The William Sydney Thayer and Susan Read Thayer lectures in clinical medicine : Lecture 1, The hereditary factor in some diseases of the haemopoietic system. Lecture 2, Some diseases in the Jewish race / by Sir Humphry Rolleston Bart., K.C.B., M.D., Regius Professor of Physic in the University of Cambridge.

With the Lecturer's Compliments

THE WILLIAM SYDNEY THAYER AND SUSAN READ THAYER LECTURES IN CLINICAL MEDICINE

BY

SIR HUMPHRY ROLLESTON BART., K.C.B., M.D.,

Regius Professor of Physic in the University of Cambridge

Reprinted from Bulletin of the Johns Hopkins Hospital
Baltimore, 1928, Vol. XLIII, pp. 61–80; 117–139.

Made in United States of America

Reprinted from BULLETIN OF THE JOHNS HOPKINS HOSPITAL
Vol. XLIII, No. 2, pp. 61–80, August, 1928

THE HEREDITARY FACTOR IN SOME DISEASES OF THE HAEMOPOIETIC SYSTEM

LECTURE I OF THE WILLIAM SYDNEY THAYER AND SUSAN READ THAYER LECTURES IN CLINICAL MEDICINE (1928)[1]

SIR HUMPHRY ROLLESTON, Bart., K.C.B., M.D.
Regius Professor of Physic in the University of Cambridge

INTRODUCTION

It is indeed a great and happy honour to be asked to give these lectures named after the friend of many years—more, perhaps, than he and I may wish to count—the one in the United States I have been privileged to know longest. This Foundation is affectionately dedicated to William Sydney Thayer and Susan Read Thayer his wife, that gracious spirit, inseparable from him in the minds of their friends as a true counterpart to him who is left alone with the memory of "the light that was." Richly endowed with the charm and social gifts characteristic of the South, she freely gave her life first to the service of the suffering in the Johns Hopkins Hospital, then to humanitarian work in other directions and to seconding her husband in encouraging and guiding his pupils in the footsteps of the great clinicians. In the last stage of a long and trying illness the light of her nobility and unselfishness shone more brightly than even before.

With the changing fashions of thought, inevitable to the passing years, there has been some tendency to magnify the cleanly cut decisions of the laboratory at the expense of bedside experience, and to imagine that a clinical physician can be evolved with little trouble or time from the well drilled scientific student. It has been said that, like the poet, the clinical physician is born, not made, and no doubt

[1] The William Sydney Thayer and Susan Read Thayer Lectureship was established through the generosity of friends of Dr. and Mrs. Thayer. This is the first series of lectures to be given under this foundation. For an account of the presentation of the Thayer Lectureship to the University, see *Bulletin of the Johns Hopkins Hospital*, 1927, xli, no. 1,—ED.

there is an element of truth in this, for some are certainly inherently unfit from the absence of the essential qualification of character and temperament. But this is not all; the fine and finished product results only from wide knowledge, including not only that of the laboratory but that of human nature, and long experience of the manifold aspects of disease. While a pathological training is essential, a man cannot at once blossom out into a clinical physician by the simple process of transferring his laboratory mind and methods from the pathological block to the wards. "There are few short-cuts in medicine; all the acquisitions of recent years have not shortened by a day the time that he who would be a skilled clinician must pass by the bedside."[2] An apprenticeship—longer than that of Jacob—must be served before what Robert Louis Stevenson called "the flower of our civilisation," the physician, can be brought to perfection. This ideal is admirably exemplified by Thayer's work, career, and influence, and should he ever be depicted, as many of the London physicians were in past times by "Spy," in Vanity Fair, the only appropriate legend below the cartoon would be "Clinical Medicine." It was a happy event in the medical history of the United States when at Washington, D. C., on 18 May, 1927, his friends and admirers presented this lectureship to the Johns Hopkins University, which he has served so long, so faithfully, and with such distinction. Of the numerous eponymous lectureships few, like this, have been founded during a man's active life, before "the sere, the yellow leaf," retirement, or complete rest from his labours have made a permanent memorial appropriate by the absence of the inspiring personality. There are exceptions to Thayer's own lines—

> 'Tis only those who're gone beyond recall
> That leave enduring shadows on life's wall.

In 1897 the Neurological Society of London established the Hughlings Jackson Lectureship to commemorate "the Founder of the New Neurology," as Sir Thomas Barlow happily expressed his preeminence; their first President (1885) Hughlings Jackson was appointed the first lecturer, and so escaped the embarrassing experience

[2] Thayer, W. S.: *Bull. Johns Hopkins Hosp.*, Baltimore, 1927, xli, 10.

of listening, as would otherwise have been inevitable, to a lecture containing the expression of warm affection and intense admiration felt by his pupils and colleagues. Perhaps the same wise course was planned in this instance, but frustrated by William Sydney Thayer's true modesty which has very definitely dictated that in these two lectures there should not be any attempt at appreciation of his work, as I have known it since 1891, when we first met through a mutual friend A. A. Kanthack (1863–98), whose career of the highest promise was, to the great loss of British pathology, cut short after little more than a year's tenure of the Chair of Pathology at Cambridge. Much has changed since those far off days, but as the years have added up, my regard has only grown into increasing affection for Thayer. We in Old England regard him as another Osler whose tradition of unity, peace, and concord means so much to us, and even more to you as better able to judge of these two Masters of Medicine who have captured not only the minds but the hearts of their colleagues and pupils.

THE HEREDITARY FACTOR IN SOME DISEASES OF THE HAEMOPOIETIC SYSTEM

The new knowledge of heredity, which like statistics has now become too complicated for the plain medical man in the street, and the revival of interest in the constitutional factor in disease, which suffered an eclipse as the result of the rise of bacteriology, have coincided with an elaboration of the various forms of disorders of the haemopoietic system. New diseases of the blood-forming organs are constantly described based on histology, and in some instances on microchemical methods—data which provide information on the essentials of the hereditary and constitutional factors of disease. It may therefore not be out of place briefly to review our knowledge of the hereditary character of some morbid conditions of the haemopoietic system, an expression at once more accurate and inclusive than the old term "diseases of the blood." Such a consideration is of course attended by the underlying problem of heredity versus environment, for the less accentuated cases of hereditary influences may remain latent from lack of an exciting factor. Indeed, an extremely

interesting observation is the existence of latent manifestations in the blood and blood-forming organs, such as fragility, sickling of the red cells, and the persistence of haemoblastic foci in the liver in pernicious anaemia. These may not give rise to haemolytic anaemia until some additional factor, such as infection or toxaemia, intervenes. The practical distinction between hereditary and familial diseases may in some instances at least depend mainly on the age incidence and early mortality, for example, in grave familial jaundice of the newly born in which out of 130 collected cases 100, or 77 per cent, proved fatal. No doubt variations occur in the degree of the constitutional tendency, so that in some instances little in the way of an external environmental factor is needed to bring out the disease, whereas in others considerable intensity of the exciting factor is necessary.

Haemophilia

Haemophilia, first described by John C. Otto of Philadelphia in 1803, is the prototype and most characteristic of hereditary diseases, and is so well established that there is not any need for discussion. It is sex-limited and transmitted by females who do not suffer from the disease and are remarkably prolific. The transmission according to Nasse's law, or what Herringham called "Mother's son inheritance," without, as Bulloch and Fildes showed from analysis of 900 papers, any authentic female case, is very remarkable; for, as Nettleship pointed out in colour blindness and Leber's hereditary optic atrophy which are in like manner transmitted by unaffected females to males, females are occasionally attacked. It would be interesting to know if adrenal virilism in a female of a bleeder stock would prove an exception to Nasse's law. Haemophilia is imitated by hereditary pseudo-haemophilia and hereditary thrombopenia, in both of which females may be affected as well as males, and it has been suggested that purpura haemorrhagica is the female form of haemophilia (Hess[3]); the recognition of these and some other rare and somewhat obscure haemorrhagic conditions explains the difficulty in diagnosis when faced with what seems to be a female haemophiliac. As Giffin[4]

[3] Hess, A. F.: *Arch. Int. Med.*, Chicago, 1916, xvii, 203.
[4] Giffin, H. Z.: *Am. Journ. Med. Sc.*, Phila., 1928, clxxv, 44.

points out in recording a haemorrhagic disease, without the characteristics of haemophilia or purpura haemorrhagica, attacking women in four generations, there is much to be discovered about haemorrhagic diseases of this nature.

Chlorosis

Chlorosis is specially interesting as a disease, probably with an inborn tendency, in which the extrinsic or exciting factor has become rare. It has indeed been suggested that the universal decline in the incidence of this once familiar disease is more apparent than real, and due to the more frequent detection of cases of secondary anaemia, which before the era of focal infection and of blood counts as an almost routine practice were included under the caption of chlorosis (Aubertin and Mouquin); but at the best this would appear to be a very partial explanation, and perhaps naturally does not appeal to those who, only too familiar with the disease in the 'nineties of the last century, now look in vain for a case. Cabot twenty years ago excluded this explanation on the ground that there was then an actual diminution in the number of cases diagnosed as secondary anaemia without demonstrable cause. The striking diminution amounting almost to disappearance of chlorosis since the end of the last century in Europe and America has been ascribed to several factors, for example, to improved hygienic conditions, such as better ventilation, more open-air and exercise, to a diet containing more iron, to diminished alcoholism on the part of the parents (Schauman), the effect appearing some twenty years later, and with probably more justification to the passing of the once popular corset and tight lacing (Rosenbach; Weber), and thus to be a disease due to fashion.

The clinical impression that chlorosis is hereditary and familial was expressed by Potain and Clifford Allbutt, but statistics on this point do not appear to be available. Lloyd Jones' observations showed that the specific gravity of the blood in chlorotic females is low, and that this character is shared to a certain extent by their male relatives; he found that chlorotic families are remarkable for their fertility, and suggests that the condition of chlorotic blood, characterized by corpuscular defect, plasma of a normal specific gravity and excessive in quantity, is favourable to fertility, and indeed may be regarded

as an index of fertility of the mother and possibly of the facultative fertility of her offspring.

Erythraemia

Erythraemia, which has been shown by Christian to be accompanied by clinical manifestations curiously like those of pernicious anaemia and to resemble those of cerebral anoxaemia, usually occurs in persons between thirty-five and fifty years of age, and might therefore be thought to be more probably due to environmental influences than to constitutional factors. Weber (1921), after referring to cases recorded in early life, raised the possibility of a congenital incidence and the hypothesis that they may represent an extreme degree of a congenital plethoric tendency in some persons, but expressed his scepticism of their existence. Lately, however, its familial and constitutional incidence has attracted attention from Curschmann, Signorelli, and Trevor Owen; Engelking recorded the condition in three generations, grandmother, mother, and five children, and from the occurrence of infantilism in all the five children argued in favour of a defect in the germ plasm. Weber (1927) quotes familial and hereditary cases (Bernstein, Nichamin, Tancré, and Moewis), and now considers that in all kinds of primary and secondary polycythaemia a constitutional tendency—hereditary or familial—may play an important part; for example, in the presence of hyperpiesia or granular kidney this constitutional factor may convert the clinical picture into that of Geisböck's polycythaemia hypertonica.

Harrop and Heath, in a paper to which Professor W. T. Longcope has kindly drawn my attention, point out that lowered functional capacity of the lungs for gas diffusion may be an inherited character and occur in members of a family including an erythraemic patient, as is supported by the detection of apparently healthy relatives with a high red blood count and splenomegaly. From investigation of 7 cases they obtained evidence that there was diminution of the diffusion constant, and that disturbance of gas diffusion led to the compensatory erythraemia. This interference with pulmonary gas diffusion may be due to some structural abnormality in the pulmonary epithelium. The condition of erythraemia may remain latent for years and only become embarrassing with the advent of pulmonary em-

physema, fibrosis, high blood pressure and cerebral arteriosclerosis. An acquired condition, unique of its kind, of microscopic infiltration of the walls of the pulmonary alveoli by myosarcomatous metastases causing erythraemia (Barnes, Thompson, and Lamb) is analogous, though not homologous, to the constitutional defect in the pulmonary epithelium postulated by Harrop and Heath.

