An Address
ON
THE CONSTITUTIONAL FACTOR IN DISEASE.

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BY

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It would seem obvious that in the practice of medicine the man is as worthy of study as the malady with which he is afflicted. But during the last twenty-five years the great advances in knowledge which have followed the application of bacteriological, biochemical, and physical methods to the investigation of disease have led to the comparative neglect of the constitutional factor, and the whole question of diatheses has come to be regarded as hardly worth serious consideration by the scientific physician. The illuminating studies on constitution by such great clinicians of the nineteenth century as Laycock[1] and Jonathan Hutchinson[2] have unfortunately been almost forgotten by the present generation.

There are signs that a renewal of interest in constitution is taking place on the Continent and in America, where a clinic for the investigation of the subject has been started by Draper,[3] but with the exception of the classical work of Garrod on the rare conditions grouped by him as "inborn errors of metabolism," and a recent lecture by my colleague J. A. Ryle,[4] very little has been written on the subject in England. Since the war my investigations on the pathogenesis of gastric and duodenal ulcer, Addison's anaemia, and asthma have led me to regard a study of the constitutional factor in the causation of disease as a most promising field for research.

Without discussing with any thoroughness the fundamental meaning of constitution or the difficult problems of heredity, I shall confine myself mainly to a consideration of the constitutional factor in certain diseases in which I have been specially interested for many years, together with a more cursory consideration of certain other conditions in which the constitutional factor has been too much neglected, though it appears to be of paramount importance.

I do not think it is possible to improve upon Draper's conception of constitution as the sum of the anatomical, physiological, immunological, and psychological characters with which each individual is born. These depend in part upon heredity and in part upon other factors the nature of which is quite unknown. Acquired characteristics do not play any part in what I understand by the term constitution, though in the course of years they may profoundly influence it.

It is natural that considerable variations should occur among different normal individuals in each of Draper's four "panels" of constitution—anatomical, physiological, immunological, and psychological; many conditions formerly regarded as pathological are indeed nothing more than extreme examples of such normal variations. Some of these variations may be advantageous to the individual, whereas others may make him more liable than the average person to develop certain diseases. It is the latter type of variations that constitute diatheses, which may be defined as the inborn and often inherited characteristics which make an individual liable to react to physical, chemical, or psychological stimuli in such a manner that a condition of disease results.

A better knowledge of constitution and diatheses should make it possible to prevent some diseases hitherto regarded as unpreventable, to recognize others in an earlier stage than is at present possible, and to avoid recurrences in recurrent disorders when one attack has been overcome.

THE ANATOMICAL AND PHYSIOLOGICAL BASIS OF GASTRIC DIATHESES.

(a) *Variations in Tone, Position, and Length of Stomach.*

Though atonic dilatation of the stomach was a common diagnosis before the days of *x* rays, and though hypotonus is still frequently diagnosed by radiologists, the condition is rare. In 100 consecutive cases of abdominal disorder examined with the *x* rays by Dr. P. J. Briggs at New Lodge Clinic hypotonus was present only in 6, and in only one of these did it appear to have any direct or indirect connexion with the symptoms present. Though gastric hypertonus is a diagnosis frequently made by radiologists, I doubt whether it ever really occurs. Accurate observation has proved that the tone of the high, so-called hypertonic stomach is no greater than that of the stomach of average position, or than that of the so-called dropped stomach.

The term "dropped stomach" is as incorrect as "hypertonic stomach," for "gastroptosis," or dropping of the stomach, should indicate that the stomach has fallen from a higher position which it had at one time occupied. But there is never any evidence that this has occurred; as I first pointed out twenty years ago, the condition thus described is quite common in healthy people with excellent abdominal muscles who have always been thin, and it also occurs, though less frequently, in comparatively stout individuals. On the other hand, the so-called hypertonic stomach may exist in people who have lost much weight and whose abdominal muscles have become very weak; nothing, in fact, will make such a stomach drop materially, just as nothing will make the so-called dropped stomach rise to the level of the average stomach.

