Observations ON DIABETIC COMA;

WITH SPECIAL REFERENCE TO BETA-OXYBUTYRIC ACID AS AN ETIOLOGICAL FACTOR.

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THE majority of the numerous pathological questions at present under consideration are being attacked from the standpoint of bacteriology and histology, but there are various diseases whose sombre problems still await full elucidation, and which one feels must be approached mainly from the side of pathological chemistry. Among these are eclampsia and diabetes mellitus. With regard to the former, in spite of all the histological and bacteriological work that has been done, we really know very little more now about its essential nature than we did a dozen years ago, nor shall we, I am convinced, until the blood, the liver, the placenta, and the liquor amnii have been subjected to the strictest scrutiny by the pathological chemist; while, in the case of diabetes, the explanation of such a matter as the "coma diabeticum" lies almost entirely along chemical lines.

Without entering into details of the pathology of diabetes, I may be permitted to emphasize certain outstanding features in the disease. In a genuine case we have a patient exhibiting the presence of large quantities of glucose in the urine, and practically always a distinct though not great increase in the sugar of the blood, the latter consisting in part of glucose and in part of a combination of glucose with lecithin. Such a patient suffers from polyuria on account of the larger amount of fluid required to act as a solvent for the sugar, and, although the appetite may be voracious, there is a loss of flesh. It is in general accepted that the increase of sugar in the blood is due not to increased production, but to defective utilization, or as v. Noorden puts it, "diabetes is a disease in which the capacity of the organism for burning up grape sugar is morbidly depressed." As to the precise cause of this defective combustion, one cannot make a positive statement, and it is likely that it is not the same in all cases.

The established connexion between the complete ablation of the pancreas and the development of the classical symptoms of diabetes in lower animals, and the occurrence of pancreatic lesions in at least 50 per cent. of the fatal cases in man, have led to the suggestion of this plausible theory that from those peculiar groups of cells in the organ called the "islands of Langerhans" some internal secretion is added to the circulation which aids in glycolysis or the breaking down of the sugar molecule, and that when the gland is removed or has become the seat of disease this so-called secretion is lost and diabetes develops. A parallel, in short, is drawn between this disease and the gland associated with it, and myxoedema and the thyroid. I may say, however, that this simple theory of the matter is by no means free from objections, and that we do not as yet know the rôle which the pancreas plays in diabetes or the prevention of it. Let us now turn to the aspect of the subject with which we are specially concerned, and consider what is the most probable explanation of the causation and nature of diabetic coma, that most grave of eventualities that may arise in the course of the disease.

Of coma there are three types:

1. The typical and most common form, often met with in young subjects and where the symptoms develop with comparative suddenness. To begin with, the patient complains of digestive disturbance and vomiting, abdominal pain, muscular weakness, and drowsiness which passes into coma. The breathing is often deep (though not rapid), as if the patient was longing for air; this constitutes the *Lufthunger* described long ago by Kussmaul. Death may occur in 24 hours.

2. A form met with after fatigue, especially in elderly patients, where the symptoms are those of profound collapse.

3. A third variety in which the gait may become ataxic and the speech confused. It is with the first of these that we are particularly concerned. A careful study of the urine from the chemical standpoint shows that we have present in it in severe cases several substances which are calculated to throw

light on this matter. Sugar, abundantly present though it may be, we may dismiss at once.

A substance nearly always present in severe cases is acetone, CH_3COCH_3 . It is not peculiar to diabetic urine, but may be met with in cancer, fever, and digestive disturbance. It is usually regarded as having its origin in an excessive destruction of albuminous tissue or from fat. Acetone is a volatile, clear liquid when pure, and can easily be distilled off from urine. It is readily recognized by Lieben's test, in which iodoform is produced, and in a distinct case of diabetes the amount excreted per diem may, according to Hirschfeld, reach to 0.6 to 0.8 gram. (8 to 12 gr.). It is practically certain that it is not the cause of coma. The next substance to be mentioned is diacetic or aceto-acetic acid, whose formula is $\text{CH}_3\text{COCH}_2\text{CO}_2\text{H}$, being acetic acid where one atom of hydrogen in the methyl group has been replaced by the radicle acetyl CH_3CO . It is found in certain other pathological states, but most frequently of all in diabetes, and then usually in severe cases. In fact, acetone and diacetic acid in a diabetic's urine usually indicate that the outlook is somewhat grave. It is readily recognized by Gerhardt's test, and is easily driven off by boiling. If we compare the formulae of those two bodies we see the diacetic acid is acetone *plus* a molecule of CO_2 . They are related chemically and physically, and usually occur together. In looking over my notes of the last forty-three examinations made in severe cases of diabetes, I find that acetone was present on thirty-seven occasions, while diacetic acid occurred thirty-two times. On no occasion was diacetic acid present without acetone. The amount present in a severe case may be a few grams, and although it may possibly contribute to some extent to the causation of the coma, it is not regarded as playing any serious part in its genesis. The third and most important substance of the class found in diabetic urine is β -oxybutyric acid, and it merits some close degree of attention, since it is regarded by most clinicians as playing a large part in the development of coma. It is found in practically all very grave cases, and may be present in large amount. Its formula is $\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{CO}_2\text{H}$, and its relationship to acetone and diacetic acid are as follows:

Now the acid content of diabetic urine is very high, and is due chiefly to the presence of this acid. One need not be surprised at this, if it be borne in mind that from 20 grams to 30 grams or 1 oz. of this acid may be excreted in a single day; and in this connexion we may take note of the fact that diabetic urine in such cases is remarkably rich in ammonia, the amount excreted being often eight or ten times that met with in health. And if we ask why this alkali should be present in such large quantity, the answer is that it is needed as a base for the oxybutyric acid. This is a point of importance, and will be referred to again.

As regards the detection of this acid, the method I employ is Kùlz's, where the urine, after full fermentation, filtration, and concentration is distilled with strong sulphuric acid, whereby the oxybutyric acid loses water and distills over as α -crotonic acid, thus:

The latter is obtained as feathery crystals with a melting point of 72°C . In 36 analyses performed on 15 cases of diabetes, most of them severe, I found the acid present on 19 occasions, the amount being distinct in 10 instances and scanty in 9. In one case ending fatally by coma which was examined only twice, it was found in the urine the first time, but in a second specimen removed by catheter after coma had set in I found none. The distillate in this case had a peculiar fruity odour which I had already noticed in another fatal case, and which suggested that some other organic body might be present.

The amount of ammonia required for neutralization of the β -oxybutyric acid is 1 gram for 5 of the acid. In one of the last cases I examined the ammonia was estimated, and found to be 1.95 gram. As this is about 1 gram above that usually met with in health, it suggests that that excess was required for the oxybutyric acid which was present, and, as a matter of fact, it was computed that the acid in this case was about 5 grams for the day—just what we should have expected. Indeed, it has been suggested that the estimation of the ammonia in the urine (which is not a troublesome operation)

might be taken as a fairly accurate measurement of the β -oxybutyric acid it contains.

And now to explain the precise relationship of the acid to the coma—a relationship first suggested by Stadelmann. I incline distinctly to the opinion shared by many others, that we are dealing here with an acid-intoxication, or acidosis as it is sometimes termed. The acid for its elimination requires a base, for it does not appear in the urine in the free state. It cannot obtain from the body enough soda or potash, and therefore unites with ammonia (which explains the high excretion of this substance), this ammonia being the result of the metabolism of proteids, and destined under ordinary circumstances to become urea. This ammonia is given up to protect the alkali of the blood. If now, as a result of gastric disturbance or defective nutrition this supply is cut off, the acid utilizes the alkali of the blood as a base, reduces its alkalinescence, and stupor supervenes. In support of this view may be mentioned the fact proved experimentally by Walther that the introduction into the system of large quantities of dilute mineral acid, such as hydrochloric, can cause the onset of coma and dyspnoea in dogs and other mammals. It is further supported by the fact that in the gravest cases of diabetes the acid is almost always present, and greater in amount the nearer the coma is, while on the other hand relief has been obtained in cases actually in stupor by the subcutaneous or intravenous injection of saline alkaline fluid, or even by the administration by the mouth of massive doses of sodium bicarbonate. It does not necessarily follow because coma results from an excess of acid in the system that it is due to a specific toxic effect of that acid. Indeed, it has been shown experimentally that β -oxybutyric acid is not in itself a noxious substance. The acid probably acts by diminishing the alkalinescence of the blood, and so preventing the normal elimination of carbonic acid by the lungs. Indeed in coma the patient may be actually cyanosed. And it is this interference with internal respiration which gives rise to the *Lufthunger* of Kussmaul—the dyspnoea and gasping for air.

It is right to state that other substances have been regarded as the cause of coma besides oxybutyric acid. Sternberg, for example, finding that the introduction of the latter into a healthy mammal did not cause stupor, suggested that it might be β -amido-butyric acid that caused the fatal symptoms, since its administration to animals could produce deep insensibility, laboured breathing, and increased blood pressure. The acid has the formula: $\text{CH}_3\text{CH}(\text{NH}_2)\text{CH}_2\text{CO}_2\text{H}$. The facts just stated regarding its effects have been substantiated by Grube, and Lépine, in a paper published about three years ago, also seems inclined to favour this view. It may be noted that on hydration this acid yields β -oxybutyric acid and ammonia, thus: $\text{CH}_3\text{CH}(\text{NH}_2)\text{CH}_2\text{CO}_2\text{H} + \text{H}_2\text{O} = \text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{CO}_2\text{H} + \text{NH}_3$, and Lépine thinks that in this way he may explain the high ammonia output in diabetics. Other chemical bodies of known composition have from time to time been suggested as the cause of the coma, among which may be mentioned trimethyl-amine (Senator) and paraldehyde (Latham). Schmitz has propounded the view that the stupor develops as a result of an auto-intoxication from loaded bowels; while Klemperer, and to some extent Von Noorden, incline to attribute the fatal ending to a toxin developed within the system as a result of the destruction of albuminous substances.

