreted as evidence of a benign ulcer crater at the level of the hiatus in the diaphragm. Ulceration in this area has frequently been described in association with paraesophageal or combined types of hiatus hernias and has been related to the pressure on the stomach of the diaphragmatic ring. It was felt therefore that a similar mechanism might be operative in the present case.

The patient was explored via a thoraco-abdominal incision and it was promptly evident that there was a huge recurrent carcinoma involving practically the entire intrathoracic portion of the stomach as well as the part in the hiatus extending distally. There were pleural and peritoneal as well as hepatic metastases. Biopsy showed undifferentiated carcinoma with signet-ring cells.

The roentgen findings in this case demonstrate the considerable difficulty in recognizing even an extensive carcinoma of the stomach which primarily involves the wall and spreads intramurally without forming any remarkable ulceration or filling defect. Under normal circumstances after an esophagogastric resection, the intrathoracic portion of the stomach remains distended and dilated with air and fluid. The lack of contractility in this patient, of this area, did not appear to be remarkable. The ulceration demonstrated on the roentgen examination was an incident in the progressive course of this man's disease. It is likely that it is peptic in character, that is, related to the presence of a rather high gastric acidity although the basis for the ulceration is the underlying infiltrating carci-



Case 92, Fig. 1. Barium meal shows no delay to the passage of barium into the thoracic portion of the stomach which is distended with air and secretions. Barium passed freely through the hiatus but the stomach is narrowed at this level and a discrete smooth ulcer crater is evident (arrow). This has the appearance of a benign ulcer. The remainder of the stomach does not appear remarkable.

noma. It is of special interest that the ulceration occurred at the site of pressure due to the diaphragmatic ring as in patients without tumor with similar gastric herniation.

Final Diagnosis: RECURRENT SPREADING CARCINOMA AFTER ESOPHAGO-GASTRECTOMY SIMULATING "PRESSURE" PEPTIC ULCER.

CASE NO. 93

This was the second admission of a 68 year old white female. Three years previously the patient was operated on for a squamous cell carcinoma of the middle third of the esophagus. No nodes were found at that time and a supra-aortic esophagogastric resection and esophagogastrostomy were performed. The liver was seen at that time and showed no evidence of metastases. She was well until three months prior to the current admission when she developed hoarseness. Laryngoscopy revealed an abductor paralysis of the right vocal cord. Radio-



Case 93, Fig. 1A. Barium meal examination shows the dilated supradiaphragmatic portion of the stomach which contains considerable secretions or retained food. Barium, however, promptly entered the infradiaphragmatic part of the stomach through the hiatus of the diaphragm. On the posterior wall of the stomach (arrow) there is a hemispherical filling defect narrowing the AP diameter of the lumen of the stomach. Within the defect there is a huge irregular ulceration. The distal part of the stomach does not appear to be involved and barium left the stomach promptly.

therapy was administered to the mediastinum, the patient's voice improved and the right cord appeared to regain some movement. Two to three weeks prior to admission she began to complain of increasing pallor and dyspnea on exertion, weakness, malaise and anorexia and noted that her stools were black.

On admission, physical examination showed a thin, pale, chronically ill, white female in no acute distress. The liver was felt three fingerbreadths below the right costal margin. Its edge was smooth and non-tender. Multiple stool guaiacs



Case 93, Fig. 1B. In the postero-anterior projection, the irregular ulcer crater is seen en-face. The relative lucency of the barium surrounding the ulcer crater in the proximal portion of the stomach is indicative of the filling defect involving the posterior wall.

were positive. Hemoglobin was 5 grams per cent, white blood count 3200 per cu. mm. with a normal differential count. A gastric specimen was coffee-brown and showed 4+ guaiac. Free acid was present after histamine stimulation.

Barium meal examination (Figs. 1A, & 1B) showed the anastomosis to be located at the thoracic inlet. The deformity in this area appeared to be operative and there was no delay to the passage of the barium into the thoracic portion of the stomach. This portion of the stomach was filled with a considerable amount of air and secretions or retained food although the barium passed promptly through the region of the hiatus into the infradiaphragmatic portion of the stomach. Immediately below the hiatus, however, on the posterior wall of the

stomach there was evidence of a large filling defect which was irregularly ulcerated. The distal portion of the stomach did not appear to be remarkable and barium left the stomach promptly to outline the duodenum.

The appearance of the lesion in the stomach on roentgen examination was that of an ulcerated mass. Despite the realization that the involvement of the stomach might be secondary to retroperitoneal lymph nodes from the original carcinoma of the esophagus, the possibility of a second primary carcinoma of the stomach or even a benign calloused ulcer could not be excluded. Extensive involvement of the stomach of this type as a result of metastases to the retroperitoneal lymph nodes from a squamous cell carcinoma of the esophagus is not common. The patient was therefore explored and it was demonstrated that the gastric mass represented extension from adjacent involved nodes. One of these nodes was removed and on microscopic section showed metastatic squamous cell carcinoma.

Final Diagnosis: METASTATIC SQUAMOUS CELL CARCINOMA TO THE STOMACH FROM A PRIMARY ESOPHAGEAL LESION.



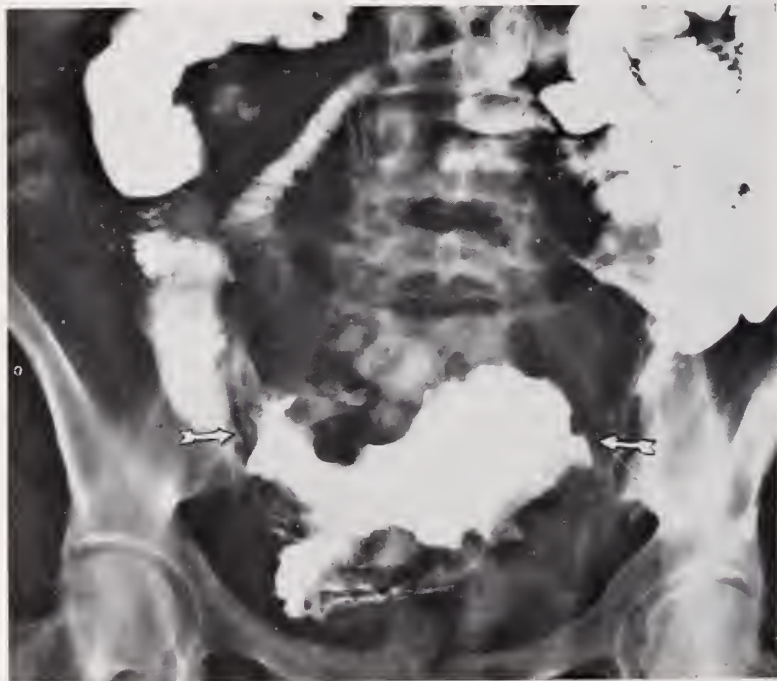
Case 94, Fig. 1. Double contrast portion of the barium enema examination demonstrates extrinsic pressure over two short segments of the proximal loop of sigmoid (arrows). There is a diffuse homogeneous soft tissue density extending for some distance above this area.

CASE NO. 94

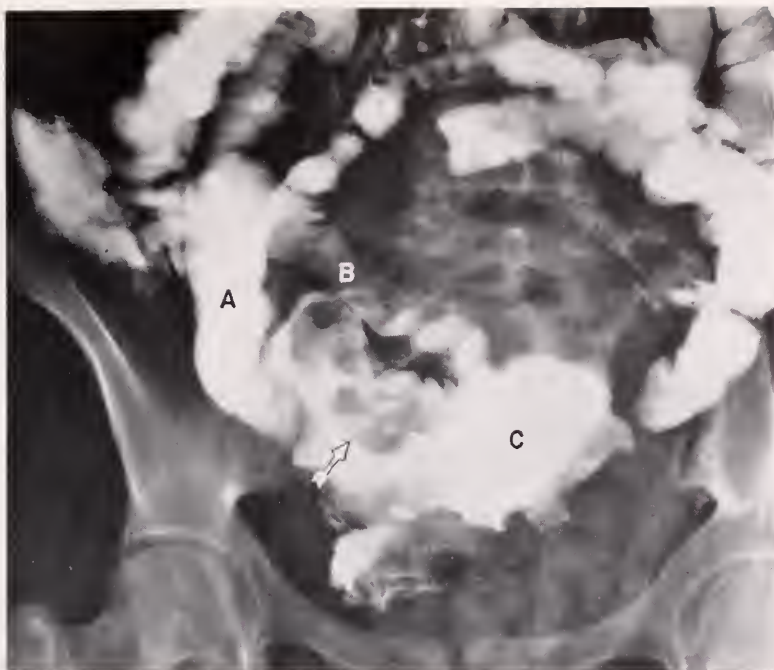
This was the first admission of a 54 year old white female with the chief complaint of weakness for nine months. At the onset of this complaint, an anemia was discovered which was treated with iron, vitamin B₁₂ and parenteral liver without benefit. In the six months prior to admission, she had lost 25 pounds and complained of anorexia and mild nausea. Chills and temperature as high as 102°F. occurred intermittently for about a day every week or two. Recently she complained also of mild constipation and lower abdominal discomfort and pressure.

Physical examination showed a pale, chronically ill female. In the lower abdomen and extending into the pelvis was a palpable mass about 10 cm. in diameter which was slightly irregular and non-tender and did not appear to be connected to the uterus or ovaries. Hemoglobin was 6 grams per cent, white blood count 16,000 per cu. mm. with a normal differential count. Red blood count was 2,800,000 per cu. mm. Sedimentation rate was markedly accelerated. Stools were guaiac positive on three occasions.

Barium enema examination (Fig. 1) showed no evidence of an intrinsic organic lesion of the colon but there appeared to be extrinsic pressure on the superior aspect of the proximal sigmoid. Barium meal examination with serial observa-



Case 94, Fig. 2A. Small bowel examination shows a huge, irregular, scalloped collection of barium (arrows) in the center of a homogeneous soft tissue density at the level of the brim of the pelvis.



Case 94, Fig. 2B. Later in the examination, adjacent "afferent" and "efferent" loops of small bowel, A and B, are evident with extrinsic pressure on the medial of these loops. The huge collection of barium (C) remains. To the right of this collection, a large lobulated filling defect is present (arrow). In retrospect, this filling defect protrudes into the lumen of a widened segment of ileum intervening between loops A and B and the barium extends through a perforation into a huge excavation (C) within the in-tramesenteric mass.

tions of the small bowel (Figs. 2A, & 2B) demonstrated a huge markedly irregular collection of barium in the midst of a soft tissue mass at the level of the brim of the pelvis. The outlines of this collection of barium were markedly nodular and in one area these nodules appeared to be confluent. There was no obstruction to the flow of barium through the small bowel or into the colon and no evidence of dilatation in the small bowel. The lesion was located in the proximal or mid-ileum. An adjacent loop of small bowel appeared to be compressed.

It was obvious from the roentgen examination that a huge excavated neoplasm involving the ileum was present. Since there was no evidence of narrowing, the suggestion of a sarcoma, presumably a lymphosarcoma, was made.

After multiple transfusions, the patient was explored and a large soft cystic mass occupying the lower abdomen and pelvis was exposed. It was densely adherent to the anterior peritoneum and also to the peritoneum over the bladder. The mass was dissected free of the bladder and also from two areas of the sigmoid where it was adherent to the appendices epiploica. Three loops of small

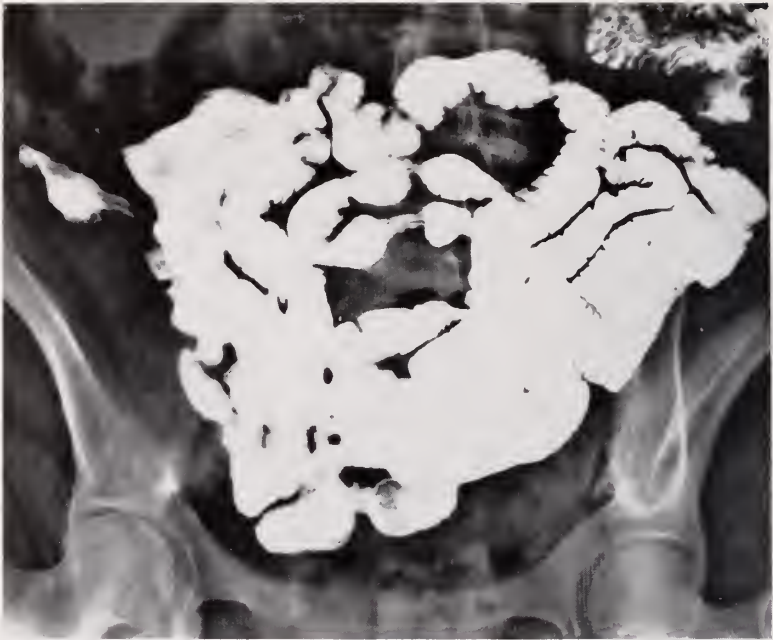


Fig. 3. Small bowel series done about one year after the operative procedure shows no evidence of local recurrence.

bowel appeared to enter and leave the tumor and accordingly three small bowel resections and end-to-end anastomoses were performed. The specimen consisted of three segments of small intestine adherent to a large intramesenteric cystic mass that measured 16 x 18 x 8 cm. The mass was covered by serosa over its entire surface except for one small area which presumably represented the root of the mesentery. Two of the segments of small bowel after careful dissection were demonstrated to be adherent to this mass but to have uninvolved mucosa. On opening the third segment, however, a bulky tumor mass measuring 5 cm. in diameter was found protruding into the lumen and widening the lumen. The edges of this mass were firm, raised, and covered by mucosa. The central portion was deeply ulcerated, the ulceration measuring about 3 cm. in diameter. In the center of the ulceration, there was a perforation about 1½ cm. in diameter which communicated with the large intramesenteric cyst which contained about 200 cc. of dark red blood and fragments of necrotic tumor. The wall of the cyst was composed of soft fleshy tumor tissue up to 3 cm. thick, with numerous areas of hemorrhage and necrosis. Microscopic examination demonstrated the mass to be a myosarcoma which apparently had arisen in the mesentery and perforated into the small bowel. No lymph nodes were identified although a mass 2 x 2 cms. in diameter adjacent to the main mass was also removed and also showed myosarcoma.

The patient did very well post-operatively for about one year. Repeat

small bowel observations at this time (Fig. 3) showed no evidence of recurrent tumor. However, shortly after this, she developed abdominal pain, jaundice and vomiting as well as progressive hepatic enlargement and was considered to have extensive metastatic disease.

Final Diagnosis: EXOENTERIC MYOSARCOMA.

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THE JOURNAL OF
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FURAZOLIDONE (FUROXONE) IN THE TREATMENT OF
SALMONELLA INFECTIONS

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Salmonellosis, a disease of protean manifestations, is still capable of producing significant mortality in spite of chloramphenicol (Chloromycetin[®]) and other antibiotics, especially when caused by certain types, e.g., *S. choleraesuis*. Thus, Saphra and Wassermann (1) reported a mortality rate of 21 per cent in 329 infections caused by this microorganism between 1940 and 1954, and more recently, Eisenberg, et al. (2) noted an over-all mortality of 20 per cent, in spite of treatment, in 75 cases produced by a variety of *Salmonella* strains. However, the latter rate was reduced to 5.3 per cent when corrected to those instances where death could unquestionably be attributed exclusively to salmonellosis. In the opinion of these authors, chloramphenicol, either alone or with other agents, exerted little if any influence upon the fatality rate in their series.

Chloramphenicol, currently the drug of choice for the treatment of salmonellosis, has a number of limitations. It is capable of producing serious and fatal blood dyscrasias, including granulocytopenia (3), so that its administration in a disease characterized by a leukopenic tendency is not without risk. Its clinical efficacy has been subject to question not only by the above authors, but also by Le Riche and Peacock (4) who compared the results obtained in a large series of untreated typhoid fever cases with those receiving the antibiotic. They found that although mortality was lower in the treated group, the reduction in deaths did not appear to be statistically significant. In addition, although average duration of hospital stay was shortened slightly and complications were fewer in the treated group, untreated controls had fewer relapses than individuals to whom chloramphenicol had been administered. Despite chloramphenicol, the relapse rate in this disease remains high and the chronic carrier state, a not infrequent sequel (1, 2), is extremely difficult to eradicate with it. Finally, the action of chloramphenicol is primarily bacteriostatic rather than bactericidal.

Furazolidone (Furoxone[®]) a recently developed antimicrobial nitrofuram (5) with a wide spectrum of antibacterial activity including *Salmonella* and *Shigella*, has been previously reported (6, 7) as being of value in the treatment of infections caused by these organisms. In the light of the shortcomings of chloramphenicol, as noted above, it was believed of value to investigate the activity of this compound *in vitro* against all *Salmonella* strains isolated during the past

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This study was supported by a grant-in-aid by Eaton Laboratories.

year and to subject it to clinical trial upon patients from whom these strains had been recovered.

The tube dilution method was employed for the sensitivity studies, both bacteriostatic and bactericidal concentrations being determined. Tests were performed in 2 ml. amounts by adding 1 ml. of a six hour culture at 37° C, diluted 10^{-6} , to a series of tubes containing 1 ml. of varying concentrations of furazolidone standard as well as to a growth control tube containing no antimicrobial agent, after which all tubes were incubated at 37° C. Minimal inhibitory or bacteriostatic concentration for each strain was the least amount of drug capable of inhibiting growth, as determined visually, after 48 hours. Minimal bactericidal concentration or the amount needed to completely kill each strain was determined by pipetting under sterile conditions approximately 0.05 ml. from each of the clear tubes of the above assays into individual tubes containing 5.0 ml. of nutrient medium to neutralize the growth inhibitory effect of the drug by dilution, thereby permitting any viable bacteria, if present, to then grow out. These subcultures were grown an additional 48 hours at 37° C and the bactericidal concentration of furazolidone for each strain under test was ascertained by noting the tube containing the least amount of antibiotic where no growth on subculture ensued.

RESULTS OF SENSITIVITY TESTS

Minimal bacteriostatic and bactericidal concentrations of furazolidone for each of the *Salmonella* strains included in this series are noted in Table I. As may be readily observed from the table, growth of all strains was inhibited by concentrations ranging from 0.6 to 3.0 mcg/ml., whereas bactericidal concentrations ranged from 1 to 6 mcg/ml., thereby indicating that all were sensitive *in vitro* to the action of the drug under consideration. Moreover, its action is primarily bactericidal since amounts needed to kill each test inoculum were not much greater than that needed to inhibit their growth.

TABLE I
Sensitivity of Salmonella Strains to Furazolidone (Furozone) in Vitro

Salmonella Serotypes	Total Strains Isolated	Minimal Bacteriostatic Concentration (mcg/ml)	Minimal Bactericidal Concentration (mcg/ml)
<i>S. Choleraesuis</i>	3	2; 2; 3	2; 2; 4
<i>S. heidelberg</i>	1	0.8	2
<i>S. newport</i>	1	1	1
<i>S. norwich</i>	1	2	4
<i>S. oranienburg</i>	1	1	2
<i>S. paratyphi A</i>	1	2	3
<i>S. paratyphi B</i>	2	2; 3	3; 6
<i>S. taksony</i>	3	0.6; 3; 1	2; 6; 2
<i>S. tennessee</i>	1	1	1
<i>S. typhosum</i>	3	3; 3; 0.8	3; 4; 3

CLINICAL RESULTS

Thirteen of the patients from whom the above strains had been isolated were subjected to clinical trial with furazolidone and a short case history of each patient follows. Unless otherwise specified, all were treated with 100 mg. orally four times daily for 10 days.

Case Histories

Patients #1 and #2 (21 year old white male, and 18 year old white female, student nurses). *S. tennessee* and *S. taksony*, respectively, were isolated in routine stool cultures. Both patients were asymptomatic. A course of furazolidone was administered to each after which all follow-up cultures were consistently negative for salmonella.

Patients #3 and #4 (21 year old colored female, and 19 year old white female, student nurses). Acute onset of fever, abdominal pain and diarrhea. Stool cultures revealed *S. heidelberg* and *S. taksony*, respectively. Furazolidone was administered with prompt alleviation of all symptoms. Follow-up cultures all have been negative.

Patient #5 (11 month old white male). Several weeks prior to the onset of the present illness the child had recurrent bouts of tonsillitis and otitis media which responded to penicillin. During one of these episodes there was no apparent response to penicillin and chloramphenicol therapy was started. Twenty-four hours subsequently, while receiving the latter antibiotic, he developed vomiting, diarrhea and fever. The vomiting subsided within a few hours but the diarrhea persisted. Chloramphenicol was continued but the patient's clinical condition, although slightly improved, persisted. A stool culture taken at this time was found to be positive for *S. norwich*. Chloramphenicol was continued for two weeks during which time there was a gradual return of temperature to normal and a decrease in frequency of stools. However, salmonella organisms of the same type continued to be isolated from his stools even after completion of the course of treatment. Furazolidone therapy was then started. The patient received 50 mg. daily in divided doses for a two week period. During this time the appetite was poor and the child was unusually cranky but these symptoms promptly disappeared within 12 to 24 hours after cessation of therapy. Three consecutive daily stool cultures taken one week following furazolidone therapy all failed to reveal salmonella. Subsequent periodic stool cultures have all remained negative and the child has been asymptomatic.

Patient #6 (35 year old white female). The patient entered the hospital with a history of weakness of 13 days duration following a fall on her buttocks while ice skating. A laminectomy was performed and an epidural abscess was discovered and evacuated. A few days post-operatively, a stool culture taken because of a bout of gastroenteritis and elevated temperature grew out *S. taksony*. She was treated with furazolidone in the routine manner and gastrointestinal symptoms and fever promptly subsided and all subsequent stool cultures for salmonella have been negative.

Patient #7 (48 year old white male). The patient presented a three year history of periarteritis nodosum for which steroids had been administered regularly. Six weeks prior to the present admission he developed a perforated gastric ulcer which was attributed to the steroid therapy. A subtotal gastrectomy was performed. The patient's post-operative course was uneventful. Six hours prior to the present admission, the patient first noted gross hematuria, rectal bleeding of bright blood and diarrhea unassociated with abdominal pain. Urine and stool cultures revealed *S. choleraesuis*. Furazolidone was administered in the usual fashion for 10 days without untoward symptoms. Follow-up cultures after completion of therapy and subsequently all have been consistently negative. Stools are now normal in frequency and consistency and there has been no further evidence of rectal or urinary bleeding. Steroids have been reinstated for treatment of the periarteritis.

Patient #8 (67 year old white male). Four months prior to the present admission, the

patient had fever to 103°F. for three to four weeks. He was treated with penicillin without benefit. Upon admission to the hospital, his temperature was found to be 103°F. and a blood culture was taken which proved to be positive for *S. choleraesuis*. He was treated with chloramphenicol. Improvement was evident within 36 hours. Therapy was continued for two weeks until discharge. He was readmitted three and a half months later with a recurrence of fever, weight loss and severe lower abdominal and lower back pain. Stool and blood cultures were again found to be positive for the same salmonella type. Furazolidone was started at once but on the second day he suddenly went into shock and subsequently expired. Post mortem examination revealed rupture of an abdominal aortic aneurysm, a recently described complication of Salmonella infection (8). Cultures of the lung, spleen and an osteomyelitic focus in the 3rd and 4th lumbar vertebrae all grew out *S. choleraesuis*.

Patient #9 (60 year old white male). Seven years prior to the present admission a partial cholecystectomy with removal of stones had been performed. His present admission was because of a tender mass at the previous incisional site and weight loss of 25 pounds in three months. The mass was incised revealing an abdominal wall abscess, the contents of which were cultured. *S. choleraesuis* was isolated and therapy with chloramphenicol was started. The incision failed to heal and a fistula developed while he was receiving the antibiotic. Culture of the fistula tract and stools both revealed the presence of *S. choleraesuis* organisms. He was again operated upon and the gall bladder, which contained several stones, and part of the fistula tract were removed. He was immediately started on a course of furazolidone and did very well post-operatively. The fistula tract closed completely, he returned to his original weight and all subsequent stool cultures have been negative.

Patient #10 (18 year old Negro male). This patient, who attended the Food Trades High School and worked as a food handler at a number of department stores on week ends, had been entirely well prior to the present illness. Ten days before admission he began to complain of anorexia, constipation, nausea, vomiting, throbbing headache, fever, malaise and melena. Upon admission he was found to have a temperature of 105°F., relatively low pulse rate, palpable spleen and bloody diarrhea. He was treated with chloramphenicol and penicillin and for the first five days his temperature ranged between 102° and 105°F. Culture of the urine was found to be positive for *S. typhi* as were subsequent blood and stool cultures. Chloramphenicol was discontinued and treatment with furazolidone was begun. His temperature gradually decreased but he continued to be lethargic, anorexic and nauseated. His blood pressure was 100/60. During the second week in the hospital he appeared to improve gradually and his temperature ranged between 99.0 and 100.5°F. Urine cultures became negative but his stool cultures remained intermittently positive. A second course of furazolidone therapy was started after a one week interval and 2 grams of chloramphenicol daily was added to the therapeutic regime. All subsequent stool cultures were consistently negative. The patient continued to be asymptomatic and afebrile and was discharged five weeks after admission.