The only satisfactory explanation for the remarkable difference between the appearances of the so-called hypertonic and the so-called dropped stomach is to regard them as anatomical variations from the average normal length. Moody[5] and his colleagues have shown that the high stomach occurred in 17 per cent. of 300 healthy young men and 7 per cent. of 300 healthy young women, and that the low stomach occurred in 3.6 per cent. of the men and 15 per cent. of the women. This means that there are great variations in the normal length of the stomach, just as there are great variations in the normal length of the trunk and the limbs; according to Faber,[6] measurements on the *x*-ray screen show that the length of the stomach of normal individuals varies between 18 and 84 cm.

The stomach swings between the part of the oesophagus which passes through the diaphragm about one inch above the cardia and the junction between the duodenal bulb and the descending retroperitoneal portion of the duodenum. If it is short, it assumes the diagonal or almost horizontal position of the so-called hypertonic stomach; if it is long, it assumes the vertical position with the steeply ascending pyloric part of the so-called dropped stomach. These types of stomachs should be renamed respectively the "short stomach" and the "long stomach," and they should be regarded as nothing more than normal anatomical variations from the stomach of average length.

(b) *Variations in Gastric Secretion.*

All the earlier investigations on gastric secretion were carried out on patients suffering from disorders of the stomach. It is therefore not surprising that hyperchlorhydria was regarded as a pathological condition, sometimes secondary to gastric ulcer and sometimes primary; achlorhydria was also thought to be always pathological, and a result of cancer of the stomach or gastritis. The introduction of the fractional test meal by Rehfuss and his colleagues, and their investigations, together with those of Bennett and Ryle[7] on normal individuals, have shown that both hyperchlorhydria and achlorhydria are simply extreme variations from the average normal secretion, occurring respectively in about 10 and 4 per cent. of healthy people. They are therefore constitutional conditions, and are compatible with perfectly good health. It is doubtful whether hyperchlorhydria is ever a secondary condition, though achlorhydria is not an uncommon result of gastritis

and carcinoma of the stomach. Hyperchlorhydria predisposes to duodenal ulcer, but does not result from it; its supposed association with gastric ulcer is now known to be a myth.

Gastric Diatheses.

Campbell and Conybeare[8] have shown that the short stomach is often associated with hyperchlorhydria, and occurs most commonly in the hypersthenic type of individual. I have elsewhere described the condition in which this short rapidly emptying stomach, which secretes an abundant and very acid juice, occurs as the *hypersthenic gastric diathesis*.[9]

The long stomach is generally associated with a normal or low gastric acidity. In contrast with the short stomach, it occurs especially in individuals of asthenic type with long chests and narrow intercostal angle. It may appropriately be referred to as the *hyposthenic gastric diathesis*.

In normal individuals the stomach contains food throughout the day (T. I. Bennett), whereas in those with the hypersthenic gastric diathesis there are several hours in which it is empty except for the continuous secretion of acid gastric juice. Many of the latter individuals are habitually hungry already three hours after a meal, and for this reason they may form the habit of taking a little food or drink at such times. If this is not done the duodenal bulb is bathed with very acid juice for several hours each day; when for any reason an acute ulcer develops in the duodenal bulb of such an individual, instead of healing very rapidly without the production of symptoms, as it would in an average person, a chronic ulcer is likely to form. The hypersthenic gastric diathesis is, in fact, the essential predisposing cause of duodenal ulcer. The motor and secretory signs of the diathesis are as obvious in very early cases as in late ones, and they persist after the ulcer has healed. As the diathesis is frequently familial, duodenal ulcer also often occurs in more than one member of a family; in other cases there is evidence of the diathesis without ulceration in some members of a family, one or more of which have an active ulcer. In one family the father and two out of nine children were dyspeptic, and four others had duodenal ulcer, one dying from a perforation; in another the mother and all three sons and one grandson had duodenal ulcer. The hyposthenic gastric diathesis probably bears a similar relation to gastric ulcer; as it is also familial, gastric ulcer frequently occurs in more than one member of the same family, but in the very unusual cases in which a gastric ulcer occurs in one member and a duodenal ulcer in another, there is sometimes evidence of one diathesis in the father's family and of the other in the mother's.

The relative frequency of the two diatheses in men and women in health found by Moody and his colleagues explains both the greater incidence of duodenal than gastric ulcer and the relative frequency of the two conditions in men and women, especially when the effect of excessive smoking, which is rare in women, on the pathogenesis of duodenal ulcer is also taken into account.

