WHERE CHEMISTRY AND MEDICINE MEET.*

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THERE was a time, not so very long ago, when this country could challenge comparison with any other as regards the number of able and zealous workers who were engaged in the study of the chemical aspects of disease. Those were the days of Prout, of Alexander Marcet, and of Bence Jones, and others whose names occupy distinguished places in the roll of honour of British medicine, and who, following in their footsteps, carried on and extended their work. Of these, the veteran Dr. Pavy is still among us, and hands on the tradition to younger generations. Yet it must be admitted, with regret, that of recent years we have tended to fall behind, and to leave to investigators in other lands in which the organization of research has been more developed than with us, the task of unravelling many of the problems which await solution. Our workers in this field are not less zealous than their predecessors, but their numbers are fewer in proportion, and the development of fresh fields of pathological study has opened out many attractive lines of investigation in other directions. Although the profession at large, in this country, gives an ungrudging recognition to the importance of chemical pathology, it prefers for the most part to admire at a distance, and to a medical audience a discourse on this subject is not always acceptable. This is in part the fault of the labourers in the field, who have somewhat neglected the task of exposition. If the workers are few, textbooks are still fewer, and the results obtained are seldom discussed in our medical societies. Yet in these days of press activity the omission to add largely to the bulk of the writings with which the busy medical man is expected to cope will be regarded leniently as a vice which makes a near approach to virtue. May the scantiness of such writings in our own language serve as an excuse for my incursions into the chemical field, in response to the invitation to address you with which I have been honoured.

In few branches of scientific investigation have greater advances been made of recent years than in that which deals with the chemistry of living things, but it is no easy task which he enters upon who sets himself to investigate the metabolic processes at work in the animal organism, and the derangements which these processes undergo in disease. It may be compared with that which confronts a man who wishes to study the manifold activities of a great chemical factory which he is forbidden to enter. He is able to examine the raw materials which are brought to the factory, the finished products which emerge from it, and the waste substances which are washed away in the drains, escape from the chimneys, or are thrown upon the dust heap. Upon such examinations, supplemented by an occasional peep through the windows, he must rely for his information as to what goes on within.

Nevertheless, with no better means at their disposal, chemical physiologists and pathologists have found out much about the chemistry of the human body, and are year by year making fresh incursions into the vast territory of the unknown.

All such knowledge is of importance to us as practical medical men. It enables us to gain clearer ideas of many problems which confront us, it arms us with new weapons for our fight with disease, and corrects many misconceptions which have been handed down for generations, and which tend to warp our practice.

It is of the general bearings of this increased knowledge upon our science and art that I propose to speak this afternoon, and I hope to be able to show that no special chemical training beyond that which forms an essential part of medical education is necessary for the appreciation of its import, whatever may be the case as regards the more technical details.

I cannot more fitly begin my discourse than by referring

briefly to the immense advances made in the study of that great group of complex compounds in which all albuminous substances are included. The proteins are the essential constituents of living organisms, and it is upon their properties that the very possibility of life depends. Thanks to the labours of a body of indefatigable workers, among whom the great German chemist Emil Fischer stands pre-eminent, our knowledge of proteins is no longer limited to a knowledge of their ultimate compositions, of the various temperatures at which they coagulate, and other chemico-physical data. Their complex molecules have been taken to pieces, and it has been shown that they are built up of a number of comparatively simple fractions which can exist as independent chemical substances, and which, widely as they differ in structure, have this in common that they belong, almost without exception, to the group of amino-acids. Some of these fractions of proteins are old friends, long known as occasional constituents of the excreta, such as leucin, tyrosin, and cystin, in which last the sulphur of proteins resides; and from others equally familiar excretory products or products of putrefaction are derived, such as indol from tryptophane, cadaverin from lysin, and putrescin from arginin. In the elaborate protein molecules these various fractions play parts which may be compared with those played by atoms in simpler chemical molecules, and they are so numerous, and are capable of such various groupings, that from them may be formed an almost infinite variety of compounds of the protein class. Some proteins are peculiar in that from them certain of the primary fractions are absent. Thus gelatin contains no tyrosin, and zein, the protein of maize, no tryptophane. It is now believed that in the process of digestion the protein molecules undergo much more complete disintegration than used to be supposed, and that instead of being absorbed as proteins and incorporated as such in the organism which digests them, they are taken to pieces more or less completely, and are reconstructed to form the proper tissue proteins of the new host.

Even if there were no other grounds for this belief, it could hardly be avoided in view of the demonstration by means of the delicate ultra-chemical precipitin reactions, that the proteins of which the tissues of animals are built up are not identical for the different species, and that the more nearly two species are related, the more closely do their proteins approximate.

Seeing that the boundaries of species are not rigid in any strict sense, it follows of necessity that similar but even more subtle differences must exist between the tissue proteins of individuals of a species. The notion must be abandoned, once and for all, of a multiplicity of structure and form, but a uniformity of chemical process throughout the animal kingdom.

Such considerations, although they appear at first sight to have a merely theoretical interest, have a real practical importance for us, and this altogether apart from the medico-legal applications of the precipitin test.

