Practical Points of Diagnosis and Treatment in Medicine.

BIOCHEMISTRY IN RELATION TO MODERN MEDICINE.

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THE increasing use of chemical, and even physical, methods in physiological and medical research has led to the use of the term biochemistry to denote the whole of biology that is so investigated. It has thus become a major science, incorporating, as it does, so much of all the biological sciences ; in fact, the journals of physiology, experimental medicine, pathology and other similar periodicals all now contain papers of biochemical interest. Originally the chemical methods and conceptions used, as for example, by the physiologists, were relatively simple, and it is only in more recent times that expert chemists have interested themselves in biological problems and have used methods which were not available to biologists and physicians who had not the requisite training. Thus the physiological chemist is now recruited from the ranks of the pure chemists and there have resulted advances on all fronts which have changed the aspect of modern medicine. We have travelled a long way from the empirical use of cod-liver oil in rickets to our present-day knowledge of vitamin D, the isolation of which is due so largely to the work of that master chemist, Windaus, whose studies of cholesterol and the bile acids were originally so purely a chemical interest.

It follows that much of biochemistry becomes less and less comprehensible to the average medical practitioner, however ready he may be to grasp the possible applications of such work to his particular problems. Further, the range is very wide, as we see when we consider such different aspects as the synthesis of hormones such as adrenalin or thyroxin, the isolation of an extremely active hormone from male urine to the extent of 15 mg. from 25,000 litres, the increasing field of chemotherapy, the concentration of antitoxins as in antiscarlatinal and antipneumonic sera, the application of micro-chemical analysis to routine medical work, the problems of animal nutrition, &c. The medical student now needs his preliminary chemical studies more than ever, and certainly more than the detailed knowledge of anatomy which he spends so much time acquiring and so little time forgetting ; he finds his knowledge of the composition of foodstuffs more useful than, for example, his knowledge of the branches of the subclavian artery.

In everyday medical work biochemical methods are in increasing use, and though exaggerated claims are often made as to the necessity of their application in certain diseases, in many cases it is impossible to make diagnoses or provide rational treatment without recourse to the chemical laboratory. To a large extent this latter utility is due

to the improvement in methods of micro-analysis of biological material, whereby minute amounts of these can be analysed with sufficient accuracy for clinical purposes. Many of the methods used would hardly satisfy the criteria demanded in rigid chemical analysis, as where, for example, a method depends on a colorimetric measurement of a colour reaction which is neither specific nor stable. Nevertheless, if the possibility and size of the errors are borne in mind, information of great utility is easily obtainable. Blood "sugar", for example, can be estimated on 0.1 c.c. of blood; the values obtained vary according to the method of estimation, and further, the values represent the amount of reducing substances oxidized by the main reagent, and hence include other bodies besides glucose. To the clinician, however, it is of little significance whether blood-sugar is 0.15 per cent. or 0.16 per cent. in a particular estimation or, say, 0.26 per cent. or 0.28 per cent. in another. A medical man will hardly achieve any greater accuracy than this in methods involving so much use of the pipette and burette, the calibration of which he generally takes for granted. Values such as those just mentioned represent sufficiently well the extent of a hyperglycæmia and enable diabetes mellitus to be so controlled that a diabetic patient's metabolism becomes normal enough for the maintenance of health, freedom from symptoms and secondary damage.

It is impossible to give in such short compass any comprehensive account of the applications of biochemistry to medicine, but a consideration of certain aspects only may be of assistance in assessing their value to the physician.

For many years efforts have been made to estimate the functional efficiency of the kidney. Generally these depend on estimating either the degree of retention of certain metabolites, the result of their slow excretion, as for example by evaluating the blood-urea or creatinin, or by determining the actual rate of excretion either of metabolites such as urea or chlorides, or of foreign bodies such as phenolsulphonephthalein or indigo-carmin. Largely as a result of the findings of the French workers there arose the conception of a dual nature of renal impairment. This seemed so definite that nephritis was divided into two forms, the azotæmic and the hydropigenous, the former marked by nitrogen retention and vascular changes, the latter by water and chloride retention associated with varying degrees of œdema or anasarca. This division of nephritis on the ground of certain biochemical findings, though elegant and simple, was misleading in many ways, for it did not really correspond with the clinical facts. We now know that gross nephritic œdema is correlated with the loss of protein from the plasma through the leaky kidneys, and though other factors may be operative, the appearance of such œdema requires sufficient chronicity and sufficient degree of albuminuria. Every nephritis shows impairment of function of the same nature and the predominance of œdema or of azotæmia depends on the chronicity of the lesions and on the *stage* of the disease. In early nephritis œdema largely occupies the clinical picture, the nephrotic syndrome in fact; in late nephritis, nitrogen retention and vascular change take its place. In the more chronic cases these syndromes are developed often consecutively, in acuter forms they overlap and may even appear together.

