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INSULIN DEFICIENCY AND INSULIN INEFFICIENCY*

BY

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The work I wish to present to you had its origin in a chance observation by Claude Bernard (1877) He noticed that when starving dogs were allowed to satisfy their hunger with carbohydrate food sugar appeared in their urine. This phenomenon was amply confirmed by subsequent workers, but little further progress was made towards understanding its significance until the invention of reliable methods for estimating the blood sugar enabled Bang (1913) to demonstrate that starvation impaired the blood glucose-tolerance curve. Ten years later Adlersberg and Porges (1926, 1929) in Vienna and Sweeney (1927) in America, and soon many other workers, showed that diets rich in fat were associated with a similar impairment of the glucose-tolerance curve and, further, that diets rich in carbohydrates resulted in an improvement of the tolerance curve. This sudden renewal of interest in the effect of diet upon sugar tolerance was directly attributable to a revolution that had occurred in the therapeutics of diabetes mellitus.

Influence of Carbohydrates on Insulin Sensitivity

The discovery of insulin, although it altered the whole prognosis for diabetic patients, was not a revolution in that it required a change in our ideas regarding the disease. The existence of insulin had been accurately foreseen, and when it became available its effects on diabetes mellitus were in accordance with our expectations. But shortly after the use of insulin became general a revolution in the true sense of the word occurred. Up to this time it had been assumed that increasing the amount of carbohydrate in the diabetic's diet would necessitate a corresponding increase in the dose of insulin required. When, however, this supposition was put to the test, to everybody's surprise it was found that in many diabetics this dietetic change necessitated no increase in their insulin requirements and in some cases actually led to a decrease. Such a paradox naturally attracted considerable interest, and in the effort to find its explanation attention became redirected to the effect of dietetic change upon the sugar tolerance of healthy people.

In Fig. 1 is shown the effect upon the blood glucose-tolerance curve of a healthy person of changing the diet from one poor in carbohydrates and rich in fat to one rich in carbohydrate and poor in fat. It will be seen that on the former diet the blood-sugar curve is high and prolonged, indicating impaired carbohydrate tolerance, while on the latter diet it is low and short, indicating improved

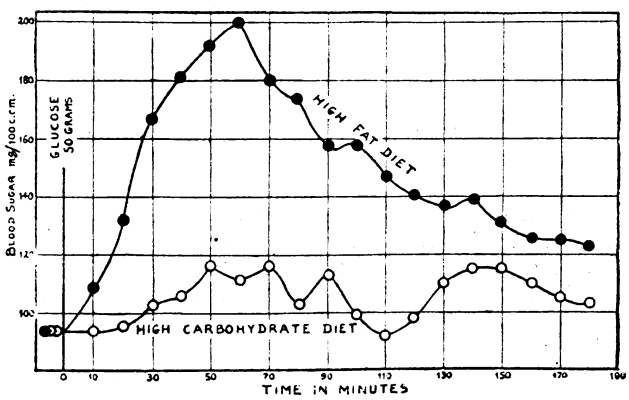

FIG. 1.—Two blood glucose-tolerance curves from the same normal subject—one when taking a low carbohydrate–high fat diet and the other when taking an equicaloric high carbohydrate–low fat diet. On the former diet the glucose tolerance is impaired, on the latter it is improved (Himsworth, 1934b).

tolerance. The first question which arises is, to what dietary change can the alteration in glucose tolerance be attributed? By testing suitable series of diets the responsible factor was disclosed. Neither the caloric value nor the fat content nor the protein content of the diet has any influence. The sole dietetic factor influencing glucose tolerance in healthy people is the absolute amount of carbohydrate in the diet. Increase of dietary carbohydrate improves the glucose tolerance, decrease of carbohydrate impairs it (Himsworth, 1935).