It will be evident that the optimum diet of a man must contain not only a sufficiency of protein in general, but must also contain an adequate supply of each individual fraction of the protein molecules which enter into the structure of the human tissues.

As you well know, the balance of the nitrogen in the excreta against the nitrogen of the food affords a measure of the quantities of protein broken down and built up on a particular diet. When the output of nitrogen exceeds the intake, this shows that tissue breakdown is in excess of reconstruction, whereas when active reconstruction is in progress the intake of nitrogen exceeds the output in the urine and faeces.

Again, it is a well-established fact that an even nitrogen balance may be maintained upon diets of very different protein content, and may also be maintained upon a diet much poorer in protein than that which is usually taken by healthy men, and which represents the level instinctively arrived at by mankind, civilized and uncivilized alike.

Yet it does not follow from this fact that the reduced diet, although it maintain the nitrogen balance, is an optimum diet, and more probably we need to take habitually excessive quantities of food proteins, in order that we may get from our diet all that we need of each individual fraction of the protein molecules.

* An address delivered to the Gloucestershire Branch of the British Medical Association.

You will remember the stone bricks which were so popular as children's toys some years ago. They were of different colours, shapes and sizes, and with them could be constructed a variety of buildings of different kinds—houses, churches, temples, and the like. However, if the bricks of some particular kind had been lost, as was often the case, although abundance of others were available one could not construct some special kind of building which was wanted. So it is with protein reconstruction. A protein which has some special deficiency, such as gelatin which lacks the tyrosin bricks, does not form a satisfactory substitute for other kinds of protein foods. The organism does not need protein alone, but demands tyrosin as an essential building stone for its tissues, and the same is true of other fractions also. According to the more modern views, which are associated with the name of Folin, large quantities of the ingested proteins are merely stripped of their nitrogen and burnt as fuel, just as fats and carbohydrates are, and from this excess we may suppose that the organism readily picks out the particular fractions which it needs, and in the proportions necessary for the reconstruction of its tissues, for which purpose only a small fraction of the total supply is utilized.

There is another practical lesson to be learnt from what has gone before—namely, that the more nearly the proteins of the food approximate in structure to the tissue proteins, the more completely satisfactory and easy of utilization will they prove to be. This may be supposed to be of special importance to the newborn animal whose digestive ferments are as yet only imperfectly developed; and accordingly Nature has provided, in mother's milk, an optimum diet at that period of life. This is, perhaps, the reason why no substitute is as good for an infant as mother's milk. We may, with care, rearrange the constituents of cow's milk so that its several constituents are represented in proportions almost exactly similar to those in which they occur in breast milk; but however completely we may humanize cow's milk, it is not in our power to make it human, nor to give to its proteins the peculiar stamp of specificity.

At first sight this appears to be an argument for cannibalism; but it is not really so. As the infant grows into the child, and the child into the man, he is quite able to dispense with these slight advantages which may be of inestimable value in his earliest days of life. Even those animals which are by instinct and practice vegetarians, who reconstruct their tissues from proteins which are not even of animal kinds, are nourished with maternal milk at the beginning of their lives.

It is in the proteins of the tissues that chemical specificity and individuality resides. The simpler molecules of fats and carbohydrates admit of no such range of variation. Glucose wherever met with is one and the same substance, and, although the composition of the fats of animals varies in different species, it is probable that these variations are mainly due to differences of diet. When an unusual fat is administered to an animal it is stored as such in its adipose tissues.

The clearer insight gained into the structure of proteins also throws a flood of light upon many urinary problems. We see that various abnormal constituents of urine, the origin of which was previously quite obscure, are in reality protein fractions which have escaped destruction in the ordinary way, or products of the incomplete breakdown of such fractions.

The evidence available tends to show that each individual protein fraction follows its own path of breakdown its destruction being effected step by step by the action of enzymes, a fresh enzyme taking up the work where another has left it. Thus the study of the rare and interesting congenital anomaly of metabolism known as alcaptonuria has thrown much light upon the ordinary fate of the aromatic protein fractions tyrosin and phenylalanin; whereas in the sister anomaly, cystinuria, the cystin fraction of proteins in part escapes the fate which normally overtakes it, and is excreted unchanged in the urine. Moreover, it appears that the derangement of the catabolism of one such fraction does not necessarily involve the implications of others also.

On the other hand, the ductless glands appear to exert a controlling influence upon metabolism as a whole, as witness the stimulation thereof which results from excessive thyroid activity in exophthalmic goitre, and the

slackening which characterizes the converse malady, myxoedema. It would seem that the thyroid secretion has a power of activating many enzymes.

The several metabolic paths for different substances, which have doubtless been shaped by evolutionary influences, are in the main permanent routes, and it is probable that when a patient excretes an abnormal product, or abundance of a product normally excreted in mere traces, this is not due to the deflection of the metabolic paths into new and abnormal lines, but rather to arrest at an incomplete stage of catabolism, or to excessive calls upon mechanisms but little utilized in health.

The fact that the organism has provided itself with means of defence against certain chemical poisons with which it is often called upon to cope, is not opposed to, but is rather confirmatory of, this view.

