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ON

PREDESTINATION IN DISEASE.

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BY

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THE word "predestination" brings the grim figure of Calvin before the mind. But it is not with the theological aspects that I wish to deal. The flames of hell have lost their terror, but as man must be frightened about something, he terrifies himself about germs or cancer or whether he is eating enough vitamins. This fills the void, which disbelief in hell has left, quite satisfactorily. True, the scientific doctrine of determinism approximates to predestination. On that view every act is predetermined by our reaction to some afferent impulse—determined by our original make-up as modified by the effect of previous impulses. This doctrine has been carried to its logical conclusion by Freud when he maintains that slips of the tongue or pen and forgetfulness are the result of causes which can be discovered and which throw light on the working of the unconscious level of our minds. On this view the only variable factor in a man's behaviour comes from his environment, which may vary the kind of stimulus he receives—the rest is predestined.

Now I would like to say, in passing, that while I object to the doctrine of the verbal inspiration of Freud, and while I think he bases his views of the origin of the instincts too much on one instinct, I do really feel that when the dust of controversy has cleared away Freud will be recognized as one of the most original thinkers of our time, and his scientific achievement equal to that of Darwin. But I do not intend to-night to delve into the mysteries of the unconscious. Mine is a less ambitious task—that of estimating the effect that modern work has had on the doctrine of diatheses.

DIATHESSES.

Even in the days of Hippocrates the doctrine of diatheses was taught, and it survived into the latter half of the nineteenth century. What exactly is meant by diatheses? Jonathan Hutchinson, in his lectures on "The pedigree of disease," in 1884, defined a diathesis as any bodily condition, however induced, in virtue of which the individual is, for a long period, or usually through the whole life, prone to suffer from some peculiar type of disease. Some diatheses, he said, are inherited, others are acquired. Of some the effects are permanent or constant, of others they are transitory, or recurrent after intervals of health. Later on, in the same course of lectures, he defined diathesis more briefly as "any condition of prolonged peculiarity of health giving proclivity to definite forms of disease."

But the bacteriological conception of disease that had been initiated by Pasteur had already thrown the doctrine of diatheses under a cloud. The scrofulous diathesis was a conception which was particularly open to attack. Not only were some observers confusing syphilitic with tuberculous diseases under that heading, but even those who were free from this gross error did not sufficiently distinguish between the tendency to infection by tubercle and a condition in which such infection had already occurred. It may be said that both syphilis and tubercle are infective granulomata, but it must certainly be admitted that a definition which does not draw a clear distinction between them is really worthless. Moreover, the strumous diathesis was open to a similar criticism, that it did not distinguish between the liability to, and infection by, tubercle. Nothing much can be said in favour of a classification which con-

fused some cases of glandular tubercle with syphilis and attempted to separate others into two different diatheses. Yet, curiously enough, it was exactly the same point which, after helping to overthrow the doctrine of diathesis, then helped to dethrone the bacteriological factor from its supremacy. When it was realized how ever-present the tubercle bacillus was, how exposed everyone was to its inroads, and how comparatively few submitted to those inroads, it was forced upon our attention that the seed was not all-important, the soil must also be considered. Fortunately that seed falls upon stony ground in most of us. And so back came diatheses, with a difference. A new interest was awakened in the subject of natural immunity.

But despite Jonathan Hutchinson's gallant attempt to stem it, the tide was to run strongly against diatheses for some years to come. Nor is this surprising if we read those lectures. Surely never was the saying that the wisdom of one generation is the foolishness of the next better illustrated. Here was a man of unique clinical insight, extraordinary powers of observation, and great experience, making inevitable mistakes which would not be tolerated to-day in a candidate for his diploma—inevitable because he had not the data on which to base a correct opinion. Who to-day would dare to speak of the malarial diathesis, or who would attribute leprosy to the eating of unwholesome fish? Yet mingled with these errors are numerous shrewd guesses at future developments. Thus he quotes Spencer Watson as saying, in 1882, that "free exposure to sunlight and warmth would do much to enable a child improperly fed to effect assimilation in such a way as to keep clear of rickets." And he concludes thus: "We may certainly believe it probable that our climate and the narrow, sunless streets of our large towns take their share in the production of rickets." Yet it was not until after the war that this view was set on a sound scientific basis. We shall be very lucky if, forty-five years hence, our theories and conclusions of to-day stand the test of time as well as those of Jonathan Hutchinson.