Now you will remember that the most striking feature of the therapeutic paradox was that increasing the carbohydrate content of the diet of diabetics did not necessitate a proportionate increase in the insulin requirements. A possible explanation of this observation is that the composition of the diet influences not only the sugar tolerance but also the efficiency with which insulin acted. Accordingly the effect of dietary changes upon the speed and degree with which a standard intravenous dose of insulin depressed the blood-sugar level in healthy subjects

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was investigated. It was found at once that subjects taking a high carbohydrate–low fat diet were much more sensitive to insulin than were subjects taking a low carbohydrate–high fat diet (Fig. 2). The subjects were then given the same series of test diets used in determining which dietary

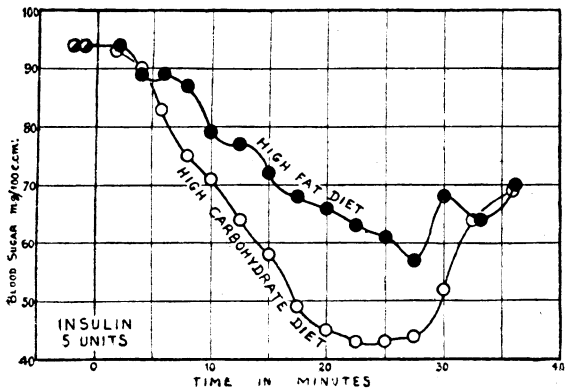

FIG. 2.—Two insulin-depression curves from the same normal subject—one when taking a low carbohydrate–high fat diet and the other when taking an equicaloric high carbohydrate–low fat diet. On the first diet the insulin injected intravenously comes into action more slowly and to less extent than when the subject takes the second diet (Himsworth, 1934b).

constituent was responsible for the change of glucose tolerance, and it was similarly found that the sole dietetic factor influencing insulin sensitivity is the absolute amount of carbohydrate in the diet (Himsworth, 1935). This result clearly has a direct bearing on the observation that in certain diabetics increase of dietary carbohydrate requires no increase in the insulin dosage. But it has a further significance. It shows that the efficiency with which each unit of insulin acts in the body is not fixed, but is dependent upon the factor of sensitivity of the body to insulin. Realization of this point revealed the possibility that a type of diabetes mellitus might exist which was due not to lack of insulin but to insensitivity to insulin. The state of knowledge at this stage of the investigations was not unfavourable to such a conception, for it was then well established that in many fatal cases of diabetes mellitus the islets of Langerhans in the pancreas were apparently unscathed by the disease.

At first sight it would appear easy to put this possibility to the test by simply comparing the speed and degree to which a standard dose of insulin depressed the fasting blood-sugar level in different diabetic patients. This line of approach is, however, impracticable. The effect of insulin varies with the height of the blood-sugar level, so that the higher the blood-sugar level the greater the effect of insulin. In different diabetics the blood-sugar level varies widely and thus renders incomparable the effects observed after intravenous insulin in different patients.

The Insulin–Glucose Test

A new test was therefore devised. This was based on the observation previously made on animals that the effect of insulin in suppressing the rise of blood sugar following the injection of glucose was proportional to the animal's sensitivity to insulin (Himsworth, 1934a). The technique of the insulin–glucose test is as follows: Three samples of blood for estimation of the blood sugar are taken from the fasting patient. Insulin, 5 units per square metre of body surface, is then injected intravenously, and the patient immediately drinks a solution of glucose containing 30 grammes of glucose for every square metre of his body surface. Further samples of blood for analysis are then taken at frequent intervals. On applying this test to diabetics it was immediately apparent that two different types of response are obtained (Himsworth, 1936). In one the injected insulin comes into action rapidly and suppresses the immediate rise of blood sugar which should follow the ingestion of the glucose. This type of response we have called the insulin-sensitive. In the other the injected insulin comes into action only slowly and fails to suppress the rising blood sugar. This type of response we have called the insulin-insensitive. The question which now arises is whether these two types of response correspond to two distinct types of disease each of which manifests itself as the syndrome of diabetes mellitus. On applying the insulin–glucose test to diabetic patients Kerr and I found that all the responses obtained were of one or other type (Himsworth and Kerr, 1939b). We saw no group of patients who gave responses of an intermediate type, and therefore we concluded that the insulin–glucose test differentiated two distinct types of diabetes. In support of this view we found that the two types of case reacted differently to changes in diet. When the amount of carbohydrate in the diet of the sensitive diabetic was increased while the insulin remained unchanged no increase of glycosuria occurred, the fasting blood-sugar values did not rise, and the blood sugar-tolerance curve either improved or remained unaltered. On the other hand, the insensitive type of diabetic reacted to increase of dietary carbohydrate by an increase of glycosuria, and a tendency to elevation of the fasting blood-sugar level and to impairment of the glucose-tolerance curve (Himsworth and Kerr, 1939b). Corresponding to the cases giving one or other of the two types of response to the test two clinical groups of patients can be distinguished, and these two groups bear a remarkable similarity to the two clinical types of diabetic patients distinguished by Falta (1936). The clinical distinction is not, however, precise, as cases which clinically are of the type usually giving an insulin-sensitive response may be found on testing to give an insensitive response, and vice versa. On the whole the insulin-sensitive diabetics tend to be younger, to be thin, and to have a normal blood pressure and healthy arteries. In them the disease is sudden and severe at onset; they easily develop ketosis and react to a slight excess of insulin with a hypoglycaemic attack. The insensitive diabetics, on the other hand, tend to be older, obese, and to have hypertension and arteriosclerosis. In them the onset of the disease is insidious; they rarely develop ketosis and can tolerate overdosage of insulin without showing symptoms of hypoglycaemia (Himsworth and Kerr, 1939b).