The protective mechanisms, which recall the more subtle defences, as yet beyond the ken of the chemist, by which the organism is guarded against bacterial poisonings, are of no small medical interest. In principle they all agree more or less closely; the harmful substance is rendered harmless by combination with some intermediate or final product of metabolism, and so combined is got rid of in the excreta. The metabolic product made use of plays the part of a watchful policeman, who, finding the toxic substance loitering in the organism, presumably for an unlawful purpose, takes it by the arm and conducts it outside the door.

It is a well-known fact that when benzoic acid is taken by the mouth hippuric acid is excreted in the urine. This is an example of such a protective arrangement. Benzoic acid, like most aromatic compounds, has toxic properties, whereas hippuric acid is relatively inert. Hippuric acid is a product of the combination of benzoic acid with glycine, the simplest of the primary protein fractions and presumably a product of metabolism. Some other aromatic compounds of similar nature to benzoic acid are similarly combined with glycine and excreted, for example, salicylic acid, which appears in the urine as salicyluric acid.

There is an alternative and even more important method of dealing with aromatic poisons, namely, by combining them with the sulphuric acid which is formed by the oxidation of the cystin fraction of proteins. Aromatic sulphates so formed are present in all human urines, even in health, for we all take in aromatic poisons with our foods, or form them in our intestines.

In health about one-tenth of the sulphuric acid of the urine is in such forms, but when the intake or formation of aromatic poisons is excessive, the proportion is far higher, and in carboluria nearly all the sulphuric acid is so combined.

The decomposition of proteins in the alimentary canal by the action of intestinal bacteria is an important source of such poisons. In ordinary circumstances fluctuations of the output of aromatic sulphates in the urine are mainly due to such decomposition, and hence the proportion of the total sulphates so combined affords some measure of intestinal putrefactive changes. The so-called indican of urine is such a compound, an indoxyl-sulphate formed from indol which is derived from the tryptophane fraction of proteins under the influence of intestinal bacteria, and its abundant presence also testifies to the activity of protein putrefaction.

Another most important protective mechanism is that by means of which the organism is guarded against poisoning by acids and vegetivora, which from the abundance of the alkalis in their diet run comparatively little risk of such poisoning, appear to lack this means of defence. It is far easier to kill a rabbit with acids than a dog. The fixed alkalis of the tissues are urgently needed for more important uses than the mere neutralization of acids, and any excessive call upon them for that purpose has disastrous results; but by the breaking down of proteins, and the stripping off of the amino groups from the various protein fractions, ammonia is abundantly found, and normally goes to the making of urea. In acid poisoning more or less of this ammonia is intercepted, is employed for neutralization, and appears in the urine as ammonium salts.

Hence it comes about that the amount of ammonia in the urine affords a measure of the quantities of abnormal acids in circulation in the organism, and when sodium bicarbonate is freely taken in cases of acidosis there is

less need of ammonia for neutralization, and the output is accordingly diminished.

Although under the stress of special conditions the ordinary metabolic scheme is departed from in certain directions, and, indeed, is more or less deranged in almost all diseases, it is highly improbable that the body chemistry ever goes wrong on its own initiative, and in this, as in other connexions, the epithet "idiopathic," now seldom used, is a survival of an age of ideas which are fast becoming obsolete.

Whether if placed in a perfect environment the human body would survive much more than a hundred years may still be looked upon as an open question, despite the brilliant writings of Metchnikoff and his well-known views upon the subject. In every chemical process there is some loss, by formation of by-products, and it may well be that the cumulative effect of such infinitesimal losses, in the constant breaking down and repair of the cells of the body, would, in any circumstances, bring the machine to a standstill in time. In all such speculations the crux of the problem is why the average duration of life of different animals varies so widely—why a dog becomes senile almost before his human contemporary is out of the nursery—and the intestinal theory hardly seems to explain this.

However, comparatively few human beings die of senile decay. Many succumb in early life to the invasions of the bacteria which surround us. Many, again, succumb to what may be styled the maladies of the second half of life, granular kidney and its congeners, some of which may well be effects of the accumulated minimal insults to which the organism is exposed, of trifling injuries, and minor indiscretions of diet and hygiene.

Advancing knowledge tends to bring the conviction that all diseases come from without, save such as are inborn (not merely acquired *in utero*) and which are less diseases than structural or functional peculiarities, inherited and bred in the bone. Such inborn peculiarities are met with in the domain of metabolism, as well as in that of structure. By coming from without I do not mean to imply that all maladies are due to invasion of the organism by vegetable or animal parasites. The alimentary canal is, strictly speaking, an external region, and an important rôle as exciters of disease must be ascribed to poisons introduced into the alimentary canal, or formed by the action upon food materials of the bacteria which abound therein.

The disturbances of metabolism which result from disease are often slight and inconspicuous, but in some maladies, which are often spoken of as diseases of metabolism, such disturbances dominate the clinical picture. Yet "diseases of metabolism" is a misleading term, for the chemical processes in the organism do not go wrong on their own initiative, and metabolism is no more truly diseased, than a machine is out of order because it goes wrong or comes to a stop when a stick is inserted among the wheels.