When I entered St. Bartholomew's Hospital in 1894, only one of my teachers referred to diatheses without an apologetic smile. Sir Dyce Duckworth alone maintained a robust faith in them. Yet at that very time Weismann, the Calvin of biology, was laying down the rigid doctrine of the germ plasm. No acquired character was transmitted, he averred, for acquired characters only affected the somatic cells, and in the germ plasm alone did heredity reside. Later on the discovery of the chromosomes and the rediscovery of Mendel's work seemed to place this doctrine on an assured basis. This inevitably brought the idea of predestination into medicine. The progress of human thought is always in a spiral; the turn of the spiral had now been reached, and, as I have already said, back came diatheses, with a difference.

It is interesting to see how, even in some matters of detail, the old ideas have been coming back. In 1862 Dr. Laycock published his lectures on "Physiognomical diagnosis," in which he called attention to certain facial types which assisted in the diagnosis of the diseases from which their owners were suffering; and Draper at Columbia University is at present studying this subject anthropometrically, and trying to establish by direct measurements the existence of certain types, such as the gall-stone type, the peptic ulcer type, and the pernicious anaemia type. He has collected a mass of data in his book *Human Constitution*, and has certainly revived an interest in the subject of diathesis. I have had the pleasure of his company in my wards at St. Bartholomew's Hospital, and it was clear that his system enabled him to make shrewd and often correct guesses at the diagnosis, though I think he will have to do far more work before his conclusions command wide acceptance.

My main purpose is to discuss certain recent investigations which give us some hopes that we are arriving at clearer views as to the factors which go to determine liability to disease, factors which admit of some accuracy of determination, some degree of measurement. I refer to such subjects as inborn errors of metabolism, idiosyncrasy, endocrine balance, and the posture of the viscera. I will deal first with those which express themselves through some recognizable chemical disturbance.

Inborn Errors of Metabolism.

This term was introduced by Sir Archibald Garrod to describe certain congenital abnormalities which could be diagnosed by chemical tests. They are so rare that a man may spend his whole professional life in busy practice and never see a case. They may lead to a disease in some instances, but they more frequently cause no discomfort. It might be thought, therefore, that their study is a wasted endeavour. But by years of careful observation Sir Archibald Garrod was able to arrive at certain general conclusions which have thrown much light on the way in which the body works, and on some important factors in our constitutional make-up.

The inborn errors which are at present recognized are albinism, alkaptonuria, cystinuria, pentosuria, and porphyria. Four out of the five, therefore, are characterized by the presence of an abnormal substance in the urine. But each of these substances, though not normally excreted, is a normal intermediate product of metabolism. The peculiar feature, then, is that in persons suffering from such conditions the ordinary breaking down of their tissue cells stops short at a certain point, and the product formed at that stage is excreted. In the remaining example, albinism, there is evidently a closely similar state of affairs. The albino is unable to manufacture any pigment containing melanin, and if he is given melanin he merely excretes it as such, although he can manufacture the pigments of blood and bile just like an ordinary man.

Now we have been gradually forced to recognize that each successive step in the building up or breaking down of all tissue components, even of individual fractions of proteins and of individual sugars, is the work of special enzymes or ferments set apart for each particular purpose; and, to quote Garrod: "If any one step in the process fail, the intermediate product in being at the moment of arrest will escape further change, just as when the film of a cinema is brought to a standstill the moving figures are left, foot in air." Very curious, you may say, but not important, considering the rarity of these conditions. But wait a moment; Garrod quotes a far-seeing remark which Claude Bernard made in 1880: "Would anyone dare to maintain that it is necessary to distinguish the laws of life in a pathological state from those laws in a normal state? That would be like distinguishing between the laws of mechanics in a house that falls down and in a house that remains standing." In other words, the great value of the study of these inborn errors of metabolism is that they have shown us some of the intermediate steps taken in the ordinary metabolism of tissues and have helped to prove that each step requires its own special ferment.