Taken together this evidence strongly suggests that two distinct types of diabetes exist, but sure proof that the two different responses to the insulin–glucose test distinguish two different disease processes can only be given by the demonstration of two different pathological mechanisms each giving rise to diabetes mellitus.

Implications of the Two Types of Response

Inspection of the two types of insulin–glucose curve gives a hint of the essential nature of the difference underlying the response. This is more easily seen when the glucose-tolerance and the insulin–glucose curves from a healthy subject, a sensitive diabetic, and an insensitive diabetic are compared (Fig. 3). The insulin–glucose response of the sensitive diabetic is essentially normal, the insulin injected having changed the abnormal glucose-tolerance curve which follows glucose alone to a normal insulin–glucose curve. Thus the abnormality in the sensitive

diabetic is corrected by insulin, suggesting that the disease in the sensitive diabetic is due to the lack of insulin. In the insensitive diabetic, however, the injected insulin has not this effect, and the insulin–glucose curve remains as abnormal as the tolerance curve after glucose alone. This suggests that the disease in the insensitive diabetic is due not to lack of insulin but to inefficient insulin action.

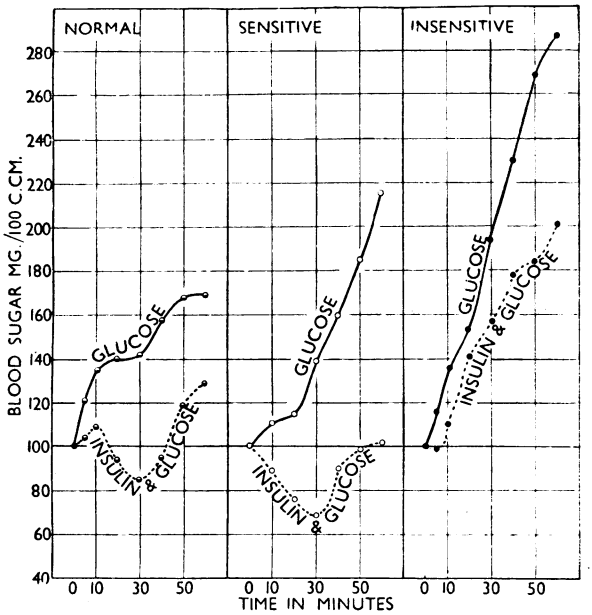

FIG. 3.—Glucose-tolerance and insulin–glucose curves from a normal subject, from an insulin-sensitive diabetic, and from an insulin-insensitive diabetic. The composition of the diet was approximately the same in each case (Himsworth and Kerr, 1939b).

Now, perhaps the most characteristic action of insulin is its ability to increase the rate in which the peripheral tissues remove sugar from the blood. In man a rough idea of the extent to which the peripheral tissues are abstracting the sugar can be obtained by comparing the glucose content of the capillary blood with that of the venous blood leaving a limb. As the capillary blood sugar rises after ingestion of glucose the capillary–venous blood-sugar difference increases, and this increase is attributed to the pancreatic insulin secreted in response to the rise of blood sugar. If the experiment is repeated, but the insulin is injected intravenously at the same time as the glucose is taken by mouth, it will be found that the injected insulin has caused an enormous increase in the capillary–venous difference.

