INSULIN SHOCK THERAPY.

I.—CARBOHYDRATE METABOLISM IN SCHIZOPHRENIA.

(PRELIMINARY OBSERVATIONS.)

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INSULIN shock treatment of schizophrenia is to-day a recognized part of our therapeutic armamentarium in mental disease, and with selected cases is yielding results which are more encouraging than those given by other methods. At the same time the method is largely empirical, and the theories of its mode of action are only equalled in number by the hypothetical causes of the disease itself.

On *a priori* grounds, the individual response of any patient to injections of insulin depends, *inter alia*, upon the carbohydrate reserves of the body as represented by the stored glycogen, and the state of functional balance between the pancreas, the pituitary and the adrenal glands.* Originally we had hoped that by assessing the state of these factors we would be able to predict the response of the patient to insulin. Unfortunately this has not been possible. However, even at this early stage of our work some interesting facts have been brought to light, and in this paper we have summarized our preliminary results in broad outline. At present our series is small and we have investigated only twenty-one patients, so that it is impossible to make any hard and fast deductions. We are here simply recording what might be called a series of pointers, in the hope that even if they do no more, they will at least stimulate a degree of constructive criticism.

Previous workers who have investigated the carbohydrate metabolism in schizophrenia have used the oral route for the administration of a known amount of glucose to a fasting subject, and indeed this method is almost general throughout the realm of medicine. But such a method, old established though it is, appears to us to be fraught with pitfalls, not least of which is the

* It is interesting to note that one ætiological theory of the disease postulates a disturbance of the vegetative nervous system, with a parallel adrenaline imbalance.

fact that the resulting " tolerance " curve by no means represents the way in which the body deals with glucose. The curve is an indecipherable complex of two curves, of which the most important is the curve of glucose absorption from the alimentary tract, and the least significant the curve of its removal from the blood. It is an unscientific test in that it is uncontrollable, and we have abandoned it as a means of assessing carbohydrate metabolism ; we reserve it more particularly as an index of the rate of glucose absorption. In its place we have substituted an intravenous test in which 10 grm. of glucose (in 50% solution) are injected into an arm vein within 30 seconds ; blood samples are taken immediately after the injection, and at intervals of 5, 10, 15, 20, 30, 40, 50 and 60 minutes thereafter. Two persons are required to perform this test properly, for the " immediate " blood sample must be taken as soon as the plunger of the syringe is home. The initial rate of removal of glucose from the blood after injection is so rapid that a delay of even 30 seconds will result in a fall of 20 or more mgrm. per 100 ml. of blood. We refer to this test as the glucose utilization test (G.U.C.).

An example of the difficulty in assessing oral glucose curves was provided by two schizophrenic girls, each in the early twenties, in adjacent beds. On successive days oral and intravenous glucose curves were made on each under identical conditions ; they were both on the same diet. The results are shown in Fig. 1. In both the fasting-sugar level was low (80 and 83 mgrm./100 ml.). However, the one in thirty minutes had absorbed sufficient glucose to raise her blood sugar to over 200 mgrm./100 ml., and after an hour excreted more than a gramme of sugar in her urine; two hours afterwards the blood sugar was still nearly 180 mgrm./100 ml. The blood sugar of the other, by contrast, rose no higher than 116 mgrm./100 ml., and she, of course, excreted no sugar in her urine. That these totally dissimilar curves are functions of absorption and not of utilization is strikingly shown by the intravenous curves, which at each time interval were almost milligram for milligram identical. Woodyatt, in 1915, said that " glucose tolerance tests are a function of velocity and not of weight "—the resulting curves vary more with the speed at which glucose is introduced into the circulation than with the amount which is so introduced. It is only by standardizing the conditions and rate of administration that accurate and comparable results are attainable.

Some comment upon the collection and analysis of the blood samples is pertinent. As far as is practicable, it is essential to reduce the arterio-venous sugar difference to a minimum. This is most conveniently done by taking blood from the finger when the whole arm has been immersed in a bath of hot water. Just before the required time, the arm is taken out of the bath and dried ; the pulp of the finger is pricked with an automatic needle to the depth necessary to yield a large drop of blood. The blood is run into a small tube containing sodium fluoride which inhibits *in vitro* glycolysis. Squeezing of the finger, which produces a venous stagnation, should be avoided.