Although caused, no doubt, by an unusual degree of tonic activity of the vagal nuclei, this is strictly localized to that part which controls the activities of the stomach, as it is not accompanied by a slow pulse, nor any special tendency to asthma; I do not believe that such a condition as general vagotonia exists. It might have been expected that the hypersthenic gastric diathesis would be associated with a tendency to hyperpiesia, as both conditions occur particularly in people of hypersthenic build, and that the hyposthenic gastric diathesis would be associated with hypopiesia. However, the average systolic blood pressure of 20 consecutive cases of duodenal ulcer (11 men and 9 women) seen at New Lodge Clinic was 134.7 mm., which is almost identical with that of 20 cases (11 men and 9 women) of gastric ulcer (134.2 mm.).

In his investigations on the facial characteristics of individuals suffering from various diseases, Draper[3] unfortunately grouped the cases of gastric ulcer and duodenal ulcer together. He records, however, the interesting experience of seeing three cases of perforated gastric ulcer lying side by side in a hospital in New York.

"The likeness of the three, one to another, was striking, and anthropometrically their measurements and proportions were almost superimposable, yet they had their origin in three distinct racial roots—one an Anglo-Saxon, one a Pole, and one an Italian from the shores of the Mediterranean."

In an individual with the hypersthenic gastric diathesis the nervous dyspepsia caused by overwork, the reflex dyspepsia caused by chronic cholecystitis or appendicitis, and the toxic dyspepsia caused by excessive smoking all tend to simulate the clinical picture of duodenal ulcer, although the *x* rays show no deformity, the stools contain no occult blood, and removal of the exciting cause without any dietetic or drug treatment rapidly leads to complete disappearance of the symptoms.

Constitutional Achylia Gastrica.

Achlorhydria was present in 4 out of the 100 normal students examined by Bennett and Ryle. It occurs in early childhood and is often present in several members of a family. In such cases it is presumably due to an inborn error of secretion, a constitutional and often familial achylia gastrica, which is not associated with any known structural changes in the mucous membrane of the stomach.

The absence of normal gastric digestion and the loss of what Knott has described as the antiseptic barrier of the stomach, which normally prevents the access to the intestines of bacteria derived from the food or from pathological secretions in connexion with the teeth, tonsils, or nasal sinuses, may lead to a great variety of ill effects, though it is remarkable how many people who are known to have had complete achlorhydria for many years, and perhaps for all their lives, are apparently none the worse for it. The chief digestive symptoms are nausea, flatulence, and heartburn, with vague epigastric discomfort; diarrhoea is very common, achlorhydria being the most frequent cause of intermittent attacks of diarrhoea lasting for many years. The dyspepsia of achlorhydria is often associated with acne rosacea (Barber and Ryle[10]), which, like the dyspepsia, is rapidly cured by the administration of acid.

The absence of hydrochloric acid must predispose to infections derived from food or water, such as typhoid fever and bacillary and amoebic dysentery. Streptococcal infection of the caecum from the mouth or nasopharynx often leads to chronic appendicitis, achlorhydria being found in 33 per cent. of cases (Bonar[11]).

Knott[12] has shown that achlorhydria not only allows the access of bacteria from the mouth to the duodenum, but, by causing an increase in the alkalinity of the small intestines, it permits bacteria to spread from the colon to the small intestines, the reaction of which normally inhibits their development. The consequent invasion of the duodenum with pathogenic strains of *B. coli* often leads to ascending infection of the biliary passages; thus achlorhydria is found in about 25 per cent. of patients with cholecystitis (New Lodge Clinic statistics) and 49 per cent. with gall stones (Bonar[11]).

In rheumatoid arthritis if the primary oral or nasopharyngeal sepsis is associated with achlorhydria secondary streptococcal infection of the intestines occurs; this is found in about 40 per cent. of cases, and especially in the severe and chronic, in which incomplete recovery or relapses follow eradication of the primary foci of infection.

The Constitutional Basis of Addison's (so-called Pernicious) Anaemia and Subacute Combined Degeneration of the Spinal Cord.