Though medical biochemistry in this way misled us for a time we have, however, gained an ability to measure the progress of a case in terms of loss of renal function. Much credit is due to the work of Addis and his collaborators who have devised a test

in which the kidney is forced to work up to its maximum capacity, when the estimation of the rate of removal of urea from the blood, expressed as the volume of blood cleared from urea, under their carefully defined conditions has been shown to provide a measure of the amount of functioning renal tissue. An application of this test has demonstrated that no rise of blood-urea occurs till more than 50 per cent. of the kidneys is, as it were, out of action. Addis' ratio, as it is termed, is not an easy test applicable to all cases, but it has shown the value of a *quantitative* estimation of the amount of functioning kidney substance. Most other tests of renal capacity, however, provide only qualitative values with perhaps the exception of Van Slyke's urea clearance coefficient which is similar to Addis' ratio, much more simply estimated but correspondingly subject to much greater limits of variation.

It should be noted that such estimations of the amount of functioning renal tissue are not necessarily guides to prognosis in the absence of common clinical knowledge. An acute nephritis may show renal efficiency reduced by say 80 per cent. and yet complete recovery be possible, whereas, on the other hand, a reduction of renal capacity to a lesser degree in the slow march of a chronic nephritis only marks a stage of progress, and the prognosis depends on the rate of destruction of the kidney. From the surgeon's viewpoint estimations of renal efficiency are very helpful in distinguishing cases which are or are not a reasonable operative risk, but again the tests are not all-sufficient; an asthenic patient with a foul, dry tongue is not necessarily operable even if the renal efficiency is apparently fairly good.!

To the clinician a more advanced state of affairs is seen in the control of diabetes mellitus. Progress here has been due in the main to the discovery of insulin and to the common use of blood-sugar estimation. Insulin is now readily

Diabetes. obtainable in concentrated preparations of high purity, and the introduction of a quadruple strength has added a further facility; the administration of the hormone need be attended by no extraneous ill-effects. One might notice firstly, the ease with which diabetes mellitus can be distinguished from other conditions associated with glycosuria by the use of glucose tolerance tests. As a general rule such investigations are not required, the diagnosis in the presence of the usual symptoms associated with high blood-sugar values is enough, and an injudicious glucose tolerance test with the administration of a large dose of glucose may unnecessarily delay the recovery of the patient's tolerance during treatment. The control of the ordinary diabetic by the use of fixed carbohydrate intakes and administration of insulin once or twice a day is generally quite easy; once a suitable balance is found blood-sugar estimation is rarely required; examination of the urine and avoidance of hypoglycæmic symptoms provide a sufficient index. Some cases, such as those with a high renal threshold for sugar or the much rarer case with a low threshold, cannot be dealt with satisfactorily unless the balance of carbohydrate and insulin is frequently checked by blood-sugar determinations. Much more difficulty is met with in the presence of complications such as sepsis. Here the loss of sugar tolerance may rapidly increase, large doses of insulin must be used till the sepsis has been dealt with, and then the insulin is reduced as tolerance for carbohydrate recovers.

Surgical procedures are no longer to be feared in the diabetic, even when the disease has not been adequately controlled. In such cases the administration of glucose per os or per rectum and of insulin removes the danger of coma. Choice of anæsthetic is

nevertheless important as prolonged unconsciousness is objectionable, hence local anæsthesia or gas and oxygen are preferable. There is no longer any urgency in the treatment of complications such as gangrene. In pre-insulin days the mortality of this occurrence was very high, and the successful cases were those who had survived a "high" amputation or from those who had been left alone. Now amputation is rarely necessary, the diabetic under complete control separates off his gangrenous parts, aided if necessary by local operation only.

More recently there has been a considerable change in the diets used in diabetics. Hitherto the diets were low in carbohydrate and high in fat content, the latter to provide the essential caloric value. The fat intake was only limited by the necessity of avoiding ketosis. With such diets, the insulin to carbohydrate ratio tends to be rather high, and it is now thought that better results are obtained by using a diet high in carbohydrate and low in fat. With this diet large doses of insulin are required at first, up to say 100 units a day, but it is possible quite rapidly to reduce the amount of insulin administered to quite manageable figures. For example, a patient might be given 120 gm. of carbohydrate daily, allowing of reasonable quantities of bread, potatoes or fruit, and yet finally be balanced with only 10 to 30 units of insulin a day. Such diets are very advantageous in that they allow of foods which the patients generally prefer, and further in that they provide a combination of foodstuffs more in accordance with average *normal* requirements. In the management of diabetic complications much better results are obtained by using high carbohydrate diets giving perhaps 200 gm. per day. After all it is reasonable to suppose that if such a complication as atherosclerosis and gangrene is consecutive to the prolonged mal-metabolism of carbohydrate, then the nearer this metabolism is brought to the normal the better.