In gout, which is one of the diseases commonly included under this name, uric acid is the villain of the piece, but not, I believe, nearly so truculent a villain as it is often depicted. Indeed, I would venture to assert that uric acid has acquired in the public mind, and in that of many members of our profession, a pathological importance wholly beyond its deserts.

Some fifty or sixty years ago, soon after the discovery of an excess of uric acid in the blood of the gouty, the question of the pathology of gout appeared to have been solved to a great extent. It was taught that, owing to an impaired power of excreting uric acid by way of the kidneys, the observed accumulation occurs in the blood; that at intervals the power of the blood to hold uric acid in solution becomes overtaxed, and deposition of sodium biurate results in those tissues, such as cartilages, in which the conditions are least favourable to its remaining in solution, and that such deposition is the exciting cause of the acute paroxysm of gout. Since that time much elaborate work has been done upon the metabolism of the gouty, and by methods far exceeding in accuracy any which were available sixty years ago. Theories have arisen and theories have gone to the wall. Opinion has swung, like a pendulum, now towards the views that even in gout itself uric acid plays only a small and secondary rôle, then towards the attribution to this substance of a predominant influence in many diseases besides gout.

It has been maintained that the gouty deposits are formed *in situ*, and even that the uric acid in the blood is derived from the deposits, and not the deposits from the accumulated uric acid in the blood. Again, the view has been advocated that it is the uric acid in solution which does the mischief, and not its deposition from solution.

And yet, of recent years, the opinion of most of those who have studied the subject most closely has steadily tended back to something very closely resembling the original theory. Recent researches have corrected not a few minor inaccuracies, mainly due to the lack of adequate methods and a more embryonic stage of chemical knowledge, such as the view that the deposition is determined by lowering of the alkalinity of the blood. On the other hand, there seems to be no way of escape from the conclusion that uric acid is present in excess in the blood of gouty patients because it is imperfectly excreted. In no other way can the undoubted fact be explained that the excess in the blood is not accompanied by any excess in the urine, and often by some diminution of the output. Only for short periods during or immediately after the acute attacks has any increased excretion been observed.

If the excretion of uric acid were unimpaired, excess in the urine would go hand in hand with excess in the blood, as is actually the case during an excessive intake of purin substances—for example, when thymus gland is freely eaten, and when there is an excessive formation of uric acid, as is the case in some forms of leukaemia. Nevertheless the cause of the impaired excretion, and whether it be due to failure of renal functions or some unusual combination or state of the uric acid which hinders its excretion, is still unknown. Many other problems of gout still remain unsolved. It is uncertain in what combination the uric acid exists in the blood, what are the actual conditions which determine the deposition in the tissues, and how far the many symptoms which are commonly diagnosed as gouty, often upon very flimsy evidence, are directly connected with true gout, and are in any way dependent upon the uric acid error.

I lay stress upon the impairment of uric acid excretion, because there is a very widespread belief that the urine of a gouty patient is loaded with uric acid, and even that the existence of a gouty state can be diagnosed by examination of the urine. No one can diagnose goutiness by such means, and the erroneous belief doubtless had its origin in the frequency of uratic deposits in the urine of gouty patients, or the presence of abundant crystals of uric acid. These phenomena have no necessary connexion with an excessive daily output, but are rather due to concentration and other conditions unfavourable to solution. Excessive output is a cause, but only one of the causes, of such deposits.

Again, it is very generally assumed that because a drug is a good solvent of uric acid it is therefore of value in the treatment of gout. From the standpoint of the chemist this is a most unsound assumption. However soluble the urate of a metal may be, there is little chance that by administering a salt of that metal by the mouth we shall be able materially to promote the excretion of uric acid. Combinations of acids and bases are controlled by rigid chemical laws, and the bases with which an acid combines are determined by the relative amounts of the several bases on the spot. There is little hope that by giving a particular base in medicinal doses we can secure its presence, in any given region of the body in such quantities that it will have a chance against the sodium which is so abundant in the blood and tissues. The uric acid will show no preference for the base with which it forms a more soluble compound; and that base must take its chance with the rest in the general scramble. Thus it will be seen that there is no scientific ground for the use of substances which form specially soluble urates in the treatment of gout.

Our notions as to the place of uric acid in metabolism have undergone profound change in recent years. It is recognized that this substance can no longer be looked upon as an intermediate product in the formation of urea, but that it is a special product of the breaking down of one particular class of protein substances, the nucleo-proteins. A second mode of origin, by synthesis, is perhaps operative, to some extent, in the human body, and must play an important part in birds and reptiles, the bulk of whose nitrogenous excretion is in this form.

Obviously this change of view cannot fail to modify profoundly our ideas as to the optimum diet of gouty patients. Our aim will be to avoid adding to the excess of uric acid in the blood, by limiting the intake of its parent substances, the purin bodies and nucleo-proteins. To this end it no longer appears necessary to restrict protein foods generally, unless the kidneys be actually diseased, but rather to restrict such foods as are rich in the constituents referred to, namely, the extractives of meat, the glandular organs, such as sweetbreads and kidneys, and the varieties of meat which are specially fibrous, and therefore rich in nucleo-proteins. Other restrictions which are imposed, and with good cause, are made upon empirical grounds, and mainly on the testimony of those best qualified to judge of their desirability, namely, gouty sufferers themselves.