Patient #11. A Negro man with chronic osteomyelitis of 16 years duration was admitted for incision and drainage of an abscess of the left thigh, and for sequestration and saucerization of the bone lesion. Culture of material obtained at operation revealed *S. typhi* as did stool cultures taken at the same time. Furazolidone treatment was started immediately, the post-operative course was completely uneventful and there was excellent wound healing. Of three consecutive stool cultures taken one week after conclusion of treatment, the first two were negative and the third questionably positive. Another course of treatment was instituted and all subsequent stool cultures have remained negative for salmonella.

Patient #12 (59 year old white female). During World War I, while living in Eastern Europe, the patient became ill during an epidemic of typhoid fever. She migrated to the United States a few years later and remained entirely asymptomatic. In 1931 her stepson became ill with high fever which was proven to be typhoid fever. Because of this, stools of all members of the family were cultured and the patient was discovered to be a carrier. She was followed regularly by the New York City Department of Health but did not receive any

treatment. Her present admission was for the purpose of cholecystectomy. At operation her gall bladder was found to be chronically inflamed. Stones were found in the gall bladder, cystic and common ducts and a large stone was found impacted in the Ampulla of Vater. Culture of the gall bladder was positive for *S. typhi*. She was treated with chloramphenicol post-operatively but two days later her temperature rose to 102°F. and continued to be high for 14 days in spite of the fact that the bacterial strain that had been isolated was sensitive to the antibiotic *in vitro*. At this time an abscess was noted around a retention suture which was unroofed and drained. Culture of the contents of the abscess as well as of the stool at this time was positive for *S. typhi*. Furazolidone was then administered and continued for 10 days. On the second day of this therapy there was found in the incision scar a new abscess which healed within a week without incision. She remained afebrile and without complaints throughout the therapeutic period. Daily follow-up stool cultures unfortunately proved to be consistently positive. The patient was treated with another course of furazolidone with the same dosage for two weeks but cultures taken after completion of this course were still positive. She was discharged uncured as an asymptomatic chronic carrier.

Patient #13 (59 year old white male). This patient gave a history of pain in the right upper quadrant, chills, fever, diarrhea and jaundice two years ago. Cholecystectomy was performed at that time and thereafter he had intermittent bouts of fever and jaundice. Stool culture taken during one such episode revealed *S. oranienburg* and follow-up cultures taken periodically thereafter always produced extremely heavy growth of the same organism despite a number of therapeutic courses of chloramphenicol to which the strain remained sensitive *in vitro*. In an attempt to eliminate this carrier state, a course of furazolidone was administered in the usual dosage. During this period a number of stool cultures were found to be negative but on cessation of treatment stool cultures promptly reverted to positive. Another course of treatment was immediately started, during which the patient complained of occasional nausea, tiredness and dryness of the mouth. At the end of ten days, the dosage was reduced to 100 mg. twice daily, but on the thirteenth day of the second course he developed a diffuse morbilliform eruption with some petechiae and itching, which promptly subsided after therapy was discontinued. Follow-up cultures were positive. Subsequent attempts to clear the patient's carrier state with courses of neomycin orally, chloramphenicol and synnematin B parenterally, to all of which the strain was sensitive *in vitro*, have all proven futile.

A resume of the clinical status of each patient treated as well as of the therapeutic results achieved with the test compound is contained in Table II.

Nine of the 13 patients treated with furazolidone achieved good results. One patient (Patient #8) expired suddenly of a ruptured abdominal aorta 24 hours after the start of treatment so that adequate evaluation of the drug's efficacy could not be made. In the case of acute typhoid fever (Patient #10), recovery ensued but since the clinical course was not materially different from what could have been expected in the natural course of the disease and since the patient also received chloramphenicol concomitantly during the second course of therapy, no valid conclusions could be properly derived in this instance. Attempts to eradicate the carrier state of the two chronic carriers (Patients #12 and #13) ended in failure.

No serious untoward effects of the drug were noted in this series. Some of the patients complained of slight nausea and loss of appetite, but this could not be ascribed to the drug entirely. In no instance was it necessary to discontinue treatment because of intolerance. One patient (Patient #13), on the 13th day of the second course of treatment developed a generalized morbilliform eruption with petechiae which subsided promptly when the drug was stopped. No evi-

TABLE 11

Clinical Status of Patients with Salmonella Infections and Therapeutic Results Achieved with Furazolidone (Furoxone)

Cases	Age, Sex, Color	Clinical Picture	Etiological Type	Sites of Isolation	Side Effects	Therapeutic Results
Pt. #1	21, M, W.	Asymptomatic carrier	<i>S. tennessee</i>	Stool	None	Cure
Pt. #2	18, F, W.	Asymptomatic carrier	<i>S. taksony</i>	Stool	None	Cure
Pt. #3	21, F, C.	Fever and gastroenteritis	<i>S. heidelberg</i>	Stool	None	Good
Pt. #4	19, F, W.	Fever and gastroenteritis	<i>S. taksony</i>	Stool	None	Good
Pt. #5	11 Mos., M, W.	Vomiting, diarrhea, fever	<i>S. norwich</i>	Stool	Poor appetite, cranky	Good
Pt. #6	35, F, W.	Fever and gastroenteritis post incision and drainage of epidural abscess	<i>S. taksony</i>	Stool	None	Good
Pt. #7	48, M, W.	Periarteritis nodosum, pyuria, hematuria, rectal bleeding, diarrhea	<i>S. choleraesuis</i>	Urine Stool	None	Good
Pt. #8	67, M, W.	Fever, weight loss, septicemia, ruptured abdominal aorta, death	<i>S. choleraesuis</i>	Stool Blood	None	Inconclusive
Pt. #9	60, M, W	Incision and drainage of abdominal wall abscess, fistula formation, cholecystotomy, fistulectomy	<i>S. choleraesuis</i>	Abscess Stool Fistula tract	None	Good
Pt. #10	18, M, C.	Acute typhoid fever	<i>S. typhi</i>	Urine Blood Stool	Anorexia Nausea	Equivocal
Pt. #11	32, M, C.	Abscess, chronic osteomyelitis	<i>S. typhi</i>	Bone marrow Stool	None	Good
Pt. #12	59, F, W.	Post typhoid fever, chronic stool carrier, cholecystectomy, post operative fever, abdominal wall abscess	<i>S. typhi</i>	Abdominal wall abscess Stool Gall bladder	None	Failure
Pt. #13	59, M, W.	Recurrent bouts of fever and jaundice post-cholecystectomy 2 yrs., chronic stool carrier	<i>S. oranienburg</i>	Stool	Nausea Dryness of mouth Morbilliform eruption	Failure

dence of renal, hepatic or hematological toxicity presented itself during or after treatment.

In the patients who failed to respond, sensitivity tests performed upon the residual positive cultures failed to reveal development of resistance on their part to the action of furazolidone *in vitro* so that the drug's inadequacy in this regard could not be attributed to this factor.

While an evaluation of the efficacy of any drug in the treatment of salmonellosis is extremely difficult because of the highly variable nature of this disease with respect to severity, duration, complications, etc., furazolidone did appear

to elicit a favorable therapeutic effect in many of the cases in this limited series although it failed completely to eradicate the chronic carrier state in two of the patients so afflicted. The number of cases treated, however, is too few to permit valid conclusions as to its value in this disease and a more extensive clinical trial is indicated before its position in the available therapeutic armamentarium against salmonella infections can be definitively established.

SUMMARY

Furazolidone (Furoxone[®]), a new antibacterial compound, has been subjected to laboratory and clinical evaluation in the treatment of salmonella infections. All 17 strains isolated from clinical material during the past year proved highly sensitive to its action *in vitro*. Its effect is primarily bactericidal. Nine of 13 patients treated with the drug achieved a satisfactory clinical response. Result of treatment in one case of acute typhoid fever was equivocal, one patient died suddenly from a ruptured abdominal aorta too soon before the drug could possibly exert any effect, and attempts to eradicate the chronic carrier state in two patients resulted in failure.

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THE DIAGNOSIS OF CAROTID ARTERY OCCLUSION

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Among the many changing facets of the present hospital practice of medicine is the attitude of neurology house staff officers towards patients presenting with cerebrovascular accidents. Whereas in previous years, such a patient was shunned as "another stroke," and was begrudgingly admitted to the hospital because he could not be disposed of elsewhere, the same patient today is received by the neurology resident with considerably more interest and enthusiasm. The explanation for this change in attitude lies in the application of the technique of arteriography to the study of cerebrovascular disease, and the subsequent recognition of the relatively great frequency of occlusive disease of the carotid arteries as a cause for the common "stroke."

Interest in carotid occlusive disease has been further nourished by several recent reports of successful therapy. Since such therapy has generally been of value only when instituted early in the disease, prompt diagnosis of a carotid occlusion seems mandatory. The purposes of this communication are: (a) to discuss those features of carotid occlusion which are reported to allow an early diagnosis, and (b) to indicate the frequency of occurrence of these "diagnostic" features in 50 patients in whom carotid occlusions were verified at The Mount Sinai Hospital.

CLINICAL MATERIAL

The presence of a carotid occlusion was proven in all 50 patients by arteriography, surgery or autopsy. The criteria for arteriographic proof have included visualization of the tip of the Cournaud needle on the x-ray film. Thirty of these patients have been personally observed by the author during the last two years. The information to be presented concerning the other 20 patients was obtained from a review of their charts.

INCIDENCE OF CAROTID OCCLUSION

At the present time over 500 arteriograms are performed annually at The Mount Sinai Hospital. The presence of carotid occlusion is demonstrated in approximately one of every 25 such procedures (1). It has been reported elsewhere that one of every five patients who present with an acute "stroke" syndrome may have an angiographically demonstrable carotid occlusion (2), and that a similar occlusion can be anatomically demonstrated in one of every ten unselected consecutive autopsies (3).

CLINICAL FEATURES OF CAROTID OCCLUSION

The usual signs and symptoms produced by carotid occlusion are indistinguishable from those observed with cerebral lesions of other etiologies. The

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acute onset of hemiparesis with maximum deficit in the upper extremity, may thus be identical with the clinical picture of middle cerebral artery occlusion (4-7). The presence of headache, focal seizures, and progression of symptoms may make the clinician think first of a cerebral neoplasm. Craniotomy may unfortunately follow if air studies are undertaken and a displaced ventricular system (the result of cerebral edema) is demonstrated (8, 9). The great variability of the clinical picture of carotid occlusion is further shown by the several reports of patients with completely asymptomatic occlusions (3, 5, 10, 11).

Monocular Blindness and Contralateral Hemiparesis

The classical textbook description of the "syndrome of the internal carotid artery" includes loss of vision in the eye on the side of the occlusion, and a hemiparesis (and possible hemisensory and homonymous visual field defect) on the opposite side. The blindness is supposed to represent interference with the blood supply through the ophthalmic artery, the first branch of the internal carotid. This monocular blindness may be transitory and recurrent early in the disease (12, 13). If this syndrome is present, it is quite suggestive for occlusive carotid artery disease; however, in the actual analysis of patients with carotid occlusions it is only rarely observed. Thus, only 5 per cent of the 107 patients with carotid occlusions collected by Johnson and Walker (14) were reported to show monocular blindness, and only three per cent of the 65 patients Sastrasin (15) presented had the syndrome. Only 10 per cent of the 50 patients in the present series were found to have involvement of vision in the eye and ipsilateral to their occlusions. This percentage may be higher than those previously reported due to the deliberate attempt to elicit a history of possible fleeting monocular blindness in the patients personally observed.

Ipsilateral Optic Atrophy

Atrophy of the optic nerve on the side of a carotid occlusion, presumably the result of impaired ophthalmic artery flow, is another "diagnostic" feature of carotid occlusion which occurs more often in textbooks than in patients. Ipsilateral optic atrophy has been observed only rarely in patients with carotid occlusions (32), and is found in only three per cent (15) to ten per cent (14) of such patients. Only one patient (two per cent) in the present series was observed to have optic atrophy.

Ipsilateral Horner's Syndrome

A contracted pupil on the side of a carotid occlusion has occasionally been described (3, 16-18). O'Doherty and Green (19) have recently reported the presence of an ipsilateral Horner's syndrome in 12 of 18 patients with carotid occlusions, and suggested that the findings of miosis and ptosis contralateral to a hemiplegia may be diagnostic for carotid occlusion. This disturbance in the cervical sympathetics is supposed to be due to decreased blood flow through the vasa nervorum arising from the carotid artery. Anhidrosis of the face is reported to be absent if the occlusion is confined to the internal carotid, and present if the common or external carotid is involved (19).

A Horner's syndrome, however, would also appear to be only an infrequent finding with carotid occlusive disease. Miosis was thus described in only nine per cent, and ptosis in only six per cent of the 107 patients with carotid occlusion collected by Johnson and Walker (14). A partial Horner's syndrome was noted in only four per cent of the patients in the present series. In one patient the pupil ipsilateral to the carotid occlusion was found to be markedly dilated.

Dilation of the Superficial Vessels of the Face

If the collateral circulation to the brain in patients with internal carotid artery occlusions is derived from the ipsilateral external carotid artery (20), such increased flow through the external carotid may produce dilatation of the ipsilateral superficial temporal artery. Dilatation and tortuosity of the vessels on the face and temporal region on the side of a carotid occlusion have thus been reported to be of some diagnostic value (17, 21, 22). Such dilatation, however, was noted in only two per cent of the patients in the present series.

Recurrent Cerebral Episodes

Many patients with partial carotid occlusions will present with recurrent unilateral signs and symptoms of cerebral dysfunction (23). This syndrome has been referred to as "transient cerebral paralysis" by Pickering (24), as "intermittent insufficiency of the carotid arterial system" by Millikan and Siekert (25), and as "transient ischemic attacks" by Fisher (26). Although the syndrome has been discussed quite frequently in the recent literature (27-29), its precise etiology remains unclear. Among the factors possibly responsible for these transient recurrent cerebral symptoms, hypotension, diminished cardiac output, cerebral vasospasm, recurrent emboli, and transitory failure of collateral circulation have all been cited.

Intermittent symptoms were present in 40 per cent of Johnson and Walker's 107 patients with carotid occlusions (14), and in 63 per cent of the 65 patients studied by Sastrasin (15). Such symptomatology occurred, however, in only 11 per cent of the 27 patients reported by Jacobsen and Skinhos (30), and in 27 per cent of the 63 patients analyzed by Webster, et al. (31). Twenty-six per cent of the patients in the present series had these recurrent cerebral episodes.

While this syndrome may occur not uncommonly in patients with carotid occlusive disease, many other patients with intermittent episodes of unilateral cerebral dysfunction and perfectly patent carotid arteries at arteriography have recently been observed in this hospital. In a few of these patients the presence of a cerebral neoplasm was eventually demonstrated. (An unobtainable complete history, or the inability of the physician to observe the patient during an episode may make differentiation between "ischemic" episodes and post seizure phenomena impossible (26). Thus, recurrent cerebral episodes can by no means be considered diagnostic for carotid occlusion.

Diminished Carotid Pulsations

Although Hunt (32) called attention to the diagnostic importance of diminished carotid artery pulsations in the neck on the side of a carotid occlusion as far

back as 1914, the pulse usually felt in the neck is that of the external or common carotid artery. Thus, diminished carotid pulsations are rarely felt in the neck with occlusions of the internal carotid artery alone. Absence of the carotid pulsation in the neck together with loss of the superficial temporal pulse, however, are probably diagnostic for the relatively rare occlusion of the common carotid artery (33-35). Dunning (13, 36, 37) has reported that internal carotid artery occlusions may be diagnosed by palpating the carotid pulsation within the pharynx, a site where the internal and external carotid arteries are supposedly well separated. It has been the experience, however, of almost all other writers that palpation of neither the pharyngeal nor neck pulses is particularly helpful in recognizing carotid occlusions (7, 8, 38-40).

Information was available concerning the equality of the carotid pulses in the neck in 43 of the patients in the present series. Diminished pulsations on the side of the occlusion were reported in 12 (28 per cent), but differences of opinion were expressed by other observers regarding the certainty of these findings. Only five of the 30 personally observed patients had diminished carotid pulsations; the common carotid was occluded in one of these patients. An attempt was made to feel pharyngeal pulsations in all 30 subjects. In no cases were unequal pharyngeal pulsations noted.

Carotid or Intracranial Bruit

Occasionally patients with carotid occlusive disease may report "noises" in their heads, and the examiner may hear an intracranial or carotid bruit. Thus, Harbitz (41) in 1926 reported a patient with bilateral carotid occlusions whose symptomatology included "noises in the ears". Similar subjective and objective head murmurs in patients with carotid occlusions have been reported by others (42-44). Cohen and Miller (45) suggested auscultation over the eyeball, and presented three patients with proven carotid occlusions and "eyeball bruits". In a recent presentation of several more cases, Fisher (46) noted that the murmur occurs on the side opposite a completely occluded carotid, and suggested that it may be due to collateral circulation via the patent carotid. Others (7, 47-49) have claimed that a bruit heard over the carotid artery represents partial occlusion at that site. Crevasse and Logue (48) claim that the systolic carotid murmur changes to a continuous murmur with the development of "carotid insufficiency". These murmurs may vanish with the correction of anemia (46, 48), or the development of a relative hypotensive state (47).

It should be noted, however, that there are many conditions other than carotid occlusion which can be responsible for a carotid or intracranial bruit. These include anemia, hyperthyroidism, Paget's disease, aortic valvular lesions, vascular malformations and certain neoplasms (hemangioma, carotid body tumor) (45, 50).

An attempt was made to hear a carotid or intracranial bruit in 37 patients with verified carotid occlusions from the present series. Carotid murmurs were heard in only five patients (14 per cent). The carotid murmur radiated to the mastoid bone in one patient; no other intracranial bruits could be heard in this series.

Carotid Compression

The collateral circulation to the brain is derived from the patent carotid in about 65 per cent of patients with a carotid occlusion (20). Manual compression of this patent carotid may therefore produce signs of cerebral ischemia (syncope and/or seizures), and thus be of some aid in the recognition of a contralateral carotid occlusion.

As far as could be determined, the first "positive" carotid compression test (i.e. the production of syncope or seizures) was reported in a patient with a probable carotid occlusion in 1930 (51). Positive tests in two patients with common carotid occlusions were cited in 1941 (33), but these may well have been manifestations of carotid sinus hypersensitivity. The diagnostic significance of carotid compression was first suggested by Bommal, et al. (52) in 1952, and reemphasized by Ochs, et al. (53) in 1954. The subsequent writings of Webster and Gurdjian (54-58) have established the technique of carotid compression as a valuable adjunct to the neurological examination.

Patients with carotid occlusions may show several signs and symptoms when their patent carotid is compressed. Thus, syncope and/or seizures may result (20, 52-58), contralateral paresthesias and hemiparesis can occur (59-61) and electroencephalographic abnormalities may be produced (20, 23, 61-65).

Positive carotid compression tests have been reported to occur in 80 per cent of 52 patients with carotid occlusions (57). The test has been performed in 40 patients in the present series and was positive in 26 (65 per cent).

While it is usually possible to distinguish between the effects of this test and carotid sinus hypersensitivity (66), it should be stated that many patients without carotid occlusions will have positive tests from carotid compression. The list of conditions other than carotid occlusion in which positive tests have been observed is quite large (20), and this may well limit the diagnostic value of the procedure. It should also be noted that carotid compression tests may not be completely without risk (66).

Ophthalmodynamometry

Since the ophthalmic artery is the first branch of the internal carotid artery, diminished pressure in the retinal artery on the side of an occluded carotid may well be expected. The technique of ophthalmodynamometry which allows measurement of the central retinal artery pressure, and the results of its preliminary application to the study of patients with carotid occlusive disease, have recently been described (67).

The first recorded ophthalmodynamometric diminution of retinal artery pressure in a patient with a carotid occlusion was described in 1936 (68). Milletti (17) recognized the diagnostic value of the procedure in 1950, and reported that manual compression of the patent carotid reduced the pressure in both retinal arteries (the "tonometric retinal syndrome"). Thomas and Petrohelos (69) in 1953 collected 15 instances of significant ophthalmodynamometric changes in 19 patients with carotid occlusions from the literature, and reported five patients, four of whom had positive tests.

The value of ophthalmodynamometry as a simple diagnostic test for carotid occlusion has been repeatedly confirmed (20, 52, 70-73), although rare false positive tests have been reported (73, 74). Heyman, et al. (75) found significant differences in retinal artery systolic pressures in 80 per cent of 16 patients with carotid occlusions, and Hollenhorst (76) has written that 72 per cent of 116 patients with the clinical picture of carotid insufficiency or occlusion had diminished ipsilateral retinal artery pressure. Ophthalmodynamometry was adequately performed in 23 patients with proved carotid occlusions in the present series. Diagnostic results were obtained in 16 (70 per cent).

CLINICAL DIAGNOSIS OF CAROTID OCCLUSION

The admission diagnosis recorded by the senior examiner, after his initial history and examination, on the charts of each of the 50 patients with verified carotid occlusions in this series may indicate how variable the clinical picture of a carotid occlusion may be. Thus, cerebrovascular lesion was diagnosed in 19 patients, brain tumor in 14, carotid occlusion in 13, subdural hematoma in two, and subarachnoid hemorrhage and brain stem lesion in one patient each. Only two of the 13 correct diagnosis of carotid occlusion were made prior to 1957.

The frequency of the so-called "diagnostic" features of carotid occlusion, as obtained from the present series, is summarized in Table I. With the possible exceptions of positive carotid compression and ophthalmodynamometric studies, these "diagnostic" features occur only infrequently in patients with carotid occlusions. Those features that do occur commonly are unfortunately also seen in patients without carotid occlusions. For these reasons, and because of the great variability of the clinical picture of a carotid occlusion, the clinical diagnosis of carotid occlusive disease can hardly ever be made with certainty. A definitive diagnosis, however, can almost always be established with the help of carotid arteriography, a simple procedure, which has proven to be safe even in elderly patients with occlusive vascular disease.

ANGIOGRAPHIC DIAGNOSIS OF CAROTID OCCLUSION

For adequate arteriographic diagnosis of a carotid occlusion, all cerebral arteriograms should include visualization of the vessels in the neck so that a

TABLE I
Incidence of Diagnostic Features of Carotid Occlusion

Monocular Blindness and Contralateral Hemiparesis.....	10%
Ipsilateral Optic Atrophy.....	2%
Ipsilateral Horner's Syndrome.....	4%
Dilatation of Superficial Vessels of Face.....	2%
Recurrent Cerebral Episodes.....	26%
Diminished Carotid Pulsations.....	28%
Carotid or Intracranial Bruits.....	14%
Positive Carotid Compression.....	65%
Diminished Retinal Artery Pressures.....	70%



FIG. 1. Angiographic features of partial carotid occlusions.

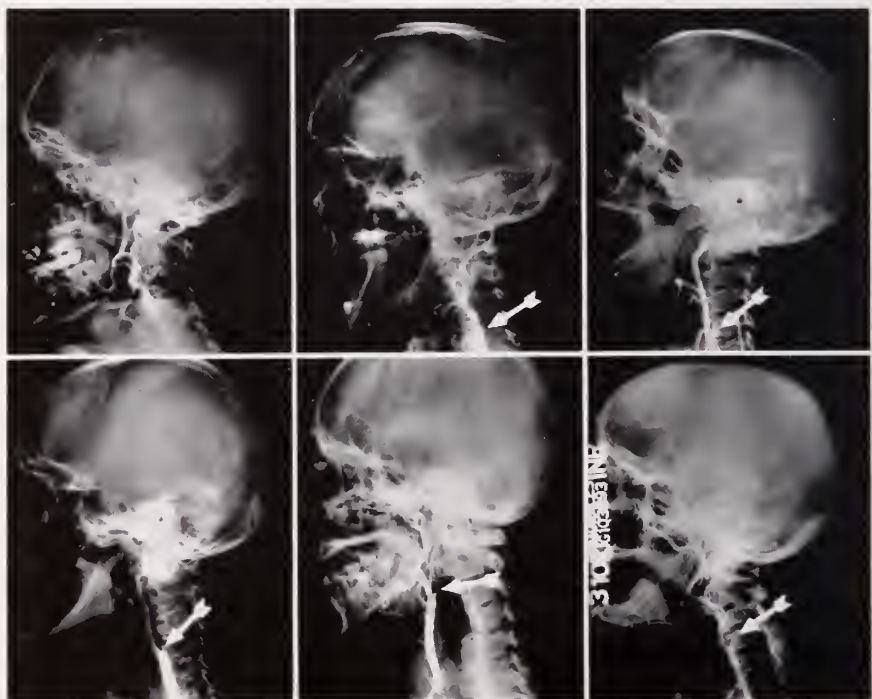


FIG. 2. Angiographic features of complete carotid occlusions.

partial carotid occlusion (examples of which are shown in figure 1) is not left unrecognized. If no contrast medium is seen in the internal carotid artery, the tip of the Cournaud needle must be visualized on the x-ray film before the diagnosis of carotid occlusion is made. Thus, improper insertion of the needle into the external carotid artery, or insertion of the contrast media into the sheath of the vessel may be identified as the cause of the non-filling internal carotid artery. The typical angiographic picture of a complete carotid occlusion is that of a small nubbin of contrast media just at the expected origin of the occluded vessel. (Examples of this are shown in figure 2.) The demonstration of collateral circulation may also be of diagnostic value.