The only disease in which achlorhydria is always or almost always present is the syndrome of Addison's anaemia, subacute combined degeneration of the spinal cord, and Hunterian glossitis. (For the sake of brevity the components of the syndrome will be referred to as A.A., S.C.D., and H.G. respectively.)

The disease is caused by infection of the small intestine, as a result of which a haemolysin and a neurotoxin are produced in varying proportions. In about 85 per cent. of cases of A.A. symptoms or signs of S.C.D. appear before death, and the characteristic pathological changes are found *post mortem*, and in all cases of S.C.D. megalocytosis and generally more or less well marked A.A. develop at some stage in the disease. In a large majority of both conditions H.G. is found, and I have seen a few cases in which

the latter was the earliest and most prominent symptom but signs of very early A.A. could also be detected.

It has long been known that achlorhydria is almost invariably present in A.A., and in 1922 Bell and I[13] drew attention to its constant presence in S.C.D. In 50 cases of A.A. at New Lodge Clinic and in the Medico-Neurological Clinic at Guy's Hospital achlorhydria was present in all except one, in which the symptoms had developed as a direct sequel of chronic obstruction of the end of the ileum, and among several hundred published records in not more than 1 per cent. was any free acid found. Test meals have been given to 33 of our cases of S.C.D. and to 2 cases of H.G.; achlorhydria was present in all, and Vanderhoof[14] obtained a similar result in all of 29 cases of S.C.D. In a discussion before the Royal Society of Medicine in February, 1925, Dr. H. J. Macbride threw doubts upon the constancy of achlorhydria in S.C.D. as a result of statistics collected from the records of the National Hospital. He tells me, however, that his more recent experience confirms our views, and he now doubts the accuracy of the observations upon which his original statistics were founded.

The achlorhydria precedes the development of the disease: 21 cases have now been recorded in which it was known to be present from one to twenty-five years before the onset of symptoms of A.A. or S.C.D., and in many others digestive symptoms clearly due to achlorhydria have been present for many years. Achlorhydria occurred in several cases of mine in which the haemoglobin percentage had not yet fallen below 80 or 90, but the characteristic megalocytosis was found, the blood having been examined on account of the presence of symptoms of S.C.D. or simply of H.G.

There is nothing characteristic about the achlorhydria. In an analysis of 43 private cases of the A.A.-S.C.D.-H.G. syndrome[15] I found that in 6 (14 per cent.) the achlorhydria was clearly secondary to gastritis arising from food poisoning. I have also seen 3 cases in which it was secondary to alcoholic gastritis and 2 to cancer of the stomach, and others have been recorded in which it followed gastro-enterostomy and complete gastrectomy. In the remaining cases I believe it is due to the constitutional achylia gastrica, which occurs in about 4 per cent. of normal people, although, of course, only a small proportion of these ever develop the disease. Perhaps the strongest evidence in favour of this view is the frequency of a family history of A.A. or S.C.D. in patients suffering from these diseases; it occurred in 12 of the series of 43 cases (28 per cent.) just referred to, and has been recorded in 65 cases by other authors.* In several instances three, four, and even six members of a family have been affected, occasionally in three generations. Still more striking is the frequency with which achlorhydria is found in other members of the family: A.A. occurred in one or more members of the family of six patients of mine suffering from various conditions, who were found to have achlorhydria but a perfectly normal blood picture and nervous system, and twenty-six similar family histories have been recorded by other authors.

The constitutional basis of Addison's anaemia is associated, according to Draper, with a characteristic appearance of the individual. Addison himself had some idea of this when he described the disease as occurring "chiefly in persons of a somewhat large and bulky frame, and with a strongly marked tendency to the formation of fat." Draper has found that they were short-chested and had broad features with unusually widely separated eyes and large jaw angles (Fig 1).