On performing these two experiments on each of the two types of diabetic a striking difference is revealed (Himsworth, 1936). In the sensitive diabetic insulin causes the normal increase in the capillary–venous difference, but in the insensitive diabetic it has little effect. In the sensitive diabetic the action of insulin in accelerating the rate at which the peripheral tissues remove sugar from the blood is normal; in the insensitive diabetic it is impaired. It appears, therefore, that in the insensitive diabetic, even if the normal amount of insulin were available from the pancreas, the insensitivity of the peripheral tissues to insulin is such that the secreted insulin would be unable to promote the removal of sugar from the blood at normal rates, and thus diabetes mellitus would result. From a study of the changes of the glucose-tolerance and insulin–glucose curves in normal subjects when sensitivity to insulin is varied by means of dietary change it can be deduced what would be the nature of the insulin–glucose response in diabetes due on the one hand to lack of insulin and on the other to insensitivity to insulin. These theoretical deductions accord with the observed measurements of the insulin–glucose test in the two types of diabetic patients (Himsworth and Kerr, 1939b).

Up to this point we have been considering only the first hour of the insulin–glucose curve—that is, we have been concerned more with the rate at which the injected insulin came into action than with the total effect of the insulin in suppressing the alimentary hyperglycaemia. On examining the insulin–glucose curves over longer periods, however, it will be seen that the total effect of insulin in suppressing alimentary hyperglycaemia tends to approximate in the two types of case. This observation suggests that insensitivity to insulin results from a retardation of insulin action rather than from a neutralization or a destruction of insulin. It appears, therefore, that the sensitive type of diabetes can be explained on the grounds of insulin deficiency, while the insensitive type of diabetes must be explained by inefficiency of insulin due to a retardation of insulin action in the peripheral tissues (Himsworth and Kerr, 1939b). At the time when the conception first emerged there was no known substance which would thus inhibit the peripheral action of insulin; but one has since been found in the anterior pituitary gland.

Pituitary Gland and Diabetes Mellitus

The association between disease of the pituitary gland and abnormal carbohydrate metabolism has been known since Pierre Marie recorded the frequent occurrence of glycosuria in acromegalics. Later the recognition by Cushing of the frequency of glycosuria in cases of pituitary basophilism has strengthened the clinical evidence for this association. Within the last few years the connexion has been established through the brilliant work initiated by Houssay (1937). He showed that removal of the pituitary gland ameliorated the diabetes of depancreatized dogs and that injection of extracts of the anterior pituitary gland into normal animals would temporarily produce a diabetic state. Pituitary extracts contain a factor which inhibits insulin action in the intact animal, and it has now been shown that this inhibition takes place largely, if not entirely, in the peripheral tissues (Marks, 1936; Himsworth and Scott, 1938b). This anti-insulin factor therefore has the property required to produce the state of insensitivity to insulin characteristic of one type of diabetic patient, and it was found that after injection of such an extract into a normal animal the previously normal sensitive insulin–glucose curve was changed to an abnormal insulin-insensitive type (Fig. 4).

At this stage the important work of F. G. Young can be considered. He has shown that after a course of injections of crude anterior pituitary extract dogs become permanently diabetic (Young, 1937). It might have been expected that the permanent diabetes in these animals would prove to be of the insensitive type, but it has now been shown that the disease is of the sensitive type (Young, 1939), associated with gross changes in the islets of Langerhans and grave deficiency of insulin.

Evidence both experimental and clinical is available that a substance identical with or similar to the anti-insulin factor can be secreted by the anterior pituitary gland. If the pituitary gland is removed from the normal animal then the usual changes in insulin sensitivity which follow variations in dietary carbohydrate do not occur, but in such an animal these changes can be mimicked by injecting the appropriate amounts of the pituitary extracts

(Himsworth and Scott, 1938a). The inference is that the substance responsible for insulin insensitivity is secreted by the pituitary gland. Clinically the evidence is provided by studies on the diabetes of cases of Cushing's syndrome and acromegaly. The diabetes associated with these two types of hyperpituitarism has been found to be of the insensitive type. It has been shown in such cases that