A few instances of non-filling of the internal carotid artery not due to carotid occlusion have occasionally been reported. Thus, it is said that "spasm" of the artery, secondary to mechanical trauma, may result in a false angiographic diagnosis of carotid occlusion (7, 77, 78). The contrast media may be injected into the intima of the vessel producing a valvula which, when distended with contrast media, may simulate an occluded vessel (79). The needle puncture may result in bleeding within the wall of the artery which may also mimic the angiographic picture of a carotid occlusion (80). The position of the patient's head during arteriography may be important (7), and compression of the internal carotid artery by the transverse process of the atlas may result in non-filling of the vessel (81). Non or poor visualization of the internal carotid artery has also been reported in a few terminal patients with acutely increased intracranial pressure (82, 83). These arteries were found to be patent at autopsy, and the explanation for the erroneous angiographic picture of carotid occlusion is obscure.

While these "false-positive" angiographic diagnoses of carotid occlusion have been reported, their occurrence is quite rare. Angiography remains not only the sole means of allowing the definitive diagnosis of carotid occlusion to be made with any degree of certainty, but it also gives information concerning collateral circulation which may be of value for prognosis and therapy.

SUMMARY

Certain clinical features of 50 patients with verified occlusions of the carotid arteries are described. Many of the features previously thought to be diagnostic for carotid occlusion are only infrequently present, and the clinical pictures produced by such occlusions are quite variable. While ophthalmodynamometric and carotid compression studies may be of some help in recognizing carotid occlusions, a definitive diagnosis requires arteriography.

ACKNOWLEDGMENT

I am indebted to several members of the Departments of Neurology and Neurosurgery of The Mount Sinai Hospital for permission to study their private patients, and to Dr. Morris B. Bender for his pace-setting inspiration and patient advice.

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PATHOLOGIC FEATURES OF PIPESTEM FIBROSIS OF THE LIVER DUE TO SCHISTOSOMIASIS

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Since the original description of white-clay pipestem cirrhosis in hepatic schistosomiasis by Symmers (1) in 1904, several conflicting theories have been presented as to the pathogenesis of the lesion and the mechanism of its most important clinical manifestation, portal hypertension (2-6).

Some of the difficulties in understanding the development of the lesion arise from a lack of knowledge regarding (a) the cause and nature of intraparenchymal alterations, (b) the mechanism of portal fibrosis, and (c) factors in the development of portal hypertension.

In an attempt to explore these problems further, liver tissue from a group of patients with pipestem fibrosis was examined.

MATERIAL AND METHODS

Autopsy specimens were obtained from eight patients and surgical biopsy specimens from two patients with chronic hepatic schistosomiasis due to *Schistosoma mansoni*. Five patients were seen at The Mount Sinai Hospital and five at Presbyterian Hospital, New York. All tissues were fixed in buffered neutral formalin. Routine histological examinations were carried out after staining with hematoxylin eosin. In addition, the following special stains were used: Chromatropene aniline blue for connective tissue, silver impregnation for reticulum, periodic acid Schiff (PAS) reaction for polysaccharides, and Weigert's stain for elastica. Ultrathin sections (one micron) were cut in the Porter-Blum microtome after double embedding. These sections were all stained with the same methods used on routinely cut sections except that the elastica stain was omitted. Deparaffinized sections were also mounted in low fluorescence immersion oil and examined in the fluorescence microscope.

RESULTS

Alterations were noted in the general lobular architecture of the liver, in the epithelial liver cells, in the intralobular mesenchymal elements, and in and around the portal tracts.

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Supported by the Research and Development Division, Office of the Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-790.

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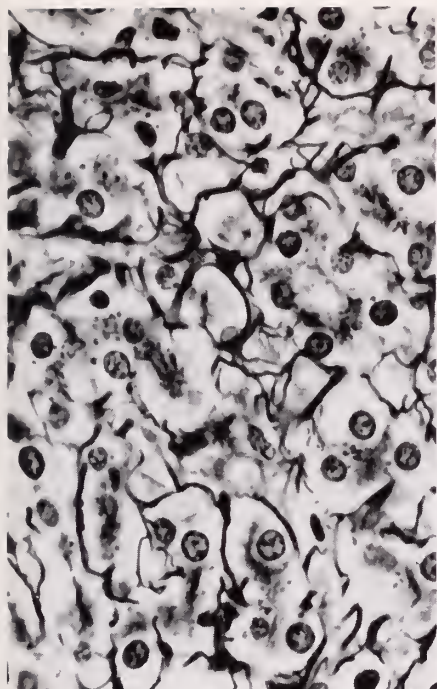


FIG. 1A.

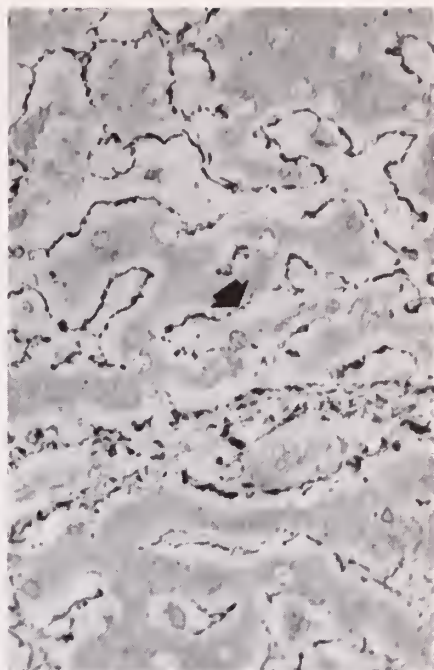


FIG. 1B.

FIG. 1. Increase of reticulum fibers within the parenchyma as demonstrated by Gomori's silver impregnation. A) Five micron thick section: Duplication of reticulum framework, which is represented by continuous frequently branching and crossing membranes. B) One micron thick section showing the reticulum framework consisting of cross sections of individual fibres (arrow) which in most places seem to overlap superficially to produce a continuous layer ($\times 4000$).

TABLE I

Pathological Features in Each of the 10 Cases of Hepatic Schistosomal

Case No.	Granulomas	Phlebitis	Thrombosis	Thickening of Arteries	Nodules	Subcapsular Fibrosis	Ductular Proliferation
1	Periportal and intralobular	+	-	+	-	+	+
2	-	+	+	+	Pseudo-nodules	+	+
3	Portal tract and vicinity	+	+	+	-	+	+
4	-	+	-	+	-	+	+
5	-	+	-	+	-	+	+
6	-	-	-	+	-	+	+
7	-	-	-	+	-	+	+
8	Portal tract	-	-	-	-	+	+
9	Intralobular	-	-	-	-	+	+
10	-	+	+	+	-	+	+

General Lobular Architecture

The lobular architecture was preserved in all cases except in the subcapsular zone where conspicuous fibrosis and collapse were noted with dissection of lobules and formation of small pseudonodules. The parenchymal cells in the pseudonodules were in plates only one-cell thick, in contrast to the several cell thick plates of the regenerative nodule of cirrhosis. True regenerative nodules

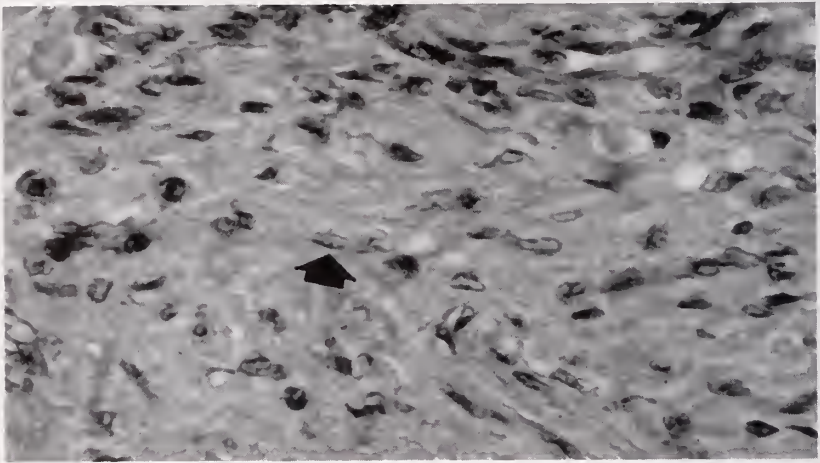


FIG. 2. Large amount of fibroblasts with spindle shape nuclei, some with double nucleol in fibrotic portal tract (H&E \times 600).

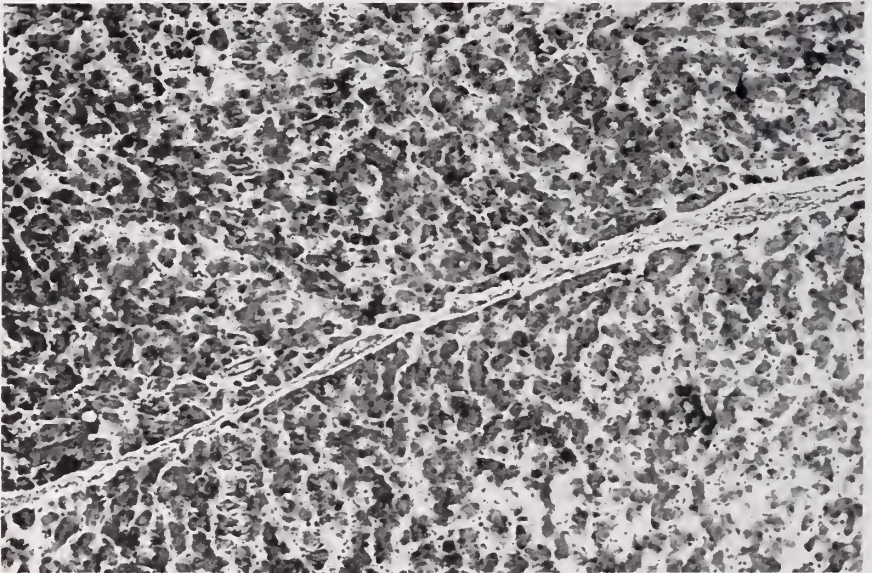


FIG. 3. Thin connective tissue septum extending through the parenchyma without relation to the lobular architecture (H&E \times 63).

were not seen in any of the cases. Glisson's capsule was thickened in all cases in which a portion of the capsule was present in the section.

Epithelial Liver Cells

The epithelial liver cells appeared normal with hematoxylin-eosin stains, in that the cytoplasm was uniform, and basophilic nuclei were well stained, and neighboring cells were alike. However, with the PAS reaction, fine PAS positive granules were seen in scattered cells with no zonal predilection. In addition, small amounts of fine, granular, brown pigment was seen in some cells. Small scattered areas of focal necrosis were seen in severe cases. No evidence of bile stasis was found in any of the cases.

Sinusoids and Kupffer Cells

The sinusoidal border of the liver cells was thickened in chromatrope aniline blue and PAS stains (Fig. 1A) in cases number 8 and 6 respectively (Table I). With silver impregnation, in ultrathin sections, the reticulum appeared as a continuous line rather than the normal series of fine dots (Fig. 1B), in eight of the cases (Table I). The Kupffer cells were increased in size and number. They contained many strongly PAS positive granules and clumps of brown pigment. The pigment was not fluorescent.

Portal Tracts

The smallest portal tracts were infiltrated by lymphocytes, monocytes and eosinophiles. Fibroblasts were present in large numbers (Fig. 2). The larger

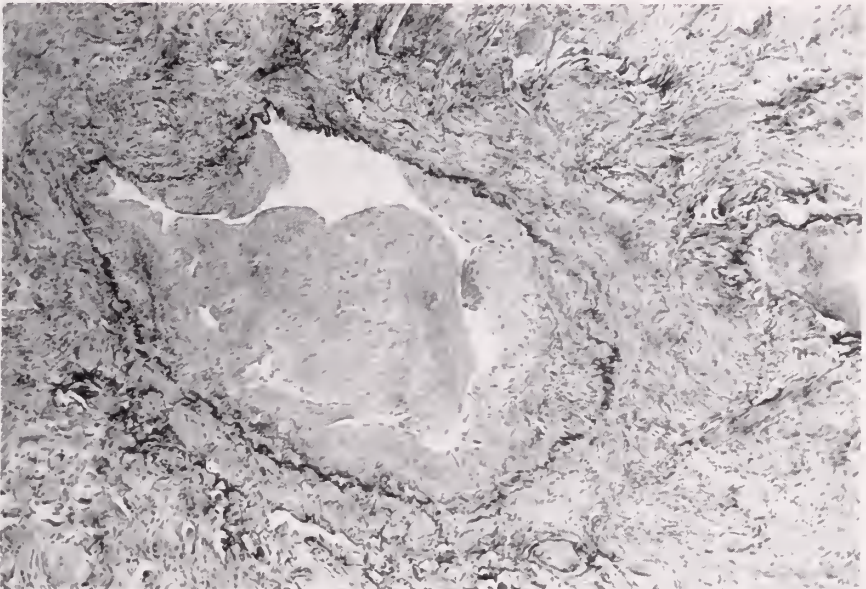


FIG. 4. Partial thrombosis of branch of portal vein in an extremely fibrosed portal tract ($\times 63$ orcein elastic stain).



FIG. 5. Symmers' lesion within thick walled veins and arteries (arrow), as well as multiple nerves (curved arrow) (H&E \times 63).

portal tracts appeared as very broad bands of fibrous tissue containing reticulum and collagen fibers in equal amounts and a few elastic fibers. The collagen fibers were longitudinal and wavy, and passed vessels without surrounding them. Infiltration similar to that seen in the small portal tracts was present in the broad bands. Ductular proliferation was present in the portal tracts in all cases without necessarily periductular infiltration. Intralobular bile ducts were normal. Very thin, long and straight fibrous septa extended from the broad fibrosed portal areas into the parenchyma, sometimes across several lobules (Fig. 3). The greatest amount of pigment was in the portal tract, particularly in macrophages. Its characteristics were the same as in the Kupffer cells.

Vessels

The central veins were normal. Chronic phlebitis of portal vein branches in the portal tracts were seen in six cases (Table I) with endothelial proliferation, infiltration with mononuclear cells, and thickening of the vein walls (Fig. 4). Thrombosis of portal vein branches had occurred in three cases. Many newly-formed vessels were seen in the portal tract in all cases and, in two, these assumed an angiomatoid character. In eight cases, medium-sized and small-sized arterioles presented a striking thickening of the media in the fibrotic areas (Fig. 5). The arteriolar lumens were not appreciably narrowed. The walls of both the veins and arteries contained much PAS positive material diffusely distributed both in the media and in the intima.

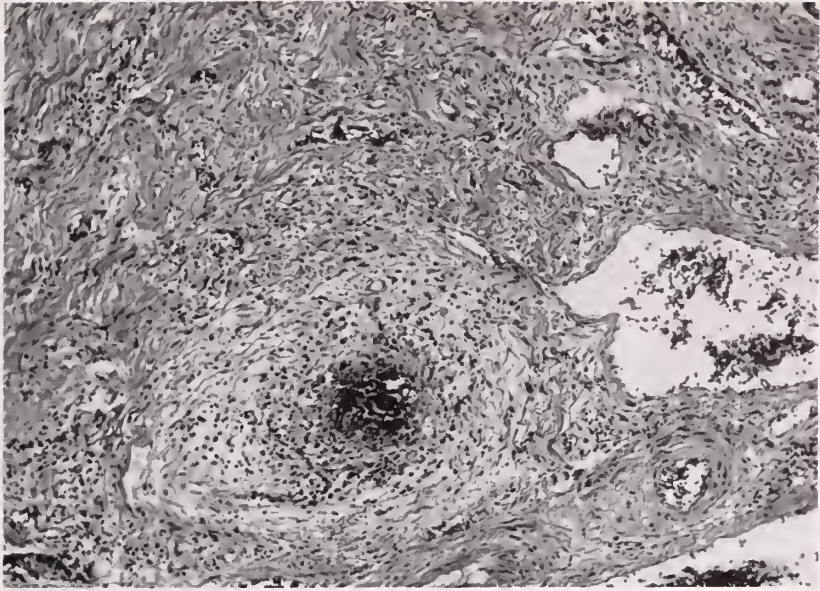


FIG. 6. Symmers' lesion with extensive fibrosis of the portal tract which contains an older granuloma with central ovum of *Schistosoma* (H&E $\times 63$).

Granulomas

Distinct granulomas with epithelioid and foreign body giant cells were found in three cases with the shell of the ovum in two and an intact ovum in one (Fig. 6) (Table I). The granulomas were located in the portal tract, in the parenchyma adjacent to the portal tracts, and in both areas. When granulomas were in the small portal tracts, they occupied the entire area, apparently obliterating the portal vein branches. The reticulum stopped at the border of the granulomas and sometimes encircled them in a concentric onion peel-like fashion.

DISCUSSION

In all the cases described, the morphologic picture was characteristic and easily permitted the diagnosis of Symmers' pipestem fibrosis. The presence of the ovum-containing granuloma led to an unequivocal diagnosis, although the distribution of broad bands of fibers around portal vein branches in the absence of granulomas sufficed as a diagnostic criterion. From the broad fibrous bands, very thin septa extended through several normal lobules, appearing longer and straighter than in cirrhosis.

The picture is strikingly different from that seen in either postnecrotic or septal cirrhosis, when septa are shorter, thicker, and surround nodules in which the liver cell plates are two or more cells thick, especially on the periphery. Furthermore, in schistosomiasis, fibrosis is associated with the presence of many fibroblasts which are very sparse in cirrhosis.

The differential diagnosis is particularly based on the absence of regenerative nodules and the lack of portohepatic venous anastomosis in schistosomiasis. If cirrhosis is present, it probably is an independent disease process (5). Diagnosis of pipestem fibrosis from needle biopsy specimens may be difficult if tissue is removed from nonfibrotic areas, thus appearing normal, or from the subcapsular zone when it may be difficult to distinguish from cirrhosis (7, 8). Peritoneoscopic needle biopsy or laparotomy are preferable means of obtaining tissue.

The PAS positive material in the Kupffer cells and along the sinusoidal border of the liver cells, together with an increase in the reticulum fibers along the sinusoids is similar to that which is seen in many types of hepatic injury often leading to fibrosis. This fibrosis usually develops in the absence of fibroblasts in contrast to that which was seen in portal tracts. It possibly represents a reaction to the portal inflammation rather than a response to the injury which caused the portal inflammation since it is so much milder in degree.

Since granulomas were seen in the periportal area in addition to within the portal tract, the ova in some instances had to migrate through the wall of the portal vein branch and into the parenchyma. Köhlschütter and Koppisch claim that the ovum attaches itself to the vein wall and migrates through, producing the granuloma and localized phlebitis in the process (9, 10). The variations in the location of these lesions throw some doubt on the role of the granuloma in the development of pipestem fibrosis and portal hypertension. Furthermore, the uniform thickening of the larger vein walls is not characteristic of active or healed granulomas. The presence of much PAS positive material uniformly distributed throughout the vessel walls suggests a more diffuse process. However, some portal tracts were seen to be completely filled with granulomas, with apparent obliteration of portal veins suggesting that granulomas *per se* may contribute to portal hypertension in the early phases of the disease. In addition to obliteration by granulomas, portal vein branches may be occluded by thrombi or narrowed by phlebitis. Lichtenberg stressed the finding of all three features (6), and Köhlschütter and Koppisch felt that phlebitis was most important (9). Thrombi were found in only three cases whereas phlebitis, with increase in elastic tissue in the wall, was present in six. The thickness of the vein wall indicates that the phlebitic process is a chronic one which is still active in the absence of granulomas as evidenced by the presence of inflammatory cells and PAS positive material. As a result either of the narrowing or of the occlusion of the veins, new veins form around the original channel. In injection preparations these appear as a mossy covering of the vein branch. Bogliolo thinks that much of the portal blood flows through these newly-formed vessels but because of the narrow lumens and tortuous courses the flow is slow (11, 12). It is difficult to explain uniform thickening of portal venous channels on the basis of a series of focal lesions, *i.e.* granulomas. Rather it seems that some irritant is acting on larger and medium-sized vessel branches and spares some smaller ones. The most likely factor is the presence of the worm or its ova in this locale before or during their passage through the wall.

Many parasite proteins excite rather violent responses in the host and possibly

the portal fibrosis is a result of prolonged exposure to such a protein. As a result of occlusion and narrowing of portal vein branches and slowing of blood flow in tortuous newly-formed channels, pressure in the portal vein increases, leading to the clinical picture of portal hypertension.

The obliteration and narrowing is similar in effect to thrombosis and phlebitis of extrahepatic portion of the portal vein while the mossy new veins simulate multiple small cavernomatous transformations. Thus, hepatic schistosomiasis produces portal hypertension in the same way extrahepatic portal vein disease does (13, 14). The fibrosis itself is not an important factor. Portal hypertension in pipestem fibrosis is presinusoidal rather than post-sinusoidal as in cirrhosis. This has been substantiated by portal pressure estimation of splenic pulp pressure and wedged hepatic vein pressure in the same patient in whom splenic pressure was high and the wedged pressure low (15). The thickening of the arteriolar walls is probably the result of local inflammatory (or hypersensitivity) reactions, since it is seen only in areas of fibrosis. Proliferation of arterioles was not seen and therefore it is unlikely that the arteriolar changes play a significant role in portal hypertension. Furthermore, since the lumens were not much narrowed, it is doubtful whether a decreased arterial blood supply aggravates the lesion.

SUMMARY

In ten cases of hepatic schistosomiasis with pipestem fibrosis, the histologic appearance of the liver was sufficiently characteristic to permit the diagnosis even in the absence of ovum-containing granulomas.

Fibroblastic portal fibrosis with inflammation, thrombosis, and new formation of portal vein branches was seen in large and medium-sized portal tracts.

Diffuse changes in the lobules, such as thickening of the sinusoidal border of the liver cells with increased reticulum, were found, when ultra-thin sections were examined.

Narrowing or occlusion of the original portal branches and thin and tortuous new vessels are felt to be responsible for the portal hypertension. Because of the uniform nature of the lesion, in large and medium-sized portal veins, local reaction to the ova and worm is suggested as an important etiologic factor, rather than migration of the ova through vein walls.

ACKNOWLEDGMENTS

Thanks are due to Dr. Harry P. Smith, Department of Pathology, Columbia Presbyterian Medical Center for making available some of the material used in this study, and to Dr. Hans Popper, Department of Pathology, The Mount Sinai Hospital for help in the interpretation of the findings and in the preparation of the manuscript.

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HYPOTENSIVE THERAPY OF ACUTE INTRACRANIAL HEMORRHAGE: FURTHER STUDIES

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INTRODUCTION

This communication is a description of a non-surgical method of treatment of patients with acute subarachnoid and/or intracerebral bleeding due to single and/or multiple aneurysms primarily, but which may be used in cases of hemorrhage due to arteriovenous malformation, as well as those in which no cause of bleeding can be found. Intracranial bleeding due to head trauma and less common disorders such as hemorrhage occurring in a brain tumor, infection or a blood dyscrasia should not be treated by this method.

The rupture of an aneurysm, arteriovenous malformation or any cerebral vessel occurs when the intraluminal pressure exceeds the maximum pressure that the vascular wall can withstand, or if there is a rupture of the wall. As yet, there is no means of increasing the strength of the weakened vascular wall to avoid breakthrough by the intravascular tension. However, it is possible to decrease the intraluminal pressure through the use of hypotensive drugs and thus perhaps reduce the chances of rupture. This method of avoiding rupture depends upon "monitoring" or "titration" of the blood pressure and neurologic status throughout the day. The lowering of the blood pressure must be done with care. Induced hypotension without such caution is hazardous. Just as uncontrolled high blood pressure may be a factor in causing hemorrhage, uncontrolled low blood pressure may cause infarction.

PURPOSE OF THE THERAPY

Hypotensive therapy in the type of cases mentioned above has three objectives. First, to prevent recurrent (and perhaps current) hemorrhage by maintaining a lower blood pressure* in the region of the circulatory break. Second, the transitory elevations of blood pressure that occur in any patient's lifetime may be reduced by the medications. This latter is emphasized in those cases wherein the patient's blood pressure range before bleeding occurred would be considered normotensive. Recent experimental work tends to support this

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Aided by U.S.P.H.S. Grant #3-B-9084.