These inborn errors of function are the chemical analogues of structural malformations; they do not tend to get worse, but they may predispose to further trouble. Alkaptonuria passes a urine which darkens on standing and reduces Fehling's solution, thus perhaps leading to an erroneous diagnosis of, and unnecessary treatment for, diabetes. But he may also develop a special form of arthritis and be inconvenienced by ochronosis, a pigmentation of his conjunctivae and of his cartilages similar to that which may be developed by prolonged use of carbolic acid—for example, as a dressing—and essentially due to a similar chemical cause. The cystinuria has no inconvenience unless he contract an infection of his urine, when he may develop a cystin stone in his kidney or bladder. The pentosuria is unable to deal with the special sugar which is set free in the breakdown of the nucleo-proteins of his cell nuclei, but will suffer from no inconvenience unless he tries to insure his life, when he is very likely to be unnecessarily rejected. As for the porphyria, we know that the haematoporphyrin of the blood pigment is a sensitizer to light. If haematoporphyrin is injected into each of two albino rabbits and one is kept in the dark no harm will result to it, but if the other is allowed to run about in sunlight it will die. It has no protective pigment, and the free haematoporphyrin makes it fatally sensitive to light rays. Haematoporphyrin in the combined state enables actinic rays to reach the hidden recesses of our body through the blood stream, but the individual who is unable to decompose it when red blood corpuscles die a natural

death is so sensitive to light that every summer he is apt to develop a vesicular rash on any exposed part.

Such errors of metabolism fulfil Jonathan Hutchinson's definition of a diathesis—"any condition of prolonged peculiarity of health giving proclivity to definite forms of disease." A further point of great interest is that these inborn errors of metabolism are liable to occur in several members of the same family, most often in collaterals of the same generation, born of normal parents. Direct transmission from either parent to child is very rare. Like many such abnormalities, they are specially liable to occur in the offspring of marriages between first cousins. Much has been said against such marriages, but it is generally admitted to-day that the mere fact of consanguinity of parents cannot cause "an anomaly to appear *de novo* in their children, but it is obvious that the reappearance of a latent character which both parents tend to transmit is likely to be favoured by the mating of members of certain families" (Garrod). What is often forgotten by opponents of such marriages is that favourable variations are just as likely to reappear as unfavourable ones. Hereditary genius has apparently been fostered by the marriage of first cousins. Of course, if such intermarriages were frequently repeated in a family, the ordinary bad effects of prolonged inbreeding would assert themselves.

The proportion of first-cousin marriages in this country is estimated at between 3 to 5 per cent. of all marriages, yet of 34 cases of alkaptonuria 15 were in the children of first cousins—that is to say, 44 per cent. of the cases sprang from marriages which constitute less than 5 per cent. of the total marriages. The late Professor Bateson pointed out that the mode of incidence of alkaptonuria finds a ready explanation if the anomaly in question be regarded as a rare recessive character in the Mendelian sense. Naturally such recessive characters are more likely to occur when the parents are consanguineous.

I have dwelt at some length on this rare group because of the light they throw on questions of wider interest. They show that each step in metabolism requires its special ferment, that the absence of some special ferment may induce a predisposition to a disease, and that this lack may be transmitted according to the Mendelian laws of heredity. Such clear-cut results in this narrow field will doubtless find applications in wider fields. In gout we have an error of metabolism, which is sometimes clearly inherited, but sometimes apparently acquired. Yet that apparent acquisition may perhaps only be a latent inborn tendency made active by habit or environment. The chemical factor is an inability to deal with the uric acid set free by the breakdown of nucleo-proteins, yet it often requires the presence of a low-grade sepsis to make it effectively noxious. Routine analyses of the blood have shown that many more people have excess of uric acid than have ever had gout. Of all hereditary disease haemophilia is the most striking, both because of its dramatic and often tragic manifestations, and because, as a corollary of this, of the detailed knowledge we have of its method of transmission. Cases have been traced back in an exalted family as far as 1500; Dru Drury mentions a family in South Africa, springing from old Dutch settlers, in which haemophilia has been traced back for twelve generations, over a period of 250 years and affecting 610 individuals.