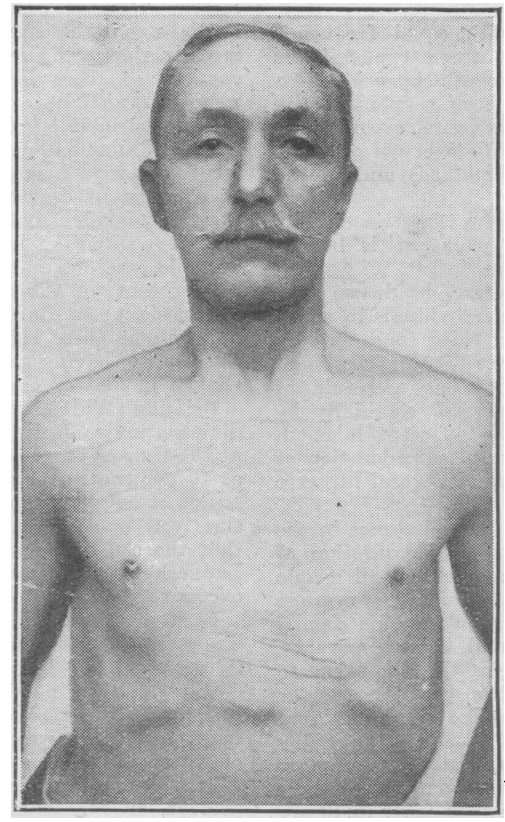

FIG. 1.—A patient with Addison's anaemia showing typical facies and wide epigastric angle.

Gastric Diatheses in Prophylaxis and Treatment.

The knowledge that the three gastric diatheses I have described predispose to certain diseases should make it our ambition to recognize them before the latter have developed, so that we may give such advice that successful prophylaxis can be instituted. The brothers, sisters, and children of patients with the A.A.-S.C.D.-H.G. syndrome should be given test meals. If they are found to have achlorhydria, they should, in common with everybody else in whom the condition is discovered, be advised to take a drachm or more of hydrochloric acid, fasting, in the morning and at lunch and dinner for the rest of their lives; given with sweetened orangeade or syrup of grenadine it makes a very palatable beverage. Such an acid drink would provide an admirable prophylactic measure in the tropics against enteric, dysenteric, and other intestinal infections among individuals predisposed to them on account of constitutional achylia or hypochlorhydria.

Important as the prevention and treatment of pyorrhoea alveolaris and nasopharyngeal sepsis are in everybody, they are doubly important in patients with any one of the three gastric diatheses, in whom the sepsis may act as the exciting cause of some serious disease.

People with a family history of gastric or duodenal ulcer should be told to choose a diet free from mechanical or chemical irritants. In the case of the hypersthenic diathesis intermediate feeds are desirable, and smoking should be kept within strict limits, as it is the most important single exciting cause of duodenal ulcer. In such individuals the slightest indigestion calls for a thorough physical and radiological investigation and examination of the stools for occult blood; if this is done, an ulcer should be discovered in the early and easily curable stage.

When a patient has recovered from a gastric or duodenal ulcer as a result of medical treatment and the removal of all foci of infection, it is essential that he should be given definite instructions with regard to diet, intermediate feeds, and restriction of tobacco and alcohol, which he must follow for the rest of his life; he should be told that he has the ulcer diathesis, and that there is likely to be a recurrence unless he strictly follows the directions he has been given. If patients upon whom an operation has been performed for ulcer were given similar rules, the frequent occurrence of jejunal ulcer and of other less serious ill results could almost always be prevented.

When a patient recovers from Addison's anaemia, as shown by the normal blood picture (except sometimes for persistent megalocytosis) and negative van den Bergh's test, it is often said that his recovery is only apparent and a relapse is inevitable. The truth is that he has recovered from the disease, but not the diathesis; he is therefore likely to reinfect his intestines and develop a new haemolytic or neurotoxic attack, just as patients with the hypersthenic gastric diathesis who have recovered from duodenal ulcer are likely to develop a new one, unless sufficient care is taken. It is therefore essential that he should continue to take acid, however well he may feel, and he

*I have never obtained a family history of the disease in hospital patients, whose knowledge of the medical history of their relatives is generally so incomplete and inaccurate as to be quite valueless.

should have his mouth, throat, and nose periodically inspected in order to arrest the development of any new focus of infection at the earliest possible moment.

THE RELATIVE IMPORTANCE OF CONSTITUTION, PREGNANCY, AND INFECTION IN THE DEVELOPMENT OF GALL STONES.

There are three well established facts about gall stones.