Reserpine (Serpasil[®]), Syrosingopine (Singoserp[®]) and Hydralazine (Apresoline[®]) were supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J. Chlorothiazide (Diuril[®]) was supplied by Merck, Sharpe and Dohme, Inc., Philadelphia, Pa.

* The reduction in blood pressure by hypotensive medication usually occurs to a much greater extent in the systolic phase than in the diastolic, therefore, often producing a pronounced decrease in pulse pressure. Because of this and because of the greater difficulty in accurately obtaining diastolic pressure, this study has been concerned mainly with systolic readings.

concept (1). Assessment of any of these objectives ideally would involve local pressure measurements especially at the base of the brain; however, such determinations cannot yet be done. The available evidence for reduction of blood pressure without reduction in cerebral blood flow, and reduction in blood pressure with reduction in cerebral blood flow but without reduction in cerebral metabolism is discussed elsewhere (2). The third objective of this treatment is to reduce the severity of symptoms, especially headache, during the acute stage of hemorrhage. This objective had not been sought initially but developed during the course of the pilot study because some patients seemed to have had less headache during the induced hypotension. On at least one occasion, this change was sudden and striking. Treatment with opiates in combination with barbiturates has at times failed to control the severe headache. Furthermore, opiates may induce severe constipation and or nausea with the possibility of recurrent hemorrhage through straining at stool or vomiting. It has been said that intracranial pressure may be increased by the administration of opiates. At no time thus far has there been any need for the use of either an opiate or a barbiturate in cases treated by the hypotensive method. Aspirin (or a compound containing it) has been given as the only analgesic and the patients have been surprisingly comfortable.

METHOD

The following technique which is presently used is basically the same as that originally used (3) but with improvements brought about through experience and the availability of newer anti-hypertensive agents. As before, cases are selected to meet two conditions (2). First, the patient must be able to communicate. This requirement is needed because the treatment is based upon the induction of a completely reversible, transitory state of cerebrovascular insufficiency. The evaluation of this change depends upon such parts of the neurologic examination as orientation and perception of specific stimuli. These data are unavailable in the uncommunicative patient. In the latter instance, induced hypotension cannot be safely quantitated and should not be used. For these cases, other methods of treatment possibly hypothermia must be sought. Thus early treatment is emphasized. The second condition is simply that the hemorrhage not be due to trauma, tumor, infection or blood dyscrasia. The problem of the hemorrhagic infarct will be discussed later. The above degree of selection is less restrictive than that which is commonly used by surgeons (4). The experience of the author suggests that the mortality of a comparable group treated by bed rest and sedation may be 30 to 40 per cent.

As soon as the diagnosis of intracranial hemorrhage is confirmed by lumbar puncture, studies for blood dyscrasia are initiated. Cerebral angiography is performed as soon as feasible so as to obtain as much information as possible. After angiography, the patient is returned either to a bed, the entire length of which can be tilted or, preferably, to a padded tilt table. He is placed in the supine position. The head of the bed or tilt table is then elevated at least 45 degrees. This simple maneuver has proven to be an effective safety mechanism

in the event of excessive induced hypotension. Vasopressor drugs to counteract excessive hypotension should be avoided. Instead, lowering of the head of the bed, elevation of the foot of the bed or noxious stimulation have sufficed to alleviate the effects of the anti-hypertensive agents.

Parenteral pentolinium is administered but, if possible, limited to a single dose. Although excellent for the initial phase of treatment, continuation of this drug carries with it the necessity of counteracting its often annoying side effects. The dose is small, 1.25 to 2.5 mg. subcutaneously or intramuscularly. Subsequently the patient is observed for a change in neurological status from the pre-treatment "base line" (accepting the unavoidable factor of spontaneous fluctuation). The systemic blood pressure sometimes begins to decrease as early as five to ten minutes after the injection, so the patient must be observed carefully. As the pressure decreases, a range will usually be reached wherein brain dysfunction occurs. Presumably this is due to cerebrovascular insufficiency. It is this range of blood pressure which is taken to be the approximate lower limit ("compensatory mechanisms" may reduce this limit subsequently). Immediately, lowering of the head of the tilt table or bed is begun and continued until the blood pressure has risen (usually a very slight reelevation is necessary) and the symptoms of cerebrovascular insufficiency have completely disappeared. This blood pressure range, usually much lower than the pre-treatment levels, is taken as the range to be sought by other anti-hypertensive medication. If signs of cerebrovascular insufficiency are not readily encountered, the functions of the other organ systems must be very carefully observed especially if there is any past history of dysfunction. This includes measurement of intake and output of fluids, serial blood urea nitrogen determinations, serum electrolyte and hematocrit values, electrocardiograms, liver function tests, examination of the lungs for hypostatic or aspiration pneumonia and examination of stool for blood. The etiology of any antecedent hypertension is investigated and such causes as coarctation of the aorta, Cushing's syndrome, primary aldosteronism, pheochromocytoma and pyelonephritis are ruled out.

Since agitation is a common problem, parenteral reserpine is frequently used, the initial dose usually being about 0.3 mg. When using this agent, its side-effects e.g. signs of extra-pyramidal dysfunction or an increase in gastric secretion must be considered. The latter may aggravate gastrointestinal ulceration which sometimes occurs as a complication in patients with severe brain damage. An antacid should be prescribed (if necessary by stomach tube) even if reserpine is not used. Stool specimens are examined periodically for the presence of occult blood. Parenteral reserpine is later replaced by oral reserpine (or a reserpine derivative). When it is given orally, this drug is a far less potent hypotensive agent than it is parenterally. In general, eventual transfer to oral medication for an indefinite period after discharge from the hospital is desired. Oral reserpine when used with other hypotensive agents augments the hypotensive effects. It may also provide a tranquilizing effect. The dose should be kept to a minimum, occasionally as little as 0.05 mg. per day to minimize the chance for psychic depression. A reserpine derivative, syrosingopine, may be substituted later to

further lessen the possible occurrence of side effects. The regimen includes the use of chlorothiazide, starting with 125 to 250 mg, and, if necessary, hydralazine may be added. The use of chlorothiazide necessitates observation of the electrolyte (especially potassium) balance and sometimes even the addition of the vitamin B complex if congestive heart failure is also present, although a vitamin-mineral combination is now routinely used. Chlorothiazide may be given intermittently when it is employed as a diuretic. However, for the smoother blood pressure course desired in the treatment of intracranial hemorrhage it is preferable to give it every day. The administration of hydralazine is sometimes followed by headache, chest pain or less often a systemic lupus erythematosus-like syndrome. This drug also is begun in very small doses; as little as 5 mg. The use of anti-hypertensive drug combinations reduces individual drug side effects. The veratrum group of anti-hypertensive agents has been avoided because of the common side effects of nausea and vomiting and therefore the possibility of recurrent hemorrhage through straining. The patient's diet is usually full because hypotensive agents greatly lessen or eliminate the need for salt restriction.

With this technique, continuous observation of the patient is mandatory. The degree of effectiveness of this method depends upon the degree to which careful observation by the physician is carried out. (This method does not require the use of any special or complicated apparatus. It could conceivably even be carried out in the patient's home in an emergency). During the most acute stage of hemorrhage, approximately the first twenty-four hours, serial examinations of the patient, including the blood pressure (the latter as often as every three or five minutes) are necessary*. There is only one way to become familiar with each patient's blood pressure range, its response to the medications, the side effects of the medications and the all important changing neurological status of the patient. That is by observation at the bedside, because there is a great deal of individual variation in all of these factors. There is great difficulty in demarcating the "most critical period" e.g. the first week, the first two weeks, the second and third weeks, et cetera. In general, the longer the patient survives, the better are his chances to keep on surviving. However, the persistent seriousness of the illness, especially in the earliest stages needs re-emphasis. Just when the physician begins to feel that the patient is getting better and "doing very well", a fatal recurrent hemorrhage can obliterate previous efforts. Thus, the lowest possible safe blood pressure range must be achieved and *maintained*, especially during the earlier periods which may mean the first three weeks. Beginning with the second day of treatment, a nurse must be present constantly with specific instructions regarding the total management of the patient. (If results justify more widespread application of this method, automatic devices for regulating the elevation of the bed as indicated by blood pressure changes might be considered). The use of mimeographed sheets has consolidated many of the important data.

* For the purpose of developing this method, it has been necessary for the author to remain with these patients throughout the period described. However, after the first two days, coordination of work with the neurologic house staff would make the management of these cases just as feasible as the management of any other critically ill patients.

Over a period of several weeks, the patient is gradually ambulated. Any motor disability secondary to the hemorrhage may be managed by the usual rehabilitative methods. The dosage of hypotensive agents changes as the patient ambulates progressively and thus the regimen with which he goes home may be quite different from the earlier ones. It is preferable to administer the heavier dose of anti-hypertensives at bedtime since the increase in blood pressure due to the reclining position is usually greater than the decrease in blood pressure due to sleeping. In addition, the decrease in diurnal dosage reduces the likelihood of symptoms of excessive hypotension during the more often erect postures of daytime.

After discharge, the patient is followed periodically. As a result of a great many observations of blood pressure changes and correlation with the occurrence of symptoms and signs, the patient is given very few "rules" to observe. He is to avoid lying flat. This mild restriction has sometimes reduced to a surprising degree the amount of medication needed. The patient is to avoid bending the head far forward or far backward because this maneuver has been associated with unpleasant symptoms in several patients. Enemas are contraindicated because sudden reductions in blood pressure (30 to 40 mm.) have been observed during either a rectal examination or an enema when hypotensive drugs are administered. The patient is observed during such procedures as barium enemas. Other procedures such as dental ones, may require the use of local anesthetics without epinephrine. Alteration of environmental pressure such as air travel, is avoided until more data become available from the study of a large series of patients.

DISCUSSION

It has been emphasized that the primary goal of this treatment is to prevent recurrent hemorrhage. The precise mechanisms involved are yet to be assessed. Prevention of hemorrhage might be achieved simply by indefinitely preventing the occurrence of an intraluminal pressure high enough to break the vascular wall, in which case it would not be necessary to "cure" the underlying pathological cause itself. Even total surgical obliteration of an aneurysm may not correct the basic defect in the wall of the artery at the site of origin of the aneurysm. Insulin does not "cure" diabetes nor does digitalis "cure" congestive heart failure. Withdraw such drugs and the patient may become seriously ill; continue them, and a normal or near normal life is usually possible. In a like manner, hypotensive agents may be continued indefinitely for the prevention of recurrent intracranial hemorrhage. On the other hand, if an occasional aneurysm is apparently "sealed off" during the hypotensive procedure, so much the better. Some aneurysms, originally demonstrated angiographically will, without surgery, no longer fill on repeated angiographic study performed years later (5). However, angiography can be falsely negative whether medical, surgical or no treatment has been used. Angiographic studies are now being repeated in patients with previously demonstrated aneurysms who have been treated with hypotensive medications continuously for more than three years. One of these follow up examinations disclosed an aneurysm which looked the same as it had on the

original angiogram performed more than three years previously. The patient has had continuous hypotensive therapy. Her recovery has been complete and she has had no recurrent hemorrhage in more than three years. She will therefore continue with her treatment indefinitely with the hope that there will be no recurrence of bleeding. This is the procedure recommended for all these patients regardless of the results of follow-up angiography.

In monitored hypotension the selection used is less restrictive than that usually employed by surgical methods. In hypotensive therapy there is no restriction with regard to age, location of aneurysm or adequacy of cross-circulation. There is *no limitation of cases* through the delaying of treatment for any specific length of time, i.e., the cases are treated as early as possible. This is the most difficult and most important period of all. Although this is the time wherein treatment is most urgently needed since it is when the mortality is highest, this is also the time when surgeons often (and perhaps rightfully) believe that the presence of the edema-swollen hemorrhagic brain constitutes the poorest surgical risk and yields the poorest surgical results. Therefore, they frequently will defer operation. As recently as July, 1958, this opinion has been once again stated (and by a surgeon): "it is a well known fact that an operation at an early stage is considerably more dangerous than if performed later after the acute signs and symptoms of bleeding have subsided" (6). This very situation of edema and hemorrhage may make the brain, perhaps through an increase in cerebrovascular resistance, the organ most sensitive to a decrease in systemic blood pressure even if it is suggested that it had not been so before the hemorrhage. Therefore it would be the organ most likely to give the earliest warning, through neurologic monitoring, of readily correctable excessive induced hypotension.

The present technique thus far has been utilized only in cases of aneurysm with bleeding. Its application in cases of unruptured aneurysm or arteriovenous anomaly in which the clinical problem concerns dysfunction secondary to a non-hemorrhagic (i.e. not extravasated) mass has not yet been explored. This requires a separate therapeutic investigation. With regard to the cases of hemorrhage, if some form of this or other medical therapy is by itself effective, all well and good. If not, and with regard specifically to cases of aneurysm, it is not inconceivable that hypotensive therapy be used *initially* i.e. in the acute stage, when surgical mortality is prohibitively high. Later, after recovery from the acute phase the patient might be a candidate for surgery. The not uncommon problem of multiple aneurysms as well as that of less accessible aneurysms e.g. those occurring in the posterior part of the Circle of Willis, present additional obstacles to surgical methods of treatment but have no effect on the application of the hypotensive method. Occasionally with a patient who has a subarachnoid hemorrhage, one can not only demonstrate an aneurysm; one can also bring out a state of cerebrovascular insufficiency. The latter may be due to an associated anomaly of the Circle of Willis and/or postural hypotension. This state of cerebrovascular insufficiency can be diagnosed by careful observation and can be incorporated into the hypotensive therapy of the patient's subarachnoid hemorrhage. Some untreated patients survive subarachnoid hemorrhage and at least

some of those patients have demonstrable cerebrovascular insufficiency. Whether or not the insufficiency (provided it is not excessive) has afforded protection in these cases remains to be assessed.

Where no aneurysm can be demonstrated, the problem of differentiating a hemorrhagic infarction from other causes of hemorrhagic cerebrospinal fluid is important. This can be difficult even at the post-mortem table and may be impossible clinically in certain instances. This is especially true when there is hemorrhagic cerebrospinal fluid without an apparent source of embolization. In such a situation, consistent non-filling of a blood vessel on cerebral angiography may suggest a total occlusion of that vessel. Although this may sometimes be merely an artifact (due to technical difficulty), it should be remembered that an anomalously narrow vessel may not fill and thus appear angiographically similar to an occluded blood vessel. The exact significance of the anomalous cerebral blood vessel with regard to cerebral infarction and/or hemorrhage is still under investigation (2). Hemorrhagic infarction may be an occasional obstacle not only to hypotensive treatment of intracranial hemorrhage but also to anticoagulant treatment of intracranial occlusive disease. The latter treatment should be used only when the cerebrospinal fluid is non-hemorrhagic, but absence of blood in the cerebro-spinal fluid does not exclude hemorrhagic infarction or even intracerebral hemorrhage. The clinico-pathologic aspects of the hemorrhagic infarct include part of the features of each of these two cerebrovascular disease groups. Apropos of this discussion, there are cases in which the cerebro-spinal fluid is hemorrhagic but complete angiographic study is "negative". It is sometimes stated that the prognosis in such instances is better than it would have been if, for example, an aneurysm had been demonstrated. First, this statement needs verification. Second, some of these cases might be examples of hemorrhagic infarction. Not much is known about the prognosis of this type of hemorrhagic infarct, and at present, a patient with a hemorrhagic infarct might best be left alone. Data on hemorrhagic infarction are being collected (7).

An interesting observation concerns one of the patients (treated earlier in the study) during the "wearing off" of a hypotensive drug. The patient, while the blood pressure was kept low, had no complaints and was responsive. The hypotensive medication was withdrawn, permitting the blood pressure to rise. It did so in a progressive fashion; ultimately the patient complained of a severe headache and became unresponsive. Lumbar puncture was repeated and revealed a recurrent hemorrhage. This finding is emphasized because it is sometimes said that the headache always precedes the rise in blood pressure and that the elevated blood pressure is necessary and compensatory.

Some of the treated cases of hemorrhage occurred during the menopause. It should be noted that some of the symptoms of excessively induced hypotension used in therapy are difficult to distinguish from those of the menopause per se. Regulation of the hypotensive medications during the menopause might be somewhat confusing if one were to depend on symptoms only. The data of some workers suggest that subarachnoid hemorrhage affects females more than males (8). One might be tempted to correlate an excessive incidence in women with

additional stress put upon the cerebral circulation by changes occurring during the menopause (and perhaps the menses).

CONCLUSIONS

The value of hypotensive agents in these cases must be considered according to whether the patient is in the acute "bleeding" phase or the more chronic phase. It is not always easy to separate these two phases. Treatment should be directed primarily toward prophylaxis in both instances. From the available data, the impression thus far is that hypotensive therapy is of value in the treatment of acute subarachnoid hemorrhage due to rupture of an aneurysm. This represents the largest single group of cases of intracranial hemorrhage treated by this method. It is re-emphasized that this acute "bleeding" phase is the one most often avoided when surgical methods are attempted. Yet this period, the first few weeks after hemorrhage, is the one of greatest mortality whether bed rest and sedation or surgery is used. However, this most dangerous period is deliberately sought for the type of hypotensive therapy outlined above. There is also to be considered the significant group of cases that are inoperable but can be treated by hypotensive therapy in both the acute and the more chronic phases. It is too early as yet to compare long term results of this and other methods of treatment. The regimen has been used for only three years. It is noted that neither the available medical nor surgical methods have been sufficiently effective to guarantee against eventual recurrence.

With regard to the safety of hypotensive agents in these cases, when carefully used, they can be very helpful and are not dangerous. In fact, they have a very wide margin of safety. The side effects of the medications are usually very mild and are the same as those encountered in the treatment of essential hypertension. They are minimized or eliminated by careful adjustment of dosage.

SUMMARY

A description of a method of management of acute subarachnoid and or cerebral hemorrhage by monitored hypotension is presented. Significantly, the only special apparatus used is a tilt table and even this may be omitted. A very long-term follow-up, probably many years, will be required to assess the value of any form of treatment, medical or surgical, of this group of cerebrovascular diseases. Although almost all of the patients treated have thus far survived and are fully active, the number of cases treated is still too small for statistical evaluation and the follow-up period (more than three years) is still too short to permit any definite conclusions.

ACKNOWLEDGMENTS

The author wishes to thank Drs. Morris B. Bender, Israel S. Wechsler, Hans Strauss, and Irwin H. Feigin for their helpful suggestions.

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ANTEPARTUM FETAL DEATH DURING ANTICOAGULANT THERAPY FOR THROMBOEMBOLISM

REPORT OF THREE CASES

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The treatment of thrombophlebitis and thromboembolism with anticoagulant drugs in the nonpregnant patient has become routine practice. Their use, however, during pregnancy has been of recent origin; the first report having appeared in 1945 (1). Subsequent reports (2, 3) of larger series indicate increasingly frequent use of these drugs in pregnancies complicated by thrombophlebitis and pulmonary embolism.

Employing anticoagulants in the prenatal period, however, is not without danger to the fetus. The increasing number of reports (3, 4) of fetal death from hemorrhage resulting from fetal coagulation deficiencies, both in utero and in the early neonatal period serve to emphasize the deleterious effect upon the fetus. Attention, therefore, has been focused on evaluating the various anticoagulant derivatives and especially their effects on the viable fetus.

This report adds to the literature three cases of antepartum fetal death associated with the use of Coumadin® in the treatment of antepartum pulmonary embolism. All three patients were in the 27th to 30th weeks of pregnancy at the time of hospitalization. Since long term anticoagulant therapy was anticipated and two of the patients were to continue treatment at home, the use of Coumadin® rather than heparin seemed more practical. Prothrombin time was determined regularly by reputable laboratories and the dose of Coumadin® was prescribed accordingly. Nevertheless, all three fetuses died in utero before the onset of labor.

CASE REPORTS

Case #1

A. P., a 30 year old white woman, was a para 0-1-0-0 whose expected date of delivery was 11/7/57. Her first pregnancy, in 1955, was complicated by pre-eclampsia and she delivered a premature, macerated fetus at 26 weeks. Her past history otherwise was negative. Subacute lupus erythematosus disseminata was first diagnosed during this pregnancy and she was treated with 15 mgm. daily of meticorten. Because of chest pain during the 27th week of her pregnancy, she was admitted to another hospital where the diagnosis of deep thrombophlebitis of the leg and pulmonary embolism was made. Coumadin® therapy was begun and the prothrombin time was maintained at approximately twice the control level. The patient was discharged from the hospital under the care of a medical consultant and Coumadin® therapy was regulated according to the prothrombin determinations. She was given 100 mgm. of Coumadin® intramuscularly every six days. The last dose was administered on 8/28/59. The patient was admitted to The Mount Sinai Hospital on 8/30/58 in early labor. She was 31 weeks pregnant, had not felt fetal movements for several days and

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no fetal heart was heard on admission. After a 10 hour labor, she was delivered of a macerated immature 870 gram infant. Coumadin[®] therapy, 5 to 10 mgm. daily, was continued throughout labor and for several weeks postpartum without any coagulation defects in the mother. Because of the maceration, the autopsy examination of the fetus did not reveal evidence of hemorrhage.

Case #2

A. E., a 27 year old white female was delivered of a normal child in 1955 and a premature infant that died in 12 hours in 1957. Otherwise her past history and routine laboratory findings were normal. On 6/13/58 she had chills and fever with pain in the chest and right thigh. Her physician made a diagnosis of chest involvement, possibly a pulmonary embolism. On 6/16/58 she was admitted to the Obstetrical Service at The Mount Sinai Hospital where the diagnosis of pulmonary embolism secondary to a deep thrombophlebitis of the thigh was established. Coumadin[®] therapy was instituted and a maintenance dose was given which kept the prothrombin time at about twice the control. At no time in the hospital did the patient's prothrombin time exceed 22 seconds. The fetal heart was heard daily throughout her hospital stay and the uterus was the size expected of a 30 week gestation. The patient improved and was discharged on 6/29/58 under the care of the medical consultant. Her prothrombin time was determined regularly at a reputable laboratory and the Coumadin[®] dosage was regulated accordingly. The average daily dose was 10 to 15 mgm. On 7/17/58 examination revealed a growing uterus and good fetal heart sounds. Her prothrombin time was 26 seconds and the control was 14 seconds. Examination on 7/24/58 revealed no fetal heart sounds and the patient had felt no fetal movements for several days. On 8/12/58 the patient was delivered of a 2380 gram macerated fetus. Coumadin[®] was discontinued during labor but given again for several weeks postpartum. There were no coagulation defects in the mother. Autopsy examination of the fetus showed no hemorrhagic accidents. There was marked maceration of the fetus making positive pathological diagnosis difficult.

Case #3

A 22 year old Puerto Rican woman, para 4-0-0-4, was admitted to the Obstetrical Service on 6/24/58. Her past history and routine laboratory findings were normal. She was admitted at 27 weeks gestation because of chest pain diagnosed as pulmonary embolism secondary to a deep thrombophlebitis. The fetal heart sounds were good. A medical consultant advised heparin, 7.5 mgm. intramuscularly every 4 hours until desired prothrombin time values were established, then Coumadin[®], 60 mgm. initially and 5 to 15 mgm. daily depending on the prothrombin levels. These were maintained at approximately twice the control time.

In spite of adequate Coumadin[®] therapy, the patient complained of repeated attacks of chest pain that were thought to be repeated embolizations, but the exact diagnosis could not be established. Because of this it was decided to keep the patient in the hospital under careful supervision and labor was to be induced when the fetus appeared large enough.

The average daily dose of Coumadin[®] was about 7.5 mgm.; the lowest was 2.5 mgm., and the highest was 15 mgm. The average prothrombin time was about 24 to 30 seconds with two readings at 34 seconds and one at 41 seconds on 7/5/58. The average control time was about 12.5 seconds.

The fetal heart sounds were present throughout her long hospital stay until 8/3/59 when they were no longer heard. There were no fetal movements. Labor was induced on 8/6/58, at 33 weeks gestation, and she was delivered of an 1860 gram severely macerated fetus. Coumadin[®] was continued throughout labor and the postpartum period without coagulation defects in the mother. Autopsy of the macerated fetus failed to show any evidence of hemorrhagic accidents.

DISCUSSION

All three patients were about 27 to 30 weeks pregnant when they were hospitalized because of leg and chest pains due to thrombophlebitis and pulmonary embolism. Each patient was receiving good medical supervision and the anti-coagulation therapy was carefully controlled. In case #1 the patient received 100 mgm. of Coumadin® intramuscularly every six days, but the other two patients received the more conventional daily dose of 5 to 15 mgm. In none of the patients did the prothrombin time ever reach unusually high levels; the average time was about 25 to 30 seconds with occasional readings of 35 seconds. The average levels were maintained at approximately twice the control time.