In every case the method of transmission is the same—by the female line, though only males are affected. This gives us some clear evidence to go upon, for sex is a Mendelian characteristic, dependent on a chromosome. Females have an even number of chromosomes, males have an odd number, being one short. This odd one is called the X chromosome, but some sperm cells contain this, others do not. The union of an egg cell with a sperm cell containing an X will result in the offspring being female, while such union with a sperm cell which does not contain an X means that an unpaired X will result, and the offspring will be male. It would therefore appear that haemophilia is due to the transmission of an X chromosome derived from the egg cell which has remained unpaired at fertilization. If it is paired this peccant chromosome is rendered harmless. We know that in certain

animals particular characters are transmitted by particular chromosomes, but this, as far as I know, is the only instance in which we can apparently associate the transmission of a disease in man with one recognizable chromosome. But, further, we know that the haemorrhagic tendency to haemophilia, unlike purpura, is due to a delay in the coagulation time, and that this delay is due to a lack of one of the constituents of the fibrin ferment—namely, thrombogen. Here, therefore, we have a deadly disease due to the lack of a particular ferment which is transmitted according to definite Mendelian laws. In other words, it fulfils the same criteria as those demanded by the rare and seldom serious inborn errors of metabolism.

The transmission of the pseudo-hypertrophic form of muscular dystrophy is similar—that is, it is transmitted by the female line but usually attacks males. However, girls occasionally suffer from the disease, though it is five times more common in boys than in girls, but this is sufficient to destroy any idea of its necessary connexion with the X chromosome. Spiller's remark in Osler and McCrae's *System of Medicine*, that "it seems extraordinary that sex should influence the onset of this disease, especially at so early an age," ignores the fact that sex is dependent on the chromosomes, and is determined at the moment of fertilization.

Another rare familial disease which has some interesting bearings on my topic is familial haemorrhagic nephritis, of which I have seen examples in two different families. The most striking group is the family described by Hurst, of which I saw two members. In this family there were 27 persons in three generations, of whom 16 suffered from nephritis. The males were much the most seriously affected, all the affected ones having succumbed with the exception of one child in the third generation, while the females were involved to a much lesser degree, and only two succumbed. In the early stages there was merely haematuria, and Leonard Guthrie, who studied some of the earlier cases, preferred not to label them as nephritis; but later on undoubted nephritis developed, and typical uraemia has closed the scene in several. In the two patients I had the opportunity of seeing, the passage from haematuria to nephritis was distinctly observed in the boy, but not in the girl. Dr. Hurst kindly made some biochemical tests, and we found it possible to predict the onset of the haemorrhage by noting an increased concentration of the urine and an increased output of neutral sulphur. This suggested to us that some abnormal protein breakdown was the immediate cause of the haemorrhage, and that repeated irritation of the kidney in this way led to nephritis. It is an interesting fact that in some members of the family certain articles of diet, especially black currants or claret, would induce an attack. I strongly suspect, therefore, that the nephritis in this family was the consequence of some error in metabolism which resulted in the excretion of intermediate products in a form damaging to the kidney. This has an interesting bearing on Aschoff's views as to the importance of a pre-renal factor in inducing nephritis, while bringing the familial type into close relationship with the other errors of metabolism I have mentioned.

Idiosyncrasy.

I next come to the subject of idiosyncrasy as a factor in predestination in disease. Sir Humphry Rolleston considers that idiosyncrasy is a semi-popular rather than a scientific term, but briefly defines it as an unusual physiological equation. It is a special instance of allergy, a term introduced by von Pirquet to describe all forms of altered reactivity of the organism. It therefore includes hypersensitiveness on the positive side and immunity on the negative side, but is now commonly confined to the former condition. Very often allergy is restricted to an inborn sensitiveness, while the term "anaphylaxis" is applied to an acquired sensitiveness. Here we are only concerned with an inborn sensitiveness. Morley Roberts has made the profound remark that "immunity is assimilation." There is one flesh of birds and another of beasts. From the welter of amino-acids which result from the disintegration of food proteins each animal has to build up its own characteristic and specific tissues. Specificity is chemical