Sickle-celled blood

In 1904 Dresbach described an elliptical condition in 90 per cent of the red cells in a healthy mulatto; in 1910 J. B. Herrick gave an account of peculiar elongated red cells in a jaundiced negro with severe anaemia, leucocytosis and an ulcer of the leg. Cases by Washburn, Bishop who found two in a family, Mason, and others, were recorded as curiosities. In 1923 Huck showed that it was not rare as a latent condition, and from study of 11 persons in one family concluded that it conforms to the Mendelian law for the inheritance of a single factor and is dominant over the normal condition. In 1924 Sydenstricker observed 80 cases in 10 families, 71 being latent sicklaemia. Archibald recorded a case in an Arab boy in the Sudan. Cooley and Lee examined 400 negro children attending hospital, though not for anaemia, and found 30, or 7.5 per cent, with sickle-cells; they employed the word "sacklaemia" as a synonym for sicklaemia. Hahn and Gillespie suggested the words drepanocyte, from δρεπάνη = a sickle, for the sickle-cell, drepanocytaemia for the latent cases without symptoms, and drepanocytic anaemia for the active cases with anaemia, haemolytic jaundice and often ulceration of the legs and splenic enlargement; from investigation they found that the formation of sickle-cells is induced by anoxaemia, and that the spleen plays a secondary part, namely in excessive haemolysis of the sickle-cells, and is damaged in the process, passing through the stages of enlargement to subsequent atrophy. This may explain the percentage of 15 as the incidence of splenomegaly in the reported cases of sickle-celled anaemia (Hahn, 1928). In Hahn and Gillespie's case, which was at first regarded as chronic haemolytic jaundice although the resistance of the red cells to haemolysis by hypotonic salt solutions was recognised as inconsistent with this diagnosis, splenectomy was followed by great improvement in the blood count, but the condition

of sickling persisted; persistence of sickling was subsequently reported after splenectomy in two coloured children aged 1½ and 2½ years by Bell, Kotte, and Mitchell and another by Hahn (1928). These observations suggest that the spleen is not responsible for the sickle-cell trait; this is analogous to the persistence of fragility after splenectomy in chronic haemolytic jaundice.

The sickle-cell trait, which has been the subject of many papers in America, has been regarded as confined to negroes and as a hereditary anomaly of the red cells. It has, however, been recorded in a white Cuban boy without any direct negro ancestors (Stewart), in an Italian boy (Castana), and in 6 white adults by Lawrence. Possibly these exceptional cases belong to the at present small group isolated by Huck and Bigalow who collected 5 cases, including those previously reported by Dresbach and Bishop, in whites as well as blacks, of elliptical red cells in otherwise normal individuals. This condition is regarded by Huck and Bigalow as in no way related to the sickle-cell trait, for the abnormal cells are found in fresh blood and no change is induced by standing, as occurs in the sickle-celled form. The suggestion is thus made of an abnormal poikilocytosis which is distinct from sicklaemia. On the other hand Lawrence's observations tend to throw doubt on a sharp racial limitation of sickle-celled anaemia and on an absolute distinction between sickle or elliptical cells in whites and sickle-celled anaemia in negroes; in a white woman under his care with moderate anaemia and numerous sickle-cells he suggests that the condition may "represent a mild form of sickle-celled anaemia or some intermediary condition." Further, his results showed that in normal individuals of white and negro race there is very little difference in the incidence of the deformed cells, which were found in 2 per cent of negroes and in a slightly higher percentage of the whites examined.

It is interesting to compare sickle-celled anaemia with another hereditary blood anomaly, also regarded as possessing dominant Mendelian characteristics, namely, chronic haemolytic jaundice: both may be latent, though the increased fragility in chronic haemolytic jaundice has very rarely been reported in otherwise normal persons; nucleated reds in small numbers occur in chronic haemolytic jaundice and sickle-cells may be nucleated. The resistance of the reds to

hypotonic salt solutions, which is characteristically diminished in chronic haemolytic jaundice, is normal or even increased in sickle-celled blood.

Hahn and Gillespie figure a wet smear culture of blood, 48 hours after preparation, of sickle-celled anaemia showing "apparent colonization of the corpuscles around granular areas," a condition not previously reported. The figure suggests auto-agglutination, and my colleague Professor H. R. Dean tells me that though auto-agglutination is not constant in pernicious anaemia its presence is to his mind diagnostic.

Pernicious anaemia

Hereditary and constitutional influences have recently been raised as underlying factors which enable infection to excite the syndrome of pernicious (Addisonian) anaemia. The difficulties of getting a reliable history from hospital patients may in some degree account for the paucity in the past of reference to the heredo-familial factor; Cabot's analysis of 1200 collected cases in 1908 provided 2 examples only of its familial incidence, and Hurst (1927) never succeeded in obtaining a history of its family occurrence in hospital patients, though he and others have observed and collected many examples among private patients. The familial tendency appears to be more frequent than the hereditary; Mustelin's, Hurst's (1924), and Todd's records of the disease in three generations are rather exceptional; but there are many in two generations; B. Bramwell described 7 and Bartlett 8 cases in two generations; and in 1918 Ossian Schauman collected 24 families with a history of hereditary pernicious anaemia, either idiopathic or associated with tapeworm. Among 143 cases of pernicious anaemia in hospital and private practice, analysed by Levine and Ladd, there were 9, or 6.3 per cent, in which the disease occurred in relatives—parents, brothers, sisters, or children. It has been regarded as a dominant factor from a Mendelian point of view (Mustelin).

In contrast to sickle-celled anaemia, there is not any evidence of inherent defect in the red blood corpuscles preceding the onset of, or responsible for, the pernicious anaemia. But as achlorhydria is generally accepted as the early change in pernicious anaemia, Baumgartner and Hubbard's observations on the blood picture in achlor-

hydria may be quoted: among 153 persons on whom fractional gastric analyses were done, 40 were found to have pernicious anaemia, but among the remaining 113 there were only 16 with definite anaemia, 3 having less than 3,500,000 red cells. The increased resistance of the red cells in pernicious anaemia to hypotonic salt solutions contrasts with their fragility in chronic haemolytic jaundice. The achlorhydria, almost constant in pernicious anaemia (according to Hurst in 98.3 per cent), is thought to favour the incidence of anaemia by allowing the bacterial flora of the gastro-intestinal tract to grow in unrestrained profusion. Martius, in 1897, regarded achlorhydria as a true benign constitutional condition, and more recently it has been found in otherwise normal relatives of patients with pernicious anaemia; Hurst considers pernicious anaemia, sore tongue and subacute combined degeneration of the spinal cord as constitutional conditions, inasmuch as they depend on constitutional achlorhydria. Among healthy persons achlorhydria occurs in 4 per cent and among these pernicious anaemia will supervene in 16 per cent, and subacute combined degeneration of the cord in others. The question must then arise as to the degree of the immediate exciting cause—infection—that determines the anaemia, Hunterian glossitis or the spinal cord lesion. Hurst and Bell argue that together with a haemolysin a neurotoxin is produced in the alimentary canal by bacterial activity, and that according to the relative amounts of these two toxins anaemia or nervous manifestations are predominant. This explanation of the cord changes, which Woltmann found in 80.6 per cent of 150 cases of pernicious anaemia, is attractive, but has not escaped opposition; Piney argues from the absence of cicatricial (gliotic) tissue and reaction around the degenerations that they are not toxic but due to abiotrophy—a premature wearing out due to inherent defect in formation.

Knud Faber, while firmly convinced that pernicious anemia is due to an intestinal toxin, vigorously criticizes the view that achlorhydria is due to any constitutional or inborn defect, and brings forward much evidence to shew that achlorhydria is the result of gastritis; he admits that achlorhydria is the most frequent, but not the only, antecedent of pernicious anaemia, and in support of his contention refers to his report of 5 definite cases without achlorhydria. As

gastritis or gastro-enteritis, due either to direct damage or to toxins brought by the blood-stream, may produce temporary or long-continued achlorhydria in young children, the argument that its occurrence in early life is in favour of a constitutional origin is invalidated. It might be suggested that an inherent want of resistance to microbic invasion may play a part in the occurrence of pernicious anaemia, and that if achlorhydria, from whatever cause, occurs in such an individual, pernicious anaemia is more likely to ensue.

A different hypothesis bearing on the familial incidence of pernicious anaemia has been propounded by Piney; he finds constantly in the blood channels of the livers of these patients nests of pure megaloblastic tissue which can only produce megaloblasts, and argues that as the result of their abnormal persistence the red bone marrow fails in its function of producing normoblasts; thus he concludes that pernicious anaemia occurs only in those persons with this congenital malformation of a persistence of megaloblastic tissue in the liver. Oral or other sepsis, syphilis, and tapeworms in the intestine will in such disposed persons produce pernicious anaemia, but in persons with normal livers sepsis will lead to secondary anaemia only. In support of this argument it is significant that only a small proportion of persons with sepsis or tapeworm develop pernicious anaemia; in Scandinavia a large proportion of the inhabitants have tapeworm, in Finland one-third, and only a small proportion of these carriers, it is said 1 in 1,000 in Sweden, suffer from pernicious anaemia. Piney also rather tentatively suggests that the achlorhydria and subacute combined degeneration of the spinal cord seen in pernicious anaemia may be correlated phenomena, the cord changes being of the nature of an abiotrophy. The remarkable benefit that has followed the administration of liver substance (Minot and Murphy) or of a non-protein ether-insoluble, alcohol-precipitable, water-soluble fraction of beef protein (Minot, Murphy, Cohn, Stetson, and Lawson) to patients with pernicious anaemia and sprue and its apparently usual failure in secondary anaemia has been explained on the hypothesis that it stimulates the maturation of the megaloblasts which are present in large numbers in the bone marrow in pernicious anaemia, but not in secondary anaemia. Minot and Murphy also consider that the anaemia is primarily due to a defect in the formation of the red blood

cells and not to haemolysis. The difficult question arises if and to what extent this therapeutic effect of liver bears on the etiology of pernicious anaemia; does it lend support to Piney's view that one of the six conditions which he describes as coming under the syndrome of pernicious anaemia is due to a malformation of the liver; or is it compatible with the hypothesis that pernicious anaemia is of the nature of a deficiency disease, as might be suggested by the statement that the value of the treatment by liver substance depends on its content of vitamin E and iron (Simonds, Becker, and McCollom)? These are questions for future decision.

In connection with the question of a constitutional factor in pernicious anaemia, which may enable intestinal infection or tapeworm to precipitate the syndrome, the relation of sprue to pernicious anaemia is of considerable interest. These two conditions have recently been regarded as very closely allied (B. Bramwell); Wood (1925) suggests that "they may be types of a single condition," and accepts Ashford's view that sprue is due to infection by *Monilia psilosis*, this fungus having been isolated in all his recent cases of pernicious anaemia. It may be remembered that liver substance is an old remedy in Ceylon for sprue (Chalmers and Castellani). On the other hand, Baumgartner and Smith, who found achylia in 5 only and *Monilia* in 14 out of 15 cases of sprue, and out of 17 cases of pernicious anaemia 4 only with *Monilia*, dispute the identity of the two conditions, and the etiological bearing of yeast-like fungi on both sprue and pernicious anaemia has recently been denied by Nye, Zerfas and Cornwell. Christian, writing on "The Achlorhydria Family Tree of Disease," discusses their relationships and recognizes pernicious anaemia as a sequel of sprue, but points out that in sprue achlorhydria supervenes after the intestinal symptoms have been present for some time, whereas it precedes the blood changes of pernicious anaemia. It would therefore appear that sprue produces achlorhydria and thus paves the way for the development of pernicious anaemia. Thus achlorhydria, whether inherent and constitutional or acquired, would appear to be the antecedent to the blood picture of pernicious anaemia. But as only a certain proportion of the subjects of achlorhydria suffer from pernicious anaemia another factor is necessary; this may be the degree of intestinal toxaemia rendered possible, or there may be some in-

herent susceptibility to these toxins or, as Draper and Barach suggest, a change in the permeability of the intestinal wall or a peculiar genetic fault in the bone marrow.