Quenneville *et al.* (5), in a recent paper on this subject, suggest that the Coumadin® derivatives can be used over long periods without harm to the fetus if the prothrombin time is kept below 35 seconds. In our cases the levels were well below this upper limit and yet the three fetuses died in utero. The average time that elapsed between the start of Coumadin® therapy and fetal death was about five weeks.

Because of suspected repeated pulmonary embolization the third case was kept in the hospital until she was delivered. Heparin, which has a molecular weight of 20,000 does not pass the placental barrier. Drugs like Coumadin®, however, which have a molecular weight of less than 1,000 apparently enter the fetal circulation. Heparin, therefore could have feasibly been used with less danger to the fetus.

Although the pathological examination of the macerated fetuses failed to show any hemorrhagic complications, the fetal loss associated with Coumadin® therapy suggests a cause-effect relationship, rather than a coincidental, unrelated finding.

SUMMARY

A. Three cases of pregnancy complicated by antepartum thrombophlebitis and pulmonary embolism are presented. All of the patients were treated with Coumadin®, and all of the pregnancies terminated with antepartum fetal death.

B. The fetuses died in utero before labor about five weeks after the institution of anticoagulant therapy.

C. Although the fetuses were dead the three mothers showed no evidence of unusual coagulation defects beyond those attributable to the anticoagulation therapy. There was no evidence of hypofibrinogenemia in the three mothers.

D. At no time were the prothrombin levels excessive. The average prothrombin time was well below 35 seconds which was about twice the control time.

E. The three patients were hospitalized during the 27th to 30th weeks of gestation. Good fetal heart sounds were heard when Coumadin® therapy was instituted.

F. Although no evidence of hemorrhagic accidents was found in the three macerated fetuses at autopsy, it is believed that the intrauterine fetal deaths

associated with Coumadin® therapy are more than coincidental, and that a cause-effect relationship is strongly suggested.

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AN EVALUATION OF THE SURGICAL TREATMENT OF CARCINOMA OF THE PERIAMPULLARY REGION

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In spite of the fact that carcinoma of the periampullary region has been a well recognized clinical and pathological entity for more than a century, attempts at definitive treatment have been accompanied by controversy and skepticism. Beginning in 1935 with Whipple's epoch-making proposal of radical resection (1), the pendulum of thought has swung back and forth between an aggressive, optimistic approach and a conservative, pessimistic outlook toward cancer in this region.

In recent years palliative operations have been the choice of some surgeons. The primary reason is the high operative mortality attendant upon the Whipple or similar procedures. However, the results of radical pancreatoduodenectomy reported within the past few years and the sporadic reports of long term survival following resection for pancreatic carcinoma, call for a re-evaluation of the prevailing attitude. Accordingly, a review of the experience from 1951 to 1957 on the ward service of The Mount Sinai Hospital has been made and is reported here.

MATERIAL

During this period, 60 patients with carcinoma of the periampullary region were operated upon. These include all patients with carcinoma originating in the region of the distal common duct, i.e., ampulla of Vater, head of the pancreas and common bile duct. Radical resection was performed in six patients. The remaining 54 were treated by some type of palliative procedure. Patients who had an exploratory laparotomy only are not included in this report.

In the group of patients subjected to radical resection, four had a Whipple type of procedure and two had total pancreatoduodenectomy. Four deaths occurred in the postoperative period between the first and the fourteenth day; two of these were in patients who had total pancreatectomy. Two patients who left the hospital died eight, and 26 months later with widespread metastases (Table I).

Palliative surgery in the form of side-tracking operations was performed in the remaining 54 patients, without attempting to extirpate the tumor. The

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This work was supported by the Surgical Research Fund.

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TABLE I
Results of Radical Resection

Patient's Age	Procedure	Result	Cause of Death
72	Total Pancreatectomy	Died, 14th P.O. Day	Shock
77	Total Pancreatectomy	Died, 1st P.O. Day	Myocardial infarction
53	Whipple	Died, 8 months post-op.	Carcinomatosis
65	Whipple	Died, 10th P.O. Day	Massive GI bleeding
58	Whipple	Died, 26 months post-op.	Carcinomatosis
53	Whipple	Died, 14th P.O. Day	Pulmonary edema

TABLE II
*Results of Various Palliative Procedures**

Procedure	Immediate Post-op. Deaths	Number Followed	Avg. Length of Survival (Months)
Cholecystogastrostomy.....	4	18	8.7
Cholecystojejunostomy.....	2	9	5
Cholecystojejunostomy (Roux-en-Y).....	0	6	5
Cholecystoduodenostomy.....	1	1	7
Choledochoduodenostomy.....	0	3	7.5
Choledochojejunostomy.....	0	2	12
Totals.....	7	39	7 (Avg. survival)

* 8 patients were lost to follow-up.

various procedures included 27 cholecystogastrostomies, 12 cholecystojejunostomies, six cholecystojejunostomies Roux-en-Y, two cholecystoduodenostomies, four choledochoduodenostomies, two choledochojejunostomies and one choledocostomy. Seven patients (12.9 per cent) died in the immediate postoperative period. Eight additional patients were lost to follow-up, leaving 39 patients available for this study. The range of survival in the last group was between one and 36 months, with an average of seven months. Only five patients lived one year or more. Conversely, 86 per cent of those who survived operation were dead within a year. The type of by-pass did not influence the operative mortality, nor the duration of survival (Table II).

These results with palliative surgery in cancer of the periampullary region confirm the expected dismal outlook, and are similar to those reported elsewhere in the literature (2-7).

DISCUSSION

It is evident that the practice at The Mount Sinai Hospital has been to attempt resection in only a small number of the cases. However, in the hands of those with extensive experience the mortality attendant upon radical pan-

creatoduodenectomy does not differ markedly from that of a bypass procedure. Moreover, the duration of survival has been reported to be greater after resection (2, 5, 6).

Cattell (8) reported a mortality of 12.9 per cent in 102 pancreatoduodenal resections; his mortality for carcinoma of the ampulla was 6.6 per cent and 17.3 per cent for carcinoma of the head of the pancreas. Waugh (9) had 17 deaths in 85 resected cases (20 per cent) with a mortality of 4.2 per cent and 26.2 per cent for carcinoma of the ampulla and head of the pancreas, respectively. It should be mentioned that his mortality of 22.5 per cent from 1941 to 1947 was reduced to 17.5 per cent in the period 1949 to 1952. Smith (10), in his series of 34 pancreatoduodenectomies, reported a mortality of 8.7 per cent. All deaths were in patients with carcinoma of the head of the pancreas, and there were no deaths in 25 instances of resection of carcinoma of the ampulla. Rhoads (11) has recently reported four deaths in 25 resections (16 per cent) for ampullary carcinoma. These figures represent a marked reduction in the mortality over the early reports for pancreatoduodenectomy (1-3, 5, 12-16) which ranged between 30 and 35 per cent. Mortality in the older patients is only slightly higher. Moore (5) performed 11 resections in people between 70 and 84 years of age with four deaths (36 per cent).

In one series, follow-up of patients who survived resectional surgery disclosed a five-year survival of 15.8 per cent for carcinoma of the head of the pancreas and 38.4 per cent for carcinoma of the ampulla (9). Cattell (8) has reported a five-year survival of 11 per cent and 30 per cent, respectively, for these two lesions. Rhoads had six five-year survivors among 17 cases available for study (29 per cent). Noteworthy are the results given by Smith, who reported 50 per cent survival of five years or more for carcinoma of the ampulla (10).

The operative mortality and survival figures cited above are comparable to results obtained in radical surgery for carcinoma of other organs, e.g., esophagus, stomach and lung (17-19), and tend to negate the widespread hopeless attitude toward carcinoma of the periampullary region.

It has been suggested that radical surgery should be undertaken for ampullary carcinoma, but not for cancer of the head of the pancreas. This point of view can only be accepted with reservation. At the time of operation the surgeon often finds it difficult to identify the site of origin of neoplasms in the periampullary region. This is difficult even for the pathologist (20, 21). Thus, many authors identify tumors in this region as one entity, under the term carcinoma of the periampullary region. Nevertheless, where study of resected specimens and autopsies has determined the exact site of origin of the tumor, carcinoma of the ampulla of Vater has been found to be the more localized lesion, with a lower incidence of metastases (22, 23).

Outerbridge (21) found that only 22 per cent of 110 cases of carcinoma of ampulla of Vater, seen at the time of autopsy, had metastases. Bagenstoss (20) reported 15 cases free of metastases in 26 post-mortems performed for carcinoma of the ampulla. These figures are in marked contrast to those reported for carcinoma of the head of the pancreas by Silver et al. (24), who found that 82.5 per cent of these lesions had metastases at the time of autopsy.

Miller (25), who studied resected specimens, noted a 30 per cent incidence of involved lymph nodes in carcinoma of the papilla and a 65 per cent incidence in carcinoma of the head of the pancreas. He found the perineural lymphatics involved in 60 per cent of cases of carcinoma of the head of the pancreas, and the transected end of the common duct was invaded in 15 per cent. None of these structures were involved in the resected specimens for carcinoma of the ampulla. These findings have been confirmed by others (26, 27). The presence of metastases in local lymph nodes should not, in itself, be considered a contraindication to resection. Five-year survivals in patients who had involved lymph nodes at time of surgery have been reported (2, 9, 28, 29).

Invasion of the portal vein was seen by Miller in 37 per cent of cases of carcinoma of the head of the pancreas, and in six per cent of the cases of carcinoma of the papilla (25). Child (30, 31) has presented experimental and clinical evidence of the feasibility of resection of the portal vein and its branches during pancreatectomy. Sweet (32) and McDermott (33) have reported successful resection of a portal vein involved by tumor, and implantation of the superior mesenteric vein into the inferior vena cava. Daniel (34) has attempted, in dogs, the bridging of defects in the portal vein with plastic tubes and homografts. Brunschwig (35) and Moore (36) resected the superior mesenteric vein *en bloc* with the tumor.

An additional problem that confronts the surgeon at the time of operation is the determination of the exact nature of a mass in the periampullary region. In the absence of metastases, there is nothing in the gross characteristics to differentiate between benign and malignant lesions (37, 38). Biopsy is often not helpful due to the secondary changes that occur in the pancreas as a result of obstruction of the ducts. Gross pancreatitis was reported in 23 per cent of cases of carcinoma of the head of the pancreas, and microscopic evidence of pancreatitis in 85 per cent (39). Cases of pancreatitis which were resected because of the impression that they were malignant have been reported (5, 37, 38). Fraser (4), reviewing 1035 cases of obstructive jaundice due to pancreatic disease, found a seven per cent incidence of benign lesions which were considered malignant, and a 16 per cent incidence of malignancies which were mistaken for benign lesions. Bowden (37) reported comparable figures of eight and 26 per cent, respectively, for these errors in diagnosis. On this basis, he feels that the chance of survival of a patient who has a resection for a benign lesion that is mistaken for a malignancy is greater than that of a patient who has a carcinoma of the pancreas that is not resected, because it is assumed to be a benign lesion. The following case report illustrates this difficulty in diagnosis.

R. T. (#87710), a 58 year old white woman, was admitted to The Mount Sinai Hospital on September 7, 1958, with a two month history of right upper quadrant pain radiating to the back and right shoulder, and jaundice of one week's duration. Physical examination revealed a jaundiced patient, in good general condition, with a large palpable gall bladder. The significant findings in laboratory studies consisted of a bilirubin of 7.3 mgm. per cent indirect and 4.9 mgm. per cent direct, and an alkaline phosphatase of 52 King-Armstrong units. On September 27, 1957, the patient was explored under general anaesthesia and a markedly distended gall bladder and common duct, without evidence of intrinsic disease, were found. A mass, 4 x 6 cm., occupying the head of the pancreas and firmly adherent to the duodenum, and large lymph nodes along the porta hepatis, were encountered. A biopsy

of several of the lymph nodes was reported negative on frozen section for carcinoma, and biopsies of the pancreas in three different sites were reported as chronic pancreatitis. These reports were confirmed by paraffin sections. In view of the negative biopsies, a cholecystoduodenostomy was performed. Postoperatively, the patient developed a left subphrenic abscess and a left pleural effusion which subsided. She was discharged on November 21, 1957. On May 11, 1958, she was readmitted with severe back pain, anorexia and weight loss. Physical examination at that time revealed a large liver, a palpable spleen and a mass in the epigastrium. Biochemical studies of the liver were normal. There was no evidence of jaundice. Smears taken of cells obtained on duodenal aspiration revealed carcinoma. The patient received bilateral splanchnic blocks, and was discharged relieved of the pain. She died in August, 1958, 11 months after the original exploration, of carcinomatosis.

The high incidence of associated pancreatitis has also been the cause of overestimation of the size of the tumor, and the consequent declaration of non-resectability. Bowden (40) reviewed 16 cases of carcinoma of the head of the pancreas with this problem in mind, and found that there was a marked discrepancy between the surgeon's impression and the pathologist's measurements. Furthermore, in five cases there was only microscopic evidence of tumor and these were described originally by the surgeon as a tumefaction from 1.5 cm. to 8 cm. in size.

With the aforementioned problems in mind, it is necessary to examine the factors responsible for the low survival rate in those cases in which resection is undertaken. Cattell and Pyrttek (41), analyzing their results, feel that partial pancreatoduodenectomy is unsatisfactory for carcinoma of the pancreas, and suggest that total pancreatectomy should be the next step to improve the prognosis. This opinion has been supported by others (6, 14, 42). McDermott and Miller cite the high incidence of local recurrence in patients who died some time after subtotal pancreatoduodenectomy. Grauer (43), in 29 cases classified as carcinoma of the head of the pancreas, found that the tumor was localized to the head as a single mass in only 14 cases. In the remaining 15, beside the mass occupying the head, there was microscopic as well as macroscopic evidence of tumor scattered throughout the remainder of the gland. Furthermore, Sommers (44) has noted the high incidence of papillomatous and adenomatous hyperplasia (41 per cent) in the uninvolved segment of pancreatic ducts in cases of carcinoma. He feels that this type of hyperplasia bears an etiologic relationship to the development of carcinoma in the gland.

Evans and Ochsner (42), in a detailed study of the lymphatics of the pancreas, have shown that lymphatic vessels of the head travel along the body and tail and empty into suprapancreatic and infrapancreatic nodes. These nodes are in close proximity to the superior mesenteric, middle colic, and splenic vessels. For this reason, they suggest that a radical operation for carcinoma of the head of the pancreas should include a total pancreatectomy, resection of the superior mesenteric vein and the middle colic vein.

Cole (45) and Hutcheson (12) have pointed to the presence of carcinoma cells in the pancreatic juice, and the consequent contamination of the peritoneal cavity during transection of the pancreas. This could explain those instances in which diffuse carcinomatosis follows shortly after pancreatoduodenectomy for a

localized lesion. These facts support the choice of total pancreatoduodenectomy as the treatment of choice for carcinoma of the periampullary region. However, this procedure still carries a high mortality. In a series of cases collected by Cattell, he has reported a mortality of 43.5 per cent for malignant lesions and a 20 per cent mortality for benign lesions. Zimmerman (46) has recently reported five consecutive total pancreatoduodenectomies without mortality.

SUMMARY AND CONCLUSIONS

A. The results of the treatment of carcinoma of the periampullary region on the ward service of The Mount Sinai Hospital from 1951 to 1957 have been presented.

B. Only 10 per cent of the patients operated upon underwent radical resection, with a mortality of 66 per cent.

C. The remaining patients had a palliative bypass procedure for relief of jaundice with a mortality of 12.9 per cent, and an average survival after discharge from the hospital of seven months.

D. The widespread pessimistic attitude toward radical resection for periampullary carcinoma has been discussed. Analysis of the mortality and survival statistics reveals that this attitude is unwarranted, and the prognosis following resection is comparable to that of malignant neoplasms of other organs.

E. The difficulty in diagnosis, and in evaluation of the origin and extent of the tumor, at the time of surgery, has been considered.

F. The factors influencing local recurrence, and therefore the nature of the resection to be undertaken, have been discussed.

G. A consideration of these factors indicates that radical total pancreatectomy should be recommended in any attempt at curative resection.

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MANAGEMENT OF TOXEMIA OF PREGNANCY

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Accurate evaluation of management of toxemia, or specific hypertensive disease of pregnancy, has two inherent handicaps. First, despite much investigative effort, this remains a disease of undetermined etiology. Second, in those clinics which stress adequate prenatal care, the disease is becoming less common. Proper prophylaxis in supervised pregnant patients has almost eliminated toxemia of pregnancy in its severe and fulminating form, replete with multiple alterations in body physiology (1). There remains a hard core of patients whose underlying hypertension, renal disease, or diabetes mellitus makes them particularly vulnerable to toxemia and at the same time especially resistant to treatment. These patients represent the major problem in this field today.

At The Mount Sinai Hospital (1953 to 1958), 26,041 patients have been delivered. The incidence of toxemia and essential hypertension and the fetal results in this group are presented in Table I.

These figures compare favorably with those reported elsewhere (Table II), bearing in mind differences in population and medical climate and variations in classification and reporting.

When the perinatal losses in this group are compared with the overall perinatal rate at The Mount Sinai Hospital for the same period, 21.4 per thousand live births, the major therapeutic problem in toxemia becomes evident. Reversal of the secondary manifestations of toxemia—hypertension, edema, and central nervous system irritability—can be accomplished readily with several different therapeutic regimens. Only when the perinatal loss, ranging from three times greater than normal in pre-eclampsia to ten times greater in pre-eclampsia superimposed on chronic hypertension, is reduced will there be any indication that therapy is influencing the basic disease process.

A second measure of therapeutic efficacy might be reduction in maternal mortality. This is not a sensitive criterion for us, since of all 1091 patients described in Table I there was only one maternal death: a 34 year old negress who had no prenatal care in her seventh pregnancy, whose course was complicated by rheumatic heart disease with mitral stenosis and essential hypertension with superimposed toxemia, who entered the hospital at 32 weeks gestation with premature rupture of membranes and in congestive heart failure, developed severe pulmonary edema when labor started 24 hours later, and died four hours post-partum; the premature newborn survived. It would be difficult to evaluate therapy by attempting to reduce a maternal mortality figure already lower than 0.1 per cent.

Our approach to the management of toxemia of pregnancy has been conserva-

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TABLE I
Toxemia and Hypertension in Pregnancy
*(The Mount Sinai Hospital, 1953-1958)**

Diagnosis	Number of Cases	Per Cent	Fetal Loss (Cases)	Perinatal Loss (Per 1000 Live Births)
Pre-eclampsia	695	2.7	47	67.6
Eclampsia	9	0.03	0	0
Chronic hypertension without toxemia	310	1.2	23	74.1
Chronic hypertension with toxemia	77	0.3	16	207.8
Total	1091	4.2	86	78.8

* These data are based upon 26,041 deliveries during this period.

TABLE II
Fetal Loss in Toxemia
(Perinatal deaths/1000 live births)

Authors	Pre-eclampsia	Eclampsia	Hypertension	
			Without toxemia	With toxemia
Cosgrove and Chesley (2, 3) (1935-1939)	171		185	500
Wellen (4) (1935-1950)	71	221	393	
Browne and Dodds (5) (1931-1940)	130	480	92	635
Taylor et al. (6) (1931-1950)	66		157	
Dieckmann (1) (1941-1950)	45	107	87	300
The Mount Sinai Hospital, 1953-1958	68	0	74	208

tive, partly because the small number of fulminating cases in our experience mitigates against extensive trials of new therapies, and partly because of our interpretation of the pathophysiology of this disease. We consider that the clinical manifestations of toxemia of pregnancy are secondary to the basic disease process. The generalized vascular spasm and resultant hypertension (7-9), responsible in major degree for maternal mortality (10) and the point of attack for therapy, may well be a protective mechanism whereby the body provides adequate circulation to the fetus. Whether the initial precipitating changes occur in the placenta (11) or other organs is not known. The finding on electron microscopic examination of renal biopsy specimens in pre-eclampsia of a deposit of amorphous material between the basement membrane of the renal glomerulus and the capillary wall, previously described with light microscopy as "swelling

of the basement membrane" (12), raises the question of a primary renal etiology for this syndrome. Under these circumstances, a reasonable approach to therapy is containment of the clinical manifestations of toxemia within boundaries which would assure maternal safety without interfering with the body's efforts at homeostasis.

PHARMACOLOGIC CONSIDERATIONS

Theobald (13) has summarized the numerous drugs proposed for the treatment of pre-eclampsia and eclampsia, and is of the opinion, shared by Eastman (14), that many of these patients have suffered from overtreatment. In an attempt to evolve a rational approach to therapy, we have considered the more popular drugs currently in use and their influence on representative vital functions in toxemia: blood pressure, cerebral blood flow and cerebral oxygen uptake (as measures of central nervous system ischemia and convulsive propensity), and renal blood flow (as a measure of renal function and representative of splanchnic and therefore uterine flow). These considerations are detailed in Table III.

Several inferences can be drawn from this analysis. Barbiturates, though effective in high doses in suppressing central nervous system irritability, have undesirable effects on other vital functions. Chlorpromazine (Thorazine®) and

TABLE III
Effect of Drugs in Toxemia of Pregnancy

Drug	Blood Pressure	Cerebral Blood Flow	Cerebral Oxygen Uptake	Renal Blood Flow
Depressant Drugs:				
Barbiturates	sl. D	D	D	D
Morphine . . .	sl. D	N	N	N
Magnesium sulfate	D	sl. I	sl. I	N
Chlorpromazine	D	D	D	D
Promethazine	D	D	D	D
Rauwolfia derivatives	sl. D	sl. D	N	sl. I
Adrenergic Blocking Agents:				
Hydergine®	D	N	N	N
Ganglionic Blocking Agents:				
Hexamethonium	D	D	D	D
Trimethidinium methosulfate	D	sl. D	sl. D	D
Veratrum Derivatives:				
Veratrum viride	D	N	N	sl. D
Cryptenamine	D	I	I	sl. D
Hydralazine	D	I	I	I

D = decrease; N = no change; I = increase; sl. = slight.

Data collated from references 15 to 28.

promethazine (Phenergan®) are in the same category. The use of the latter two drugs has had the greatest vogue in India, where unsupervised pregnant women present with fulminating eclampsia of a severity rarely seen by us (22, 23, 29, 30). The major problem in such cases is the reduction of maternal mortality with inadequate medical personnel; this the drugs have accomplished, the maternal death rate being reduced from 49.0 to 4.5 per cent in one series (22) and reported as zero in a second (23). The overall fetal mortality, however, in the respective series was 39.0 and 53.5 per cent. These drugs seem to offer no particular advantage in our circumstances. Of the depressant drugs, morphine and magnesium sulfate have the most physiologic effects in pre-eclampsia (18-21), and the rauwolfia derivatives are most helpful in the long term management of chronic hypertension in pregnancy (24).

Both adrenergic and ganglionic blocking agents are disappointing. Though effective in decreasing blood pressure, they do so by relatively more peripheral than splanchnic vasodilatation, and hence do not correct the renal ischemia characteristic of toxemia. The veratrum derivatives are markedly effective in increasing cerebral blood flow. Hydralazine (Apresoline®) seems from the pharmacologic data to exert the most beneficial effect, but has the disadvantage of a relatively high incidence of side effects when used in full dosage. A better therapeutic result may therefore be achieved by employing a combination of agents with lesser doses for each, i.e., a veratrum derivative plus hydralazine (31).

THERAPEUTIC REGIMEN

Current therapy at The Mount Sinai Hospital for toxemia of pregnancy is based upon the foregoing pharmacological considerations. In the Toxemia Clinic, to which are directed all pregnant women with essential hypertension, renal disease, evidence of pre-eclampsia in the current pregnancy or history of pre-eclampsia in previous gestations, the emphasis is on prophylaxis and symptomatic treatment. The patients are followed bi-weekly, encouraged to restrict weight gain with low caloric, low salt diets, and treated actively with diuretics at the first evidence of edema. Chlorothiazide (Diuril®), in doses of 500 milligrams daily for four consecutive days, has become the mainstay of therapy. With this dosage, and intermittent therapy, potassium depletion has been no problem; the patients are encouraged to use citrus fruits and juices liberally. Meralluride (Mercurhydrin®), 2 cc. intramuscularly, is used in patients refractory to or unable to tolerate oral diuretics. Reserpine in appropriate dosage has been used in patients with chronic hypertensive disease, but without effect in improving fetal salvage. Predisposing medical factors such as renal infection or diabetes are treated at the same time.

Sometimes the pregnant patient presents either without or despite prenatal care with sudden eruption of severe hypertension, marked edema, and intensive proteinuria. In such patients hospitalization and therapy are promptly instituted so that the clinical course can be stabilized. Salt diuresis, heavy sedation, and antihypertensive therapy are combined judiciously; the need for immediate

treatment is particularly pressing if any signs of impending eclampsia such as severe headache, muscle irritability, or epigastric pain are present.