as well as morphological. To some foreign proteins we are naturally immune—that is, we can assimilate them automatically; to others we acquire immunity—that is, we learn to assimilate them; but to some foreign proteins immunity is neither congenital nor acquired. The tissues continue to resent the intrusion of such. They will not assimilate them. Such proteins excite anaphylaxis, or, more strictly, allergy, in varying degrees. Richet has defined anaphylaxis as the last stand of the race against adulteration of its protoplasm. In extreme degrees anaphylactic shock is fatal because assimilation would mean too profound an alteration of bodily structure. In less degrees both allergy and anaphylaxis declare themselves in violent attempts to get rid of the foreign invader. These attempts take the form of diarrhoea and vomiting, of giant urticaria, or of asthma. Hypersensitiveness, then, is the refusal on the part of the individual's protoplasm to attempt to deal with certain foods and drugs in order to conserve its own identity. If inborn errors of metabolism indicate a difficulty in katabolism, idiosyncrasy indicates a difficulty in anabolism. It gives a scientific basis for the old saying that one man's meat is another man's poison. The substances which excite these reactions are not in the least toxic to the ordinary individual. Freeman has injected himself intravenously with doses which would be fatal to a sensitive subject without any symptoms resulting. He has given rabbits enormous doses of an extract of grass pollen, such as would kill a pollen-sensitive asthmatic, without any results. Indeed, one can hardly imagine a rabbit being sensitive to grass pollen. Such rabbits could not survive in the struggle for existence.

Some years ago I saw an extreme example of hypersensitiveness to eggs in a young man. He was made very ill by the minutest trace of egg-white, whether he was conscious of taking egg or not. He did not know that a roll might be glazed by egg-white until it produced the following distressing symptoms—an immediate tingling sensation on the tongue, followed by a shudder; then copious salivation, first frothy, then in long viscid strings, difficult to spit up; next, spasmodic contractions in the throat, rendering it most difficult to swallow even saliva; then severe abdominal pains and cramps, continuing for about eight hours. A larger quantity of anything containing egg albumen would cause violent diarrhoea and vomiting, with alarming collapse. I have noted that egg-sensitive persons are liable to be upset by eating chicken, and it is well known that if one emanation from an animal causes a reaction others from that animal will do likewise. The man who gets asthma from horse dandruff will get a violent rash and joint swellings from an injection of horse serum, and may have an alarming and even fatal collapse. On this fact the protein skin tests have been based, and it has been claimed that in this way the peccant protein may be discovered. Unfortunately this method has not proved the success in practice that was anticipated. The patient may show a reaction to a large group of substances, and is not constantly sensitive to the same substance. Thus I saw a patient who was emaciated and profoundly depressed, but whose chief objective trouble was a painful swelling of the tongue and lips. His skin reactions showed that he was highly sensitive to cereals, which were accordingly removed from his diet, and he made a dramatic improvement, gaining 16 lb. in weight in one month. Later on he relapsed, and a repetition of the skin tests showed that, although he was no longer sensitive to cereals, he gave a marked reaction for some other groups.

Intradermal tests are the best, and the Schick test for diphtheria and the Dick test for scarlet fever, which are based on that method, have proved of great value in distinguishing between those who are naturally immune to and those who are susceptible to these diseases.

Briefly to summarize this section—immunity and hypersensitivity are the opposite poles in an assimilative process; if the cell can assimilate a substance it is immune to any toxic results that substance might produce; if it is hypersensitive to that substance this is because it cannot assimilate it. From the make-up of their protoplasm some individuals are quite unable to do this, and are therefore predestined to suffer if exposed to material which for them may be highly toxic.

The Sympathetic-Endocrine Balance.

Time will not allow of my making more than a brief reference to the important factor of the endocrine balance. That some individuals inherit an imperfect equipment of endocrines is well recognized; a family tendency to thyroid disturbance is frequently seen—and, curiously enough, the balance may lead to overaction in one member and to underaction in another of the same family. Now there is a very interesting point in connexion with Graves's disease. It is always accompanied by a persistent and usually enlarged thymus. The thymus should have atrophied before puberty; it is an infantile gland which retards the development of sexual maturity. On the other hand, Graves's disease seldom develops before puberty, so that it would appear that only those patients in whom the thymus fails to atrophy are capable of developing Graves's disease. Here, therefore, we have again a family liability to a disease, in this case associated with the persistence of an infantile gland. Cases of hypopituitarism also tend to run in families. As for pluriglandular syndromes, these are, in my experience, usually associated with a gonadal defect, which naturally interferes with fertility. In this way a family in which the endocrine balance is too grossly disturbed tends to die out. Mott has shown that exactly the same thing happens in some families liable to mental disease. The mental trouble tends to occur earlier and earlier in each generation until, by producing dementia praecox, in which there is usually gonadal deficiency, the propagation of this inherited defect is checked. It is to be regretted that this method of eliminating mental disease is not more widely adopted by nature.