Diabetic coma need rarely occur in treated patients, but even in neglected cases the prognosis is still fairly good, excepting where a factor such as sepsis cannot be located. These latter cases probably provide the so-called insulin-resistant types, and a patient in coma with an undiagnosed perinephric abscess or a quiet empyema of the gall-bladder may not yield to treatment with insulin.

An interesting group of cases has been defined in which, as opposed to the hypo-insulinism of diabetes, a hyper-insulinism occurs. These cases are generally due to pancreatic islet tumours and the symptoms are those of persistent hypoglycæmia. They are not easily controlled by a high carbohydrate intake, nor is operative treatment entirely satisfactory, possibly because of the difficulty of removing all the tumours.

The comparison of this condition with hyperparathyroidism is striking. The study of cases of hyperparathyroidism due to parathyroid tumours provides a remarkable example of the importance of biochemistry to medicine, and has helped enormously to elucidate the physiology of this gland and of calcium metabolism. Briefly, the excessive activity of tumours of this gland leads to a drainage of calcium from the bones from which ensues a high blood-calcium and an increased urinary excretion of this substance. In the course of time the process of decalcification of the bones becomes obvious as osteitis fibrosa cystica, and this condition can now be adequately diagnosed and then treated by surgical removal of the parathyroid tumours.

Here too one might mention vitamin D, the action of which on calcium metabolism is very different from that of the parathyroid secretion. Hypo-vitaminosis D leads to

failure of calcium and phosphate absorption and retention and hence to rickets. Administration of vitamin D, either as cod-liver oil or in pure form, facilitates calcium and phosphate retention. Hyper-vitaminosis D, from excessive administration of the principle, leads to excessive calcification and even to the deposit of calcium in some soft structures such as the aorta or other arteries.

The study of gastric secretion by means of test meals has been disappointing in many ways in the diagnosis of gastric disease, but on the other hand it has thrown valuable light on the nutritional nature of certain of the anæmias such as pernicious anæmia and achlorhydric (microcytic) anæmia. In Addison's anæmia the deficiency of the gastric secretion is such that some essential extrinsic factor is not elaborated or liberated from the foodstuffs, and in the absence of the extrinsic factor the typical anæmia is produced. The intrinsic factor absent from the gastric juice is not hydrochloric acid or other known substance. The extrinsic factor can be supplied by the administration of liver. In achlorhydric anæmia the absorption of iron and perhaps other important heavy metals is at fault and, once the diagnosis of such an anæmia is established, treatment by large doses of iron is extremely effective.

A class of case in which accurate diagnosis is almost entirely dependent on biochemical analyses is seen in the occurrence of alkalosis due to high intestinal obstruction or to overdose of alkalies. A patient with incomplete pyloric obstruction treated with alkalies may rapidly become uræmic and present a blood-picture of increased alkali reserve, marked nitrogen retention but low blood-chlorides. Such a condition can be rapidly fatal; where the intestinal obstruction has not been suspected and alkalies have not been administered the differential diagnosis between uræmia of primary renal origin and uræmia, the sequel of alkalosis due to pyloric obstruction, can be very difficult. The differentiation is, of course, exceedingly valuable, for the latter type of uræmia rapidly yields to treatment by intravenous and rectal salines, with suitable operation such as jejunostomy under local anæsthesia. It is interesting that the well-marked renal changes produced in these cases are apparently the result of a purely metabolic disturbance.

It would be easy to add further examples of the use of biochemical methods in everyday medicine, as in estimation of liver efficiency and of basal metabolic rates. The latter is dependent on that most beautiful demonstration by Lavoisier in the eighteenth century of the applicability of the laws of conservation of energy and of mass to living animals. How Lavoisier, in addition to all his epoch-making scientific researches, found time to interest himself in politics is difficult to understand, but it led him to the guillotine, and the world lost one of its greatest savants and a pioneer in biochemistry many years before Wohler opened new vistas to the biologist by synthesizing urea at a time when it was considered impossible to synthesize organic compounds found in living structures.