Addison described the physique of patients with pernicious anaemia as chiefly of a somewhat large and bulky frame and with a strongly marked tendency to the formation of fat; G. Draper from anthropometric measurements finds that the chest is short, deep and has a very wide costal margin, the profile characterized by a very wide jaw angle, a massive lower jaw in proportion to the other facial measurements, wide face with very great interpupillary space (Draper, Dunn, and Seegal), and that males have the longest upper extremities of any disease pattern. Writing with Barach, he has come to the conclusion that there is a psychical as well as a physical pattern in the pernicious anaemia race which represents an approach to the neuter or species type characterized by an arrest of differentiation in the psyche and the stroma; this hypothesis will no doubt be stated more fully after further investigation. Levine and Ladd's figures show that the disease is rare in Jews and in Russians, and less often seen in the dark-haired than in the light-haired.

Chronic haemolytic jaundice

Chronic haemolytic jaundice may be (1) acquired or (2) hereditary, congenital, and familial. With regard to the acquired form which presents resemblances to pernicious anaemia the question arises whether or not it depends solely on infection or whether there is not an underlying, though perhaps slight, constitutional liability, without which the infection would not produce this effect. The hereditary form must start from an accentuation of latent tendencies in the parents, and the first case may appear to be acquired, so that subsequently the condition shews the phenomenon of anticipation and becomes familial and congenital. It would thus seem reasonable to regard the two forms usually described as the acquired and the hereditary as both dependent on a constitutional factor, though this is of different degree of intensity.

Hereditary, congenital, and familial haemolytic jaundice

In 1887 Spencer Wells removed from a woman aged 24 years the spleen which before operation was thought to be a uterine or ovarian tumour; like his operation on what was diagnosed as an ovarian cyst but turned out to be tuberculous peritonitis, the abdomen being closed with a depressing prognosis, and a happy recovery, this was an example of what may be called a fortunate mistake. Since the age of 9 years this patient had been subject to recurring attacks of jaundice, which ceased after splenectomy. In 1914 she was well, but her red blood corpuscles still shewed fragility (Dawson). This observation is important as bearing on the question whether the fragility of the reds is an hereditary character or whether it is due to the influence of the spleen. Although it has been regarded as exceptional (Moynihan), fragility of the red cells appears to persist after splenectomy (Campbell and Warner), and hence this blood trait is not dependent on the spleen and may be regarded as a constitutional anomaly. In a few recorded cases (Giffen and Sanford; Campbell and Warner) relatives of patients with chronic haemolytic jaundice have shewn the characteristic fragility of the red blood corpuscles and, though apparently normal, may convey that disease to their children. Further, according to Campbell and Warner the disease behaves as a Mendelian dominant.

The small size of the red cells, first noticed by Chauffard, was thought by Naegeli to indicate that the patients belonged to a different type of the human species; but against this interesting conception there are two points: in the first place, Meulengracht's statement that it is confined to those members of the family with symptoms and not found, as fragility has been, in their otherwise normal relatives, and secondly, that according to Whitcher the microcytosis tends to pass away after splenectomy and so is presumably due to the presence of the spleen. In regard to the effect of splenectomy it might be considered that this is not an argument of value, as this operation might interfere with the congenital anomalous mechanism responsible for the microcytosis. The number of records on the effect of splenectomy on the fragility and especially on the microcytosis is small, and further observations are desirable on the questions whether the persistence of the fragility is absolute and exactly the same as before splenectomy,

and whether the microcytosis diminishes or completely disappears. Piney, in a review of the subject, regards the excessive fragility and microcytosis as secondary phenomena, and is inclined to suggest merely an inherent susceptibility on which an additional external factor is able to produce these phenomena, and not to accept as an inherited morbid process the fragility. It is, however, tempting to anticipate further evidence to the effect that the fragility, though not the microcytosis, is an inherited anomaly and may be latent until some external factor, such as infection, stimulates the spleen to greater haemolytic activity so that anaemia and jaundice result. The analogy of sickle-celled anaemia, which is so often latent, makes this view attractive.

It is interesting to compare the conditions in pernicious anaemia, on the one hand, with those in chronic haemolytic anaemia and the sickle-celled trait and anaemia in negroes on the other hand. In pernicious anaemia there is little if anything in the way of a latent blood change, such as is present in latent cases of the sickle-cell anaemia in negroes, and, though this is not so widely established, the increased fragility in the relatives of the subjects with chronic haemolytic jaundice. Achlorhydria is almost constant in pernicious anaemia, but in the other two little is known in this respect. Professor Longcope has kindly given me the details of two cases of sickle-celled anaemia in the Johns Hopkins Hospital, which suggest that these patients are able to secrete HCl, although gastric analysis may sometimes fail to shew its presence. It might be urged that in pernicious anaemia, which is often regarded as a syndrome rather than a disease, the constitutional factor is mainly in the direction of favouring, by the existence of achlorhydria, the occurrence of the directly exciting factor, bacterial infection; whereas in chronic haemolytic jaundice and sickle-celled anaemia there is an inborn defect in the red blood corpuscles which readily undergo haemolysis when any extrinsic factor comes on the scene.

Gaucher's disease and Niemann's disease

These diseases attacking the reticulo-endothelial system, which are referred to in connection with their incidence in Jews in the second lecture, have been separated from the cases of splenomegaly called

chronic splenic anaemia. Quite recently Niemann's disease, of which few cases are as yet on record, has been differentiated from Gaucher's disease on the grounds of their micro-chemical and clinical characters, though Graham and Blacklock have contested the sharp differentiation based on the micro-chemical reactions of the material in the large cells in the two conditions.

Gaucher's disease (large-celled splenomegaly) was thoroughly investigated by the late F. S. Mandlebaum and his colleagues from 1904 to 1919. In 1926 Pick accepted 39 cases, Cushing and Stout collected 49 examples, and in 1927 Klercker brought the number up to 60. There is a distinct familial tendency, but the disease has not been shewn to occur in two generations. It has been stated to be familial in 40 per cent of the cases, and has been recorded in four members of a generation (Brill, Mandlebaum, and Libman). The familial incidence has been specially noted in cases with predominant involvement of the bones. Pick regards it as "a congenital, familial, constitutional anomaly of metabolism akin to alcaptonuria or cystinuria," and Waugh and MacIntosh argue that it is a congenital progressive systemic disease of the haemopoietic tissues, characterized by an aleukaemic dysmyelosis, *i.e.* an irregular perverse myeloid metaplasia, due to the same causes as leukaemia, and that it may be a constitutional anomaly, namely a mutation of the human species.

Niemann's disease, described in 1914 as a nutritional disease of infants of unknown nature, has been specially investigated by Pick who called it lipoid-celled splenohepatomegaly. Previously some cases in very early life had been recorded as Gaucher's disease. It contrasts with Gaucher's disease in its rapid and fatal termination and in the difference of the lipoid content of the large cells and the complex lipoprotein (kerasin) in the Gaucher cells. Among the few recorded cases it has been found in sisters (Knox, Wahl and Schmeisser; Siegmund), and in association with amaurotic family idiocy (Hamburger) and mongolism (Niemann; Bloom).

Infantile anaemia. (Synonyms: von Jaksch's anaemia infantum pseudo-leukaemica, splenomegaly with anaemia and myelaemia)

Under this heading several conditions, especially of secondary anaemia, have from time to time been included, so that the name has

become that of a syndrome rather than of a disease, and has thus been in much the same nosological position as chronic splenic anaemia of adults. But in at least one not very uncommon form the familial incidence and its occurrence in twins, of which John Thomson saw more than a dozen examples, have naturally suggested that there is an underlying hereditary anomaly (Marquard) which enables defective dietary or infection to cause anaemia the more readily and of a special kind. As an indication that there may be other forms of hereditary anaemia reference may be made to oligochromaemia porphyrinurica (megalosplenica congenita) described by Sato and Takahashi as a familial condition characterized by splenomegaly from birth, chlorotic anaemia, porphyrinuria, purple teeth, and a cutaneous eruption of the same nature as in congenital porphyrinuria.

Hodgkin's lymphogranuloma or lymphadenoma

Hodgkin's lymphogranuloma or lymphadenoma has in rare instances been known to attack two in the same family or twins (Senator; Peacock), thus suggesting that a special tissue susceptibility or constitution, such as status lymphaticus (Arkin), favours its incidence. As in the case of acute leukaemia which has been recorded in a nurse after contact with a case (Obrastzow) and in a brother and sister (Eppinger; Schereschewsky), and in which the question of hereditary and familial disposition has been considered by Bauer and Weber, the explanation that infection is responsible must arise; until the causal agents of these diseases are established it is impossible to deny that, as in the case of malignant disease, some constitutional factor may play a part in their incidence. But the cases clinically supporting the contention of a heredo-familial incidence are so rare that the evidence is not so definite as in the case of the tuberculous diathesis or the heredity of malignant disease.

REFERENCES

Chlorosis

ALLBUTT, CLIFFORD: System of Medicine (Allbutt), 1898, v, 483.

AUBERTIN ET MONQUIN: Nouveau traité de médecine (Roger, Widal et Teissier), Fasc. ix, p. 4, 1927.

CABOT, R. C.: Modern Medicine (Osler and McCrae), 1908, iv, 640.

JONES, E. LLOYD: Chlorosis, 1897, London.
ROSENBACH, O.: Corset und Bleichsucht, Stuttgart, 1895.
SCHAUMAN: Quoted in *Brit. Med. Journ.*, 1922, i, Epitome, No. 301.
WEBER, F. P.: *Brit. Med. Journ.*, 1925, i, 960.

Erythraemia

BARNES, THOMSON, AND LAMB: *Quart. Journ. Med.*, Oxford, 1925–6, xix, 151.
CHRISTIAN, H. A.: *Med. Clinics North America*, 1925, vi, 840.
CURSCHMANN, H.: *Acta Med. Scandinav.*, Stockholm, 1922, lviii, 228.
ENGELKING, E.: *Klin. Monatsbl. f. Augenheilk.*, 1920, lxiv, 645.
HARROP, G. A., JR., AND HEATH, E. H.: *Journ. Clin. Investig.*, 1927, iv, 53–70.
OWEN, T.: *Bull. Johns Hopkins Hosp.*, Baltimore, 1924, xxxv, 258.
SIGNORELLI, E.: *Haematologia*, 1923, iv, 437.
WEBER, F. P.: Polycythaemia, Erythrocytosis and Erythraemia, p. 54, 1921.
Idem: Med. Press and Circ., 1927, clxxv, 128.