After admission to the hospital, the immediate need is for sedation to depress central nervous system irritability. Although in the milder cases barbiturates such as phenobarbital, 10 to 60 milligrams every four to six hours, may be used, in the more severe case we have employed opiates promptly. Morphine, 15 milligrams intramuscularly every four to six hours if the respiratory rate remains adequate, has been satisfactory. Magnesium sulfate, 10 grams parenterally in 50 per cent solution as a loading dose and five grams thereafter every six hours (provided deep tendon reflexes are present and urine output is maintained at a minimum of 100 cc. in six hours) has a moderate hypotensive effect, tends to increase cerebral blood flow, and is effective in preventing convulsions. Intravenous administration of four grams of magnesium sulfate in 20 per cent solution is equally effective but more dangerous; 10 cc. of 10 per cent calcium gluconate for intravenous use should be available to counteract the respiratory depression of magnesium toxicity. Once this sedative regime has been instituted, convulsive episodes are extremely unlikely.

Diuresis should be stimulated simultaneously by administration of intramuscular mercurial diuretics. Mersaldehyde[®], 2 cc. intramuscularly, will produce a marked diuresis within hours; intravenous mercurials have been used in extreme instances, but the incidence of untoward reactions is such that this should not be a routine measure. Diuril[®] may then be employed in the usual doses for maintained diuretic effect.

Hypotensive agents have been used by us only to control hypertensive crises which arise in spite of sedation. Protoveratrine A & B (Veralba[®]), 2 mg. in 200 cc. of five per cent dextrose solution by intravenous infusion or 0.2 to 0.6 mg. intramuscularly every four to six hours, may be used to bring the blood pressure down to levels of 150 to 160/90 to 100 mm. Hg. This drug produces a moderate bradycardia and a sensation of warmth throughout the body. No attempt is made to drop the blood pressure to normal, but merely to contain the pressure within a reasonable ceiling. Ephedrine, 25 milligrams, and atropine, 0.4 milligrams, are immediately on hand for intravenous administration to counteract severe hypotension or bradycardia. Veratrum derivatives may increase cardiac excitability, and the use of these agents in patients who have been digitalized is contraindicated, since arrhythmias and fibrillation may occur. Symptoms of overdosage include progressive development of nausea, vomiting, hypersalivation, severe bradycardia and hypotension, and collapse. Drugs such as Apresoline[®], 20 milligrams, and Unitensin[®], five milligrams, combined in 500 cc. of 5 per cent dextrose solution and administered by intravenous drip, have given good results.

Patients admitted with convulsions and/or coma present an even more serious problem. It is essential to stop the convulsions and stabilize the patient's clinical condition before undertaking any obstetrical procedure. All of the aforementioned measures are employed simultaneously. In addition, general supportive measures are indicated: Intravenous fluids to provide adequate hydration and maintain urine flow; indwelling catheter to ascertain the precise renal output;

nursing care of the comatose patient; mouth gag and moderate restraints during convulsions. Oxygen is administered by nasal catheter at six liters per minute. Tracheotomy may be necessary to facilitate adequate naso-pharyngeal toilet. The patient may be digitalized prophylactically or at the first signs of cardiac failure; rotating tourniquets are used as needed for pulmonary edema. Broad spectrum antibiotics are indicated to prevent pneumonitis.

After the clinical picture has stabilized, a decision must be made whether to empty the uterus. This is generally based on two considerations: the severity of the manifestations of specific hypertension which persist after adequate therapy, and the duration of pregnancy. In severe cases of pre-eclampsia, if hypertension and proteinuria do not subside appreciably and pregnancy is sufficiently advanced to warrant termination, the uterus should be promptly evacuated; the method may be decided by obstetrical considerations. In the patient with eclampsia, it is wise to terminate the pregnancy promptly by whatever obstetrical means prove most feasible once the convulsions have stopped and the patient's status stabilized for about 24 hours. In both instances, induction of labor by intravenous pitocin infusion has been successful when the status of the cervix is favorable; the patients are well sedated during labor, permitted only a short second stage, and delivered under general or local anesthesia. Regional anesthetics such as spinal, saddle-block or caudal have the disadvantage of sometimes resulting in a sudden drop of blood pressure in a patient who must maintain a high tension for adequate blood flow to vital organs, and are therefore avoided. Although in cases of eclampsia treatment is directed toward preserving the life of the mother, the fetus will survive in many instances; N-allyl-normorphine (Nalline[®]), 5 to 10 milligrams given intravenously to the mother 10 minutes before delivery, will prevent an adverse effect of the mother's heavy opiate sedation on the respirations of the newborn. The only oxytocic used in the puerperium is pitocin, since ergot derivatives have a tendency to elevate blood pressure in these sensitive individuals.

Not uncommonly, the first detectable signs of pre-eclampsia or eclampsia may occur intrapartum or in the puerperium. Clinical manifestations occurring so late in pregnancy surprisingly may take one to three weeks to disappear. Obviously, post-partum management is simplified by the prior evacuation of the uterus.

SUMMARY

A. The major problem in toxemia of pregnancy in our clinic is the high perinatal mortality rate. Maternal mortality in registered patients has been zero, and prophylactic prenatal care has kept the incidence of eclampsia to 0.03 per cent.

B. The pharmacologic properties of drugs commonly used in the treatment of toxemia are reviewed, with special attention to alterations in cerebral and splanchnic blood flow.

C. On theoretic grounds as well as by good clinical response, magnesium sulfate, morphine, reserpine, veratrum derivatives, and hydralazine have been the mainstay of our therapy for severe pre-eclampsia and eclampsia.

D. Antepartum care, with emphasis on the prevention of toxemia of pregnancy

by means of weight restriction, low salt diet, and stimulation of salt and water diuresis in early edema, remains the best approach to the problem.

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Radiological Notes

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CASE NO. 95

This was the first admission of an 8 $\frac{1}{2}$ year old boy for investigation of recurrent meningitis. Thirteen months before admission, the child had been struck by an automobile and was admitted elsewhere with drowsiness and vomiting. Examination of the skull showed a linear fracture of the left occipital bone. The child, at the time of the accident, had bleeding from the nose but not from the ears. The hospital course was uneventful and he was discharged after twelve days. About a month after the accident, however, the child developed an ache in his left ear associated with fever, vomiting and nuchal rigidity. He was immediately re-hospitalized and a diagnosis of meningitis made after spinal tap. The spinal fluid showed many polymorphonuclear leukocytes with a protein content of 660 milligrams per cent. Prior to this hospitalization, he had received antibiotic therapy; a positive bacteriological culture was not obtained from the spinal fluid. The child responded well to antibiotics within a short period of time and was discharged. Three months later, however, the same symptoms recurred and hospitalization was required because of meningitis. The spinal fluid and blood culture of this admission were said to have shown pneumococci. Nose and throat cultures showed staphylococcus aureus. Again he was treated successfully with antibiotics and discharged after about three weeks. A similar sequence of events recurred seven or eight months later. Examination of the ears shortly before admission demonstrated the absence of hearing on the left side.

On admission, the patient appeared to be well. Temperature was 100.2°F. but in the subsequent week did not exceed 100°F. The tonsils were large and appeared to be injected. There were enlarged lymph nodes on both sides of the neck, more marked on the left. The left eardrum appeared scarred. Hearing on the left was absent and the left labyrinth was "dead." Conventional roentgenograms of the skull showed no definite evidence of fracture in the occipital bone. There was the suspicion of a fracture line in the petrous pyramid on the left side which, however, was demonstrated unequivocally by laminagraphy (Fig. 1). Examination of the mastoids showed relatively poor pneumatization on the right, most of the mastoid area consisting of diploic bone. On the left, pneumatization was even poorer and the bone was sclerotic. Pneumoencephalogram and electroencephalogram were normal. Spinal fluid was not unusual.

This case is of interest because of the insistence on the part of the clinician that there must be a persistent source of infection of the meninges related to the previous fracture, and the demonstration of the linear fracture by laminagraphy. This type of localized fracture of the superior margin of the petrous pyramid entering the bony labyrinth is uncommon. In view of the chronic tonsillar and middle ear infection, the source of recurring meningitis appears adequately explained. The absence of healing of the temporal fracture in contrast to the



Case 95, Fig. 1. Laminagraphy of petrous pyramids shows a linear fracture line (arrow) extending from the superior bony margin through the labyrinth at the site of the vestibule into the middle ear.

occipital fracture may also be the result of chronic infection. There is no doubt that a tear in the dura over the fracture is also present and unhealed. This child is under close observation with prophylactic antibiotics, with the hope that healing will occur and surgical intervention be avoided.

Final Diagnosis: RECURRENT MENINGITIS DUE TO UNUNITED FRACTURE OF THE PETROUS BONE.

CASE NO. 96

SUBMITTED BY BERNARD S. ARON, M.D.

A fifteen year old Puerto Rican girl was admitted to The Mount Sinai Hospital for the first time with the complaints of diffuse abdominal pain, occasional fever and chills, recurrent nose bleeds, for approximately a year, and scleral icterus for three weeks. Physical examination was negative except for enlargement of the liver and the spleen. The hemoglobin was 9.6 grams per cent. The serum bilirubin was elevated and multiple liver function tests were abnormal, suggesting hepato-cellular disease. Stool examinations were negative for ova and parasites but repeatedly positive for occult blood. Sigmoidoscopy and rectal mucosal biopsy were normal. Aspiration liver biopsy showed chronic non-specific hepatitis with focal necrosis and pericholangiolitis. Septa formation was present suggesting early transition into cirrhosis.

Barium meal examination showed some thickening of the folds of the duodenum



Fig. 1B



Fig. 1A

Case 96, Fig. 1A. Spot film of the right side of the colon during the course of insillation of barium shows normal distensibility and an essentially normal haustral pattern.

Case 96, Fig. 1B. A film taken subsequent to filling of the colon shows localized contraction of the cecum and ascending colon indicative of irritability of the right side of the bowel.



Case 96, Fig. 2A. Barium enema examination about five months after the examination illustrated in fig. 1 shows a very bizarre pattern of the right side of the bowel extending to the splenic flexure. These changes are most marked in the transverse colon where the mucosal folds appear to be thickened and tortuous. The entire segment appears to be limited in distensibility. Excess secretions are seen in the distal colon and sigmoid.

without evidence of any constant deformity or of an ulcer crater. Esophageal varices were not seen. Small bowel examination and barium enema examination (Figs. 1A & 1B) were essentially negative except for some irritability of the right side of the colon. The patient was treated with a high protein diet and steroids; she responded fairly well. At the time of discharge, hemoglobin was 12.5 grams per cent.

About three weeks after discharge, in the Follow-Up Clinic, it was noted that the patient was again jaundiced and febrile. Moreover, she had noted the pas-

sage of bright red blood per rectum. She was re-admitted to the hospital where the enlargement of the liver appeared to be essentially unchanged. The spleen was somewhat larger. Hemoglobin was 5.9 grams per cent. Liver function tests showed abnormalities similar to those on the first admission. Hematological study revealed multiple coagulation defects in the prothrombin group, presumably secondary to liver disease. On sigmoidoscopy, it was reported that there were multiple areas of punctate hemorrhagss in the rectal mucosa. However, on repetition of sigmoidoscopy ten days later, no mucosal abnormality was demonstrated.

Barium enema examination (Figs. 2A & 2B) showed a rather remarkable appearance during the course of barium filling, particularly in the transverse colon and ascending colon which suggested the possibility of ulcerative colitis. However, the air contrast portion of the examination showed normal distensibility except in the region of the splenic flexure where there was compression by the



Case 96, Fig. 2B. After the instillation of air, the right side of the colon appears to distend normally. The splenic flexure is limited in distensibility presumably as a result of compression by the enlarged spleen. The haustral pattern is relatively intact and the barium outlining the mucosal surfaces is continuous without evidence of serration or ulceration.



Case 96, Fig. 3. Repeat barium enema examination done six weeks after the examination illustrated in fig. 2 shows an essentially normal pattern and filling of the colon.

enlarged spleen. On steroid therapy, the liver function tests improved but stools remained persistently positive on guaiac examination. A repeat barium enema examination (Fig. 3) six weeks later showed an essential normal appearance of the colon without any remarkable irritability or abnormality in mucosal pattern. A second liver biopsy showed changes similar to, but more marked than the original findings. The patient was discharged for further observation.

The association of cirrhosis of the liver and ulcerative colitis has been commented upon by several authors (1-4). It has been postulated that mucosal changes in the colon as a result of venostasis may be a predisposing factor to ulceration. However, at The Mount Sinai Hospital this association has not been common and the case presented is of particular interest since the findings might have been interpreted as ulcerative colitis particularly of the right side of the colon. It is our belief that these changes were essentially functional in nature

perhaps associated with transitory congestion and edema. The reversal to a normal appearance within a relatively short period of time would appear to exclude the diagnosis of ulcerative colitis.

Final Diagnosis: TRANSITORY CHANGES IN THE COLON SIMULATING ULCERATIVE COLITIS IN A PATIENT WITH POST-NECROTIC CIRRHOSIS.

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CASE NO. 97

This was the first admission of a 15 year old girl. Since the age of six, the mother had noted that there was a fulness of the upper left side of the abdomen. She was also aware that this had been attributed to the presence of an enlarged spleen. At the age of four, appendectomy had been performed apparently without incident. The remainder of the history was non-contributory. There was no story of bleeding, jaundice or fever. For a period of about six months prior to admission, the parents had noted a voracious appetite and the patient was examined for this reason. After investigation, she was admitted to the hospital for operation.

Examination on admission showed a well developed, well nourished female of 15 in no distress. The only positive physical finding was an enlarged spleen which descended four fingerbreadths below the left costal margin on inspiration. The spleen was firm, non-tender and smooth. After the injection of epinephrine, the spleen appeared to shrink from five to three fingerbreadths below the left costal margin in one and a half hours. A smear of the peripheral blood after this procedure showed no evidence of malarial organisms. Because of the suspicion of Gaucher's disease, skeletal survey was done which showed no abnormality in the bones. Examination of the abdomen (Fig. 1) confirmed the presence of a huge homogeneous density occupying the left upper quadrant and extending as high as the left dome of the diaphragm. The left renal outline could be seen through this mass and did not appear to be unusual. The psoas margins were distinct.

Exploratory laparotomy was performed and a huge, thick walled cyst arising apparently from the lower pole of the spleen was found. Splenectomy was done. The cyst contained old blood and there were many other, small, cysts around it. It was lined by dense fibrous tissue with areas of calcification. In some areas, the



Case 97, Fig. 1. Examination of the abdomen shows a large, sharply demarcated, homogeneous density (arrows) with a sharp arcuate border inferiorly, extending to the dome of the diaphragm superiorly. The usual splenic shadow is not seen. The left renal outline can be discerned through the mass. The psoas borders are distinct.

lining showed squamous cell epithelium. No hair or cartilage was found but despite this the suggestion was made that the cyst was most likely a dermoid.

Final Diagnosis: CYST (DERMOID?) OF THE SPLEEN.

CASE NO. 98

SUBMITTED BY DAVID A. DREILING, M.D.

The patient was a 73 year old woman whose digestive complaints were present for at least 40 years. She suffered recurrent severe abdominal pain after meals, nausea, vomiting, multiple episodes of hematemesis and melena. At the age of

43, a thyroidectomy had been performed for Grave's disease. At the age of 50, essential hypertension was discovered. Headache, dyspnea and angina were present. At various times she had experienced several cerebral vascular accidents and on one occasion a coronary occlusion. There was no history of alcoholism.

The patient was first seen at The Mount Sinai Hospital in 1946 for symptoms of hypertension. At that time, a mass was palpated in the epigastrium and the liver appeared to be enlarged. Roentgen examination of the abdomen disclosed multiple calcific deposits in the pancreas (Fig. 1). Cholecystography showed a normally functioning and contracting gall bladder without calculi. Barium meal examination revealed a very small hiatus hernia and a duodenal diverticulum. Pancreatic secretion studies revealed findings indicative of advanced chronic pancreatitis. It was assumed that the etiology of the pancreatitis was disease of the biliary tract but in view of the absence of biliary tract symptoms and the normal cholecystographic findings as well as the patient's poor cardiovascular condition, surgical intervention was not recommended.

The patient had five subsequent admissions to the hospital. The first four admissions, one in 1953, two in 1955 and one in 1957 were all occasioned by massive hematemesis. In the interval from 1953 to 1957, the patient had six major bleeding episodes. On each occasion, the bleeding ceased after hospitalization and barium meal and enema studies showed no definite source for bleeding. Gastroscopy was also performed and there was no evidence of ulceration demon-



Case 98, Fig. 1. Examination of the abdomen shows numerous nodular and linear calcifications in the region of the body of the pancreas (arrow). These remained essentially unchanged over a period of years.



Case 98, Fig. 2. Barium meal on the patient's last admission shows marked gastric dilatation and retention with a rigid, conical, narrowed segment (arrow) involving the antrum and extending to the base of the bulb. The mucosal pattern in this area is completely destroyed and the appearance is that of neoplastic involvement.

strated. Gastric analysis revealed no free acid. Repeated secretin tests done during this interval always showed marked impairment of pancreatic function. On a number of occasions, surgical intervention was recommended but the patient's private physicians did not concur.

The patient's last admission to The Mount Sinai Hospital was in March 1959. She had been chronically ill for the last two years but had had no major gastrointestinal hemorrhage. The patient was admitted because of several months of progressive weakness, anorexia, marked weight loss and persistent vomiting. Barium meal examination on this admission (Fig. 2) demonstrated obvious marked gastric dilatation and retention. There was a conical rigid narrowing of the antrum which had the appearance of neoplastic involvement. At the four hour observation practically all of the barium remained in the stomach. From the roentgen observations, it was not evident whether the narrowed rigid antrum was the result of a primary carcinoma of the stomach or whether this was the result of neoplasm involving the stomach secondarily. In view of the long story of pancreatic disease and the presence of pancreatic calcinosis, it was suspected that the latter was true and that the patient was now suffering from a carcinoma of the pancreas with secondary involvement of the stomach. In order to relieve



Case 98, Fig. 3. Barium meal examination done six years before the examination seen in Fig. 2 shows a hemispherical indentation (arrow) on the posterior aspect of the body of the stomach which was constant and indicative of pancreatic enlargement or mass.

her desperate condition, the patient was explored. The pancreas was hard and calcific and exhibited in the body of the pancreas a large cystadenocarcinoma approximately two by three by five inches in size. There were multiple metastases in the peritoneal cavity, the lymph nodes and the liver. A large metastasis just proximal to the pylorus had involved the immediate prepyloric segment of the stomach and was the source of the obstruction. No ulceration of the gastric mucosa was felt externally nor could one be demonstrated after the stomach had been opened for the performance of a palliative gastroenterostomy. A biopsy of one of the metastatic lesions was reported as adenocarcinoma. On the fourth post-operative day, the patient suffered a coronary occlusion and died the following day.

This case is of interest because of the fact that chronic relapsing pancreatitis with pancreatic calcinosis had been present for many years. On previous barium meal examinations, an indentation on the posterior aspect and greater curvature aspect of the stomach had been repeatedly demonstrated (Fig. 3). The possibility therefore exists that this represented a cystadenoma which subsequently became

malignant, an example of an apparent increased frequency of carcinoma of the pancreas in patients with chronic pancreatitis and calcinosis.

Final Diagnosis: CYSTADENOCARCINOMA OF THE PANCREAS IN A PATIENT WITH LONG STANDING CHRONIC RELAPSING PANCREATITIS AND PANCREATIC CALCINOSIS.

CASE NO. 99

This was the fourth admission of a 70 year old white male with the chief complaints of abdominal discomfort and progressive anemia of three months duration.

Four years prior to this admission, the patient had undergone prostatectomy. He developed a persistent pyelonephritis following this and had five severe recurrent urinary infections. He also had a long history of "stomach trouble" consisting of epigastric fullness and distress, and heartburn relieved by "Tums". A barium meal examination done elsewhere was not remarkable.



Case 99, Fig. 1A. Barium enema examination shows a small polyp on a pedicle in the distal sigmoid (lowermost arrow). In addition, however, there is evidence of extrinsic pressure on the mid-sigmoid (arrow) and the terminal ileum is displaced upward with evidence of extrinsic pressure on its medial aspect (arrow).

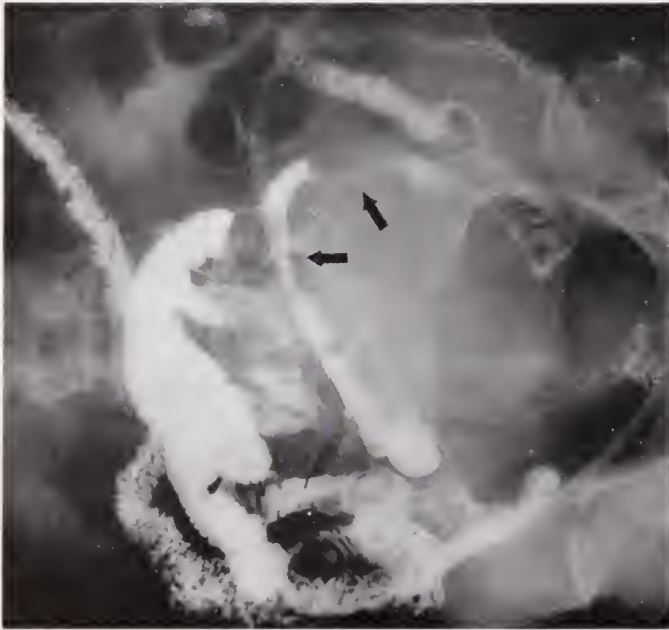


Fig. 1B

Case 99, Fig. 1B. After evacuation, additional small bowel loops above the brim of the pelvis are filled and there is evidence of compression and extrinsic pressure (arrows) as well as displacement by an extrinsic homogeneous soft tissue density.



Fig. 1C

Case 99, Fig. 1C. Double contrast portion of the barium enema examination confirms extrinsic pressure on the loops of small bowel and shows one loop that is concentrically compressed (arrow).

Two and a half months prior to the current admission, the patient had been admitted with complaints of severe anorexia, fever to 102°F., chills and weakness. Dark blood was noted in the stools. At that time, a normochromic anemia was present with a hemoglobin of 8.8 grams per cent and a red count of $3\frac{1}{2}$ million per cu. mm. The white blood count was 7,100 per cu. mm. Sedimentation time was markedly increased. The patient was treated with antibiotics and the fever subsided. Guaiac test on the stools showed a faint trace on one occasion but was negative when repeated.

The patient was readmitted because of persistent anemia, loss of weight and abdominal discomfort. Moreover, a mass on the right side of the abdomen had become palpable. This was located immediately below the umbilicus, was hard, but appeared to be movable and was not tender.

Barium enema examination (Fig. 1A) showed the presence of a small polyp on a pedicle in the sigmoid. In the lower abdomen, there was evidence of a large soft tissue density in the mid-line extending to the right, which produced extrinsic pressure on the distal sigmoid as well as adjacent loops of small bowel (Figs. 1B & 1C). After suitable preparation, exploratory laparotomy was performed and a hard, firm, irregular, solid, encapsulated tumor mass removed from the mesentery of the small bowel. On microscopic examination, this was found to have a pattern highly suggestive of paraganglioma. Very few mitotic figures were present, suggesting low-grade malignancy.

Final Diagnosis: LARGE PARAGANGLIOMA OF THE MESENTERY OF THE SMALL BOWEL.

CASE NO. 100

This was the first admission of a 55 year old male with complaints of inability to void for 24 hours and lower abdominal pain. One year prior to admission, because of hematuria, cystoscopy was performed and a large median lobe of the prostate was found. Resection was not performed. Two weeks prior to admission, he had some lower abdominal discomfort which was relieved by moving his bowels. The patient had always been constipated; there had been no recent changes in bowel habits.

Physical examination on admission showed a well developed and well nourished male, acutely ill. Temperature was 99.2°F., pulse 92. The abdomen was somewhat distended inferiorly and there was a tender mass above the symphysis and a little to the left. Hemoglobin was 13 grams per cent, white blood count 15,000 per cu. mm. with a normal differential count.

The patient was cystoscoped. There was no evidence of urinary retention and a cystogram showed only a small diverticulum of the bladder. Barium enema examination was done on the day after admission (Fig. 1), and showed no definite evidence of any intrinsic lesion of the colon. However, there was extrinsic pressure and straightening of the superior aspect of the sigmoid. No diverticulae were noted. The patient was treated symptomatically for two days without significant change in his condition except for progressive distention of the lower



Case 100, Fig. 1. Barium enema examination shows no evidence of an intrinsic lesion of the colon but there is an indentation and flattening on the superior aspect of the proximal portion of the sigmoid (arrow). Several dilated loops of small bowel are present in the mid-abdomen.

abdomen. Roentgen examination of the abdomen confirmed small bowel dilatation and the presence of a mass at the brim of the pelvis (Fig. 2). Barium was administered by mouth and serial observations made. These demonstrated moderate dilatation and an abnormal quantity of secretions in the small bowel with evidence of displacement and extrinsic pressure of several loops immediately above the soft tissue mass (Fig. 3).