First, they frequently occur in more than one member of a family. Chauffard obtained a history of the disease in the relatives of 34 per cent. of his cases. From this it has been concluded, especially by French authorities, that there is an important constitutional factor in the pathogenesis of the disease. This has been supposed to be a constitutional cholesterolaemia, as Chauffard found excess of cholesterol in the blood in 95 per cent. of 46 patients with gall stones, Bell, and subsequently Shiskin, in 60 per cent. of 101 cases under Moynihan, and Alexandresco-Dersca in 75 per cent. of 41 cases, though Campbell found no excess in 10 cases under my care.

Secondly, gall stones are found with equal frequency in men and in childless women, but for every childless woman with gall stones there are four who have had one or more children. From this it has been concluded that pregnancy is a very important exciting cause, a conclusion which appeared to be confirmed by the discovery of constant excess of cholesterol in the blood (Chauffard) and in the bile (McNee) in pregnancy.

Thirdly, in the vast majority of cases there is definite clinical and pathological evidence of cholecystitis having preceded the development of the stones.

The general conclusion might, therefore, be drawn that cholecystitis gives rise to gall stones in individuals in whom the quantity of cholesterol in the blood and bile is excessive, either as a result of an inherited constitutional deficiency in cholesterol metabolism or as a result of pregnancy. This is the view put forward especially by French physicians, and I was inclined to accept it until, in preparing this address, a more careful consideration of the data upon which it was based revealed several hitherto unsuspected fallacies.

In the first place the high incidence of gall stones in the general public was ignored in discussing the question of heredity. The bodies of about 10 per cent. of all people dying in adult life contain gall stones. An average individual, in replying to a question about his family history, will think of his brothers and sisters, parents, uncles, and aunts, and grandparents. If three is taken to be the size of an average family, then he will consider four grandparents, two parents, four uncles and aunts, and two brothers and sisters, a total of twelve. Supposing two of the uncles, aunts, brothers, and sisters died before they reached adult life, ten relatives are left, and of these one is likely to have had gall stones, as they occur in 10 per cent. of adults. The conclusion is that everybody is likely to have a near relative who has gall stones or will have gall stones before his or her death. Supposing that the diagnosis is made in only one case out of three, we are left with 33 per cent., which is the figure given for the occurrence of a family history of the disease in patients with gall stones. It is clear, therefore, that such a history is no more common among patients with gall stones than would be expected from its incidence in the general population.

With regard to the influence of the hypercholesterolaemia of pregnancy on the pathogenesis of gall stones, it is necessary to remember that about four women out of every five have one or more children before they die. It is obvious that, apart from any special liability to the disease, four women who have had children will have gall stones for every one woman who has had no children. The relatively much greater incidence in women than in men cannot therefore be due to the influence of pregnancy.

We are thus left with cholecystitis as the only indisputable predisposing cause of gall stones. Common as gall stones are, cholecystitis is still more common, but why some patients with the latter should develop stones while others do not remains for the present a mystery. It is, of course, possible that a non-familial constitutional factor is responsible. Thus it is noticeable how frequently a patient with gall stones gives a history dating from childhood of intolerance to fats or to some special forms of fatty food. This might very well be an expression of the same constitutional abnormality in fat and cholesterol metabolism which predisposes to the production of gall stones and is sometimes associated with hypercholesterolaemia. The anthropometric studies of Draper also tend to show that gall stones occur in a definite type of individual with a deep chest, wide subcostal angle, and wide rounded face with relatively narrow eyes. Possibly, too, certain congenital variations in the anatomy and motor functions of the gall bladder and biliary tract, which predispose to biliary stasis, as suggested by Berg,[16] are the determining factors in the production of stones in an infected gall bladder.

DIABETES.

The inherited predisposition to diabetes has long been known. Combining the investigations of Williamson[17] on 300 cases and Barach[18] on 350 cases, 22 per cent. had a history of diabetes in one or more members of their family; as diabetes is the cause of about 1 per cent. of all deaths, it is clear that coincidence could account for not more than one-half of these family histories. Many diabetics, who would formerly have died before they had any children, or who would have become impotent soon after marriage, are now kept alive and capable of raising a family as a result of treatment with insulin. The great increase in the number of children of diabetics is certain to result in a greatly increased incidence of the disease.