Sickle-celled blood

ARCHIBALD, R. G.: *Trans. Roy. Soc. Trop. Med.*, 1926, xix, 389.
BELL, A. J., KOTTE, R. H., AND MITCHELL, A. G.: *Am. Journ. Dis. Child.*, Chicago, 1927, xxxiv, 923.
BISHOP, F. W.: *Arch. Int. Med.*, Chicago, 1914, xiv, 388.
CASTANA, V.: *Pediatria*, Napoli, 1925, xxxiii, 431.
COOLEY, T. B., AND LEE, P.: *Am. Journ. Dis. Child.*, 1926, xxxii, 334.
DRESBACH, M.: *Science*, 1904, N. S., xix, 469.
HAHN, E. V.: *Am. Journ. Med. Sc.*, Phila., 1928, clxxv, 206.
HAHN, E. V., AND GILLESPIE, E. B.: *Arch. Int. Med.*, Chicago, 1927, xxxix, 233.
HERRICK, J. B.: *Arch. Int. Med.*, Chicago, 1910, vi, 517.
HUCK, J. G.: *Bull. Johns Hopkins Hosp.*, Baltimore, 1923, xxxiv, 335.
HUCK, J. G., AND BIGALOW, R. M.: *Bull. Johns Hopkins Hosp.*, Baltimore, 1923, xxxiv, 390.
LAWRENCE, J. S.: *Journ. Clin. Investig.*, Baltimore, 1927, v, 31.
MASON, V. R.: *Journ. Am. Med. Assoc.*, Chicago, **79**, 1318, 1922.
STEWART, W. B.: *Am. Journ. Dis. Child.*, 1927, xxxiv, 72.
SYDENSTRICKER, V. P.: *Journ. Am. Med. Assoc.*, Chicago, **83**, 12, 1924.
WASHBURN, R. E.: *Virginia Med. Semi-Month.*, 1911, xv, 490.

Pernicious anaemia

ADDISON, T.: On the Constitutional and Local Effects of Disease of the Suprarenal Capsules, p. 3, 1854.
BARTLETT, J. C.: *Journ. Am. Med. Assoc.*, Chicago, **60**, 176, 1913.
BAUMGARTNER, E. A., AND HUBBARD, R. S.: *Clifton Med. Bull.*, 1927, xiii, 71.
BAUMGARTNER, E. A., AND SMITH, G. D.: *Arch. Int. Med.*, Chicago, 1927, xl, 203.
BRAMWELL, B.: Anaemia and Some Diseases of the Blood-forming Organs, 1899.

Idem: Brit. Med. Journ., 1924, i, 365.
CABOT, R. C.: Modern Medicine (Osler and McCrae), 1908, iv, 612.
CHALMERS AND CASTELLANI: Tropical Diseases, p. 1791, 1919.
CHRISTIAN, H. A.: *North-West Med.*, 1925, xxiv, 531.
DORST, S. E.: *Am. Journ. Med. Sc.*, Phila., clxxii, 173.
DRAPER, G.: Human Constitution, 1924.
DRAPER, G., AND BARACH, A. L.: *Journ. Clin. Investig.*, Baltimore, 1927, iv, 507.
DRAPER, G., DUNN, H. L., AND SEEGAL, D.: *Am. Journ. Med. Sc.*, Phila., 1925, clxix, 322
FABER, K.: Lectures on Internal Medicine, pp. 41, 72, 1927.
HURST, A. F.: Medical Essays and Addresses, p. 89, 1924.
Idem: Brit. Med. Journ., 1927, i, 825
HURST, A. F., AND BELL, J. R.: *Brain*, 1922, xlv, 266.
LEVINE, S. A., AND LADD, W. S.: *Bull. Johns Hopkins Hosp.*, Baltimore, 1921, xxxii, 254.
MARTIUS, F.: Achylia Gastrica, Leipzig, 1897.
MINOT, G. R., AND MURPHY, W. P.: *Brit. Med. Journ.*, 1927, ii, 674.
MINOT, MURPHY, COHN, STETSON, AND LAWSON: *Trans. Assoc. Am. Phys.*, Phila., 1927, xlii, 83.
MUSTELIN, O.: *Acta med. Scandinav.*, Stockholm, 1922, lvi, 411.
NYE, R. N., ZERFAS, L. G., AND CORNWELL, M. A.: *Am. Journ. Med. Sc.*, Phila., 1928, clxxv, 153.
PINEY, A.: Recent Advances in Haematology, 1927.
Idem: Proc. Roy. Soc. Med., 1925, xviii (Path. Sect.), 5.
SCHAUMAN, O.: Quoted by Meulengracht, E., *Am. Journ. Med. Sc.*, Phila., 1925, clxix, 177.
SIMMONDS, BECKER, AND MCCOLLOM: *Journ. Am. Med. Assoc.*, Chicago, **83**, 1047, 1927.
TODD, A. T.: *Brit. Med. Journ.*, 1926, ii, 180
WOLTMANN: Collected Papers of the Mayo Clinic, 1918, x, 933.
WOOD, E. J.: *Am. Journ. Med. Sc.*, Phila., 1925, clix, 28; Modern Medicine (Osler, McCrae, and Funk), 1926, iii, 649.

Chronic haemolytic jaundice

CAMPBELL, J. M. H., AND WARNER, E. C.: *Quart. Journ. Med.*, Oxford, 1925–26, xix, 333.
DAWSON, B.: *Proc. Roy. Soc. Med.*, 1914, vii (Clin. Sect.), 86.
GIFFIN AND SANDFORD: *Journ. Lab. and Clin. Med.*, 1919, iv, 465.
MOYNIHAN, B.: The Spleen, p. 98, Bristol, 1921.
NAEGELI, O.: Blutkrankheiten und Blutdiagnostik, 4th edition, 1923.
PINEY, A.: Recent Advances in Haematology, p. 240, 1927.
WELLS, T. SPENCER: *Med.-Chir. Trans.*, 1888, liii, 255.
WHITCHER, B. R.: *Am. Journ. Med. Sc.*, Phila., 1925, clxx, 678.

Gaucher's disease

Brill, Mandlebaum, and Libman: *Am. Journ. Med. Sc.*, Phila., 1909, cxxxvii, 849.
Cushing, E. H., and Stout, A. F.: *Arch. Surg.*, Chicago, 1926, xii, 539.
Graham, S., and Blacklock, J. W. S.: *Arch. Dis. Child.*, London, 1927, ii, 267.
Klercker, Kj. O. Af.: *Acta Paediat.*, Stockholm, 1927, vi, 302.
Mandlebaum, F. S.: *Am. Journ. Med. Sc.*, Phila., 1919, clvii, 366.
Pick, L.: *Ergebn. der inn. Med. u. Kinderh.*, Berlin, 1926, xxix, 519.
Waugh, T. R., and MacIntosh, D. S.: *Arch. Int. Med.*, Chicago, 1924, xxxiii, 599.

Niemann's disease

Bloom, W.: *Am. Journ. Path.*, Boston, 1925, i, 595.
Hamburger, R.: *Jahrb. f. Kinderheilk.*, 1927, cxvi, 41.
Knox, Wahl, and Schmeisser: *Bull. Johns Hopkins Hosp.*, Baltimore, 1916, xxvii, 109.
Niemann, A.: *Jahrb. f. Kinderheilk.*, 1914, lxxix, 1.

Infantile anaemia

Marquard, E.: *Arch. f. Kinderheilk.*, 1923, lxxii, 251.
Sato, A., and Takahashi, H.: *Am. Journ. Dis. Child.*, 1926, xxxiii, 325.
Thomson, J.: Clinical Study and Treatment of Sick Children, p. 425, 1925.

Hodgkin's lymphogranuloma

Arkin, A.: *Am. Journ. Med. Sc.*, Phila., 1926, clxx, 669.
Bauer, J.: Die konstitutionelle Disposition zu inneren Krankheiten, 1924, p. 257.
Obrastzow: *Deutsche med. Wchnschr.*, 1890, xvi, 1130.
Peacock, G.: *Dublin Journ. Med. Sc.*, 1905, cxx, 85.
Schereschewsky, E.: *Zntrlbl. f. d. inn. Med.*, 1926, xlvii, 643.
Senator, H.: *Deutsche Klinik*, 1903, iii, 373.
Weber, F. P.: *Med. Press and Circ.*, 1927, clxxv, 128.

Reprinted from Bulletin of The Johns Hopkins Hospital
Vol. XLIII, No. 3, pp. 117–139, September, 1928

SOME DISEASES IN THE JEWISH RACE

Lecture II of the William Sydney Thayer and Susan Read Thayer Lectures in Clinical Medicine (1928)

The study of constitution in relation to disease, the influence of heredity on the incidence of disease, the effects of environment in the same direction, and the interplay and the question of the relative importance of these factors, which it is attractive but so difficult to decide, may perhaps justify a brief consideration of the diseases specially common among the Jews. This race, remarkable for the contrasts it presents of high culture and intellectual ability, wealth and luxury, on the one hand, with, on the other hand, an incidence of mental defectives said to be higher than in any other civilized race (Fishberg[1]), poverty and hardship, was estimated in 1910 at twelve millions, or only a small fraction of one per cent of the white population of the world. Widely spread over the globe, and though showing some tendency to resemble the nations among whom they live, the Jews have preserved their racial type in a very remarkable degree. It has been suggested that the long persecutions that the Hebrew race has suffered may have led to the survival of the fittest, but, if so, the obvious presence of many unfit shows that the process is not finished. The race would thus provide an interesting study in connection with the problem of the influence of environment versus heredity on the incidence of disease. The present crisis in Zionism may produce results difficult to forecast. There are now about $3\frac{1}{2}$ millions of Jews in the United States of America, about $2\frac{1}{2}$ millions having entered the country between 1881 and 1924, when this mass immigration was abruptly checked by the national quota system of the "Johnson Act." The Jews multiply rapidly from their comparatively low infantile mortality and longevity, not, it is said, from a high birth rate; for,

[1] Fishberg, M.: *Journ. Hered.*, Washington, 1917, viii, 543.

with the disappearance of the religious influence (Namier),[2] birth control is likely to become stricter among them even than in France. What effect in the direction of an increased number of mixed marriages the changed conditions of Zionism may induce, and so modify the constitution and morbid tendencies, remains to be seen in the future.

Some diseases are chiefly seen in, though not absolutely confined to, Jews, and in at least two of these it is noteworthy that when the diseases (cerebro-macular degeneration and thrombo-angiitis obliterans) occur in gentiles they appear later in life and are less severe in their manifestations than in Jews, thus suggesting that the inborn tendency is more powerful in the cases with a Hebrew heritage.

AMAUROTIC FAMILIAL IDIOCY

The first case of this racial and familial disease was recorded in 1881 by Waren Tay (1843–1927) from an ophthalmological point of view as "Symmetrical Changes in the Region of the Yellow Spot in each Eye of an Infant;" subsequently the disease was independently described from a neurological standpoint as "Arrested Cerebral Development" by B. Sachs in 1887. In 1892 Kingdon correlated these two separately described conditions into what is often eponymously called Tay-Sachs' disease. The name amaurotic family idiocy was suggested by Sachs in 1896. In 1894 Carter pointed out its racial incidence, and among Heveroch's 86 collected cases 61 were Hebrews; the parents are often, if not usually, poor Polish immigrants. Dr. Horsley Gantt informs me that only five cases (one in a Russian, four in Jews) have been recorded in Russia. Up to 1917 there were 100 cases on record (Cohen); 10 of these were in gentiles (among Heveroch's cases there were 7; Cockayne and Attlee; Tarr; Cohen's cases were added). Since then de Nicolo and Chalatov have reported cases in gentiles. It has been said to be a Mendelian recessive through inheritance of recessive unit characters which may be present in other surviving members of the family.