Approximately 0·3 ml. blood were taken for each sample, and duplicate estimations of the total reducing substance present were made by the Hagedorn-Jensen

technique.* No attempt has so far been made to estimate the true sugar, and the figures which we have used include the 25 mgrm. or so of non-sugar-reducing substances. The time factor in blood-sugar estimations is of importance, and although fluoride was used, in many cases the precipitation of the blood protein was made in the ward immediately after the blood sample was taken.

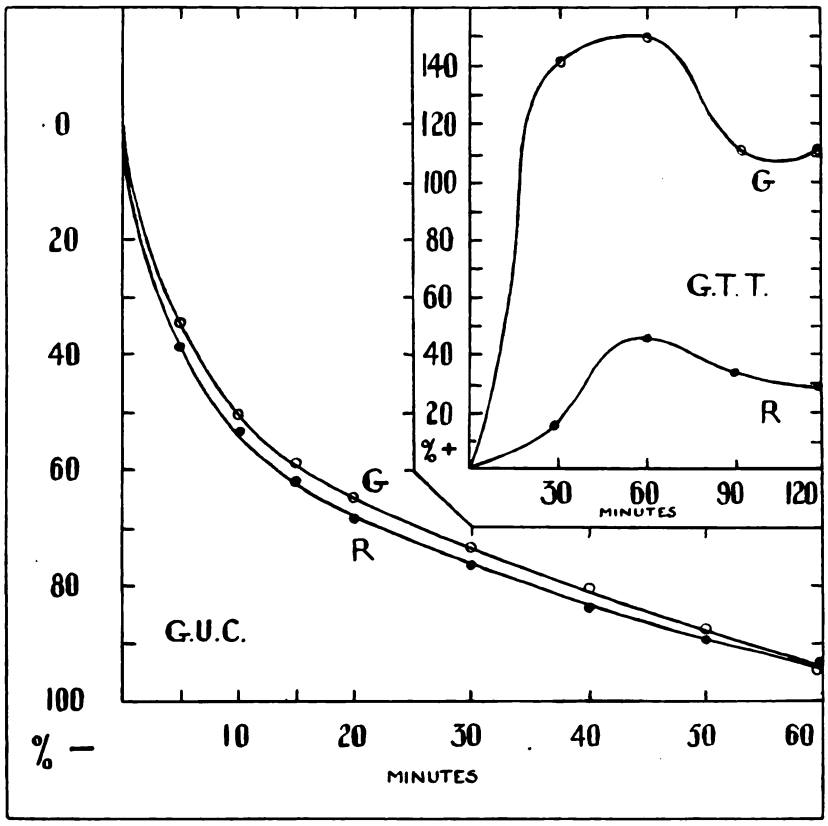

FIG. 1.—Oral (G.T.T.) and intravenous (G.U.C.) glucose curves of two female schizophrenics under similar conditions.

* We have used the Hagedorn-Jensen blood-sugar apparatus designed by Dr. H. J. Fuchs, and sold by Messrs. Baird & Tatlock, Ltd. The use of the special automatic 0·1 ml. pipette is a great asset when a number of estimations have to be made (our preliminary work has already entailed more than a thousand blood-sugar analyses), as are the funnel-topped filtration-boiling tubes. The lipped precipitation tubes are designed to hold the 6 ml. of $ZnSO_4$–NaOH mixture together with the blood sample, but do not allow for the extra 1 ml. odd of distilled water which is blown in from the automatic pipette. We have had to discard these tubes therefore, and have substituted ordinary Pyrex test-tubes.

It is important to stress the necessity for using chemicals of the utmost purity for this technique. With these, the automatic pipette and the needle-dropper, one can obtain exact duplicate results on any given sample of blood.

The remaining methods which we have used in assessing the patient's carbohydrate balance are :

1. The degree of mobilization of the glycogen reserve, measured as glucose, following the subcutaneous injection of 1 ml. of a 1/1,000 solution of adrenalin hydrochloride. Blood samples were analysed at 10-minute intervals for an hour following the injection, and at 90 and 120 minutes (adrenalin mobilization curve—A.M.C.).