It is a familiar fact that a large proportion of adult diabetics are obese at the time the disease develops. Thus 80 per cent. of 925 adults under the care of Joslin were over weight; in Barach's series of 350 cases 90 per cent. had become obese between the age of 21 and the onset of the disease, having gained an average of 59 lb. without any change in diet or occupation.

Priscilla White[19] found that 90 of 100 children with diabetes under Joslin's care were above the average height at the time of onset of the disease, but only 5 were as much as 10 per cent. over weight for their height. The average excess of height among other children of the same age and class was no less than $2\frac{7}{10}$ inches. It appears, therefore, that the constitutional inherited liability of the islands of Langerhans to degenerate is associated with a tendency to excessive stature in childhood and obesity in adult life.

In 40 per cent. of Williamson's 300 cases of diabetes there was a history of mental anxiety, worry, or sudden shock; in a quarter of these there was also a family history of diabetes. In 31 per cent. of the same series the patients had for long periods indulged in great excess of sugar or sweet food and drink, though not of starch; in a quarter of these there was also a family history of diabetes. Allowing for 9 patients in whom all three factors were present, an emotional or dietetic exciting cause existed in 47 of the 76 (62 per cent.) with a family history of diabetes. It is clear, therefore, that individuals with a diabetic family history ought, as far as possible, to avoid occupations which are likely to involve much mental stress, and they should be specially instructed to be very moderate in their consumption of sugar. It should also be remembered that acute infections, such as influenza, are not infrequently the exciting cause of diabetes; consequently the urine should be examined for sugar after, as well as during, such illnesses; this, of course, applies to everybody and not merely to those with a family history of diabetes.

CONSTITUTIONAL VARIATIONS IN THE REACTION OF THE URINE.

(a) *Nephritis.*

Osman[20] has recently shown that a special liability to the development of nephritis is present in individuals with a high acidity of the urine. Thus among 109 patients with scarlet fever, investigated with Dr. C. K. Colwill at the Monsall Fever Hospital, 14 out of 21 (66 per cent.) with a high urinary acidity (under 5 *p*H), but only 3 out of 88 (3.4 per cent.) with a low urinary acidity (over 5 *p*H), developed albuminuria or nephritis. In another series of observations on 431 cases of scarlet fever at Park Fever Hospital Osman and Woodfield found that the liability to albuminuria and nephritis could be almost completely overcome by giving 15 grains each of potassium citrate and

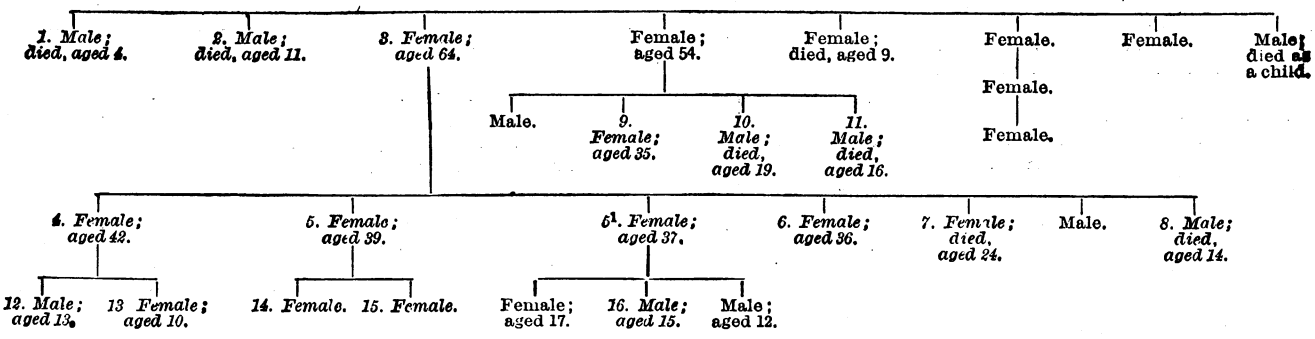

FIG. 2. Cases suffering from nephritis are italicized.

sodium bicarbonate three times a day in order to keep the urine more or less alkaline.