There is not any evidence of inflammation of the central nervous system, such as a vascular lesion, of the influence of a bacterial toxin, of malformation, arrest of development, or of a primary endocrine defect. It may be difficult to exclude the delayed action of an endog-

[2] Namier, L. B.: *New Statesman*, 1927, xxx, 103 (Nov. 5, 1927).

enous toxin of maternal origin during foetal life. According to Poynton, Parsons, and Holmes it is a primary disease of the whole central nervous system affecting the nerve cells, including those of the dorsal root ganglia and the retina, more than of the nerve fibres, due to some inherent bio-chemical property of the cell protoplasm; Mott came to the same conclusion. It is characterized by a selective degeneration limited to the ectodermal tissues with a systemic degeneration shown by demyelination of the nerve fibres. Leiner and Goodhart describe two infantile cases without myelin-sheath degeneration, thus resembling the juvenile cases which occur in gentiles, and point out that among the infantile cases there are a number of groups showing minor differences in the histological changes, but all linked together by the ectodermal selectivity and the different degrees of Schaffer's type of cell degeneration. Parsons pointed out that the cellular change is not a simple atrophy, but an excessive growth of the protoplasm which later degenerates, and that this sequence of events does not lend any support to the otherwise attractive explanation that there is an inborn want of vitality—as expressed by Gowers' word "abiotrophy" from abiosis, abiotic atrophy—of the central nervous system. Collins, however, regards it as an abiotrophy of the ganglion cells of the retina, just as he considers symmetrical familial pigmentary degeneration, which has not any racial proclivity, as abiotrophy of the cones at the macula, and retinitis pigmentosa as abiotrophy of the retinal rods and cones.

Although potentially congenital in origin, the infants appear normal at birth, and some (3 to 6) months pass before the onset of symptoms. Optic atrophy leading to complete blindness, the characteristic macular changes, progressive changes in the central nervous system resulting in dementia and muscular weakness, and death within two years, make up the clinical picture.

Infantile and juvenile forms. By its racial incidence amaurotic family idiocy is strikingly distinguished from various forms of progressive cerebral and macular degeneration, which somewhat resemble it, especially the so-called juvenile form of amaurotic family idiocy (Vogt), and familial cerebral degeneration with macular changes (F. E. Batten). There are also cases both of the infantile form (Weber) and of the juvenile form without macular changes, though otherwise

similar, and others with only retinal changes and subsequent pigmentation—primary macular pigmentary degeneration (T. Collins), as in R. D. Batten's cases in which symptoms came on in two brothers about the fourteenth year. These forms in gentiles are hereditary and familial, but usually occur less early in life than amaurotic family idiocy, about the sixth year or later, and are much milder, so that the neurological symptoms are insignificant or even absent, and the patients may survive; thus, Neave recorded familial macular atrophy in a woman aged 40 years and her two brothers. There are, thus, in the juvenile form groups of cases showing slightly different histological changes and forming transitions. In 1925 Greenfield and Gordon Holmes described this histological picture as "a primary change in the ganglion cells combined with an independent degeneration of the outer neuronic elements of the retina, which in some cases extends to the inner nuclear and inner reticular layer."

The primary macular pigmentary degeneration, often with, but sometimes without, cerebral degeneration, has some relations with the group of cases of retinitis pigmentosa which occur early in life, run a rapid course and are often associated with mental defects, such as idiocy and deaf-mutism. There is thus a connecting link with other cases of retinitis pigmentosa beginning less early in life, running a slower course, and rarely accompanied by mental defect; this latter condition is also hereditary, though sometimes discontinuous, so that Nettleship regarded the disease as then recessive in a Mendelian sense, though dominant in cases of continuous transmission. Retinitis pigmentosa has been regarded as common in Jews and due to the frequency of consanguineous marriages (vide Fishberg); but little stress can be laid on this, and there is not any mention of a Jewish proclivity to it in Bell's monograph. In connection with the inter-relations of the foregoing eye changes attention may be called to a case, recorded by Mary Buchanan, of a Jewess with retinitis pigmentosa whose infant had amaurotic family idiocy, thus suggesting "anticipation," or a more powerful and effective attack by the morbid process. In a very interesting and copiously documented paper Weber has collected material about the combination of retinitis pigmentosa with (1) hypopituitarism, described as the Laurence-Moon-Biedl syndrome by Solis-Cohen and Weiss who record four cases in an Italian family with

Fröhlich's syndrome and retinitis pigmentosa; Weber reported a case in a Jew aged thirty-five years; (2) with incomplete Recklinghausen's disease, thus showing a widespread abnormality in the nervous system.

Between the infantile type of amaurotic family idiocy, which has a predominating racial incidence, and these aberrant forms of retinitis pigmentosa there are, through the juvenile groups of macular and cerebral degeneration, a number of transitional forms of disease which make up a chain, the links of which are less early in onset, less serious, and not prominently racial in incidence. It may be pointed out that this suggests a common factor which, though not confined to the Jewish stock, is much more powerful in them than in gentiles.

The same relation existing between the infantile and juvenile types of amaurotic family idiocy is discernible between Niemann's disease (lipoid-celled spleno-hepatomegaly) and Gaucher's splenomegaly.

THROMBO-ANGIITIS OBLITERANS

Synonyms: Buerger's disease: non-syphilitic arteritis obliterans of Hebrews (Weber); die Hebraische Krankheit; glycophilia (Willy Meyer)

The name thrombo-angiitis obliterans was coined in 1908 by Leo Buerger of the Mount Sinai Hospital, New York; endarteritis obliterans had of course been described previously, but not as a special racial disease. In England Parkes Weber described early in 1908 "arteritis obliterans of the lower extremity with intermittent claudication (angina cruris)" and has often discussed the subject since. In 1924 Buerger collected 500 cases, all but 4 in Jews, and only 3 in females. Jablons found 20 gentiles among his 200 cases, and quotes Idelsohn's 40 per cent of gentiles among 226 cases: among 300 cases at the Mayo clinic just over 50 per cent were Hebrews (Allen). It is certainly becoming more widely recognized and, it is thought, actually more frequent.

The condition is characterized by its incidence almost only in men and earlier in life than senile gangrene, by absence of evidence of syphilis, by occurrence of intermittent claudication, redness or cyanosis of the feet when in a dependent position, thus resembling erythromelalgia, patches of wandering superficial thrombo-phlebitis in a certain number of cases (35 per cent Allen and Brown), and gangrene

of the extremities (137 out of Silbert's 258 cases). A leucocytosis has been recorded in the acute phase (Thomas), but Jablons contested this. It specially attacks Jews in Russia, Poland, and also in Galicia, Rumania, and European Turkey, and immigrants in America, England and elsewhere. Rich are affected as well as poor.

The process is an inflammatory thrombosis involving not only the larger arteries and veins, but their finest branches and even the capillaries (Constam). It shows (1) an acute inflammatory lesion with occlusive thrombosis and the formation of miliary foci resembling tubercles or minute abscesses with giant-cells (Buerger (1917)); these giant cells, which Buerger (1920) regarded as abortive attempts on the part of angioblasts to organize an infective focus, were not found in a British case published by Marnoch and MacRae; and in their British cases Telford and Stopford described infiltrating cells as lymphocytes and not polymorphonuclears; (2) later organization of the clot with disappearance of the inflammatory and giant-celled foci, and canalization; (3) the formation of fibrous tissue in the adventitia which binds together the artery, vein, and nerves; microscopically, the nutrient arteries of the nerves may be involved (Marnoch and MacRae). This might account for vasomotor phenomena which may make the diagnosis from Raynaud's disease difficult (Allen and Brown). Bacteriological examination has so far failed to establish a microbic cause, though Rabinowitz described a Gram-negative beaded bacillus which produced similar lesions in rabbits.

Buerger and Weber, with much experience of poor Russian and Polish Jews in the East End of London, both regarded it as a disease of Jews; this opinion has been criticized on the ground that Buerger's statistics were mainly based on observations at a Jewish Hospital. Buerger, however, quotes 120 cases collected in Japan between 1900 and 1921 (Koyano), and in a letter to Boyer and Thibault states that he has seen about 20 cases in American Christians. It is said to be relatively common among the yellow races, and in China (Whyte; Meleney and Miller). The questions of its peculiar racial incidence and whether or not it really differs from obliterative arteritis in gentiles have been much discussed. Gilbert and Coury regarded it as sharply defined from other forms of chronic obliterative arteritis, not only clinically but pathologically; and Sicard, who shared this view,

suggested that its high incidence in males was due to over-stimulation—quantitatively or qualitatively—of the adrenal medulla by the testicular hormone. It may be mentioned that von Oppel (1921), believing that excessive production of adrenalin causes hyperglycaemia arterial spasm (suprarenal arteriosis), and nutritional damage of the vessel wall leading to thrombosis and spontaneous gangrene (gangraena arteritis suprarenalis), has performed suprarenalectomy, with his Russian colleagues, in 115 cases; Leriche in France has also carried it out in 6 cases, and von Oppel has more recently advocated it again; but according to Sénèque the operation is passing out of favour.

Constam's 4 cases, in which the hands were markedly affected, were all in gentiles; he states that 80 per cent of 94 cases of thrombo-angiitis at the Mayo Clinic had been wrongly diagnosed. Telford and Stopford reported 6 cases (2 women aged 48 and 52, and 4 in men 37, 40, 44, 52) in British subjects, and the condition has been recorded in other British born men (Girdwood (male 35)) and Marnoch and MacRae (male 59)). Professor Stopford tells me that he has now seen 32 cases, none in Jews, in the Manchester district which has a large Jewish population. Telford and Stopford regarded the incidence in Jews as "a topographical accident," and Guillaume and also Lian, Puech and Viau have contested the view that it is a disease peculiar to Jews, though it is admitted that they are particularly prone to suffer from it and earlier in life than gentiles. Lian and his colleagues recorded 52 cases, all but 2 in males, and ascribed it to a metabolic disturbance occurring about the age of 50 in gentiles, but earlier in Hebrews, and argue that the characteristics of the disease as described in Jews may all occur in gentiles. Guillaume, writing on "Soi-disant maladie de Buerger," definitely opposes the argument that because it occurs earlier in life in Jews the condition is special to the Jews. He considers that the arterial lesions in gentiles differ according to the age of the patients, and regards the cases in Jews as merely a juvenile form of the endarteritis ordinarily met with in other races. Moulonguet and Pavie strongly support Buerger's contention that the thrombo-angiitis of Hebrews is the result of a special histological lesion and differs from syphilitic and juvenile arteriosclerosis, which of course may also cause gangrene and so clinically resemble it. The spontaneous gangrene ascribed by von Oppel to excessive secretion of

adrenalin causing arterial spasm and degeneration ("artériose surrénale") may well be yet another form of juvenile gangrene, which may be confused with that occurring in Jews; it does not appear that von Oppel's 115 cases were characterized by Jewish incidence. Netter, who is in favour of the racial character of the disease, supports Gilbert and Coury's suggestion that the early incidence of the affection in immigrant Jews is connected with their proneness when infants to have typhus in Russia, Galicia, or Poland, and perhaps the modified form described by Brill as sporadic in New York, the damage thus done to the vessels perhaps accounting for the earlier incidence of vascular thrombosis. But this does not explain the great predominance of male sufferers.

In all the cases of thrombo-angiitis obliterans that he examined Willy Meyer found hyperglycaemia after the ingestion of 100 gms. of glycose given after a brief fast, the high blood sugar being ascribed to the action of swallowed nicotine in the duodenum on the pancreas (1920); he therefore proposes to call the condition glycophilia, the similarity of the name to haemophilia being intended to point to its sex-limitation and other obscure features. The hyperglycaemia might be thought to be an etiological factor and, in association with the liability of Jews to diabetes, to strengthen the opinion that thrombo-angiitis is specially a disease of Hebrews. But Morrison and Ohler's results of blood sugar tests on Jews and gentiles did not support the view that race alone is a factor in the incidence of high blood sugar curves.