The only rational line of treatment that can be suggested is the introduction into the system of an alkali, either by giving very large doses of sodium bicarbonate by the mouth, or better still by administering it as a subcutaneous or intravenous injection. Cases have been reported in this country by Fagge, Taylor, Oliver, T. K. Monro, and others, where undoubted benefit occurred and in all grave cases it should be tried. I have not seen, or heard of, any case in which the inhalation of oxygen produced anything save a transient benefit.

In 1901 Schwarz, of Prague, suggested that gluconic acid might be used in the treatment of the coma. He used it in a case where coma occurred twice in the same subject, and where recovery took place each time under the administration of from 50 to 70 grams of gluconic acid in alkalized water, while at the same time large doses (140 grams) of sodium bicarbonate were given by the mouth and bowel. A third attack supervened in which no gluconic acid was available, although the soda was, and in this the patient succumbed.

In conclusion I may add that Lépine has suggested the use of some phenol, so that the toxic acid might be converted into a harmless nitrile within the tissues (nitrile-amido-

butyrate itself is innocuous for example). The phenol treatment of diabetes, however, has not been very successful, although antipyrin and phenacetin have been used a good deal in France.

SOME OBSERVATIONS ON THE TEMPERATURE OF COMA.

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A FEW years ago I made observations on many patients who were in a comatose state, and also examined the records of other cases of that condition with the view of ascertaining what variations in the bodily temperature occur in the different forms of coma, and whether a knowledge of the patient's temperature was of any value in the diagnosis of the cause of the condition. Although my observations have not perhaps been arrived at by any laborious or deep investigation, yet they are the outcome of an examination of many patients at St. Thomas's Hospital during a period extending over four years, and, although the results of this investigation are somewhat disappointing in certain respects, they appear, nevertheless, to be worthy of record on account of some interesting points which have been ascertained.

In certain conditions associated with coma the bodily temperature is well known to deviate considerably from the normal, as is the case in the high temperature of pontine lesions and in the low temperature of diabetic coma. After an examination of fifty-eight cases of coma I came to the conclusion that, while observations of the temperature might be helpful under certain circumstances, in the majority of the cases it was of comparatively little practical value in the diagnosis of the cause of the condition. Nevertheless, the changes in the bodily temperature are very constant in the different forms of coma, and, although a knowledge of these changes may only help occasionally in the diagnosis, yet, when the cause of the condition has been ascertained, the state of the patient's temperature has a distinct bearing upon prognosis. To obtain a complete record of the temperature in many of the forms of coma is naturally impossible, since the patients are often seen at varying intervals after the onset. In consequence of the examination of the patients being made at different intervals after the commencement of unconsciousness, the observations upon the temperature must vary considerably, even in cases in which the coma is due to a similar cause. For this reason, the condition of the temperature in many patients suffering from coma, when the cases are seen for the first time, does not appear to be of much diagnostic value. Notwithstanding this, the patient's thermometric temperature should always be observed, since, if it be above normal the coma is not likely to be due to alcoholic poisoning, or to be of diabetic origin, but to be dependent upon some other pathological cause; while, if the temperature be below normal, that condition may arise from the patient being in that state of collapse which occurs at the onset of many forms of coma.

In diabetic coma the bodily temperature is nearly always subnormal. I have never met with such a case in which the temperature was higher than 99°F . In those cases in which it was so before the onset of the coma, defervescence took place as the drowsiness increased. Dr. Saundby,¹ however, has observed pyrexia in this disease, and says that "death is sometimes preceded by a rise in temperature (103° to 104°F)."² It is very remarkable how rarely even slight pyrexia is found associated with glycosuria. It is not uncommon for the temperature in diabetic coma to fall so low as 96° ; the lowest record in my series was 95° , which was noted about eighteen hours before the death of the patient.

There is considerable difficulty in explaining the cause of this subnormal temperature in diabetic coma. In this disease there is a great increase in metabolism, as is shown by the large amount of urea in the urine, and as a result of this one might be led to expect an increase in the heat production. According to Sir J. Burdon Sanderson³ it is not necessary "to imagine more than one regulating centre in constant operation—that which presides over surface loss." If this thermolytic centre be injuriously affected, either by poisons circulating in the blood or by an increase in the cerebro-spinal pressure, the usual result is pyrexia. That there is very little increase in the thermolytic process is seen by the condition of the skin, which in this disease is usually dry and pale. There must, however, be a slightly increased loss of heat on account of the large amount of urine voided. By the excre-