2. The extent of the depression of the blood sugar following an intramuscular injection of insulin. We were in some difficulty in determining what dose of glucose, adrenalin and insulin to give to our patients. A weight-dose ratio seemed suitable, and for insulin we used 2 units per stone weight, the odd pounds being taken as an extra stone ; for sugar and adrenalin we used a constant dose of 10 grm. and 1 ml. respectively. Possibly the correct basis for the calculation of these doses is the surface area of the patient, which is easily calculated from the weight and height. This point is being investigated. In this test the blood sugar was estimated at the same time intervals as for the G.U.C. except that the immediate specimen was omitted. In some cases we examined the blood at 3, 6, 9, 12, 15 and 20 minutes (insulin depression curve—I.D.C.).

3. The oral glucose tolerance curve was performed by giving 50 grm. of glucose in 200 ml. water flavoured with lemon ; the blood sugar was estimated at $\frac{1}{4}$-hour intervals instead of the commoner $\frac{1}{2}$-hour intervals.

In any series of patients blood-sugar curves are not strictly comparable if expressed in milligrams per 100 ml. of blood ; at least they are not comparable graphically. To overcome this we have expressed our results for the G.T.T., A.M.C. and I.D.C. as a percentage rise or fall of the fasting sugar value. For the intravenous G.U.C. the results are given as the percentage removal of the excess from the blood, i.e., as $\frac{P-A}{P-F} \times 100$, where P, A and F represent the observed values in mgrm./100 ml. at the peak (immediately after injection), at the actual time and at the fasting level respectively.

All our patients were free from any intercurrent physical disease, and were on the same dietary level. They were fasted for 15 hours before the tests, which were made as early as possible in the morning (between 8 and 9 a.m.). The sugar curves were made on successive days. On the following day a fractional test-meal analysis and complete blood-count were made. When on a full diet a 24-hour specimen of urine was analysed completely, and this, together with a Wassermann reaction, completed the routine investigation of our patients before insulin treatment. So far we have investigated 21 patients—10 males and 11 females—and it is upon these that our preliminary observations are based.

With such a small series it is improper to dogmatize, but even at this stage we have found indications that two types of person exist when classified according to their response to glucose, adrenalin and insulin injections. It is inevitable that some patients will fail to conform to either type, but of our twenty patients, fifteen fitted into either one or other of these classes.* Quite broadly, the one type consists of the least severe and most co-operative cases

* The remaining patient—a male in catatonic stupor—will be discussed elsewhere.

of the disease, while the other contains the more florid, more excitable and more resistant patients. Frankly resistant patients have been excluded, for their curves are not true curves owing to the various physical difficulties, and the inevitable venous stagnation involved in obtaining the blood. The effect of excitement and exercise upon these curves has to be investigated, but the effect in the patients which we have so far examined was not, we judged, sufficient to produce any gross alterations in the test curves. We are not yet in a position to say whether these two " metabolic types " are pathological entities, or whether they are merely physiological variations of a normal curve. Our available evidence suggests that only one of the two types is met with in normal people, and we think that the second type represents a true endocrine imbalance in schizophrenia.

The first type is characterized by a rapid clearance of glucose from the blood, a moderate mobilization of glycogen from the liver and a steady, though variable depression of the blood sugar by insulin. The second type presents a slower sugar clearance and a delayed or lessened action of insulin, together with an abnormal sensitivity to adrenalin, evidenced by a grossly exaggerated rise of the blood sugar following its injection. Eight of our patients fell into the latter class, and seven, together with the normals which we have so far examined, into the former.

At this stage we do not propose to itemize the tests on individual patients ; the general characteristics of each type are sufficient, and these are shown well by the curves of two patients (one male and one female ; sex does not appear to influence these curves) shown in Figs. 2 and 3. The mean values for the sugar and adrenalin curves for the two groups are shown in Fig. 4.

Treating these types quite generally, a person in the first deals with intravenously injected glucose admirably and rapidly. The amount injected—10 grm.—is approximately double the amount present in the blood, yet the body is capable of removing this by oxidation and glycogenesis in about 30 minutes. None is excreted in the urine. During the second half-hour after injection there may or may not be a reciprocal hypoglycæmia. The majority of our patients did show this negative swing, but in one or two the blood sugar simply fell to its fasting level and remained there. This reciprocal hypoglycæmia appears in normal persons, and the fact that it occurs is of the utmost importance in the recovery phase of insulin-induced coma. A patient who requires intravenous glucose, irrespective of the reason for this, must, as soon as possible, be given a " backing " of oral sugar to prevent this hypoglycæmic swing. Without it, coma may reappear ; this fact is well established clinically.