It seems to be generally agreed that its victims have been heavy smokers, especially of cigarettes; it is possible that there is an underlying want of vital resistance in the vessels (Gowers' abiotrophy) and that tobacco is thus able to act with much more effect in causing vascular spasm and in favouring the attack of the unknown agent causing the acute arteritis; but it is very improbable that tobacco is the sole etiological factor; that there may be such an innate defect is suggested by the occurrence of vascular hypoplasia in some cases (Weber 1916). Among Buerger's 500 cases smoking was denied in one per cent; Parkes Weber who wrote a full account of it in 1916 had then never seen a case in a man who was not or had not been a free cigarette smoker, or in a Jewish woman or child. But Frauenthal

recorded a case in a boy aged three years. Lian, Puech and Viau found that out of 25 patients 23 smoked more than ten cigarettes daily, and considered that, as no other cardio-vascular disease showed such a high percentage of smokers, smoking is an important factor in the causation of intermittent claudication. It is interesting to recall tobacco angina in connection with the cramp in the muscles of the legs (intermittent claudication) in thrombo-angiitis obliterans. From observation of 350 cases Silbert is convinced of the importance of smoking as an etiological factor; he has never seen it in a non-smoker, has seen it delay improvement that otherwise should have followed treatment, bring on a relapse after treatment has relieved the symptoms, and has observed improvement when the habit was given up.

In some cases of thrombo-angiitis obliterans there has been erythraemia (Weber (1921); W. Meyer), and it has been suggested that this may be due to thrombosis of vessels in the spleen; it is noteworthy that in at least four of Weber's collected cases of erythraemia the splenic vein was thrombosed. On the other hand the hypoplasia of the arteries found in some cases of thrombo-angiitis might favour thrombosis in the presence of the stasis accompanying erythraemia.

The question as to the occurrence of thrombo-angiitis obliterans in other internal organs and especially in the heart giving rise to the syndrome of coronary thrombosis and infarction, first established in 1910 by Obratzow and Strachesko, is of interest. J. Heitz, who quotes cases of thrombo-angiitis obliterans combined with angina pectoris by Weber and Cawadias, reports 12 cases of his own (1 female), all about fifty years of age, in which this syndrome occurred. There is not any statement as to the nationality of the patients, and the cases were of different kinds; three or possibly 4 of his cases were syphilitic, and 2 were diabetics. In 7 of his cases the anginoid symptoms preceded the intermittent claudication. Dr. John Parkinson tells me that among a hundred cases of cardiac infarction, analyzed by him and Dr. Bedford, there was not any case of thrombo-angiitis obliterans; they believe that cardiac infarction is more frequent in Jews than in other races: in their series, 43 were Jews, but, as the London Hospital stands near a large Jewish community, they decided not to publish these figures as conclusive. Among their 100 clinical patients with cardiac infarction 93 were males, and 78 were fifty years of age or over.

Among Wearn's earlier series of 19 cases 9 were in women and 18 over 40 years of age. Jablons merely states that cardiac embolism or coronary thrombosis is a common terminal event in thrombo-angiitis obliterans, but does not give any figures. There does not appear to be any evidence that thrombo-phlebitis occurs in the retinal vessels.

To sum up: It would appear that, though the syndrome is not confined to Jews, there is a racial liability to a special arterial lesion which is responsible for the incidence of this clinical manifestation both more frequently and earlier in life, and on a provocation—smoking—which is not prone to have this effect to anything like the same extent in gentiles.

GAUCHER'S AND NIEMANN'S DISEASES

Gaucher's disease. In 1882 C. P. E. Gaucher in his Paris thesis first described the condition, which now commonly goes by his name, under the title of "épithéliome primitive de la rate." In 1926 L. Pick critically accepted 39 cases, and in 1927 Klercker brought the number up to 60. The Jewish race figures largely, but far from exclusively, among the patients, possibly 40 per cent showing this racial incidence. Mandlebaum, Pick, Bloom, and others are emphatic that the Gaucher substance which distends the reticulo-endothelial cells into the characteristic Gaucher cells is not a lipoid; the condition would therefore differ chemically from infiltration of the reticulo-endothelial cells with lipoids in the lipoid histiocytosis of Niemann's disease, diabetic lipaemia, and animals fed on excess of fats or cholesterol. But the histological appearances are so similar that it is only recently that a distinction has been drawn between the Gaucher cells and the "pseudo-Gaucher cells," as Aschoff has called them, in Niemann's disease and the other conditions in the second category. It is extremely interesting that Graham and Blacklock have by heating frozen sections up to 100°C., and so probably causing hydrolysis, found that the Gaucher cells take up the fat stain from Sudan III or Nile blue.

Niemann's disease. (Synonyms: Lipoid-celled spleno-hepatomegaly; lipoid histiocytosis.) This condition was recently separated from Gaucher's splenomegaly on the grounds that it differs in the

chemical constitution of the material—a lipoid—occupying the reticulo-endothelial cells, and clinically by its rapidly fatal course. It was described as an unknown disease by Niemann in 1914. Pick gave a fuller account of it in 1926, and Bloom called it Pick's disease. Since Bloom's paper analyzing 7 cases, others have been reported (Schiff; Hamburger), and probably, as Bloom argued with regard to the 2 Jewish infants recorded as Gaucher's disease by Knox, Wahl, and Schmeisser, other reported instances of Gaucher's splenomegaly may really have been of this nature.

Out of 7 cases collected by Bloom 5 were in Jews, so that as far as these small figures go it is more decidedly racial than Gaucher's splenomegaly; in this connection its association with amaurotic family idiocy is interesting (Hamburger); it has also been combined in two cases with mongolism (Niemann; Bloom). It is familial and proves fatal under two years of age, thus agreeing in the first feature and differing in the second from Gaucher's splenomegaly which, though it commonly begins in childhood, runs a very chronic course. In addition to the qualitative distinction between the chemical constitution of the Gaucher material (kerasin) and the lipoid histiocytosis in Niemann's disease there is a quantitative difference between them; the Gaucher cells are much more restricted in their distribution, mainly in the spleen, liver, lymphatic glands, and bones, whereas in Niemann's disease the histiocytes in general are said to be infiltrated and transformed into large cells. In Niemann's disease there is a lipoid infiltration of the histiocytes resembling that in diabetic lipaemia and that experimentally produced in animals by a diet containing excess of fat and cholesterol. But as already mentioned, Graham and Blacklock by special technique find that the Gaucher cells give a reaction for lipoids, and therefore suggest that the changes in Gaucher's and Niemann's diseases and the other forms of lipoid histiocytosis are of the same nature, namely, a reaction on the part of the reticulo-endothelial cells to abnormal products of lipoid metabolism, the differences in the several conditions depending for the most part on the nature of the lipoid substances produced.

The relation between Niemann's disease and Gaucher's splenomegaly from a racial point of view presents an analogy with that between the infantile and juvenile types of amaurotic family idiocy. In the

Jews these diseases tend to occur very early in life and to be more rapidly fatal, whereas among gentiles the allied, though structurally somewhat different, changes occur less early in life and are less severe.

DIABETES MELLITUS

The incidence of diabetes mellitus in the Hebrew race is notorious, and the statistics of Joslin, Wallach, von Noorden, and Morrison, and of the records of the Metropolitan Life Assurance Company of New York support this impression. The incidence in Jews has been variously estimated as being from twice to six times as high as in other races. Several reasons are given for this, such as the association with overweight and obesity, excessive eating of food generally and of sweets in particular, a sedentary life, and the highly nervous state so common in the race. Solis-Cohen ascribes the increased incidence of diabetes in Jewish immigrants into the New World to the cruel persecutions the race has for centuries experienced in Russia, which induce a disturbance of the autonomic-endocrine-balance.

The relation between obesity and diabetes mellitus is of interest. That obesity so frequently precedes the onset of diabetes, which may eventually lead to disappearance of the excessive storage of fat, is an established cycle of morbid metabolism. It is clear that they both may be the result of excessive and unsuitable food or of endocrine disorder. The occurrence of diabetes in obese subjects suggests that there is a common metabolic vice which by progressing in a particular manner leads to diabetes, though John's observations on the fasting blood-sugar and tolerance test suggest that there are two groups of the obese; in one diabetes is prone to occur, whereas in the other, which is due to familial tendencies, diabetes is not likely to supervene. The statistics of Anders and Jameson show that among obese persons diabetes follows in 1 out of every 12 gentiles, and in 1 out of 8 Jews, and the question arises whether the great incidence in Jews is due to a higher grade of obesity or to a greater liability to diabetes. Joslin is emphatic that diabetes is largely the penalty for obesity and is more likely to occur the greater the degree of obesity, in fact that a Jew becomes diabetic not in virtue of his race but because he is a fat Jew; for if the Jewish race were specially disposed to diabetes it should

occur in early life, but the Jewish child is not more prone than the young gentile to diabetes, and in fact the incidence of diabetes in Jews exceeds that among gentiles in the 4th and 5th decades only of life. It has been thought by Riesman and others that increased consumption of sugar is responsible both for the rise in the incidence of obesity and diabetes. According to Haven Emerson and Larimore rises and falls in the consumption of sugar in America, England, and Paris are followed with fair regularity within a few months by corresponding fluctuations in the death rate from diabetes. But with regard to overweight and obesity, which precede in many cases at least the onset of diabetes, Friedenwald and Morrison argue that sugar, as apart from other dietetic excesses, cannot be regarded as the only cause for the increased incidence.

The relation of obesity to diabetes has been further shown by the higher blood sugar curves in the fat (Beeler and Fitz; Paullin and Sauls; John), and by Friedenwald and Morrison's observation that among 45 obese Jews 31, or 68 per cent, gave an abnormal blood sugar curve, and that 8 of these were found to have mild diabetes. But that race alone is not the determining factor in producing a high blood sugar curve appears to be shown by Morrison and Ohler who found that among Jews the high blood sugar curves were all in highly strung or emotional individuals.

Obesity is stated to be familial or hereditary in a higher proportion of cases than is diabetes, though Joslin's statistics admittedly lend some support to the hereditary or familial factor in diabetes in Jews. Hereditary diabetes, according to Joslin, has a favourable prognosis, and as a rule diabetes in Jews is not severe, although, as he was surprised to find, such patients do less well than the average, probably because they do not carry out the dietetic directions thoroughly. From the data just given it would appear that the Jewish proclivity to the disease is closely bound up with obesity, though the high pressure of modern life may, especially in the highly-strung Jew, act as an accessory factor. But the question whether the frequency of obesity and so of diabetes in the Jews is entirely acquired and due to wealth and luxury, or whether it is not, in part at least, hereditary and constitutional should not be overlooked.

PENTOSURIA

The rare condition of chronic essential pentosuria is not a disease as it does not, unless detected, give rise to any ill effects; it is a chemical malformation, or inborn error of metabolism in Garrod's happy phrase, like alkaptonuria and cystinuria. It is commonly familial, but not hereditary, and a striking proportion of the reported cases have been in Jews (Cammidge and Howard).

OBESITY

The subject of obesity, which is so common in Jews, is of interest in connection not only with the high incidence of diabetes in Jews but also with other evidence of their special liability to disorders of fat metabolism, as shown by the comparative frequency of Gaucher's splenomegaly and Niemann's disease in Hebrews. The infiltration of the reticulo-endothelial cells with a complex lipo-protein, identified by Lieb as kerasin and closely allied to cerebrin, in Gaucher's disease, and of the same cells with a definite lipoid in Niemann's malady might suggest either (1) an inherent want of vitality in the reticulo-endothelial cells so that they are unable to carry on the metabolism of the infiltrating substance—admittedly a pure hypothesis and contrary to the view that, being overladen with the infiltrating substance, the reticulo-endothelial cells undergo considerable proliferation; or (2) metabolic disturbance, as stated by Mandlebaum and Downey, and supported by Schiff's observation of a lipoid state of the blood serum in Niemann's disease. In obesity the connective-tissue cells, which are distinct from the reticulo-endothelial system, are occupied by neutral fats; whereas the reticulo-endothelial cells tend to be occupied by cholesterol-esters. So although the processes in Gaucher's splenomegaly and in the lipoid-celled histiocytosis of Niemann's disease and diabetic lipaemia differ from that in steatosis, it appears probable that a vice in fat metabolism, whether inherited or acquired, underlies them both. Gaucher's and Niemann's diseases are familial, and hereditary or familial incidence is said to occur in 60 to 70 per cent of the cases of obesity.