Of all foods the thymus gland, or throatbread, is far the richest in purins, whereas some protein foods, such as eggs, milk and cheese, are, as Walker Hall has shown, almost entirely purin-free.

Remember that in these ways we are not treating the actual disease, but are trying to modify its symptoms. The accumulation of uric acid in the blood is not the cause of gout, but only that of its symptoms. It is the result and not the cause of the primary disease. Regulation of diet is helpful to a sufferer from gout, just in the same way as a restriction on different lines is helpful to a sufferer from diabetes.

Of all diseases known to us, diabetes is that in which metabolic disorders most run riot, whereas the underlying mischief usually manifests itself by no outward signs. We are accustomed to speak of diabetes as a disease, but it would be more correct to describe it as a syndrome common to several diseases. It is true that in their clinical features and developments cases of diabetes closely resemble each other, although they differ widely in their rates of progress, duration, and gravity. Any diabetic patient may acquire cataract or gangrene, may lose flesh, and is liable to suppuration after slight injuries; and any case may end in diabetic coma.

These resemblances supply no argument against diversity of origin, for the symptoms mentioned are, one and all, secondary effects of the derangement of the carbohydrate metabolism, and are either due to the excess of sugar in the blood, or to the tissue destruction which persistent glycosuria brings in its train.

The definition of diabetes as a disease characterized by persistent glycosuria is by no means adequate, for no sharp dividing line can be drawn between transitory and permanent glycosuria, nor is it a satisfactory plan to exclude from the diabetic group any case which does not go on to a fatal ending.

Some cases of diabetes are undoubtedly due to organic disease of the pancreas, which can be demonstrated *post mortem* and is sometimes revealed by the passage of fatty stools or other signs of affection of that organ appreciable during life. In other cases nothing can be found amiss with the pancreas after death, and the most recent researches of Falta and others, carried out in von Noorden's clinic, suggest that the ductless glands may play an important part in the pathology of diabetes, possibly by an influence exerted by their secretions upon the functions of the pancreas. At any rate, it is a noteworthy fact that carbohydrate metabolism is conspicuously influenced by the secretions of the thyroid, pituitary, and suprarenal glands alike. Time forbids more than this passing reference to the fascinating question of the influence of the ductless glands upon metabolism, of which much will probably be heard in the future. Again, we cannot leave out of account in discussing the pathology of diabetes the influence of the nervous system, exerted either directly or indirectly through the ductless glands, an influence which has been well recognized ever since the days of Claude Bernard.

No plan of treatment hitherto tried has succeeded in attacking diabetes at its foundations. Appropriate dietetic treatment, and to a less extent treatment by drugs, is capable of modifying its course to a remarkable degree, and undoubtedly prolongs greatly the lives of many sufferers. Yet such treatment, as applied in practice, is too often perfunctory and by rule of thumb, whereas it should be adapted to each individual case, and even to the particular stage of the patient's malady. Only in this way can the best results be obtained.

Let us pause to consider for a moment the aims of dietetic treatment in diabetes. By its means we are able, in many cases, to decrease materially, or even to arrest completely, the output of glucose, and this because we are able to diminish or to remove the excess of sugar in the blood. The loss of the potential energy of the unburnt sugar can be readily compensated by dietetic means, but the hyperglycaemia is the cause of many of the troubles to which diabetic patients are liable. Again, by resting the damaged mechanism as far as may be, we not only arrest the aggravation of the error, but even bring about, in no small proportion of cases, a remarkable recovery of tolerance for carbohydrates—a matter of no small importance. Some diabetics are able, after a course of rigid dieting, to deal with much larger quantities of starch than would have sufficed to excite glycosuria before such treatment. Whereas when starchy food is allowed without restriction a progressive aggravation of the metabolic error results, often very rapidly.

Remember that not a few diabetic subjects, in the earliest stages of their malady, pass sugar only under severe provocation as after a meal rich in starch, and unless the urine of certain times of day be examined, the glycosuria may escape notice. In such cases a restriction of carbohydrate food is eminently desirable. It is a well-known fact that a meal of sugar, provided that it is large enough—for example, some 150 to 200 grams of glucose—will excite transient glycosuria in any normal individual, but in health no amount of starch which can be taken will bring about this result, and when glycosuria is provoked by starchy as distinguished from sugary food, the patient must be looked upon as a potential diabetic at least.

Whether by a restriction of diet an individual with an inherited tendency to diabetes can be saved from developing the disease is a question which cannot yet be answered, but some limitation of the intake of sugar and starch by such persons is certainly not an unreasonable precaution.

That actual recovery does occur in some cases which are rightly classed as examples of diabetes, I firmly believe, and we may well hope that the investigations of which this malady continues to be the subject will some day enable us to treat some cases with success. On the other hand, it is little likely that any one plan of treatment will serve in all the conditions in which diabetes originates. Therapeutic measures which may prove of much service in cases in which the pancreas is not primarily involved, might well prove powerless in the face of organic disease of that gland.

