conveniently subdivided into two or three, carried out without any undue risk, the latter course is to be preferred.

After-treatment

The procedure following transurethral resection is that a retention catheter is left in for two to three days. After its removal the patient can get up, and is able to void as required. At first, owing to reaction oedema, the voidings may not be complete, and it is as well in such cases to carry out intermittent catheterization morning and evening, instilling argyrol or silver nitrate solution after the bladder is empty and before removing the catheter. This may require to be done for four to five days, after which the patient can return home. As a rule a period of a week to ten days is sufficient for the post-operative course. For debilitated, senile patients, a longer period under supervision is advisable. In cases of fibrous prostate with long-standing contracture of the vesical outlet, the bladder tone is usually much impaired, and although a free outflow has been established, some time may elapse before the detrusor tone is sufficiently established to effect complete emptying of the bladder. In such cases silver nitrate irrigations have proved of the greatest value.

A repeat operation, if the primary procedure has not come up to expectations, should not be considered until all immediate local reaction has settled and the prostate has had some time to shrink. Reinspection of the operative field after three weeks will reveal complete epithelialization, and as a rule no trace of sloughs. Each case, however, should be individually judged as to the general as well as to the local condition, before further intervention is deemed advisable. A repeat operation is invariably easier to perform and necessitates a much shorter period of care, since no further course of preoperative preparation is called for. If the procedure is carried out as above outlined there is no operative shock, and no subsequent pain, nor is the patient confined to bed for longer than a period of three to four days throughout the entire course of corrective treatment.

Conclusion

The laity tends to think that any operation carried out after the age of 60 is a "do or die" performance, but it is the duty of the profession and of science to minimize risk and prolong life. It is because such a forlorn view of prostatectomy is taken by the majority of people—including some members of the medical profession—that victims of prostatism carry on with their complaint till finally an acute obstruction brings them suddenly face to face with the fact that at last something has to be done, and they are by this time reconciled to the worst. It is just this aspect of prostatic and bladder-neck trouble which one would like to emphasize. Why allow a patient to go on with obstructive urinary symptoms till the prostate is sufficiently ripened to permit of enucleation, when all the time progressive renal impairment is taking place, and the patient's general system is becoming more toxic and less able for surgical intervention?

Now that we have the means of determining and correcting such troubles, even in their incipient stages, is it not in the interests of common sense and the community at large, that these individuals be immediately attended to, and saved unnecessary years of suffering and impairment?

It has been said: "The surgery of the obstructing prostate of to-day involves an appreciation of the necessity of its early recognition as well as its prompt correction when the patient shows his greatest credit balance in resilient arteries and other physical assets, and before he has got well along the inevitable road to material depreciation of those assets. Moreover, he can and should have this journey made easier and the road longer."

HIGH CARBOHYDRATE DIETS AND INSULIN EFFICIENCY

BY

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During the last four years the use of diets containing a relatively large quantity of carbohydrate has become more and more common in the treatment of diabetes mellitus. When these diets were first introduced they were received with many theoretical objections, but their undeniable success rapidly compelled their serious consideration and encouraged their increasing acceptance. This divergence between theoretical objection and practical success is no minor discrepancy capable of easy adjustment after careful revision of the data, but a definite conflict between two diametrically opposed conclusions. On the one hand, a well-founded theory directs that the carbohydrates in the diabetic's diet must be curtailed if health is to be preserved; whilst, on the other, a brilliant piece of clinical empiricism produces irrefutable proof that a liberal allowance of carbohydrate acts favourably on the diabetic's health. At present it may be said that the theoretical objections are securely established, not only on a logical sequence of experimental results, but also on the accumulated clinical experience of diabetes mellitus before the introduction of insulin; whilst the beneficial effects attending the use of high carbohydrate diets are inexplicable either by any known physiological or pathological mechanism, or on the basis of previous clinical experience. A probable clue as to the nature of the discrepancy is suggested by a consideration of the chronological relation of the conflicting views.

The good results following the use of high carbohydrate diets were not discovered until after the introduction of insulin treatment. This suggests that there exists in the body a mechanism capable of stimulating the utilization of carbohydrate, but which cannot exert its action in the absence of an adequate supply of insulin. It was with the object of searching for this mechanism that the present work was undertaken, and the employment of healthy men as subjects for the search was dictated by the supposition that it would only be possible to detect the unknown mechanism in subjects possessing the normal supply of insulin.