The question whether or not obesity in the Jews is purely due to environmental conditions cannot perhaps be finally settled. Environ-

mental influences, using this phrase in a broad sense to include diet and amount of physical exercise, must play a part in producing obesity, but they would obviously act at much greater advantage if there were in addition an underlying factor in fat metabolism. Obesity has been divided into three categories (1) Exogenous or simple, due to excessive feeding, in which the basal metabolism is within normal limits. This purely environmental form also accounts for conjugal diabetes. (2) Endogenous, related to endocrine inadequacy of the thyroid, pituitary, or the gonads, as seen in hypothyroidism and myxoedema, Frölich's adiposo-genital dystrophy and adiposis dolorosa, in women at the menopause and in eunuchs. In this form the metabolic rate is below normal. (3) The constitutional or hereditary form, which has been specially investigated from the metabolic point of view by Strouse in collaboration with Dye and Wang, who from a review of the literature and their own results found that obesity does occur without any relation to the food taken or to endocrine disorder in persons with a basal metabolism within the normal limits.

A distinction should be borne in mind between the hereditary and familial incidence of obesity; for although obesity is familial in perhaps 70 per cent of the cases, this may merely be due to family habits of eating and to the inheritance of a phlegmatic disposition (von Noorden; Tileston). Joslin is extremely sceptical about a fat diathesis, and suggests that in this instance an hereditary factor "may simply mean unusual exposure to an obetic environment," and Preble, from analysis of 1,000 cases, considers that it is almost always due to dietetic causes and not to hereditary errors of metabolism. On the other hand Davenport argues that constitutional and hereditary variations in the method of metabolism and the degree of appetite are essential in the explanation of fat and lean families, and that idiosyncrasies of metabolism are effected through the mechanism of the thyroid, pituitary, and gonads. It might also be urged that just as there is great hereditary variation in the bodily, muscular, and cerebral development, so must there be in the amount of storage of fats. In his experiments on hereditary adiposity in mice, especially females, at or subsequent to maturity with the A^y gene Danforth found that neither environment nor abundance of food primarily determined the obesity, and pointed out that as the trait did not appear until after

birth it presents a peculiarity which those inexperienced in genetics often find difficult to associate with heredity.

Although the medical opinions quoted are adverse to an hereditary factor in obesity, the biological view in its favour must receive due consideration.

Progressive lipodystrophy, described by Barraquer (1907), given this name by Simons (1911), and that of cephalo-thoracic lipodystrophy by Marañon and Soler (1924), is rare in its well-marked forms; Ziegler states that there are approximately 100 cases on record, and reports 7 examples in 5 of which there was diabetes. According to Weber it is possibly less rare in Hebrew than in gentile women, but is not any more confined to one race than is ordinary obesity.

ACROMEGALY

Like some other diseases, acromegaly has been thought to be common among Jews; Davidoff found that 21 of the 100 consecutive patients admitted with acromegaly into the Peter Bent Brigham Hospital, Boston, were Jews, a percentage more than six times that (3.4) of the Jews among the total American population. He quotes Lorand and Maximilian Sternberg as having also noticed the frequency of the disease in Jews. Quite recently L. P. Mark in his "Apologia of an Acromegalic" also raised the question of a special liability of the Jews to this pituitary disease on the admittedly slender evidence that out of 12 fellow-sufferers 4 were members of the Jewish community, and also on the association of acromegaly with diabetes mellitus or glycosuria, which according to various statistics holds good in from 10 to 40 per cent of cases of acromegaly. Some physicians in a position to know have told me that they do not know of any evidence of a higher incidence of acromegaly among Jews than in other nations, and have warned me that any assumption that the *frustes* forms of the condition are common in Jews should be entertained with caution, because more or less prognathism and thick negroid lips are frequent among Jews, especially when compared with Anglo-Saxons. My impression that there is a decided tendency to some excess of anterior lobe pituitarism in the Jewish race is not incompatible with the view, put forward by Keith in his lectures on the evolution of human races in the light of the hormone theory, that the peculiar effects of the

pituitary mechanism are best seen among the modern races of the Caucasian or European type.

HEREDITARY HAEMOPTYSIS

In 1919 Libman and Ottenberg described a new clinical form of haemorrhagic disease in 7 members in three generations of a Jewish family who were the subjects of haemoptysis but had never shown any evidence of tuberculosis. They could not find any signs in their cases of hereditary telangiectases, which, it may be noted, it has appropriately been suggested by Emile Weil should be called Osler's disease. They compared it to the hereditary and familial form of haematuria described by L. Guthrie and W. W. Attlee, in whose articles, however, there was not any statement suggesting that the patients were Jews; the family recorded by Guthrie was afterwards investigated by A. C. Alport and A. F. Hurst, the latter of whom tells me that they were not Hebrews, and Dr. Attlee has definitely informed me that his patients were not. But Guthrie's cases, like Kidd's, and those reported by Kidd, Pel, Eason, Smith, and Buchanan, appear to have been examples of hereditary and familial nephritis. It does not appear that familial epistaxis without telangiectasia, which affects both males and females and is transmitted by both sexes, has any special incidence in Jews (Giffin). Although their cases of haemoptysis were in Jews, Libman and Ottenberg cautiously did not lay any emphasis on the racial incidence, as their observation was practically unique.

A number of diseases have tentatively been thought to be commoner in Jews than in gentiles; among these, although there may not be any convincing evidence, some are intrinsically interesting, such as von Jaksch's anaemia infantum pseudo-leukaemica, idiopathic multiple sarcoma of Kaposi, haemophilia, polycythaemia hypertonica (Weber),[3] Hodgkin's disease (Bunting),[4] dementia praecox, and mongolism; but I do not propose to discuss these or the large question of mental and nervous disorders, and shall in conclusion refer briefly to three conditions—malignant disease, tuberculosis, and alcoholism—which, though occurring, are in some respects modified in the Jewish race.

[3] Weber, F. P.: *Brit. Med. Journ.*, 1927, ii, 98.

[4] Bunting, C. H.: Nelson's Loose-Leaf Medicine, Vol. iii, 356.

MALIGNANT DISEASE

It does not appear that the cancer mortality is lower among Jews than other races; indeed in Russia Gantt's enquiries show that it is higher than in gentiles; but there is much evidence collected by Fishberg, Theilhaber, and Vineberg that uterine cancer, especially of the cervix, is rare in Jewesses. This has been ascribed to observance of the Mosaic law limiting co-habitation during and for seven days after menstruation, and for a period after child-birth, thus ensuring freedom from irritation of the parts when in a state of congestion; Vineberg, who gives this explanation, found that at Mount Sinai Hospital, New York, uterine cancer was $7\frac{1}{2}$ times commoner among non-Jewish than among Jewish women. On the other hand malignant growths of the stomach and alimentary canal are frequent, perhaps more so than in gentiles; the same has been said about mammary carcinoma, but Dr. W. M. Feldman has told me that he has some statistical evidence pointing to the lower incidence of mammary cancer among Jewesses who suckle their children, thus suggesting that when the natural activities of the gland are balked proliferation in a malignant direction is likely to follow. It is interesting to note that among Mexican women of mixed blood the incidence is almost the reverse to that in the case of Jewesses, for uterine cancer is very common and mammary carcinoma rare (Hoffman).

TUBERCULOSIS

The comparative resistance of the Jews to tuberculosis, in spite of adverse environment, life in towns, their narrow chest measurement which would be thought to dispose them to the disease, and their special liability to diabetes which may terminate with pulmonary tuberculosis, has been proved by statistics from various parts of the world by shewing that their mortality rate is lower than that of their gentile neighbours. Even after the privations of the Great War tuberculosis appears to have run a milder course in Jews than in other races (Werner). It is important to realize that whereas the mortality rate amongst Jews is much lower than in Gentiles, this is not true of their morbidity rate.

Various hypotheses have been put forward to explain the resistance

of the Jews to tuberculosis. The attractive view was urged by Fishberg in 1911 that during the eighteen hundred years that they have lived in conditions extremely favourable to tuberculous disease those who could not adapt themselves and become relatively immune were eliminated. In support of this result of natural selection he instanced the high mortality—amounting to nearly a third of the total deaths—from tuberculosis among Viennese Jews in the 17th century. In this connection the possibility of a certain degree of acquired racial immunity might well be raised. The influence of the careful inspection of meat so as to avoid the ingestion of tubercle bacilli was insisted on by Behrend; this probably does diminish the incidence of abdominal, surgical, and generalized tuberculosis, but it would not explain so satisfactorily the resistance to pulmonary infection. Feldman believes that the greater sobriety, comparative freedom from syphilis, and care of children, characteristic of the Jews, play a part, though they are not the sole factors, in this remarkable trait.

ALCOHOLISM

The sobriety of the Jew is proverbial, and the longevity of the race has been ascribed in part at least to this factor. Though sober, the Jews are rarely total abstainers, but they are, or have in the past been, deterred from intoxication by powerful racial influence, for by the Jews of the Ghetto drunkenness was "abhorred as a sin, a disgrace, only fit for a Goe (Gentile), and not fit for one of the chosen people" (Fishberg). Feldman argues that in addition to the fear of social ostracism, the manner in which the Jew takes alcohol, namely always eating something, such as a sandwich or two, before he drinks, protects him from becoming intoxicated, for the absorption of alcohol, which takes place rapidly from an empty stomach, is delayed in the presence of food. As in the case of tuberculosis, so with regard to alcoholism it has been urged that the present sobriety of the Jews is the result of natural selection, gross intemperance in past generations having eliminated those who obtained any satisfaction from intoxication (Archdale Reid). Against this it has been stoutly denied that there is any evidence that the ancient Hebrews drank to excess; further, when the modern Jew cuts himself adrift from the influence of his race he does not remain sober. It would thus appear that the sobriety of

the Jews and the resulting freedom from alcoholic diseases, such as delirium tremens and hepatic cirrhosis, do not depend on an inborn trait but are the result of moral and social influences.

REFERENCES

Amaurotic familial idiocy

BATTEN, F. E.: *Quart. Journ. Med.*, Oxford, 1913–14, vii, 444.

BATTEN, R. D.: *Trans. Ophthalmol. Soc. U. K.*, 1897, xvii, 49.

BELL, J.: Eugenics Laboratory Memoirs XXI, Treasury of Human Intelligence, Anomalies and Diseases of the Eye, Part I.

CARTER: *Arch. f. Ophth.*, Leipz., 1894, xxiii, 126.

COCKAYNE AND ATTLEE: *Proc. Roy. Soc. Med.*, 1914–15, viii (Dis. Child.), 65.

COHEN, M.: *Arch. Ophthalm.*, 1923, lii, 140.

COLLINS, E. T.: Internat. Congress Ophthalmol., Washington, 1922, p. 103.

DE NICOLO, F.: *La Pediatria*, 1926, xxxiv, 370.

FISHBERG, M.: The Jews: A Study of Race and Environment, The Contemporary Science Series, p. 320, 1911.

GOWERS, W. R.: *Lancet*, 1902, i, 1003.

GREENFIELD, J. G., AND HOLMES, G. M.: *Brain*, London, 1925, xlviii, 183.

HEVEROCH, A.: *Wien. klin. Rundschau*, 1904, xviii, 634.

KINGDON, E. C.: *Trans. Ophthalmol. Soc. U. K.*, London, 1892, xii, 126.

LEINER, J. H., AND GOODHART, S. P.: *Arch. Neurol. and Psychiat.*, Chicago, 1927, xvii, 616.

MOTT, F. W.: *Arch. Neurol. Path. Lab. Lond. County Asylum, Claybury*, Lond., 1907, iii, 219.

NEAVE, H.: *Proc. Roy. Soc. Med.*, 1927, xx (Ophth. Sect.), 46.

NETTLESHIP, E.: *St. Thomas' Hosp. Gaz.*, 1910, xx, 37.