We know that the endocrine glands, the thyroid, adrenals, and pituitary, co-operate with the sympathetic nervous system, while the pancreas, and possibly the parathyroids, co-operate with the vagus. Eppinger and Hess have tried to classify the neurotics into two main groups—the sympathicotonic and the vagotonic. While not accepting all their conclusions, which are certainly too hard and fast, we may agree that there is a group whose tendency to an overactive sympathetic is displayed by tachycardia, overaction of the thyroid, adrenals, and pituitary, a tendency to high blood pressure, a raised blood sugar, and a liability to glycosuria. Such individuals easily develop a temperature from a trivial infection. Temperamentally they are liable to phobias. On the other hand, we have the type where the overacting vagus displays itself by a slow pulse, liability to syncope, asthma, hay fever, urticaria, spastic constipation, and low blood sugar. They react badly to infections, and their temperament is one of vague apprehension. Such patients are often a good deal benefited by belladonna, which paralyses the vagal endings. I have referred to the chemical idiosyncrasies of the asthmatic, but he is also the victim of this over-acting vagus. But this overaction may be relative rather than absolute; I mean that an underacting sympathetic may tip the balance in the direction of the vagus. Thus Widal reported the case of an asthmatic who subsequently developed myxoedema; treatment by thyroid extract not only relieved the myxoedema but also the asthma. Indeed, the relief of the asthmatic paroxysm by injections of adrenaline is another example of restoring the balance in favour of the sympathetic. These tendencies to a disturbance of the balance in one direction or another certainly run in families, and Cammidge has collected family histories which suggest that their inheritance follows Mendelian laws.

Achlorhydria.

I wish specially to call your attention to the way in which the absence of hydrochloric acid in the gastric juice may predispose to various diseases. In many respects we do not attach the same importance to gastric digestion as formerly. A man can assimilate his food after a total gastrectomy, and the pancreas is not so dependent on gastric HCl to start its secretion as Bayer and Starling concluded. But in one respect the HCl is now known to be of greater importance than was suspected, and that is in its bactericidal action. Indeed, as I pointed out a good many years ago, it may well be that the reflex hyperchlorhydria excited by some infection lower down in the alimentary tract is an attempt to check further bacterial

invasion from the mouth. Now achlorhydria may be acquired as the result of prolonged chronic gastritis, but it may also apparently be congenital. Indeed, according to Izod Bennett, it is just about as common as red hair. Bennett and Ryle in 1921 found by fractional test meals on 100 healthy medical students at Guy's Hospital, that 5 per cent. had complete achlorhydria, while 15 per cent. had hyperchlorhydria, the remaining 80 per cent. having normal curves. Now it is a well-known fact that certain diseases are always associated with achlorhydria, whether congenital or acquired, while certain other diseases are more likely to occur in its presence. Let me take, as the most striking instance, *pernicious anaemia*. When Dr. William Hunter, some thirty years ago, called attention to the association between pernicious anaemia and oral sepsis, one wondered why the disease was not far more common, considering how little attention was then paid to oral hygiene. Then it became clear that it never occurred unless achlorhydria was also present. Other sufferers from pyorrhoea might suffer from many diseases, but never from pernicious anaemia. I have seen pernicious anaemia develop in achlorhydria that has been acquired—for example, by short-circuiting—but that the achlorhydria which is responsible is usually congenital is suggested by this being an abnormality affecting 5 per cent. of the population, and is made almost certain by Hurst's observation of its more frequent occurrence in the families of patients with pernicious anaemia. The discovery of the efficacy of liver treatment in pernicious anaemia has given a new orientation to our outlook, but the primary importance of achlorhydria remains. Indeed, recent work by Castle of Boston helps to reinforce it. He showed that the normal products of the digestion of meat by gastric juice had much the same effect as liver. He concluded that this acid digest stimulated the patient's liver to produce something which prevented the breakdown of red corpuscles; the normal liver we administer contains that substance pre-formed.

Another disease which is invariably associated with achlorhydria is *subacute combined degeneration of the cord*. Collier, Batten, and Risien Russell, in 1900, showed that this disease might anticipate or follow pernicious anaemia, or occur independently. They concluded that it was due to the same toxin. Since then repeated fractional test meals have proved that it never occurs without achlorhydria, and it is also recognized that some degree of cord change is often found in pernicious anaemia, if it is carefully looked for. Once degeneration of the cord has occurred, treatment by liver is, of course, unable to restore it, but in the earlier stages, when there are only toxic symptoms and before structural changes have occurred, this remedy is of decided benefit. Curiously enough, this disease seems specially common in Newcastle, and although most neurologists would not accept the diagnosis in some of the cases reported there by Ungley and Suzman, two facts stand out—toxic symptoms resembling subacute combined degeneration of the cord were often relieved by liver treatment, and achlorhydria was common in the healthy members of the families of patients suffering from suspected or declared cord changes of this kind.