In these people the degree of glycogenolysis by adrenalin is remarkably constant ; there is a steady rise of the blood-sugar to a peak in about 45 minutes, after which the level falls and commonly returns to normal in about two hours—sometimes a little earlier, sometimes later. The word " constant " is used here quite elastically, but it is a significant fact that the curves of

six of the seven patients in this group showed a peak at 45 minutes, and that these peaks represented a 52, 54, 56, 58, 58 and 60% increase of the fasting sugar respectively.

The insulin curves of these patients are more variable. In general, however, there is a steady fall with approximately a 40% depression of the

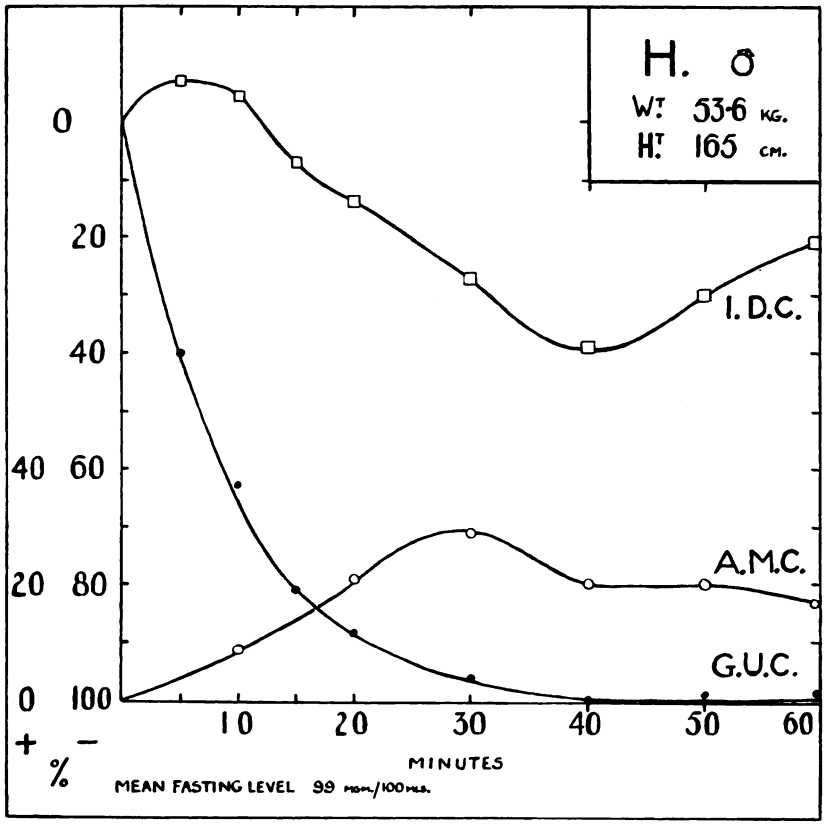

FIG. 2.—Glucose utilization (G.U.C.), adrenalin mobilization (A.M.C.) and insulin depression (I.D.C.) curves—first type. (Note that the A.M.C. is low, the more usual response being between 50 and 60% in 45 minutes—see Fig. 4.)

fasting level with the doses which we have used. The fall may or may not be preceded by an initial rise ; this rise occurs in rabbits, but its cause is uncertain. Moreover, the blood sugar in these patients regains its fasting level spontaneously, and generally there is an upward trend in the curve before an hour has passed. The absence of any grossly abnormal curves in these patients is important.

It is possible that this "metabolic type" (though "endocrine type" might be the more suitable expression) may represent the normal state of affairs. The advent of glucose into the circulation is expeditiously dealt with, and the normal sugar balance of the body rapidly regained. The secretions of the pancreas and adrenals are nicely balanced; the injection of small