PARSONS, J. H.: Pathology of the Eye, 1908, iv, 1365.

POYNTON, F. J., PARSONS, J., AND HOLMES, G.: *Brain*, London, 1906, xxix, 180.

SACHS, B.: *Journ. Nerv. and Ment. Dis.*, N. Y., 1887, xiv, 541; 1892, xix, 603.

Idem: New York Med. Journ., 1896, lxiii, 697.

SCHAFFER, K.: Ueber das morphologische Wesen und die Histopathologie der hereditär systematischen Nervenkrankheiten, 1926.

SOLIS-COHEN, S., AND WEISS, E.: *Am. Journ. Med. Sc.*, Phila., 1925, clxix, 489.

TAY, W.: *Trans. Ophth. Soc. U. K.*, London, 1881, i, 56.

VOGT, H.: *Monatsschr. f. Psychiat. u. Neurol.*, 1905, xcviii, 161.

WEBER, F. P.: *Med. Press and Circ.*, London, 1925, clxx, 416.

Thrombo-angiitis obliterans

ALLEN, E. V.: *Proc. Staff Meetings, Mayo Clinic*, 1928, iii, 40.

ALLEN, E. V., AND BROWN, G. E.: *Am. Journ. Med. Sc.*, Phila., 1927, clxxiv, 319.

BOYER, G., ET THIBAULT: *Presse méd.*, Paris, 1927, xxxv (i), 100.
BUERGER, L.: *Am. Journ. Med. Sc.*, Phila., 1908, cxxxvi, 567.
Idem: Ibid., 1917, cliv, 319.
Idem: Med. Rec., New York, 1920, xcvii, 431.
Idem: The Circulatory Disturbances of the Extremities including Gangrene, Vasomotor and Trophic Disturbances, W. B. Saunders Co., p. 277, 1924.
CONSTAM, G. R.: *Am. Journ. Med. Sc.*, Phila., 1927, clxxiv, 530.
FRAUENTHAL, W. H.: *International Clinics*, 1918, Ser. xxviii, Vol. iv, 62.
GILBERT, A., ET COURY, A.: *Paris méd.*, 1922, xlv, 13.
GIRDWOOD, E. O.: *Journ. Path. and Bacteriol.*, Edin., 1927, xxx, 643.
GUILLAUME, A. C.: *Bull. et mém. Soc. méd. des hôp. de Paris*, 1927, 3 s., li, 329; 611.
Idem: Gaz. des hôp., Paris, 1927, c, 1009.
HEITZ, J.: *Arch. des mal. du coeur, etc.*, Par., 1924, xvii, 673.
HERZBERG.: *Arch. f. klin. Chir.*, 1926, cxliii, 125.
JABLONS, B.: *International Clinics*, Phila., 1925, Ser. xxxv, vol. iii, 193.
KOGA, G.: *Deutsche Ztschr. f. Chir.*, 1913, cxxi, 371.
LERICHE, R.: *Bull. et mém. Soc. nat. de chir.*, 1926, lii, 521.
LIAN, C., PUECH, P., ET VIAU: *Bull. et mém. Soc. méd. des hôp. de Paris*, 1927, 3 s., li, 534.
MARNOCH, J., AND MACRAE, E.: *Journ. Path. and Bacteriol.*, Edin., 1927, xxx, 39.
MELENEY, F. L., AND MILLER, G. G.: *Ann. Surg.*, 1925, lxxxi, 976.
MEYER, W.: *Journ. Am. Med. Assoc.*, Chicago, 1918, lxxi, 1268.
Idem: Med. Rec., New York, 1920, xcvii, 425
MORRISON, H., AND OHLER, W. H.: *Boston Med. and Surg. Journ.*, 1923, clxxxviii, 852.
MOULONGUET, P., ET PAVIE, P.: *Ann. d'anat. path. et d'anat. norm. méd.-chir.*, Par., 1927, iv, 685.
NETTER: *Bull. et mém. Soc. méd. des hôp. de Paris*, 1927, 3 s., li, 966.
OPPEL, VON W. O.: *Lyon méd.*, Paris, 1927, xxiv, 1.
RABINOWITZ, H. M.: *Surg., Gyn., and Obst.*, 1923, xxxvii, 353.
SÉNÈQUE, J.: *Presse méd.*, Paris, 1927, xxxv (1), 451.
SICARD: *Bull. et mém. Soc. méd. des hôp. de Paris*, 1927, 3 s., li, 443.
SILBERT, S.: *Journ. Am. Med. Assoc.*, Chicago, **89**, 964, 1927.
TELFORD, E. D., AND STOPFORD, J. S. B.: *Brit. Med. Journ.*, 1924, ii, 1035; 1927, i, 1140.
THAYER, W. S.: *International Clinics*, Phila., 1923, ser. xxxiii, vol. i, 1.
THOMAS, H. M., JR.: *Am. Journ. Med. Sc.*, Phila., 1923, clxv, 86.
WEARN, J. T.: *Am. Journ. Med. Sc.*, Phila., 1923, clxv, 250.
WEBER, F. P.: *Quart. Journ. Med.*, Oxford, 1915–16, ix, 289.
Idem: Lancet, 1908, i, 152.
Idem: Polycythaemia, Erythrocytosis and Erythraemia, pp. 79, 122, 1921.
WHYTE, G. D.: *China Med. Journ.*, 1917, xxxi, 371; 1920, xxxiv, 219.

Gaucher's and Niemann's diseases

BLOOM, W.: *Am. Journ. Path.*, Boston, 1925, i, 595.
GRAHAM, S., AND BLACKLOCK, J. W. S.: *Arch. Dis. Child.*, London, 1927, ii, 267.
HAMBURGER, R.: *Jahrb. f. Kinderheilk.*, 1927, cxvi, 41.
KNOX, WAHL, AND SCHMEISSER: *Bull. Johns Hopkins Hosp.*, Baltimore, 1916, xxviii, 1.
NIEMANN, A.: *Jahrb. f. Kinderheilk.*, 1914, lxxix, 1.
PICK, L.: *Ergebn. der inn. Med. und Kinderheilk.*, Berlin, 1926, xix, 519.
SCHIFF, E.: *Jahrb. f. Kinderheilk.*, 1926, cxii, 1.

Diabetes mellitus

ANDERS, J. M., AND JAMESON, H. L.: *Trans. Assoc. Am. Phys.*, Phila., 1925, xl, 230.
BEELOR AND FITZ: *Arch. Int. Med.*, Chicago, 1921, xxviii, 804.
CAMMIDGE, P. J., AND HOWARD, H. A.: *Brit. Med. Journ.*, 1920, ii, 277.
EMERSON, H., AND LARIMORE, L. D.: *Trans. Assoc. Am. Phys.*, Phila., 1924, xxxix, 290.
FRIEDENWALD, J., AND MORRISON, T. H.: *Arch. Int. Med.*, Chicago, 1927, xl, 538.
JOHN, H. J.: *Journ. Metabol. Res.*, New Jersey, 1923, iv, 255.
JOSLIN, E. P.: The Treatment of Diabetes Mellitus, p. 134, 3rd Edit., 1923, and *Journ. Am. Med. Assoc.*, Chicago, 1924, lxxxiii, 727.
Metropolitan Life Assurance Company. *Journ. Am. Med. Assoc.*, Chicago, 1926, lxxxvii, 868.
MORRISON, H., AND OHLER, W. H.: *Boston Med. and Surg. Journ.*, 1923, clxxxviii, 852.
PAULLIN AND SAULS: *South Med. Journ.*, 1922, xv, 249.
SOLIS-COHEN, S.: *Trans. Assoc. Am. Phys.*, Phila., 1925, xl, 244.

Obesity

BARRAQUER, L.: *Neurol. Centralbl.*, 1907, xxvi, 1072.
DANFORTH, C. H.: *Journ. Hered.*, 1927, xviii, 153.
DAVENPORT, C. B.: Body-Build and its Inheritance. Carnegie Institution of Washington, 1923.
JOSLIN, E. P.: *Journ. Am. Med. Assoc.*, Chicago, 1921, lxxvi, 79.
Idem: The Treatment of Diabetes Mellitus, p. 136, 1923.
MARAÑON, G., AND SOLER, J. B.: *Endocrinol.*, Los Angeles, 1926, x, 1.
NOORDEN, C. VON: "Obesity" in Metabolism and Practical Medicine, Edited by Walker Hall, vol. iii, 693.
PREBLE, W. E.: *Boston Med. and Surg. Journ.*, 1923, clxxxviii, 617.
SIMONS, A.: *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1911, v, 29.
STROUSE, S., AND DYE, M.: *Arch. Int. Med.*, Chicago, 1924, xxxiv, 267.
TILESTON, W.: Endocrinology and Metabolism (Barker), 1922, iv, 29.

WANG, STROUSE, AND SAUNDERS: *Arch. Int. Med.*, Chicago, 1924, xxxiv, 275.
WEBER, F. P.: *Quart. Journ. Med.*, Oxford, 1916–17, x, 131.
ZIEGLER, L. H.: *Proc. Staff Meetings of Mayo Clinic*, Rochester, Minn., 1927, ii, 251.

Acromegaly

DAVIDOFF, L.: *Endocrinology*, Los Angeles, 1926, x, 462.
KEITH, A.: *Bull. Johns Hopkins Hosp.*, Baltimore, 1922, xxx, 155.
MARK, L. P.: *Med. Press and Circ.*, London, 1927, clxxv, 282.

Hereditary haemoptysis

ALPORT, A. C.: *Brit. Med. Journ.*, 1927, i, 504.
ATTLEE, W. H. W.: *St. Barth. Hosp. Journ.*, 1901–2, ix, 41.
EASON, SMITH, AND BUCHANAN: *Lancet*, 1924, ii, 639.
GIFFIN, H. Z.: *Am. Journ. Med. Sc.*, Phila., 1927, clxxiv, 690.
GUTHRIE, L.: *Lancet*, 1902, i, 1243.
HURST, A. F.: *Med. Chron.*, Manchester, 1914–15, lx, 213; and *Brit. Med. Journ.*, 1927, i, 827 (Genealogy).
KIDD, J.: *Practitioner*, 1887, xxix, 104.
LIBMAN, E., AND OTTENBERG, R.: Contributions to Medical and Biological Research dedicated to Sir William Osler, 1919, i, 632.
PEL: *Ztschr. f. klin. Med.*, 1899, xxxviii, 134.
WEIL, E.: Nouveau traité de médecine (Roger, Widal et Teissier), 1927, Fasc. ix, Affections du sang et des organes hématopoietiques, Paris.

Malignant disease

FISHBERG, M.: The Jews: A Study of Race and Environment, The Contemporary Science Series, p. 311, 1911.
GANTT, W. H.: Personal communication.
HOFFMAN, F. L.: "Cancer in Mexico": An Address delivered before the American Association for Cancer Research, Rochester, N. Y., 14 April, 1927.
THEILHABER, F.: *Ztschr. f. Krebsforsch.*, 1909–10, viii, 460.
VINEBERG, H. N.: Contributions to Medical and Biological Research, dedicated to Sir William Osler, 1919, ii, 1217.

Tuberculosis

BEHREND: *XIX Century*, 1889, xxvi, 409.
FELDMAN, W. M.: *Brit. Journ. Inebriety*, London, 1923–24, xxi, 5.
FISHBERG, M.: The Jews: A Study of Race and Environment, p. 293, 1911.
WERNER, I.: *Ztschr. f. Tuberk.*, Leipz., 1925, xlii, 130.

Alcoholism

FELDMAN, W. M.: *Brit. Journ. Inebriety*, London, 1923–24, xxi, 5.
FISHBERG, M.: The Jews: A Study of Race and Environment, p. 273, 1911.
REID, G. ARCHDALE: Alcoholism, 1901.