This patient clinically and roentgenologically posed a problem in diagnosis. The clinical findings appeared to be consistent with a diverticulitis of the sigmoid which involved the bladder externally, but the roentgen findings of a rather large mass without evidence of diverticulae appeared inconsistent with this diagnosis. Moreover, the patient was not febrile although the white blood count was elevated.

The patient was explored and a hemorrhagic mass about 12 cm. in its greater diameter was found in the left lower quadrant pressing against the sigmoid and

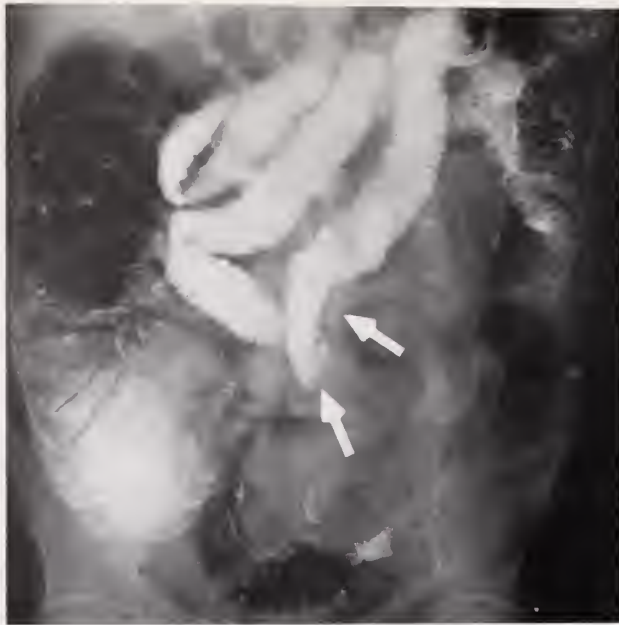


Case 100, Fig. 2. Examination of the abdomen two days after barium enema shows rather marked dilatation of small bowel loops as well as colon. This appears to be a combination of incomplete small bowel obstruction and paralytic ileus. A "window" (arrow) of homogeneous soft tissue density at the pelvic brim on the left indicates the presence of a mass.

adherent by a pedicle to an adjacent loop of distal ileum. The point of adhesion to the small bowel was over an area less than $\frac{3}{4}$ of a square centimeter. At one point, the hemorrhagic mass also pressed on the dome of the bladder and the greater omentum was adherent to it. The mesentery with the attached mass was removed. A small portion of the wall of the ileum was removed with the tumor and the opening in the ileum closed. The mesenteric portion of the mass was 7 cm. in diameter, irregular in shape and thinly encapsulated. A section of this mass showed it to be composed mainly of blood clot except at one pole where there was an irregular grayish white firm tumor mass about 3 x 4 x 2 cm. Microscopic examination showed this to be a myosarcoma with extensive hemorrhage.

The patient did well post-operatively. He was subsequently readmitted because there was some question as to whether the entire tumor at the point of the attachment to the ileum had been resected. He was re-explored and about eight inches of terminal ileum, with the old site of excision in its center, were removed. There was no evidence of any tumor in this specimen.

In retrospect, the correct diagnosis might have been suspected from the findings in Figure 3. The peculiar V-shaped configuration of the loop of small bowel



Case 100, Fig. 3. Barium administration from above shows some dilatation of ileal loops with an unusual amount of fluid within them. The small bowel loops are displaced from the pelvis and show extrinsic pressure (upper arrow). A twist in the small bowel about an anchoring point (lower arrow) is an unusual finding. The sigmoid as outlined by air shows findings similar to those seen on the barium enema examination.

with fixation to a mass at the apex of the V, and localized torsion of a short segment of bowel are unusual. A mass of this size attached to the small bowel by a short pedicle presumably pulls the involved loop of small bowel downwards in the abdomen until it becomes fixed, e.g. to the mesosigmoid. Fixation then interferes with normal small bowel motility and torsion of the loop with its attached pedicle results in hemorrhage into the neoplasm and an acute abdominal episode. The attachment to the ileum by a pedicle of a tumor which must be considered to have arisen in the wall of the bowel is also of interest and permits simple surgical excision.

Final Diagnosis: EXOENTERIC MYOSARCOMA OF THE ILEUM WITH TORSION AND HEMORRHAGE.

THE INCIDENCE OF HIATUS HERNIA IN ROUTINE BARIUM MEAL EXAMINATIONS

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A standard technique for the detection of hiatus hernias during routine "upper gastro-intestinal" series has been previously described (1). In this method, the

TABLE I

Age	Incidence of Hiatus Hernias		
	Number Examined	Number with Small Hernias	Number with Medium or Large Hernias.
10-19	16	0	0
20-29	22	1	0
30-39	30	4	1
40-49	53	15	2
50-59	114	39	11
60-69	113	46	20
70-79	42	23	9
80-89	9	6	2
90-99	1	1	0
	400	135	45

TABLE II

Age	Frequency of Hiatus Hernias		
	Percentage of Small Hernias	Percentage of Medium and Large Hernias	Total Percentage
30-39	13%	3%	16%
40-49	28%	4%	32%
50-59	34%	10%	44%
60-69	41%	18%	59%
70-79	55%	21%	76%
80-89	67%	22%	89%

patient lies on the horizontal table in the conventional right anterior oblique position with a radiolucent bolster under the abdomen. A film of the esophagus and stomach is taken while the patient continuously drinks a fluid barium-water mixture. As part of each barium meal examination, reflux from below to above the diaphragm is sought by placing the patient in a moderate Trendelenburg position, after filling the stomach with barium. More strenuous maneuvers to induce reflux are used only in selected cases.

The results of 400 consecutive patients referred to the X-Ray Department of The Mount Sinai Hospital for barium meal examination are given in Tables I and II. All of these patients were in-hospital patients and were referred for a variety of reasons. A hernia was considered "small" if the herniated portion of the stomach in the prone pressure film was definitely less than $1\frac{1}{2}$ inches in length. All other hernias were considered to be moderate or large in size.

Reflux in the moderate Trendelenburg position was noted in no patient without a hernia, was noted twice in the 135 patients with small hernias and in one-third of the patients with moderate or large hernias. Every patient who showed free reflux of barium into the esophagus in the moderate Trendelenburg position

complained of symptoms clearly referable to the hernia. There were, however, patients with medium or large hernias with similar symptoms who did not show free reflux in the Trendelenburg position. The large majority of the patients with small hernias had no significant symptoms reasonably attributable to the hernia.

It is of interest to note that the frequency of small hernias increases in adults with age in linear fashion. In contrast, medium and large-size hernias are uncommon before the age of fifty and their frequency levels off at about 20 per cent after the age of sixty. These findings appear to confirm the impression that small sliding hernias are part of the "ageing" process and that additional factors play a role in the production of large hiatus hernias.

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Clinico-Pathological Conference

HYPOGAMMAGLOBULINEMIA AND JAUNDICE

Edited By

FENTON SCHAFFNER, M.D.

A 69 year old widow entered The Mount Sinai Hospital for the fifth time, on this occasion because of jaundice of six months duration and abdominal swelling for a few days.

First admission (14 months earlier): The patient had had epigastric distress and dyspnea two years before, at which time her physician felt the spleen six fingerbreadths below the left costal margin and saw what appeared to be a gallstone on x-ray. Two months before admission she developed painless watery diarrhea, with no blood in the stool. She was found to have pancytopenia and a very low serum gamma globulin level. She had lost seven pounds in the preceding two-year period and had some ankle edema in the evening for several years.

Cysts had been removed from both breasts 20 years earlier and varicose veins were ligated 15 years before. She had traveled in many areas of the world and had had "flu" in Peru two years before. She had experienced one or two attacks of bronchitis a year for 20 years. Her father and two brothers died of arteriosclerotic heart disease; her mother died of a sarcoma and one brother of leukemia. Four sisters were living, one of whom had diabetes mellitus.

Temperature, pulse, and respirations were normal; the blood pressure was 130/76. Several discrete, soft nodes, up to one centimeter in diameter, were felt in the left axilla. A lipoma was present on the right shoulder. The thoracic spine showed scoliosis to the right. A grade I apical systolic murmur was present and transmitted to the axilla but the heart was otherwise normal. The lungs were clear. The abdomen was greatly distended, mainly by a firm smooth spleen which filled the entire left side and extended to the right midclavicular line. The liver was not felt. Pelvic and rectal examinations were negative. The extremities were normal.

X-ray examination showed the colon displaced by the spleen and an oval ring of calcium in the right upper quadrant. Aside from displacement, the stomach and small bowel were normal. A bone survey was negative. Chest x-ray showed increased markings but was otherwise normal. An electrocardiogram was normal.

Stool examinations for blood, ova and parasites, and pathogenic bacteria were negative. The urine contained a faint trace of albumin and 2 to 5 WBC/HPE. The BUN was 13.0 mg. %, blood sugar 88 mg. %, serum bilirubin 1.4 mg. % with 0.7 mg. % direct reacting pigment, serum cholesterol 132 mg. % with 74 % esters, albumin 4.0 Gm. %, globulin 2.2 Gm. %, cephalin flocculation 0, alkaline phosphatase 2.2 KA units, calcium 9.8 mg. %, phosphorus 2.6 mg. %, mucoproteins 135 mg. %, acid precipitable globulin 5.0 mg. %, zinc sulfate turbidity 1.0 units.

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Electrophoresis of serum proteins showed normal albumin, alpha 1, alpha 2, and beta globulins but very low gamma globulin. The erythrocyte sedimentation rate was 19 mm/hr. Prothrombin time was normal, as were bleeding and clotting times and clot retraction. A serologic test for syphilis was negative, as were PPD #1 and #2 skin tests and brucella and salmonella agglutinins. The hematocrit was 30.5%, hemoglobin 8.4 Gm.%, RBC 3,670,000 per cu. mm. reticulocytes 0.9%, WBC 3,450 per cu. mm. with 40% segmented cells, 20% bands, 32% lymphocytes, 2% monocytes, 6% atypical lymphocytes. The platelet count was 52,000 per cu. mm.

On the fifth hospital day the patient developed bronchitis with some fever. She was given penicillin which was rapidly followed by a rash. She was sent home on the 12th hospital day to return for splenectomy.

Second admission (1 week later): The patient returned for surgery but because an extensive rash was present, she was sent home after a blood transfusion and laboratory tests which gave essentially the same results as on the previous admission. Alkaline phosphatase activity of the white blood cells was $71.1/10^{10}$ cells.

Third admission (2½ months later): The patient returned for surgery stating that the rash had cleared very slowly despite administration of ACTH and antihistamines. Physical examination was the same as before except that many small, freely movable cervical and supraclavicular nodes were now palpable. Her blood pressure was 180/80. The results of all laboratory tests were essentially the same as on the first two admissions.

On the third hospital day, a splenectomy was performed through a thoraco-abdominal approach. Three units of blood were given. The spleen was 20 inches in its greatest diameter and 19 inches in width and weighed 2300 Gm. Postoperatively she did well until the third day when she developed a fever of 104° with daily spikes to at least 101° F. Some pyuria and serosanguinous drainage from the chest wound were present. Cultures of the spleen were negative. Chest x-ray revealed Fleischner lines on the right, a low left hilum and slight pleural reaction. The hemoglobin was maintained over 12 Gm. % while the white count reached a maximum of 44,200 per cu. mm. on the second postoperative day and the platelets rose to 260,000 per cu. mm. One week postoperatively almost all polymorphonuclear cells disappeared from the peripheral blood and remained scant in number for two weeks while many atypical lymphocytes were seen, as well as vacuolated monocytoïd cells. Paper electrophoresis showed very low gamma globulin on two strips. The bone marrow was cellular, with active megakaryocytosis, normoblastic erythropoiesis, granulocytic hyperplasia with arrest at the band stage, and an increased number of lymphocytes. A few plasma cells were seen when the section was scanned. The patient went home after four weeks, still somewhat febrile.

Fourth admission (four months later): During her first two months at home the patient did well. Then she developed a respiratory infection, and while in bed for this, she noted dark urine and became jaundiced four or five weeks prior to readmission. She had normal brown stools, no nausea or vomiting, and her ap-

petite was good. She had been gaining weight and was taking iron and vitamin tablets.

On admission, the patient was icteric and had palmar erythema but no spider nevi. Rales were present in both lung bases. A sinus tachycardia was present. The abdomen was distended with shifting dullness. The liver was firm, smooth and nontender, and extended four fingerbreadths below the costal margin. No pulses were felt in the legs below the femorals. One-plus sacral and 3+ ankle and leg edema was present.

Urinalysis showed a faint trace of bile and urobilinogen values fluctuated from 1:20 to 1:80. No occult blood was present in the stools. Hemoglobin was 12.4 Gm. %, WBC 17,500 per cu. mm. with 20% segmented cells, 16% bands, 48% lymphocytes, 10% monocytes, and 6% atypical lymphocytes. The platelet count was 202,000 per cu. mm. The red cells showed targetting and Howell-Jolly bodies. Occasional giant platelets and many pleomorphic lymphocytes were seen. The sedimentation rate was 3 mm./hr., prothrombin time was 18 sec. (control 11.5 sec.). The BUN was 13 mg. %, blood sugar 57 mg. %, serum cholesterol 189 mg. % with 60% esters, serum bilirubin was 8.2 mg. % with 5.2 mg. % direct reacting pigment. Thymol turbidity was less than 1.0 unit. Serum alkaline phosphatase was 14.6 KA units, the serum glutamic-oxaloacetic transaminase was 520 units. Albumin was 3.7 Gm. %, globulin 2.3 Gm. %. Electrophoresis revealed reduced gamma globulin but some was present in both γ_1 and γ_2 fractions. Isoagglutinin anti-B antibodies were demonstrated. The serum mucoproteins were 36.1 mg. %, acid precipitable globulin 3.2 mg. % and zime sulfate turbidity 1.7 mg. %. BSP retention was 22.5%. Gastrointestinal x-rays were negative. Intravenous cholangiography failed to visualize the biliary tree but an oval calculus was again seen in the right upper quadrant. Chest x-ray showed increased markings, focal atelectasis in the right base and Fleischner lines on the left. Electrocardiogram was normal. The patient was treated with Mereuhydrin®, chlorthiazide, vitamin K, prednisone and gamma globulin was given intramuscularly. She improved somewhat and was sent home.

Fifth admission (three months later): The patient had done poorly at home, having been continuously jaundiced and becoming weaker. Before admission, abdominal swelling was noted for several days and constipation and oliguria for one day. While at home she had bilateral thrombophlebitis migrans.

Her pulse was 100, temperature 99.6°F., blood pressure 150/80. She was dyspneic and icteric, and appeared chronically ill. Bilateral basal rales were present and a grade IV systolic murmur was heard over the entire precordium. The abdomen was distended and tympanitic but no organs were felt. Pitting edema was noted bilaterally to the knees.

The hemoglobin was 12.2 Gm. %, WBC 22,000 per cu. mm. with 56% segmented leucocytes, 14% band forms and 30% lymphocytes. The urine showed faint traces of albumin and bile, and 1:40 urobilinogen. BUN was 19.3 mg. %, blood sugar 71 mg. %, serum bilirubin 6.2 mg. % with 4.2 mg. % direct reacting pigment, serum alkaline phosphatase 15.3 KA units, thymol turbidity less than

1 unit, cephalin flocculation negative, albumin 3.6 Gm. %, globulin 2.1 Gm. %, serum sodium 136 mEq., potassium 4.4 mEq., chlorides 86 mEq. and CO_2 29.5 mEq. Bromsulfalein retention was 52.5% in 45 minutes. X-ray of the abdomen revealed distention of the colon with gas and feces. Chest x-ray showed high diaphragms, a blunted left costophrenic angle and an enlarged heart.

The patient was placed on diuretics and the distention lessened. On the fourth day, a paracentesis was performed and a liter of opalescent fluid was removed. The fluid had a specific gravity of 1.012, a protein content of 1.7 Gm. % with an A/G ratio of 1.1/0.6 and no tumor cells. The following day the patient was lethargic and her speech was thick. During the next two weeks she developed presacral edema and hemorrhoidal bleeding. The serum bilirubin had risen to 11.8 mg. % although the white count dropped to 10,050 per cu. mm. while the hemoglobin remained unchanged. The patient returned home where she died two weeks after discharge, having been comatose most of the time.

*Dr. Alexander B. Gutman**: The patient to be discussed was considered during life to have an obscure disorder which in recent years has come to be designated "acquired agammaglobulinemia", as distinguished from congenital agammaglobulinemia. My remarks will be confined to this disease, the question being whether all her varied manifestations can be accounted for by this symptom complex, or whether additional assumptions are necessary.

There are two subcategories of the acquired form of a-(better, hypo-) gamma-globulinemia. The first is associated with a recognizable underlying disorder which, one way or another, affects the biosynthesis of gamma globulins which serve as a reservoir for the formation of specific antibodies. Most commonly the underlying disease is multiple myeloma, but it may be macroglobulinemia or, occasionally, chronic lymphocytic leukemia, lymphoma or myeloid metaplasia. The second probably also is secondary to some underlying disorder but this is not readily catalogued, hence the failure to synthesize gamma globulins adequately is called idiopathic.

To get on to the facts of the case, the patient was a 69 year old widow at the time of her death. She came in at the time of her last admission because of jaundice of six months duration, with ascites. She was first seen at this hospital three years before her demise because of epigastric distress and dyspnea which had its onset two years before. Even at that early period, the physician who examined her felt the spleen six fingerbreadths below the left costal margin and observed a gallstone on x-ray. On that occasion she already had pancytopenia. A very low serum gamma globulin level was noted very early in her course. She had experienced one or two attacks of bronchitis a year for twenty years. This is important to us because it may help to localize the time at which the hypogammaglobulinemia began. One of the most prominent manifestations of this disorder is the recurrence of infections, particularly of pulmonary infections.

Dr. Siltzbach had an opportunity to go over this history with the patient and I think he has a little more information on that point.

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*Dr. Louis Siltzbach**: Actually, an enlarged spleen was first found in 1952 although our physicians first saw her in 1956. She was told she had anemia at that time. She was sent to me primarily to determine what the hepatosplenomegaly was due to. She had a Nickerson-Kveim test and it was negative. The tuberculin test, incidentally, was also negative. The patient had just recovered from an attack of pneumonia and still had some sticky rales. Chest x-ray showed a resolving pneumonia at the right base. She told me she had many attacks of bronchitis and that unlike most colds, recovery always took four to six weeks. Antibiotics in the later attacks did not seem to be nearly as helpful as they were earlier. She also had diarrhea periodically. On the basis of these facts, I suggested testing her serum for gamma globulin. We were quite surprised by the results. I was told the zinc sulfate turbidity was almost zero and that the electrophoretic pattern showed practically no gamma globulin.

Dr. Gutman: Thank you. About the only finding on physical examination of any significance was marked distention of the abdomen caused for the most part by a very large, firm, smooth spleen which was described as filling the entire left side and extending to the right of the umbilicus. The liver was not felt. The remainder of the examination was non-contributory, but the laboratory findings were of considerable interest.

One of the points to be excluded was: Did she in her travels pick up some parasite that might have lodged in her spleen or liver or both? Stool examinations for blood, ova and parasites were entirely negative, as was a search for pathogenic bacteria. The serum bilirubin on the first admission, fourteen months before her demise, was 1.4 mg.%. In other words, she was beginning to show some hyperbilirubinemia and about half of this was indirect-reacting, half was direct-reacting pigment. The serum cholesterol was somewhat low, 132 mg.%. It is interesting that her serum protein showed 4.0 Gm.% of albumin and 2.2 Gm.% of gamma globulin at this time. The cephalin flocculation was negative; the serum alkaline phosphatase was rather low: 2.2 KA units. It should be noted, as one goes down the list of tests of various kinds, that the several serological tests performed were negative. We do not know whether these were negative because the diseases searched for were not present or because she had failed to develop antibodies to them.

There were some interesting hematological findings and I have asked Dr. Rosenthal to discuss those.

Dr. Martin Rosenthal†: The patient had a hemoglobin of 8.4 Gm.%, with 3.6 million red cells, which is essentially a normochromic anemia. She had no particular reticuloecytosis, and she had a leukopenia with slight lymphocytosis. In addition some atypical lymphocytes were noted. The platelet count was diminished. Putting the three elements in the blood together, this patient had pancytopenia and perhaps some granulocytopenia. A blood picture such as this is not uncommonly associated with a large spleen, and what clinically is called hypersplenism.

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Dr. Gutman: We have established thus far that this 69 year old woman had marked hypogammaglobulinemia. Presumably this accounted for the multiple pneumonic infections and repeated episodes of watery diarrhea. She had developed a very large spleen without palpable enlargement of the liver and she had hyperbilirubinemia, in part due to indirect-reacting and in part due to direct-reacting bilirubin. She had a blood picture of pancytopenia.

In the hospital on the fifth day, the patient developed bronchitis with some fever. She was given penicillin which quickly produced a rash. In patients who have true agammaglobulinemia, with very low antibody levels in the blood, allergic reactions are uncommon and are apt to be very mild. I would think that while the gamma globulins were reduced in this patient they were not reduced to that point.

She was sent home to return for splenectomy after the penicillin reaction abated. When she was readmitted, she received a blood transfusion. Note this because of the subsequent development of jaundice and the possible relationship between the jaundice and the blood transfusions she received on this and on later occasions.

On a third admission to this hospital, she was found to have many small, freely movable cervical and supraclavicular nodes, another indication that while this patient was deficient in gamma globulin formation, she was still probably able to produce some. Some gamma globulin formation is believed to occur in the lymph nodes, with lymphocytes and plasma cells participating. It has been observed many times, at least in the male youngsters with congenital agammaglobulinemia, that they do not develop enlargement of the lymph nodes even in the face of severe local infections. But this woman did, and I take it that this was another indication that she was not completely devoid of functioning reticuloendothelial tissue. A splenectomy was performed during which three units of blood were given.

We are not told anything more about the nature of the spleen or the findings in the spleen. Because of the absence of any therapeutic measures which I am sure would have been instituted if she had a lymphoma, leukemia or sarcoidosis, I suspect no very characteristic or specific changes in the spleen were discovered. Cultures of the spleen were taken and this was another indication that nothing very specific was found on inspection of the organ. I suppose tuberculosis and fungi were sought. Apparently these studies were entirely negative.

We turn to the hematological findings following splenectomy. Dr. Rosenthal might comment on this.

Dr. Rosenthal: Post-splenectomy, this woman developed a very high white blood count. At the same time her platelet count rose rather precipitously, which would be interpreted as indicative of an excellent response to the removal of the spleen. This is at least a confirmation of the diagnosis of hypersplenism, which one really makes before hand, but never with great assurance. In other words, hypersplenism is a working diagnosis that can only be confirmed following a good response after splenectomy.

However, at one point, one week post-splenectomy, practically all of the

patient's polymorphonuclear leukocytes disappeared from the peripheral blood, which is very unusual. Usually leukocytosis develops with a good increase in granulocytes. While this did occur initially, it was followed by an almost total disappearance of the granulocytes from the peripheral blood. At that time a bone marrow aspiration showed marked increase in granulocytes with some type of arrest of the granulocytes. It was suspected that the patient was undergoing some type of cyclic neutropenia.

Dr. Gutman: On the fourth admission, which was four months after her splenectomy, the picture changed completely. She had developed a respiratory infection. While in bed for this, she noted dark urine and she became overtly jaundiced four or five weeks prior to admission. Associated with this jaundice, she had normal brown stools, no nausea or vomiting, and her appetite remained good. In fact she was gaining weight. She was obviously icteric and the abdomen was distended, with shifting dullness. The liver was firm, smooth, non-tender, and extended to four fingerbreadths below the costal margin.

The hemoglobin now was 12.4 Gm. % the WBC was 17,500 per cu. mm., with 20% segmented cells, 16% bands, and 48% lymphocytes, a quite different picture from that seen after the splenectomy. The red cells showed targetting and Howell-Jolly bodies as evidence of increased or accelerated erythropoiesis. She had occasional giant platelets and many pleomorphic lymphocytes were seen.

It is interesting to note that the thymol turbidity at this time of fairly intense jaundice was less than one unit, which may be related to the hypogammaglobulinemia. The serum alkaline phosphatase was 14.6 KA units, not in the range of obstructive jaundice. Most important of all, from a diagnostic point of view, the serum glutamic oxaloacetic transaminase was very markedly elevated, 520 units, the upper limit of normal by our method being approximately 40 units. This is a sufficient indication of severe and widespread hepatic necrosis.

She had 3.7 Gm. % of serum albumin, 2.3 Gm. % of gamma globulin, with, again, a decrease rather than complete disappearance of the gamma globulin. Electrophoresis showed some gamma₁ and gamma₂ globulins. This indicates inadequate or imperfect biosynthesis of gamma globulins rather than their complete disappearance. She also was found to have isoagglutinins, which are usually absent when true agammaglobulinemia is present.