I have been greatly struck with the frequency of achlorhydria in *ulcerative colitis*, and with the great benefit which has been derived from the administration of HCl in these cases. I was led to this by Hurst's observation of the frequency of achlorhydria in various forms of irregular diarrhoea. In such cases I have generally found a normal intestinal flora on bacteriological examination of the stools, or at any rate the absence of any definitely pathogenic organism. This indicates a weakness of defence rather than of strength of attack. I saw a man in a severe attack which cleared up on HCl which he continued to take for eighteen months after recovery. Six months after giving it up he had an even more severe attack, in which he bled so seriously as nearly to lose his life. After transfusion and routine administration of HCl he slowly recovered again, and is now apparently well. But such a man should continue to take HCl for the rest of his life.

Hunter called attention to another feature of pernicious anaemia—namely, glossitis leading to a loss of papillae. Now this raw, sore tongue is found in certain other conditions, and it is gradually becoming recognized that these are generally, if not invariably, associated with achlorhydria.

Sprue was the first of these in which this triad of symptoms—anaemia, glossitis, and achlorhydria—was recognized, and, as we know, it is characterized by a general thinning of the mucosa of the alimentary tract and by diarrhoea. We all know the neurotic woman who, generally about the time of the climacteric, complains of a sore tongue. It might be suggested by a cynic that this is due to the habitually caustic use such patients make of that organ, for their bad temper is proverbial. They are the despair of the general practitioner, for they are a mass of phobias, and naturally particularly of cancerphobia. Now it is an interesting fact that many of these patients have achlorhydria, and some of them can be benefited more by HCl and parathyroid with calcium salts than by all the nerve sedatives inside or outside the *Pharmacopoeia*. Here we have the triad of achlorhydria, glossitis, and purely functional nervous symptoms.

Lately, however, a more definite syndrome has been recognized—achlorhydria, glossitis, anaemia, dysphagia, and sometimes an enlargement of the spleen. The anaemia is usually not of the pernicious type, but is secondary in character. I take it that the dysphagia, which is referred to the oesophagus, is due to a similar loss of mucous membrane lower down than the mouth. My colleague Dr. George Graham kindly allows me to mention a case, as yet unpublished, in which the dysphagia cleared up on liver extract, although here, too, the anaemia was not of the pernicious type.

Two other conditions remain to be mentioned in which achlorhydria is very common. One is *acne rosacea*, and the other *rheumatoid arthritis*. Herein we get a therapeutic suggestion for two troublesome diseases. But by no means all cases of the latter have complete achlorhydria, though some reduction in the normal secretion of acid is very common. If a fractional test meal is normal in a case of rheumatoid arthritis, it suggests that the infective focus is below the duodenum, and it should direct our attention specially to the pelvic organs.

I believe that the real route of infection which achlorhydria permits is by way of the duodenum. Normally the duodenal contents should be sterile, but duodenal intubation will prove that in such cases marked infection is present.

We arrive, then, at the conclusion that there are certain diseases, such as pernicious anaemia and subacute combined degeneration of the cord, in which total absence of HCl is invariable, and others in which it is very common. Hurst even thinks that in *cancer of the stomach* achlorhydria exists before the new growth, and is not a result of the growth. Some years ago I saw a woman who wished for the fullest examination because her mother and daughter had died of cancer of the stomach. Nothing could be found but achlorhydria. Yet she, too, subsequently died of malignant disease of the stomach.

It is the 5 per cent. of the population who are congenital achlorhydries that we may regard as having an inborn predisposition to certain grave diseases. The recognition of this state of affairs places in our hands a valuable therapeutic weapon, for since so many of these diseases can be relieved by a drachm of the dilute HCl of the *British Pharmacopoeia* in a glass of orangeade or lemonade at meals, it is highly probable that this treatment would have a valuable preventive action also. I would suggest that it is worth while for anyone whose near relation suffered from pernicious anaemia to have the acidity of his resting gastric juice estimated, and for him to take HCl as a routine if this is found to be *nil*. And I should like to bear testimony to the splendid and indefatigable efforts of Hurst and his fellow workers in emphasizing the great importance of this syndrome of achlorhydria, glossitis, and anaemia. To my mind it is one of the most helpful generalizations of recent years.