Theoretical Objections to High Carbohydrate Diet

Before discussing the present research it is first necessary to glance at the work upon which the theoretical objections to the use of high carbohydrate diets in diabetes are based. For a long time it has been known that the excessive consumption of carbohydrate by the diabetic results in deterioration of his clinical condition. It was not, however, until a few years before the discovery of insulin that light was thrown, by the work of F. M. Allen and his collaborators, on the mechanism of this unfavourable clinical change. Allen studied the effect of diet upon the health of partially depancreatized dogs, and summed up his results by saying:¹

"Dogs which have lost a certain amount of pancreatic tissue will become diabetic irrespective of diet. Dogs which retain a sufficient amount of pancreatic tissue will never become diabetic irrespective of diet. But between these two groups is an intermediate group. On an Eskimo diet they may be found to live in health. On a Hindu diet they soon go down to fatal diabetes."

Thus if sufficient pancreas is removed from a dog so that it is on the borderline of pancreatic diabetes the animal lives, if it receives a low carbohydrate diet, and the blood sugar remains low and glycosuria does not occur. But if such an animal is given a diet rich in

carbohydrates the full clinical and chemical picture of pancreatic diabetes appears, and the animal rapidly dies. Allen further confirmed the work of other investigators, showing that, as a general rule, once pancreatic diabetes has been induced in these dogs by excessive intake of carbohydrates, then a return to the low carbohydrate diet will not cure the condition. It would appear that ingestion of excess of carbohydrate overstrained the remaining pancreatic tissue so as to produce a permanent degree of degeneration.

In the partially depancreatized dogs which died of the diabetes thus induced, histological examination of their pancreatic tissue revealed hydropic degeneration of the β cells of the islets of Langerhans, and Allen emphasized that this was also found in the pancreas of the patient dying in diabetic coma. As by this time the probability of the insular tissue's secreting an "anti-diabetic hormone" was generally accepted, conclusions from Allen's work were easily drawn. In the partially depancreatized dog excess of dietary carbohydrate, by producing a raised blood sugar, causes overstrain of the islets in the remaining pancreatic tissue; under this strain the cells break down and eventually are unable to secrete sufficient hormone to prevent the development of pancreatic diabetes. At death the β cells of the islets are in a state of hydropic degeneration; the pancreas from the diabetic dead of his disease shows similar lesions; therefore to preserve life in the diabetic the islet cells must be guarded against overstrain by maintaining the blood sugar at a low level by restriction of carbohydrates in the diet. The Allen diet—and the theoretical objections—are based on these conclusions.

Practical Experience

On its first introduction insulin was given merely as an adjunct to the Allen diet, but as its use became more widespread it began to be employed in conjunction with diets containing larger and larger quantities of carbohydrate, until the present high carbohydrate diet was evolved. It had been logically assumed that, in the diabetic needing insulin, increase of carbohydrate in the diet would necessitate an increase in the insulin dosage. But this assumption was speedily found to be false. Not only did the diabetic not require a proportionate increase of insulin for each extra gram of carbohydrate included in his diet, but his insulin requirement often remained unchanged. For example, if a patient is balanced on a diet containing carbohydrate 50 grams, protein 80 grams, and fat 115 grams and is then changed straight over to one containing carbohydrate 120 grams, protein 80 grams, and fat 76 grams, in the majority of cases no increase of insulin will be necessary. According to the current theory the excess of carbohydrate in the second over the first diet should produce the insulin requisite for its utilization by "flogging" the diabetic's already diseased islets, and the result should be rapid deterioration of the clinical condition. But the clinical condition does not deteriorate. On the contrary, the patient feels and continues to be much improved.

The only explanation so far offered of this striking paradox is on the basis of Allen's experiments on the glucose equivalent of insulin.² Working with depancreatized dogs, an attempt was made to determine how many grams of carbohydrate each unit of insulin would cause to be retained in the body. It was speedily found that there was no direct linear relation between the carbohydrate eaten and the dose of insulin needed to prevent glycosuria, and Allen arrived at the conclusion that the more carbohydrate ingested the less is the insulin required to metabolize each gram. It will be seen that this work provides no real explanation of the clinical problem, but only restates it in a different form.