Even in its graver forms disease of the pancreas is not easy of diagnosis, and in its slighter forms may wholly elude our diagnostic methods. It can hardly be doubted that, like other glands, the pancreas is the seat of passing inflammatory lesions, which, if rightly treated, may leave no permanent structural damage to the gland, but may, whilst they last, give rise to glycosuria. In this connexion I would refer you to a recent and very suggestive paper by Mr. Mayo Robson on the surgical treatment of some cases of glycosuria, and examples are occasionally met with which are best explained on such lines.

I do not propose to attempt to give even a cursory sketch of what has been learnt about the perverted chemistry of diabetes. To do so several hours rather than a few minutes would be necessary. However, the acetonæmia, which plays so conspicuous a part in this malady, calls imperatively for mention.

The presence of acetone in the urine, in the breath of the patient and in his blood, is not in itself a matter of serious moment. It serves rather as a valuable advertising sign of an important metabolic disturbance. The acetone is formed from aceto-acetic acid, the substance which yields the familiar reaction when ferric chloride is added to the urine—another valuable warning signal. Behind the aceto-acetic acid again is its parent substance, β -oxybutyric acid, the presence of which is not revealed by any simple clinical test, but which is the chief offender. In grave cases of diabetes 30, 50, or even 70 grams of β -oxybutyric acid may be excreted in the course of twenty-four hours. It is believed that this substance and aceto-acetic acid exert their malign action as acids rather than in virtue of specific toxic properties, and hence the condition under discussion is often spoken

of as acidosis. A diabetic patient may die with some of the symptoms which are usually associated with coma, although he has little β -oxybutyric acid in his blood, but it is generally held at the present day that the characteristic air hunger and the coma which follow upon it are actually due to acid poisoning. At any rate, such symptoms develop in fatal cases of acetonæmia in which there is no diabetes, for be it noted that acetonæmia is a common symptom in sick children suffering from a variety of different maladies.

Some degree of acidosis is induced by mere abstinence from food, and even by the withdrawal of carbohydrates from the diet. The acetone bodies are formed in part from the breaking down of fats, and in part from certain fractions of the protein molecules, and a diabetic patient who shows no signs of acetonæmia when on an ordinary mixed diet will usually develop a conspicuous iron reaction as his carbohydrates are more and more restricted, until that part of his carbohydrate intake with which even he is capable of dealing has been cut off.

It is generally conceded that an abrupt change from an ordinary diet to a strict one is fraught with dangers to a diabetic patient, and that the reduction should be gradual, acidosis being guarded against by the free administration of sodium bicarbonate when acetonæmia is pronounced.

Thus we are confronted with the dilemma that the therapeutic measures which experience shows to be essential are liable to increase the tendency to one of the gravest accidents of the disease, and experience teaches that it is far easier to increase acetonæmia by restricted diet than to diminish it by subsequent relaxation. Yet the restriction must be carried out, but with watchful care and circumspection.

There is no doubt that children much more readily develop such acidosis than do adults, and apart from diabetes, many of the morbid states which it complicates are characterized by vomiting, as, for example, the cyclic vomiting of children, and that very fatal and puzzling mishap known as delayed chloroform poisoning. It is a tempting hypothesis which regards the vomiting as the actual cause of the condition, in view of the starvation which it involves, but there are serious clinical obstacles to such a view. In some cases the signs of acetonæmia are present almost before the vomiting begins; in others, despite incessant vomiting, acidosis is not developed. Again, no such explanation applies to some other varieties of acetonæmia in children, such as that which so often accompanies bronchopneumonia.

It is difficult to escape from the belief that in delayed anaesthetic poisoning—for chloroform is not the only culprit—the conspicuous acidosis is the actual cause of death with symptoms so like those of diabetic coma, and it is with children, who are so prone to acetonæmia, that such accidents occur.

The fatty change seen in the liver in delayed chloroform poisoning is also observed in cases of acidosis due to other causes, and in some cases at least the free administration of alkalis has appeared to have saved the lives of the patients. One is tempted to believe that the liver is loaded with fat which has been brought to it for burning in quantities greater than it is able to deal with efficiently, with the result that, owing to its incomplete combustion, the acetone bodies are formed in excessive amounts. However, when one attempts to fit in the observed clinical facts with so simple a theory, difficulties are encountered at every turn; nor can it even be contended that the acidosis theory offers a complete and satisfactory explanation of the phenomena of diabetic coma. It is highly probable that other, as yet unknown, factors are also at work in the causation of that condition.

To turn to yet one other field, the subject of calculus formation offers many interesting chemical problems. Stones, wherever met with in the body, are formed of substances which are sparingly soluble in the surrounding media, but the mere fact that a sparingly soluble substance is present, or is even deposited from solution, does not supply an adequate cause for calculus formation. The rare anomaly, cystinuria, affords the clearest example of this fact. Cystin is an abnormal excretion product, which is very readily deposited in crystals in the urinary tract, and those who excrete it are very apt to suffer from calculi. Nevertheless, a cystinuric may pass crystals for

years and yet not suffer from stones. A catarrhal condition is necessary to bring about their formation. It is quite possible that the deposited crystals contribute to exciting this catarrh, but what has been learnt of recent years as to the infection of the biliary passages as the cause of gall stones, and as to the readiness with which the *Bacillus coli* finds its way into the urinary tract, suggests that such an infection may be an important factor in not a few instances.