Next I wish to point out that the response of the stomach to various attacks upon it will differ according to certain peculiarities, possibly inherited, which are characteristic of the individual patient. Thus, as Barclay showed, the long thin subject tends to gastropexia, while the short, stout type of man is more apt to show the hypertonic well-contracted stomach. For, as Sherrington puts it, there is a variation in the posture of the stomach by which the effect of gravity can be allowed for. But this may influence

the type of dyspepsia he may develop in response to some stress or strain. If we may take Bennett and Ryle's figures as typical of the general population they will help to explain this fact.

Digestion starts in the mouth, and indigestion often starts there too. Apart from the bolting of food, and the tendency, if mastication is difficult, to take pappy carbohydrates, which without insalivation cannot be digested in the stomach, the constant swallowing of pus from oral sepsis is now well recognized as a fertile cause of dyspepsia. It may be considered that the typical effect of this is gastritis, by which I mean a diffuse inflammatory reaction of the mucous membrane of the stomach, resulting in an increased secretion of mucus and a masked secretion of HCl. I stress this because of the tendency to use the term "gastritis" in a very vague sense—a tendency much increased by the war, since gastritis was one of the few digestive diseases a soldier was allowed to have, by regulation.

One can readily understand that if a man is one of those who naturally have a low secretion of HCl oral sepsis is more likely to produce gastritis in him. On the other hand, C. H. Miller has shown that the starting-point of a gastric ulcer is generally a septic infection of a lymphoid follicle, while Bolton has shown that hyperacidity tends to keep such an ulcer from healing. Therefore, if a man is one of those who naturally have a high secretion of HCl oral sepsis is more likely to produce a peptic ulcer in him. Then, again, take the effect of alcohol. This typically also excites gastritis, and it is this special type of gastritis which is a necessary precursor of cirrhosis. If cirrhosis occurs it will produce portal congestion, and therefore more gastritis. Thus a vicious circle is set up. And if there is another cause for gastritis, like oral sepsis, present, the chances of his developing cirrhosis are increased, which explains why one man falls a victim to cirrhosis while his equally erring brother escapes. But if the too free imbibor of strong drink has a natural tendency to hyperchlorhydria and a hypertonic stomach, he is more likely to be rewarded with a duodenal ulcer than with cirrhosis; for, as Hurst pointed out, and as my experience would confirm, not only is the hypertonic stomach practically always present when there is a duodenal ulcer, it is there before ulceration occurs and after the ulcer is healed.

It would therefore appear that such mechanical and chemical idiosyncrasies as I have described will determine the type of digestive disease that will result if one of the exciting causes is present.

Yet one more example and I have done. The liability in certain families to early arterial degeneration is well known, and one special form of obliterative arteritis is known only to attack Jews. In Osler's phrase, it would appear that in some families inferior rubber is used in the tubing.

In conclusion, although I have ranged over a large, possibly too large, an area, I hope I have been able to give some idea of the more modern views on diathesis or proclivity to certain diseases. There are peculiarities of metabolism in some individuals which may take the form of a lack of some ferment or important secretion, or may display itself in an intolerance to the assimilation of substances to which the ordinary individual is immune. Some start out with an inadequate supply of endocrines or with a disturbance in the balance between the two great divisions of the visceral nervous system—the sympathetic and parasympathetic or extended vagus. The very posture of the viscera will modify the type of disease produced by similar causes. These predispositions to disease can be shown in many instances to be inherited according to Mendelian laws and to reside in the chromosomes of the nuclei of the gonads. It might be thought that they would be such a handicap in the struggle for existence that they would lead to their own disappearance by the destruction of the individuals possessing them. In some cases this is so, but we must remember that a defect which is not fatal to propagation will continue to be propagated—not perfection, but survival, is Nature's aim. But the importance of a knowledge of the family history is greatly enhanced by these recent observations, and for that knowledge we must depend on the general practitioner, who is, and must continue to be, the backbone of our profession.