The Staub-Traugott Phenomenon

Up to the present the masterly work of Allen and his collaborators has dominated the conception of diabetes mellitus, but recently another line of research has begun to turn thought in a different direction. In 1919 Hamman and Hirschman³ described the phenomenon which is now usually referred to as the Staub-Traugott effect. They showed that if two consecutive doses of glucose are given to a healthy subject the hyperglycaemia resulting from the second dose is lower than that after the first. The current explanation of this phenomenon (Macleod)⁴ is that the first dose of glucose sensitizes the insulin-secreting mechanism, so that in response to the second dose the islet cells secrete insulin more readily and more abundantly at a lower level of hyperglycaemia. On the basis of this explanation Sweeney,⁵ in 1927, attempted to explain the variations in sugar tolerance found in normal subjects on different diets. Using the ordinary glucose tolerance test as a guide, he investigated the sugar tolerance of healthy individuals during starvation, on a fat diet, on a protein diet, and on a carbohydrate diet. He found that protein had little effect; that fat diets and starvation diminished sugar tolerance; and that carbohydrate diets improved sugar tolerance. Sweeney considered that the diminished sugar tolerance was due to the impaired sensitivity of the insulin-secreting apparatus, consequent upon the absence of the stimulus of carbohydrate ingestion, and that the improved tolerance was the result of the increased sensitivity of this mechanism, owing to greater stimulation.

Effect of Diet on Insulin Action

All the work we have considered so far has dealt with the influence of diet only upon either normal or abnormal carbohydrate tolerance. It is surprising that little attention has been paid to the effect of diet upon the action of insulin itself. A few papers, however, have appeared. Bainbridge⁶ and Hynd and Rotter⁷ showed that animals convulsed earlier after injection of insulin on a carbohydrate than on a fat diet. It appeared to me that a key to the problem of the influence of diet upon the healthy subject's sugar tolerance lay in a possible relation between the organism's tolerance for sugar and its sensitivity to insulin. If it were found that high carbohydrate diets, which improve sugar tolerance, sensitized the subject to insulin, then the effect of diet upon insulin action would have been established, and the observation that many diabetics need no more insulin on the high carbohydrate than on the low carbohydrate diet could be explained on these lines. It was accordingly determined to investigate the result of different dietetic conditions, both on sugar tolerance and on sensitivity to insulin, with a view to discovering whether a correlation existed between the two phenomena.

Methods Employed

For the purpose of this investigation healthy young men were used. They varied in age from 18 to 22 years, and as far as could be ascertained they had never suffered from any serious illness and were in perfect health during the experimental period. They were admitted to the ordinary ward of the hospital and underwent the usual routine of hospital patients, save that they were allowed up during the morning and afternoon. The special diet allotted to them was prepared and weighed in the diet kitchen of the hospital, and its consumption was checked by the ward sister. There was no reason to suspect that any of them surreptitiously supplemented his diet in any way. No experiment was carried out until the specified diet had been given for one week, and only one experiment was performed on the same day. On the day before an experiment the subject retired to bed at 6.30 p.m., and remained there (without breakfast) until 9.30

a.m. the next day. He then went to the laboratory adjoining the ward and was allowed to rest for half an hour: the experiment commenced promptly at 10 o'clock. During the whole of the subsequent procedures the patient remained at rest in an easy-chair, and precautions were taken to keep him comfortably warm. Blood specimens were taken from the ear, and the blood sugar was estimated by the Hagedorn-Jensen method.

For the *glucose-tolerance curves* three blood samples were taken in the resting state; 50 grams of glucose in 300 c.cm. of cold water flavoured with citric acid and essence of lemon were given by mouth, and blood samples were then taken every ten minutes for three hours.

For the curves following injection of insulin—*insulin depression curves*—four blood samples were collected in the resting state; 5 units of a solution of crystalline insulin were injected intravenously, and blood samples were collected, first, every two minutes, and, later, every three minutes, for thirty-five minutes. The technique for obtaining satisfactory blood samples with this frequency necessitated the training of a team of assistants, and the test is for this reason impracticable outside an experimental laboratory. It was necessary to use a solution of crystalline insulin, as commercial insulin contains an impurity which, on intravenous injection, causes a transient but variable degree of hyperglycaemia.

Results

In Fig. 1 two glucose-tolerance curves in the same subject are represented—the one (high fat diet) on a low-carbohydrate-high-fat diet; the other (high carbohydrate diet) on a high-

FIG. 1.—Two sugar-tolerance curves after 50 grams glucose; both obtained on the same healthy subject. The upper one was obtained when the subject was taking a high fat diet, the lower when he was taking an equicaloric high carbohydrate diet.

carbohydrate-low-fat diet. Both diets were of the same total calorie value. It will be seen that on the high fat diet the sugar tolerance was diminished, as indicated by a high degree of hyperglycaemia after glucose; whilst on the high carbohydrate diet the glucose tolerance was raised, as demonstrated by the low hyperglycaemia after oral glucose.