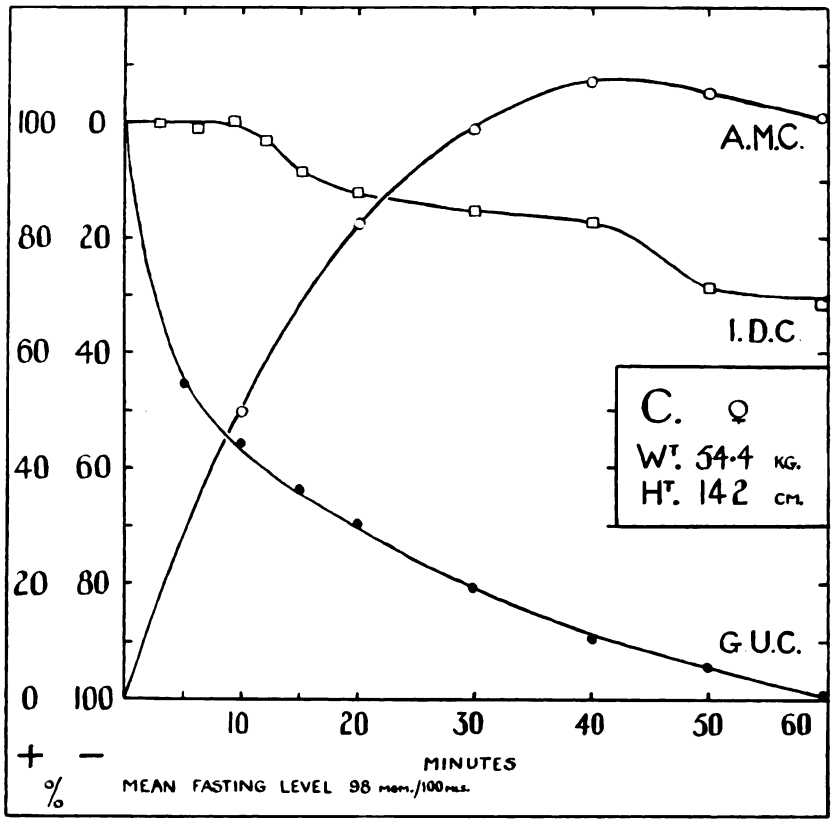

FIG. 3.—Glucose utilization, adrenalin mobilization and insulin depression curves—second type.

quantities of the one calls forth a reflex secretion of the other to preserve this balance, and by its antagonism to restore the blood-sugar level to normal as quickly as possible.

The condition of affairs in the second type is vastly different, the main characteristic being a greatly increased sensitivity to adrenalin with a parallel, though only partial insensitivity to insulin. The balance here is working, as it were, upon a hair-spring trigger—with a disturbance of the one side the

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other is called into play, and then the latter itself cannot return to normality in the usual time.

The sugar curves are entirely different in the two classes. Whereas in the former the blood sugar returns rapidly to normal, in the latter the return is