It is unknown why the urine of one healthy individual should be much more acid than that of another living under similar conditions and taking a similar diet, but it is exceedingly probable that it depends, in part at any rate, upon constitutional and inherited variations in the complicated biochemical processes upon which the reaction of the urine depends.

It will be interesting in the future to note whether the tendency to develop nephritis in certain families depends upon a familial tendency to excessive acidity of the urine. The accompanying family tree (Fig. 2) shows how extreme this familial tendency may be in exceptional cases; unfortunately my observations on members of the family were made long before Osman began his researches on the pathogenesis of nephritis, so I have no record as to the degree of acidity of their urine.

Very important conclusions can be drawn from Osman's work; alkalis should be given to all patients suffering from scarlet fever whose urinary acidity is high; the reaction of the urine of members of a family with a tendency to nephritis should be examined, and, if the acidity is high, they should constantly take alkalis; and, quite apart from the question of the alkaline treatment of nephritis recommended by Osman, the well known tendency to recurrence under unfavourable conditions in individuals who have once had nephritis could perhaps be overcome by the constant use of sufficient potassium citrate to keep the urine alkaline.

(*b*) *Phosphaturia and Phosphatic Calculi.*

Just as the urine in some individuals tends to be more acid than the average, so in others it tends to be more alkaline, the tendency being exaggerated during periods of mental strain and overwork. At such times the urine passed at the end of micturition may be milky, owing to a deposit of phosphates occurring in the urine whilst still in the bladder.

It is natural that individuals with this constitutional condition should be liable to develop phosphatic calculi. Patients sometimes have a history of passing such stones at intervals for many years, sometimes from one kidney only, sometimes from both.

A stout woman of 44 had passed phosphatic calculi at intervals during the last ten years. My clinical clerk, Mr. D. B. Smallshaw, found that one of her own stones, weighing 0.31 gram, lost 16.1 per cent. of its weight on being kept at the body temperature for four days in a test tube containing her own urine after it had been rendered acid by the administration of 90 grains of acid sodium phosphate four times a day. When not taking this drug her urine was constantly alkaline; after being kept in her alkaline urine for a day the stone increased in weight from 0.260 to 0.262 gram.

It seems reasonable to advise all patients whose urine is constantly alkaline, or who have ever passed a phosphatic calculus, to take sufficient acid sodium phosphate to keep their urine acid. If this is done, small phosphatic stones, which are not causing any obstruction to the urinary flow, and which are therefore subjected to the action of the urine flowing over them, might reasonably be expected to dissolve.

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(To be concluded.)

TUBERCULIN: IS IT A SPECIFIC?

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THE object of this article is to inquire, Is tuberculin a specific for tuberculosis in either diagnosis or treatment?

By tuberculosis I mean an infection by the tubercle bacillus of Koch—latent tuberculosis if the bacilli be living but producing no symptoms, active if living and producing symptoms, obsolete if the bacilli have died and the lesions have healed. By specific test I mean an efficient test for the presence of a disease by a reagent derived from its specific bacteria. The modern Wassermann test does not fulfil this requirement of derivation from the same species; the agglutination test for typhoid fever does; so too does tuberculin for tuberculosis; it remains to inquire, Is it efficient?

It is made by the subcutaneous injection into a patient, whose temperature is normal, of doses (usually 1, 5, and 10 mg. in succession) of (1) Koch's old tuberculin, or Koch's lymph, or, shortly, old T.; or (2) since 1911 of similar doses of albumose-free tuberculin or T.A.F., a preparation of exactly the same strength as old T., but made from tubercle bacilli grown upon a medium containing liquid extract of asparagus but neither albumin nor albumose. Evidence of the reaction is threefold—local, general, and focal. The local reaction consists in inflammation at the site of the injection; the general reaction in fever with a temperature of 100° F. or more and the ordinary accompaniments; the focal reaction in increase of symptoms and signs at the site of the disease. The local reaction may occur alone; general and focal reactions do not occur without a local reaction unless the injection has been made directly into a vein. The local reaction is obtainable also by the dermal or conjunctival application of tuberculin.

The reaction is an active response of the body cells to the stimulus of the injected reagent. Experience shows that all patients suffering from active tuberculosis give the reaction, excepting only those who have been so treated