Fig. 2 shows two insulin depression curves, one being obtained on a high fat diet and the other on an equicaloric high carbohydrate diet. It is evident that on the high fat diet insulin takes longer to act, and then acts more slowly, on the blood sugar than when the subject is given a high carbohydrate diet.

These two results are examples of a wide range of experiments on healthy men⁸ and animals⁹ which I have presented elsewhere, and it may be stated as a general rule that *those dietetic conditions which bring about improvement of sugar tolerance are always associated with an increased susceptibility of the organism to insulin, whilst those which cause impairment of sugar tolerance are invariably accompanied by a decreased susceptibility.*

Another method for improving the sugar tolerance is that exemplified in the Staub-Traugott phenomenon. One dose of glucose will lessen the hyperglycaemia resulting from a second dose; the latter, in turn, will diminish the hyperglycaemia from a third dose. Subjects habituated to a specified diet were therefore selected, and the rate at which insulin depressed the blood sugar was determined. Some days later, to the

same subject 50 grams of glucose were given, and one hour after the resulting hyperglycaemia had completely subsided the standard dose of insulin was injected and the rate of depression of the blood sugar again estimated. After glucose the blood sugar with insulin sank much more rapidly than in the fasting state; the administration of the preceding dose of

FIG. 2.—Two insulin depression curves after 5 units of crystalline insulin solution intravenously; both obtained on the same healthy subject. The upper one was taken during the high fat regime, the lower when he was taking an equicaloric high carbohydrate diet.

glucose had caused, in the subject, the development of a state of increased susceptibility to insulin. This experimental observation merits further consideration.

Discussion of Experimental Findings

Zünz and la Barre¹⁰ have demonstrated that a rise of blood sugar induces secretion of insulin by the pancreas. In the Staub-Traugott experiment the first dose of glucose brings about this secretion of insulin, but, as I have demonstrated, it also gives rise to a state of increased susceptibility to insulin. With the second dose the hyperglycaemia again calls forth the secretion of pancreatic insulin, but, the animal being now more susceptible, less insulin is required to reduce the hyperglycaemia to the normal level of blood sugar. Thus to explain the Staub-Traugott effect there is no necessity to postulate that glucose ingestion results in an increasing sensitivity of the insulin-secreting mechanism, for even if the same amount of insulin is secreted in response to each dose of glucose the consecutive improvements in tolerance can be adequately explained by the experimental observation of the progressively increasing susceptibility of the organism to insulin.

Now the maintenance of the blood sugar at normal levels is largely dependent upon the secretion of pancreatic insulin. This has recently been proved very beautifully by Gayet,¹¹ who has shown that when the pancreas is cut out of the circulation the blood sugar begins to rise; when its circulation is restored the blood sugar returns to, and remains constant at, the normal level. Consider the normal subject in the basal state. To maintain the blood sugar constant at the fasting value a certain output of insulin from the pancreas is necessary: 50 grams of glucose are now given, the hyperglycaemia is allowed to subside, and the blood sugar comes to rest within a few milligrams per 100 c.cm. of the fasting level. But we know by experiment that the subject is now more susceptible to insulin, and therefore the pancreas must be putting out less insulin than it did in the fasting state; otherwise the blood sugar would tend to hypoglycaemic levels. If the procedure is repeated we shall find that, after a further dose of glucose, when the blood sugar has returned to resting levels the animal is still more susceptible to insulin, and therefore the secretion of insulin from the pancreas must be still further reduced.

We thus arrive at the conclusion that the progressive diminution of hyperglycaemia in consecutive glucose-tolerance curves is due to the progressively increasing susceptibility of the subject to insulin, this increase being so marked that an actual decrease in the output of pancreatic insulin would appear to accompany the improving tolerance. From these considerations the explanation of the improved tolerance found in a normal subject on a high carbohydrate diet becomes clear. *The increased tolerance is due to the organism's increased susceptibility to its own insulin.* Similarly, the diminished tolerance seen in starvation and in subjects receiving a low-carbohydrate-high-fat diet is owing to their lessened susceptibility to their pancreatic insulin. Further, we have brought forward results⁹ which show that the ability of an animal to develop an increasing susceptibility to insulin after administration of carbohydrate is influenced by the diet which it is receiving. A carbohydrate diet facilitates the development; a fat diet retards it.