The same applies to other varieties of urinary calculi, oxalic, uric, and phosphatic alike. They are not mere casual agglomerations of crystals, but bodies of crystalline structure formed around an organic basis composed of catarrhal products.

It is not yet known for certain whether the condition which we call oxaluria—that is, the excretion of crystals of calcium oxalate—is ever due to a true metabolic anomaly and is independent of dietetic causes. The bulk of the oxalic acid of urine appears to be derived from the food, and an oxalate-free diet will usually, if not always, suffice to remove the crystals from the urine. After the eating of foods specially rich in oxalates, such as rhubarb and spinach, the crystals become very abundant, and by their mechanical action may excite albuminuria, and even hæmaturia.

The deposition of crystals does not by any means go hand in hand with excessive excretion of oxalic acid; such excessive output is only one of several factors, amongst which the reaction of the urine, and, as Klemperer and Tritchler have shown, the relative amounts of calcium and magnesium present in it, are amongst the chief.

Hence our aim in treatment should be to eliminate from the diet those vegetable foodstuffs which contain most oxalate, such as rhubarb, spinach, and tea, and a number of fruits and vegetables. At the same time we may attempt to influence the proportions of the bases present in the urine by cutting off foodstuffs specially rich in calcium, such as milk and eggs; and by prescribing such as are rich in magnesium and at the same time poor in oxalic acid, such as peas, beans, and coffee, and oxalate-free foods, such as all kinds of meat.

The so-called phosphaturia has, as you well know, nothing to do with increased excretion of phosphoric acid; indeed, such an increase would augment the acidity of and effectually prevent the deposition of earthy phosphates from the urine. The urine is turbid and deposits phosphates simply because it is alkaline, and therefore unable to hold the earthy phosphates in solution.

In many cases phosphaturia is associated with neurasthenic conditions, and general hygienic and tonic treatment has more effect in restoring the natural acidity of the urine than has the administration of acids, of which, as Dr. R. Hutchison has shown, acid sodium phosphate is the most efficacious. On the other hand, there is a class of cases, chiefly met with in children, which is of special interest, the true nature of which has only been revealed by the chemical investigations of Soetbeer and Tobler.

Normally the bulk of the calcium excretion of the body is effected by way of the intestine, and only a small part by way of the kidneys. In the cases referred to this relation is reversed, and owing to some morbid condition, probably catarrhal, of the intestinal wall, the bulk of the calcium appears in the urine. There is no increase of calcium excretion as a whole, but merely diversion of part of the output. As a result the urine becomes alkaline, the earthy phosphates are increased at the expense of the alkaline phosphates, and copious deposition occurs. Withdrawal of foods specially rich in calcium, such as milk and eggs, will usually suffice to stop the phosphaturia, but our treatment should also be directed to the intestinal disturbance to which the condition is due.

And now, Sir, the time has come when I must gather in the threads of my discourse, hoping that the few examples amongst many to which I have briefly alluded will suffice to prove the thesis with which I set out—that chemistry is able to lend valuable aid in the solution of problems of clinical and practical importance to medical men, and helps materially as a guide to treatment.

On the other hand, we must not expect from chemical studies more than they can reasonably be expected to give. Unlike the bacteriologist who deals with the actual *causae causantes* of many morbid states, the chemical pathologist

can only study the response of the organism to morbid agencies. He can tell us much concerning the forms which disease takes and the origin of symptoms, but comparatively little as to the actual causation of maladies.

We have been considering this afternoon examples of phenomena which can be studied by ordinary chemical methods, which are accessible to the test tube and the balance; but the advance of bacteriology is revealing responses of the organism of much more subtle nature still, and has familiarized us with theoretic substances known by such names as antitoxins, and agglutinins, precipitins, and the like. The phenomena of immunity have doubtless a chemical basis, although the substances concerned are known as yet only by single properties, just as, for a number of years, the planet Neptune was only known by its disturbing influence upon the orbit of its nearest celestial neighbour Uranus. Now, Neptune has been seen, weighed and measured, and has taken its place as a regular member of the solar system, and we may reasonably hope that in due time the substances of which we are speaking will, in like manner, be brought within the grip of the chemist, and will rank as compounds of known constitution and molecular structure.

Obviously the realization of this dream will result in an immense extension of the field in which chemistry and medicine meet.

THE ASSOCIATION OF TOXAEMIA OF PREGNANCY WITH HAEMORRHAGE.

BY

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THE following remarks are based upon a series of cases of toxæmia of pregnancy treated at Guy's Hospital during the last eleven years. Investigation of their records has shown that hæmorrhage in one form or another is not a very infrequent symptom of the disease, and that in some cases it may be so great as to constitute its principal feature.