The patient was discharged somewhat improved, and sent home. Here she did not do well and three months later required her fifth and last admission. The jaundice continued. She was becoming weaker and noted progressive abdominal swelling, continuous pain and oliguria. The cephalin flocculation test, in spite of every other evidence of progressive hepatitis, was negative, again suggesting a failure to react and form antibodies.

Paracentesis yielded a liter of an opalescent fluid which had the specific gravity and other findings of an exudate, undoubtedly a reflection of her liver damage. Toward the end, her serum bilirubin rose and the white count dropped. She was given supportive treatment, but died two weeks after discharge, comatose most of the time.

On the basis of the history, physical findings and results of laboratory tests,

I think this is in many ways a classic case of acquired idiopathic hypogammaglobulinemia. She was a woman who was in her middle 60's, the most common age period and sex for this disease. She had had a long history of recurrent bronchial infections, with delayed healing and poor response to antibiotic therapy. She did not show any evident signs of bronchiectasis (a not infrequent sequel in children), although perhaps some indication of this was found at autopsy. She had other infections, notably pyelitis and perhaps some pyelonephritis. She had abdominal complaints and stools suggestive of sprue.

Most characteristic of all, she developed hepatitis. Good and others have commented on the high incidence of severe hepatitis in patients who have agammaglobulinemia sometimes, as in this case, leading to death. This is interesting because while it is generally conceded that resistance to bacterial infections decreases, immunity to viral infections remains. But this is not always true. The fact is that these patients are particularly susceptible to hepatitis virus and sometimes to coxsackie virus, to which they may succumb.

She was demonstrated to have decreased serum gamma globulins. There was some immunological response to antigenetic challenges, shown by the various tests. We do not know whether she showed any improvement with gamma globulin replacement.

*Dr. Morton Bryer**: She received large quantities of gamma globulin and her penicillin reaction actually followed quite a large amount of exogenous gamma globulin.

Dr. Gutman: Did you get any indication of response to the gamma globulin?

Dr. Bryer: It was not clear cut. We could not be absolutely certain about it, in the sense that there was a sudden change in the hospital, but I think that her respiratory infections benefitted much. She continued to receive gamma globulin at home prior to operation. She did have fewer infections in that period.

Dr. Siltzbach: I found two other cases of hypogammaglobulinemia with penicillin reaction. I think it is believed now that reactions to penicillin and other delayed types of hypersensitivity reactions have no relation to gamma globulin or to beta₂ globulin and that they concern one of the other globulins.

Dr. Gutman: In some cases, fixed tissue antibody formation is preserved. In others, as I read the literature, it is not preserved. In her case it looks as if this site of antibody response probably was preserved.

How are we to explain the pancytopenia and the other manifestations of splenomegaly with hypersplenism in this case? It is not too unusual, in the idiopathic form of this disease, without any recognizable underlying disease, to find that the patients develop marked splenomegaly with hepatomegaly, thrombocytopenia, marked anemia and even cyclic neutropenia.

What is the significance of the final episode of severe and eventually fatal jaundice? I think this again reflects her vulnerability to hepatitis virus which, as time relationships indicate, was transmitted in the course of one or more of her transfusions. Her response clinically suggests that she had severe hepatic

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necrosis. Since she survived four or five months, perhaps she had already developed some indications of postnecrotic cirrhosis. The whole picture, varied as it is, involving so many systems and eventually terminating in death due to hepatitis virus, can all be referred to the underlying disease, acquired hypogammaglobulinemia, which I am not sure should be designated primary.

Dr. Popper, I hope in addition to explaining to us your findings at autopsy, you will comment on the genesis of gamma globulin and the role that the liver may play in this important process.

*Dr. Hans Popper**: The spleen which was removed at the operation weighed 2,300 grams and had a fleshy appearance on the cut surface. On microscopic examination of this huge spleen, we saw a somewhat disappointing picture; an almost intact architecture with lymph follicles and small germinal centers and some hyaline deposits. In the white pulp we found an abundance of cells which were primarily reticulum cells. The reticulum cell hyperplasia especially involved the perifollicular areas and not the germinal centers. On closer examination of the framework, we saw a slight increase of the reticulum framework throughout, but no severe fibrosis. Rare segmented leukocytes were present but the predominant type of cell had the nucleus of a reticulum cell. With a Giemsa stain, reticulum cell hyperplasia and not endothelial cell hyperplasia, was apparent. Some megalocytes were seen. The sinusoidal cells were not plump and did not have the characteristic enlargement which otherwise is part of reticulo-endothelial hyperplasia, but we demonstrated invasion of the sinusoid by the reticulum cells.

Summarizing the findings in the spleen, we noted an excessive splenomegaly with preserved architecture and a most marked reticulum cell hyperplasia without the usual participation of the endothelial elements (1-3). After long search, only an occasional plasma cell could be demonstrated; a few were also found in the bone marrow. Therefore at the time of the operation and at the time of severe hypogammaglobulinemia, some traces of plasma cells, the gamma globulin forming elements, were present, but in distinctly reduced number. The lymph nodes taken out at the time of the surgery showed the same lymphoid and reticulum cell hyperplasia. However, these were not the usual littoral reticulum cell, but rather cells of a more lymphoid type (1-5).

At the time of autopsy, the bone marrow was distinctly red. On microscopic examination it was a moderately cellular marrow with the great variety of cells reflecting the findings of Dr. Rosenthal. We saw megalocytes and a great number of maturing red and white cells. In some areas accumulation of lymphoid and reticulum cells were again seen.

We turned our interest to the lung in view of the long history of respiratory infections. We were disappointed since there was neither bronchiectasis nor any other chronic lesion in either lung. Microscopically, a few acute bronchopneumonic foci were seen which may have been present before on repeated occasions, but no thickening of the stroma, as evidence of chronic fibrosing lesions

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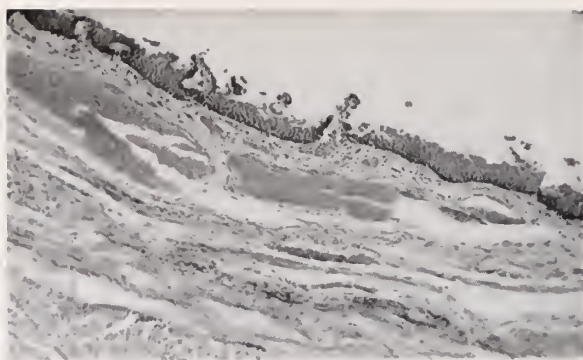


FIG. 1. Section of lower end of esophagus showing some superficial esophagitis and dilated submucosal veins, indicating portal hypertension. (H&E \times 63).

of the lungs, was found. Whatever the repeated chronic inflammatory respiratory attacks may have been, they were not reflected in anatomic changes. Remnants of old tuberculosis were present in the bronchial lymph nodes, not activated by the process under consideration.

The heart showed old rheumatic changes with thickening and merging of the papillary muscles. A recent subendocardial hemorrhage reflected the hypoprothrombinemia with which the woman died, presumably from the liver disease with severe jaundice.

The kidneys were of normal size and normal shape. A few nephrosclerotic vessels were found and were probably related to the transient elevation of the blood pressure. Bile pigment was deposited in the distal convoluted tubules as an indication of what we like to call biliary nephrosis in the presence of severe jaundice.

The esophagus showed a few enlarged vessels, evidence of varices which had not bled, and some esophagitis (Fig. 1). We thought these varices reflected portal hypertension which had already begun as a result, most probably, of the hepatic lesion.

There were small cystic adenomas in the pancreas which obstructed the duct and caused an acute focal pancreatitis. At the time of death, there was some fat necrosis, probably terminal. Despite the mechanical predisposition for an infectious process in the pancreas, nothing of this nature had led to a chronic pancreatitis.

Similarly, in the gallbladder small adenomas were found, but with no evidence of a chronic cholecystitis. The common bile duct was normal.

The liver weighed 1,100 grams. We heard that the liver was enlarged at the time of the first admission for jaundice. At death, the liver had become smaller. On the cut surface, the lobular architecture could barely be distinguished but it had not been replaced by any type of nodule which we recognized with the naked eye (Fig. 2). There was an irregular mottling which was probably due to necrosis. Cirrhosis was not grossly present. However, when we looked at the connective tissue stain, much connective tissue had accumulated throughout



FIG. 2. Cut surface of the 1100 gram liver with loss of normal architecture and irregular mottling probably due to necrosis.

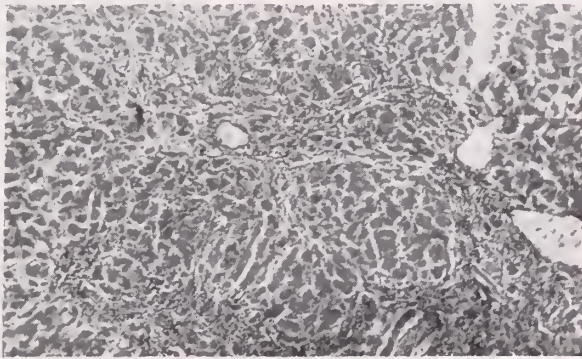


FIG. 3. Section of liver demonstrating that the lobular architecture is basically intact although connective tissue bands traverse some lobules and nodular regeneration is beginning. (H&E $\times 63$).

the entire liver. The centrolobular area had undergone collapse following necrosis. The connective tissue bands traversed some of the lobules and beginning regenerative nodule formation was seen. An outspoken cirrhosis was not present although it was in the process of developing (Fig. 3).

In analyzing the histologic changes, I believe almost everything that we would expect to find in the subacute type of viral hepatitis was present in this case. In the portal zone, proliferation of ductules was seen surrounded by mononuclear cell infiltration. There was also accumulation of reticulum cells. This ductular proliferation was associated with bile stasis in these areas. Quite often in viral hepatitis, some polymorphonuclear leukocytes are found. We assumed that they were a reaction to the biliary excretion of some irritating material which led to the proliferation of some of the ductular cells as well as to the inflammatory exudate (Fig. 4). Wherever ductules proliferated, connective tissue was deposited. This accounted for the fibrosis.

In the parenchyma we found areas of necrosis quite frequently surrounded by

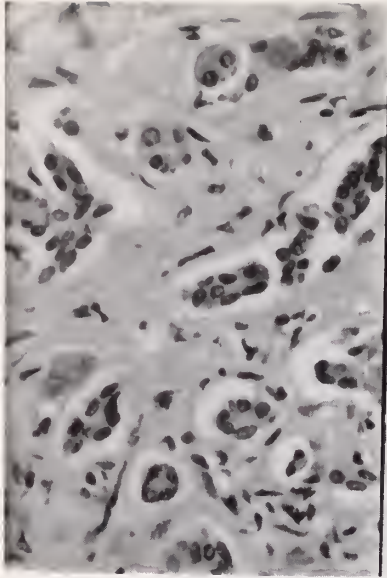


FIG. 4.

FIG. 4. Section of liver showing severe ductular proliferation, inflammatory cells within and around ductules. (H&E \times 400).

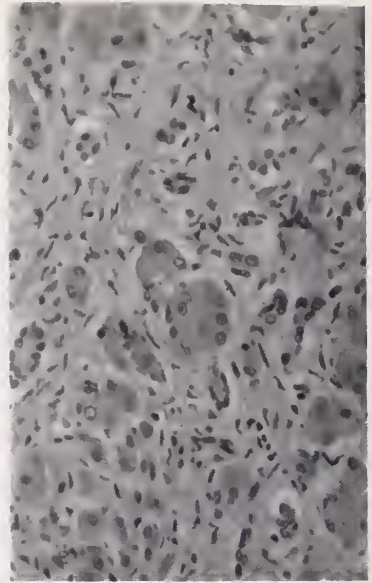


FIG. 5.

FIG. 5. Irregular regeneration of liver cells in a syncytial arrangement or in the form of giant cells. (H&E \times 240).

mononuclear cells with irregular regeneration and beginning giant cell formation (Fig. 5). We saw acidophilic bodies with pyknotic nuclei which have been incorrectly called Councilman bodies, and we also noted phlebitis of the central vein (Fig. 6). I hope we have accepted that this was viral hepatitis with massive liver cell breakdown in what may be a transition to postnecrotic cirrhosis (Fig. 7). It is an active process in which the virus seems to be destroying tissue. In the stroma, extensive areas of collapse marked the part of the parenchyma which was lost and we can understand that the patient died in hepatic failure with hardly any liver cells present.

We want to acquaint ourselves now with the reaction of the reticuloendothelial cells of the liver and its relation to the defect of gamma globulin production. We did not find one plasma cell or plasma cytoid cell in this liver, in keeping with the low gamma globulin (1, 3, 4, 6, 7). Despite the presence of postnecrotic cirrhosis in which typically the serum gamma globulin goes up to very high levels, we had no elevation in this case. The flocculation test results were normal, also in keeping with the absence of the pyroninophilic nucleic acids in the liver and in most of the other organs. The reticuloendothelial cells which we saw could perform phagocytosis because they occasionally contained fat. We saw fat in the lymph nodes as well as in the liver. Barka has shown in our laboratory that the same type of cell which usually contains pyroninophilic material also contains much polysaccharide material which give a strongly positive periodic

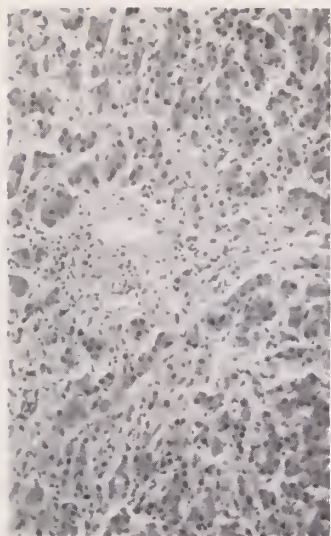


FIG. 6.

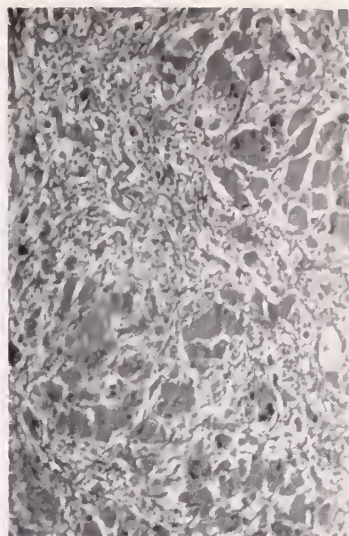


FIG. 7.

FIG. 6. Phlebitis of the central vein. (H&E $\times 120$).

FIG. 7. Nodules varying in size and shape suggesting transformation to postnecrotic cirrhosis. (Chromotrope aniline blue $\times 120$).

acid Schiff (PAS) reaction. Before this case came to our attention, we toyed with the idea that possibly these PAS positive polysaccharides may be the stimulus for the gamma globulin reflected in the presence of nucleic acids in the cytoplasm of the cells. We hoped with these methods that we possibly could stain, in the same cell, the stimulus for the gamma globulin formation (the liver cell breakdown products presumably polysaccharide) and the nucleoproteins which are related to gamma globulin formation. Independently, also in our laboratory, Cohen and Ohta have shown that in the same type of reticuloendothelial cells as in postnecrotic cirrhosis, gamma globulin can be demonstrated by fluorescent antibody methods (8) (Coons technique). Occasionally in the same type of reticuloendothelial cells, lipofuscin, which is also PAS positive and probably a liver cell breakdown product, can be demonstrated simultaneously with gamma globulin. Therefore, before this case came to our attention, we had the idea that possibly carbohydrate liver cell breakdown products might be the stimulus for the formation of gamma globulin in the mesenchymal elements of the liver, spleen and lymph nodes.

Then came this case. There was no PAS staining material whatsoever in the liver, no PAS staining material in the reticuloendothelial cells of the portal tract, despite the possibility of phagocytosis, and no pyroninophilia in these cells.

In the enlarged lymph nodes at the time of death, we saw reticulum cell hyperplasia. Another type of reticulum cell was present, namely, the littoral cells which were very much in the background before and at the time of splenectomy. The lymph nodes as well as the spleen were now rather active. This was associ-

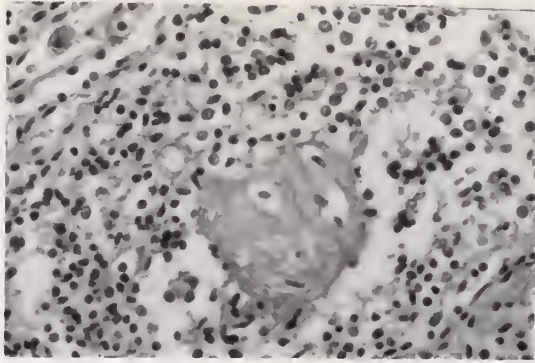


FIG. 8. Section of lymph node at porta hepatis showing PAS positive staining on a hyalinized material (globulinosis). (PAS stain $\times 240$).

ated with marked phagocytosis of fat. At this time we could see some PAS positive material (Fig. 8) indicating that formation of PAS staining material was not completely absent. It was not seen in the liver. In the lymph nodes there was some phagocytosis, but less than normally seen. In addition some plasma cells were found occasionally, quite a few staining PAS positive.

Let me summarize what we tried to present to you. We have to assume that under normal circumstances several stimuli exist for gamma globulin formation. One stimulus probably comes from infection. In addition, probably normally in the liver, cell breakdown processes of various types occur which account for the stimulation of the gamma globulin formation. The breakdown products are probably mucopolysaccharides or perhaps lipofuscin. Both may be directed to the reticuloendothelial cells. Lymphocyte and plasma cell development is associated with gamma globulin and antibody formation. In hypogammaglobulinemia, the defect lies somewhere in this area (4, 5) because neither infection nor cell breakdown products led to polysaccharide or lipofuscin in the liver or in reticuloendothelial cells. I have subsequently had the opportunity to study one case of congenital hypogammaglobulinemia. A large amount of cell breakdown material stained with PAS could be seen.

In the case under our consideration, the defect must be that either cell breakdown products are not formed, or if they are, they are probably not of the nature of neutral mucopolysaccharides. The breakdown probably goes into other channels.

In this instance, then, we have to assume that we have a temporary deficiency. Phagocytosis remains intact but cell breakdown products may have been absent, and acquired hypogammaglobulinemia developed. Other antibody formation is not necessarily impaired; the penicillin reaction may not require gamma globulin, although isoagglutinins are also present (1, 4, 7). If gamma globulin stimulation from cell breakdown is absent, even in the presence of a certain type of carbohydrate and in the presence of a severe viral hepatitis, why is this associated with reticulum cell hyperplasia?

I cannot answer this. This may be only the result of chronic infection, although

I doubt it because no infection produces a 2,300 gram spleen, (3, 7, 10) I suggest that altered cell breakdown is responsible for the abnormal lack of protein formation (9). We may also speculate that these reticulum cells normally mature into cells that require such breakdown products to produce gamma globulin.

In closing, we have presented a case which shows, as a clinical manifestation, the unusual combination of acquired hypogammaglobulinemia with death in hepatic failure. Such cases have been reported but it is indeed an unusual clinical picture. We added to it the findings of absence of carbohydrate cell breakdown products usually found in large amounts in the presence of a severe liver cell destruction. We can speculate that this may possibly be the cause of the metabolic alteration.

Final Diagnosis: SUBACUTE VIRAL HEPATITIS WITH TRANSITION INTO POST-NECROTIC CIRRHOSIS, ACQUIRED HYPOGAMMAGLOBULINEMIA, ACUTE BRONCHIO-PNEUMONIA (TERMINAL), AND FOCAL ACUTE PANCREATITIS.

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Abstracts

Papers Presented before the Research Club of The Mount Sinai Hospital

Effect of Cardiac Irradiation upon Myocardial Vascularity. Elliot Senderoff, M.D., David Kayee, M.D., Mamoru Kaneko, M.D., and Ivan D. Baronofsky, M.D. Presented February 25, 1959.

The use of cardiac irradiation as a therapeutic measure of increasing myocardial vascularity was investigated in a series of 80 dogs. These dogs were divided into a radiated and a control group. The former were subdivided into two groups receiving to the heart, a total radiation dose of 1300 and 2000 Roentgens respectively. Two hundred kilovolt radiation was used. Electrocardiographic and microscopic analysis in the pre and post radiation period revealed no evidence of harmful cardiac changes.

In an attempt to evaluate the degree of protection that radiation may afford, all dogs were subjected to acute myocardial insult by ligation of the anterior descending coronary artery at its origin. The 24 hour mortality figures reveal a significant difference between the control and the irradiated groups. Three of 30 control dogs (10.3%), eight of 25, 1300 Roentgen dogs (32%), and 12 of 25, 2000 Roentgen dogs (48%) survived ligation without fibrillation and were alive 24 hours later.

Physiological, pathological, and electrocardiographic studies were performed on surviving dogs at intervals up to six months post ligation. Peripheral coronary pressure and flow determinations measured distal to the coronary ligature revealed good retrograde flow and peripheral pressure among the radiated dogs surviving ligation. The greatest flows were observed at six months post ligation. Barium injection studies and post mortem coronary arteriograms revealed the blood to flow in a retrograde fashion from intercoronary anastomoses between the ligated anterior descending coronary artery and the unoccluded branches of the remaining arterial tree. In the radiated dogs the anastomoses are numerous and well developed. Comparison of equivalent radiated and control dogs revealed the radiated hearts to appear more vascular. Pathological studies, gross and microscopic, revealed the presence of infarcted muscle involving the entire thickness of the ventricular wall in the control dogs. The radiated dogs, of equivalent survival periods, did not exhibit this through and through infarction but did exhibit a spared area of varying degree of normal heart muscle in the sub epicardium region throughout the extent of the infarction. [More detailed reports will be available in *Surgical Forum, Proc. Soc. Exper. Biol. & Med.* 100, 1959; *Amer. J. Roentgenol.*]

Prolonged Extracorporeal Circulation Without Oxygenation in the Closed-Chest Dog. Leslie A. Kuhn, M.D., Frank Gruber, M.D., Albert Frankel, M.D. and Sherman Kupfer, M.D. Presented March, 1959.

To determine the maximum degree of circulatory support which could be maintained by a pump-oxygenator with peripheral cannulation and the chest closed, five animals with cardiac outputs reduced to zero by externally induced ventricular fibrillation were studied. Mechanically provided flow averaged 60 cc/kg/min, producing an average mean arterial pressure of 94 mm Hg and a coronary circulation sufficient to permit external defibrillation after three hours of ventricular fibrillation.

To rapidly increase coronary pressure by mechanical circulatory support with the chest closed, a method was devised to raise proximal aortic pressure, requiring a small priming volume and without the need for oxygenation. Vascular resistance was artificially increased by a balloon catheter, inserted via femoral artery, to the lowest level of the abdominal aorta at which inflation produced a proximal aortic pressure rise. (Usually at L2-3; sometimes distal, at other times immediately proximal to the renal arteries.) The distal aorta was supplied with blood drawn by gravity from the superior vena cava and pumped into the abdominal aorta below the site of obstruction. In 17 experiments, for periods up to 4½ hours, proximal aortic mean pressure averaged 156 mm Hg (control-117); distal aortic pres-

sure averaging 86 mm Hg with an average flow into the distal aorta of 44 cc/kg/min. With obstruction proximal to the renal arteries, renal function was present, though diminished, with return towards normal at the end of the procedure. The rise in proximal aortic pressure was associated with a diminution in the left ventricular work of 18 to 35 per cent, attributable to a lowered cardiac output accompanying shunting of a portion of the venous return into the distal aorta. Plasma hemoglobin averaged 160 mg per cent after four hours.

With this method, six closed chest animals with coronary embolization with plastic spheres demonstrated a marked proximal aortic pressure rise. (Average mean control pressure, 113 mm Hg; after embolization, 73 mm Hg; with aortic obstruction, proximal aorta=151 mm Hg and distal=61 mm Hg). [More detailed reports will be available in *Circulation Research*, and *Surgical Forum*.]

Brain Stem Action Potentials Correlated with Eye Movements. Howard P. Krieger. Presented June 11, 1959.

Brain stem oculomotor functions have been analyzed mainly by the methods of stimulation, destruction and clinico-pathologic correlation. This is a report on the correlation between eye movements and evoked potentials recorded within the brain stem of alert, cervically transected cats. Only points from which eye movements could be elicited by electric stimulation were studied. Single electrical stimuli evoked single potentials unaccompanied by eye movements. Repetitive stimuli of a frequency greater than c. 120/sec. elicited eye movements. The concomitantly evoked potentials had a frequency and duration equal to the stimulus. In contrast, during nystagmus, rhythmic potentials which outlasted the stimulus were recorded. Nystagmus was elicited by caloric and electric stimulation of the vestibular end organ and by brain stem or cerebellar destruction. Evidence of self-sustained electric activity was not otherwise noted.

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