It must be remembered, however, that we have not demonstrated whether the heightened susceptibility seen on the carbohydrate diet is the result of the excess of carbohydrate or of the restriction of fat in the diet, and, similarly, whether the lowered susceptibility on the high fat diet is the outcome of the restriction of carbohydrate or the excess of fat in the diet. It is possible that in the removal of the blood sugar some factor other than insulin is concerned—an unknown factor which governs the susceptibility of the animal to insulin. As to the nature of the unknown factor we have no information. It seems to be intimately connected with insulin action. There are two simple possibilities. The factor may be an inhibitor of insulin and its production be inversely proportional to the carbohydrate content of the diet; or it may be an activator of insulin, whose production is directly proportional to this content. On evidence brought forward elsewhere^{8, 12} I incline to the activator hypothesis.

Clinical Significance of the Results

The results recorded in this paper carry us some way towards the explanation of Allen's glucose equivalent of insulin. The reason behind the observation that the more carbohydrate ingested the greater the amount retained in the body by each unit of insulin is that the more carbohydrate eaten the more sensitive the organism becomes to each unit. Hence the paradox of the glucose-insulin equivalent. It will be remembered that Allen's experiments were carried out on depancreatized dogs, and thus demonstrate that such a dog under the stimulus of the administration of carbohydrate is capable of developing an increasing sensitivity to insulin.

My results show that the giving of carbohydrate raises the efficiency of both injected and pancreatic insulin in the normal subject. It only remains to prove that carbohydrate has the same action in the diabetic and the explanation of the beneficial effect of high carbohydrate diets in these patients has been achieved. Ellis¹³ has recently supplied this proof. To diabetics needing large doses of insulin he gave glucose by mouth and small doses of insulin every hour. A remarkable increase in insulin efficiency resulted. Despite the ingestion of constant large amounts of glucose the dose of insulin required to restrain the blood sugar within normal limits decreased progressively. These results show that some diabetics, though possibly not all, are capable of developing a heightened sensitivity to insulin under the stimulus of carbohydrate ingestion. Thus the improvement of diabetic patients on a high carbohydrate diet is to be ascribed not to the greater stimulation, and consequent overstrain, of their insulin-secreting tissue by the excessive

intake of carbohydrate, but rather to the rendering of the diabetic more susceptible both to his pancreatic and the injected insulin. The result is that each unit of insulin available accounts for a greater amount of carbohydrate. This, necessarily, by allowing a more economical utilization of the insulin secreted, reduces the demand of the body for insulin, with a consequent easing of the strain on the diseased islet cells. By thus lightening the burden on the cells which remain capable of function it is possible that we aid their conservation as healthy tissue, and save rather than squander the patient's own pancreatic resources.

If the augmentation of a diabetic's sensitivity to insulin is of importance in the balanced state, it is of much greater importance in the state of coma. It is well known that hundreds of units of insulin may be given in this condition with little effect on the blood sugar, when in the same diabetic after recovery 20 or 30 units will produce hypoglycaemic symptoms. Many comatose and precomatose patients seem to be relatively insensitive to insulin, and any measure directed to raise their sensitivity would appear to be of benefit. To this end glucose should be administered in large doses. The success of treatment based on this principle I have recorded previously,¹⁴ and the method has since been strongly recommended by Lawrence.¹⁵

A growing number of cases of diabetes are being reported in which the patients for no ascertainable reason are found to be resistant to insulin. In one such case doses as large as 1,600 units of insulin a day had no effect on the blood sugar. It is possible that these cases may be explained by an almost complete absence of the factor making for susceptibility. In contradistinction to these insulin-resistant diabetics, cases of spontaneous hypoglycaemia in which no hypertrophy or tumour of the islet cells can be found are continually being recorded. In such patients it is theoretically possible that the hypoglycaemia may be the outcome not of hyperinsulinism, but of the development of a state of a greatly heightened susceptibility to insulin secreted by the pancreas.

Finally, I would suggest the possibility of the existence of a type of diabetes due not to diminished secretion of insulin by the pancreas, but to a greater or less impairment of the organism's susceptibility to insulin. In such a case, although the output of endogenous insulin may be normal in quantity, the diminution or absence of the factor which is concerned in rendering the patient susceptible to insulin would produce a result identical with that of impaired production of insulin—namely, the clinical picture of diabetes mellitus.

I should like to thank Dr. J. W. Trevan of the Wellcome Physiological Research Laboratories for supplying me with the solution of crystalline insulin and Miss E. M. Marshall for controlling the diets of the experimental subjects.

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