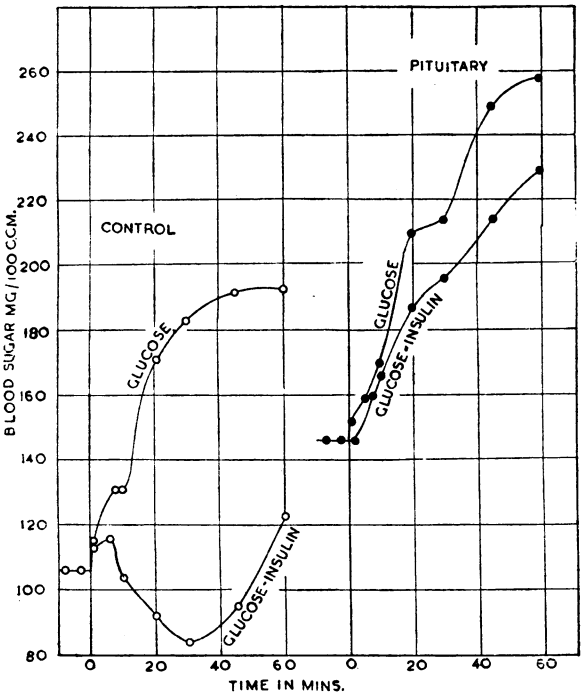

FIG. 4.—Glucose-tolerance and insulin–glucose curves from the same rabbit, before and after it had received injections of a crude extract of the anterior pituitary gland. In the untreated animal the fasting blood-sugar level is normal, the glucose-tolerance curve is normal, and the insulin–glucose curve is of the sensitive type. After the injection of the pituitary extract the fasting blood-sugar level is raised, the glucose-tolerance curve is at a high level, and the response to the insulin–glucose test is of the insensitive type.

irradiation of the pituitary region with *x* rays ameliorates the clinical severity of the diabetes and at the same time improves the sensitivity to insulin as measured by the insulin–glucose test (Himsworth and Kerr, 1939b).

In view of these facts it appeared profitable to attempt the detection of the anti-insulin type of pituitary factor in the body fluids of diabetics. No trace of any such substance was found in the blood of any case of diabetes mellitus. Neither was any trace found in the urine of sensitive or ordinary insensitive diabetics; but definite amounts were present in the urines of a case of acromegaly and two cases of Cushing's syndrome, and, further, the amount of anti-insulin substance excreted diminished with irradiation of the pituitary region (Himsworth and Kerr, in press).

Conclusion

It is convenient here to summarize the present position of our knowledge regarding human diabetes mellitus. There is considerable evidence that two types of diabetes can be differentiated on the basis of the speed with which they react to insulin. In one type, the insulin-sensitive type, insulin comes into action rapidly; in the other, the insulin-insensitive type, insulin comes into action slowly. The evidence is compatible with the suggestion that the disease in the sensitive type of case is due to deficiency of insulin, while in the insensitive type the disease is due not to lack of insulin but to impairment of insulin action. At present, although there is evidence that the anterior pituitary gland may be responsible for the diabetes associated with hyperpituitarism, the indictment of the pituitary gland as a primary factor in ordinary cases of human diabetes mellitus rests purely on analogy (Himsworth, 1939).

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STRAIN VARIATIONS IN THE RESISTANCE OF STREPTOCOCCUS VIRIDANS TO SULPHONAMIDE COMPOUNDS

BY

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The introduction of the sulphonamide group of drugs has once more brought into being hopes of a successful treatment of subacute bacterial endocarditis, and a number of papers on the application of these drugs to the disease have been published. Whitby (1938) reported two cases which were influenced by the use of sulphapyridine, and Ellis (1938) records one similar case and another influenced by sulphanilamide. Spink and Crago (1939) treated twelve fully authenticated cases of the disease, and in six of these sterility of the blood was attained, in four there was abatement of fever, and one case was apparently cured. Another case of apparent recovery is described by Andrews (1940).

Cases of Subacute Bacterial Endocarditis treated with Sulphonamides

A prominent feature of the treatment of subacute bacterial endocarditis is that some cases appear to be influenced by the drugs while others pursue their course quite unaffected by them. It seemed that the infecting organisms, though in each case a *Streptococcus viridans*, might differ in their susceptibility to sulphonamide derivatives. With this possibility in view four strains of *Strep. viridans* isolated by blood culture from patients suffering from subacute bacterial endocarditis were tested for their susceptibility to the bacteriostatic action of three drugs—4:4′-diaminodiphenyl sulphone, sulphapyridine, and the soluble sodium salt of sulphapyridine—their effects being compared with those produced by the drugs in the patient from whom the streptococcus was derived. The following are particulars of the four cases:

Case 1.—A bank clerk aged 32 had a five-months history beginning with a typical attack of acute rheumatism. A temporary improvement occurred, only to be followed by a