It may be said at once that part of this paper, which deals with antepartal hæmorrhage, concerns facts the interpretation of which is the subject of controversy, and one of my chief reasons for its publication is that very strong and, to my mind, conclusive evidence is shown of the causal relationship between toxæmia and this form of hæmorrhage. Lastly, a small group of cases occurs in which hæmorrhage, not from the uterus, was so severe as to be a very great source of danger to the patient, and, so far as I can gather, no similar condition has hitherto been described in association with toxæmia of pregnancy.

I wish here to express my thanks to the obstetric surgeons of the hospital for their kindness in allowing me to make use of their cases.

The cases of hæmorrhage fall into three groups.

I. HAEMORRHAGE FROM THE KIDNEYS.

Haematuria is mentioned as a symptom in all descriptions of eclampsia, and needs no special attention here. It is a sign of advanced degeneration of the renal epithelium, and for this reason has an importance from the point of view of prognosis.

Among the 36 cases of eclampsia treated at Guy's Hospital in the period stated above, haematuria was present in 10, and of these patients 6 died—that is, 60 per cent.—while of the total number only 11 died, or 30.5 per cent. It is therefore clear that haematuria has a grave prognostic significance in eclampsia.

I do not propose to describe these cases in detail. Suffice it to say that they were all typical examples of eclampsia.

II. HAEMORRHAGE FROM THE UTERUS.

As long ago as 1885 Winter drew attention to the fact that in many cases of accidental hæmorrhage albuminuria was found, and he expressed the opinion that a causal relationship existed between the two conditions. Since then several writers, notably the French, have supported his opinion, but their teaching has not been generally followed, and in the English textbooks of to-day, though renal disease is mentioned as a cause of hæmorrhage, it is not given any particular prominence.

I hope to show that toxæmia of pregnancy is very frequently found in association with one form of accidental hæmorrhage—namely, concealed—so frequently that it seems incredible that a direct causal relationship does not exist between the two.

On the face of it, toxæmia of pregnancy would seem likely to cause hæmorrhage from the uterus, for it is undoubted that marked changes occur in the placenta as a result of it, leading to extensive infarction, and it is natural to expect that these changes may in some cases cause separation of the placenta from the uterine wall and resulting hæmorrhage between them.

Again, it is a common experience that patients suffering from concealed hæmorrhage are frequently much more ill than the amount of their hæmorrhage would lead one to expect. If in these cases toxæmia is also present, a ready explanation at once presents itself.

During the years 1900–1910, 13 cases of concealed accidental hæmorrhage were treated, and of these 8, or 61.5 per cent., presented symptoms of what I take to have been toxæmia of pregnancy; surely more than can possibly be accounted for by coincidence. On the other hand, of 30 cases of external accidental hæmorrhage, only 1 showed signs of toxæmia.

This striking difference may be explained by the fact that in a great many cases the external hæmorrhage may have been due to low implantation of the placenta, which, however, was not low enough to be felt by the hand in the early stages of labour, and that they were wrongly classed as accidental. Probably, therefore, a greater percentage of cases of external hæmorrhage are the subjects of toxæmia than appears from these figures.

The signs of toxæmia were as follows: In most cases albuminuria occurred, and was the only sign in the five patients who recovered. That the albuminuria was toxic and not due to old-established nephritis is, I think, evident from the fact that all these patients had been quite well previously, and that in each case the albuminuria completely disappeared within a few days after the confinement, as it would not have done if a chronic lesion of the kidney had been present.

In several cases oedema was noticed, which also rapidly subsided after the confinements.

In one case (III) eclamptic convulsions occurred, and it is possible that they may have been the cause of the hæmorrhage; but as the last fit occurred three days before the hæmorrhage started, it seems hardly probable. In Case VIII the evidence is, I admit, doubtful. She had one fit before medical aid was summoned, but the description of it given by the relatives corresponded so exactly with those of eclampsia that I think it may fairly be included in the series. Unfortunately, no histological examination was made of the liver and kidneys *post mortem*. The *post-mortem* findings in the other two fatal cases were those typically found in toxæmia of pregnancy.

The retinæ were examined in those cases where a suspicion of chronic nephritis was entertained, but in all cases were found to be normal.

I think, then, that it may justly be assumed that all these patients, with the possible exception mentioned, were suffering from toxæmia of pregnancy.

The frequent association with hæmorrhage—more than 60 per cent. in cases of concealed hæmorrhage—must be more than coincidence, and the logical conclusion is that the toxæmia is the cause of the hæmorrhage, probably through its effect upon the placenta.

The preponderating frequency of concealed hæmorrhage is noteworthy, and may be explained by the fact that in these cases the uterine muscle is in an atonic state and makes no effort to expel the blood. Also I am convinced that, as I have said above, external accidental hæmorrhage is much less common than is generally supposed, many, if not most, of the cases being really due to placenta prævia.

Short Histories of the Cases.

CASE I.

Eliza W., aged 38, multipara, was admitted on January 19th, 1904. She had had nine full-term pregnancies and four miscarriages, and had always had good health. In her present pregnancy she was quite well till the end of the eighth month, when she suddenly fainted, and began to lose blood per vaginam. She was brought up at once to the hospital.