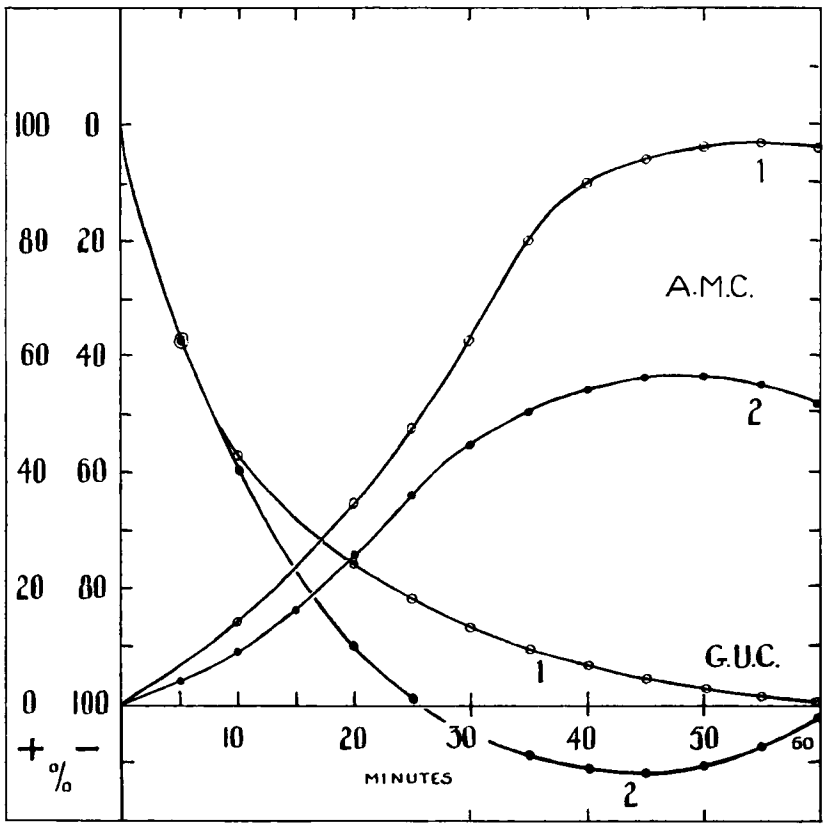

FIG. 4.—Mean glucose utilization and adrenalin mobilization curves for seven patients of first type and eight patients of second type. (1) Second type with endocrine imbalance and hyper-adrenalin response. (2) First type with balanced endocrine action and rapid removal of injected glucose.

delayed and the curve much flatter. The fasting level may not be regained in these patients for an hour or more, and the hypoglycæmic swing is conspicuous by its absence. Whether insulin plays a part in this clearance of glucose from the blood is uncertain. There is evidence to show that secretion does occur during the absorptive phase of a carbohydrate meal, and the tissues of an animal do not differentiate between sugar injected into a vein and sugar

absorbed from the intestine. Whether the insulin so secreted merely enhances the action of glycogenase or actively inhibits glycogenolysis is not clear.

In these subjects the injection of insulin may not depress the blood sugar to the extent seen in normal persons, and the initial fall is commonly delayed. But once this preliminary inertia is overcome the fall may be rapid, and the blood sugar drop to 30 mgrm./100 ml. in an hour even with the small doses which we use. It is as though its action was being restrained by adrenalin; when this restraint is overcome, control cannot be regained for some considerable time. Moreover, the injection of adrenalin increases the blood sugar to an extent never seen in the first class of patient; in half an hour it may be more than doubled, and this level be maintained as a plateau for two hours or more. In contrast again to the former type, there is a much greater variation in the individual adrenalin response, and a composite graph of these eight curves appears as a bunch of ribbons trailing in the wind instead of an intertwining skein suggested by the curves of the former class.

If we take the view that in these patients the adrenalin trigger is so lightly balanced that an abnormally small stimulus will provoke an abnormally large response the reactions of these patients are explainable. The raised blood-sugar may *per se*, or through the pituitary or through a compensatory secretion of insulin be sufficient to set it off, and the antagonism of adrenalin would be sufficient to account for the delay in sugar clearance. The injection of insulin itself may set it off, so that the sugar depression is delayed and not so marked, although once its antagonism is overcome, insulin may gain the upper hand and result in an abnormal lowering of the blood sugar with a delayed recovery. And with such an imbalance the addition of extra adrenalin to a fasting patient would result in the exaggerated degree of glycogenolysis which does occur.

Such an explanation, tentative though it is, forges an additional link in the chain of evidence implicating the vegetative nervous system in this disease. But here one is faced with the eternal problem, *propter hoc* or merely *post hoc*, and it is yet too early to decide between them. Of course, the explanation of these types may be entirely different. Although our patients have been on a balanced diet as far as possible, the fact that the carbohydrate intake may have differed cannot be ignored, for variations in this factor have been said to play an important part in modifying and altering the response to insulin. But the constancy of the types of response in the two groups would suggest that such a factor cannot be entirely responsible for the differences between the two.

We have already instanced the difficulty in interpreting oral tolerance curves, and have shown that they vary primarily, though not of course solely, with the rate of absorption of sugar from the gut. It is interesting to note that, while our patients are divisible into these types by parenteral injections, no such division is possible on the basis of oral curves. High, peaked curves appear side by side with low, flat curves in persons who appear by all the

other tests to be in an identical state of carbohydrate and endocrine balance. The curves in Fig. 5 are from two patients who fall into the second category with a slow glucose clearance and a hyper-adrenalin response. Their oral curves, however, are grossly dissimilar, the one rising to 292 mgrm./100 ml. at the end of an hour and at this time excreting 3·5 grm. of sugar in the urine, while the other never rises higher than 130 mgrm./100 ml. That this difference is a difference of absorption we think established, but why this difference

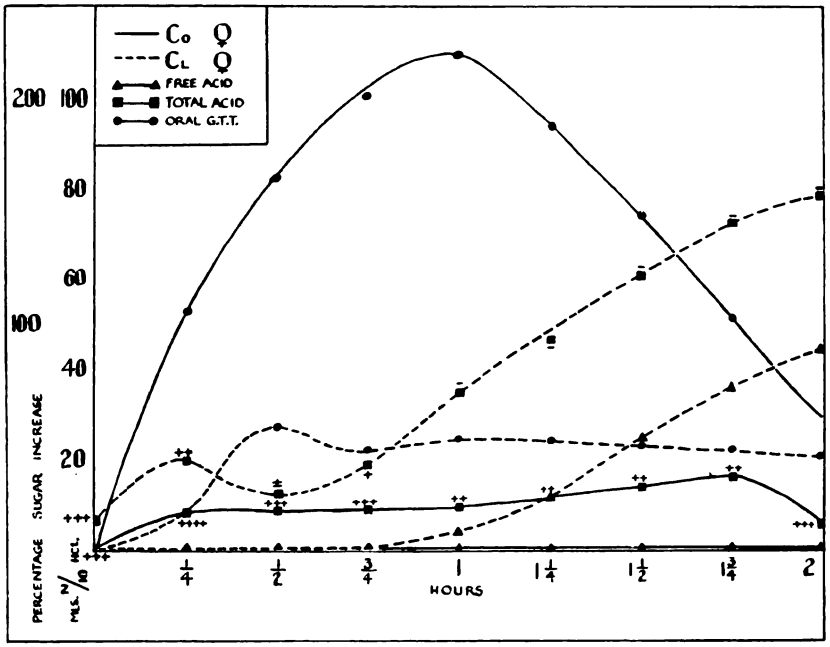

FIG. 5.—Oral glucose tolerance curves (G.T.T.) and fractional test-meal analyses of two patients of the second type with hyper-adrenalin responses. Note that the presence of free acid and mucus in the stomach does not influence the absorption of sugar. The patient with an achlorhydria to two hours eventually secreted 24 ml. free acid at 2¾ hours. (+ values indicate mucus.)

exists is more difficult to answer. The rate of absorption of glucose from the gut, and its mechanism, has been investigated by a number of workers, and is a point of the utmost practical importance in insulin therapy. Strong solutions of glucose are delayed in the stomach, while weaker ones leave the stomach quickly and then are rapidly absorbed; we are investigating the optimum strength for oral use, for the experimental evidence is in favour of weaker solutions than are generally used.

The presence or absence of free acid and mucus in the stomach is, *inter alia*, one of the factors which is stated to be important; free acid aids absorption,

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while an achlorhydria and an excess of mucus delays it. It is upon this observation, which is largely empirical, that the practice of giving acid to those patients whose gastric juice lacks it in the recovery phase of coma is based. But achlorhydria cannot be the primary factor at work, for of these two patients, the one with the rapid and efficient absorption of glucose showed a complete achlorhydria with a gross excess of mucus, while the other, with a low, flat oral curve, showed but a trace of mucus with a climbing gastric acidity (Fig. 5).

In this paper we have attempted to outline our early observations, and suggest a possible explanation for the differences which we have found. We have not mentioned any of the more practical aspects of the problem, or the many other biochemical analyses which are being made, and which will have to be made before one can gain a composite view of insulin therapy—vitamin B_1 levels and lactic acid accumulation in delayed coma; the role of the pH of the blood, the alkali reserve and the gastric contents in persistent vomiting; the Ca, K and P ratios, their changes, and the effects of changing them in particular relationship to vomiting and to the rate of glucose absorption; the effect of carbohydrate intake upon the course of coma—each of which we are investigating in detail.

The mechanism by which the repeated production of hypoglycæmic coma acts in schizophrenia is far from clear, and the position is complicated by the gaps in our knowledge of carbohydrate metabolism. In insulin therapy we have a potent weapon with which to combat mental disease. At the same time we have a golden opportunity, not only for studying the pathology of dementia præcox, but of contributing to our understanding of carbohydrate metabolism as a whole.

We wish to thank the Medical Superintendent, Dr. G. W. Shore, for permission to investigate these cases, and we gratefully acknowledge our indebtedness both to Dr. Charles Reid, of the London Hospital Medical College, for the interest which he has taken and the suggestions which he has made, and to Mr. R. F. Lane, our technical assistant, for his unflagging enthusiasm in this work.