Drug Treatment of Disease**TREATMENT OF DIABETES MELLITUS****1. INSULIN: PHYSIOLOGICAL AND THERAPEUTIC ACTIONS**

BY

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It is about 35 years since Banting and Best discovered insulin, and, in spite of a vast amount of research, the exact mode of action of this hormone is still unknown. The structure of the insulin molecule has been brilliantly demonstrated by Sanger and his colleagues (Ryle *et al.*, 1955), who showed that insulin is a protein with a molecular weight of 6,000 or multiples thereof. Each molecule consists of two polypeptide chains held together by -S-S- linkages derived from the amino-acid cystine. The A chain is made up of 21 amino-acid residues and the B chain of 30.

It is convenient to consider first the actions of insulin and then the effects of such actions, as the former are more speculative than the latter and less directly related to its therapeutic applications.

Actions of Insulin

There are at least three sites at which insulin may act to facilitate carbohydrate metabolism.

1. Action of Insulin on the Transfer of Glucose into Cells

According to Levine and Goldstein (1955) and many others the most important single action of insulin in carbohydrate metabolism is to facilitate the transport of glucose across cell membranes. There is much experimental evidence in support of the view that this process is not one of simple diffusion but is an enzyme-catalysed or "carrier" transport process upon the rate of which depends the extent of glucose utilization. Factors other than insulin, such as anaerobiosis and certain chemical substances, are also known to affect the transport of sugars into cells (Manchester *et al.*, 1958). It has been suggested that, in the absence of insulin, the transport system is shielded in some way and that insulin and other agents may act by removing this shield.

2. Action of Insulin on the Phosphorylation of Glucose

Insulin may facilitate the phosphorylation of glucose within the cell. The work of Price *et al.* (1945) and others suggests that insulin acts with hexokinase in the conversion of glucose into glucose-6-phosphate, and that it neutralizes the inhibitory action on this system of growth and adrenocortical hormones. The validity of this hypothesis remains unsettled, but many now believe that the intracellular systems are controlled by factors other than insulin.

3. Action of Insulin on Transformations in the Citric Acid Cycle

This possible site of action was suggested by Krebs and Eggleston (1938). Quite apart from whether it is the entry into the citric acid cycle or the transformations within it that are impeded by lack of insulin, the net effect is defective production of adenosine triphosphate and consequent impairment of oxidative phosphorylation. Although it is not yet possible to say with certainty how or where insulin exerts its action, it is possible to be more definite about the effects of such

action or actions; even so it may be difficult to decide whether they are directly or indirectly produced.

Effects of Insulin Action

Many effects are attributable to the action of insulin, but five only will be considered as being of particular importance in relation to the therapeutic action of insulin:

1. Increased formation of glycogen in liver and muscle.
2. Increased peripheral utilization of glucose.
3. Inhibition of gluconeogenesis and ketogenesis.
4. Increased synthesis of fat.
5. Increased synthesis of protein.

1. Opinions differ on whether the observed increase in liver glycogen produced by insulin is due to a direct effect of the hormone on the liver or entirely accounted for by the increased formation of lactic acid which results from its peripheral action.

2. The effect on the peripheral utilization of glucose can readily be demonstrated by estimation of the difference in blood-sugar level of arterial and venous blood after an injection of insulin (the A-V difference). Conversely, in diabetes utilization of glucose is impaired, and it was at one time thought that this accounted for the hyperglycaemia characteristic of the disease—the so-called "under-utilization" concept.

3. Prolonged starvation in man and animals produces a relatively small decrease in fasting blood-sugar level. If, however, an animal is adrenalectomized and then fasted, fatal hypoglycaemia is produced (Long, 1952). The same phenomenon is familiar clinically in severe Addison's disease; this tendency to hypoglycaemia is readily corrected by cortisone. The maintenance of the fasting blood-sugar level is therefore dependent on adrenocortical activity, which stimulates gluconeogenesis. This excessive production of glucose from protein and glycerol is a feature of severe diabetes, and accounts not only for the failure of carbohydrate starvation to correct the hyperglycaemia, but also for the characteristic negative nitrogen balance; it also gave rise to the "over-production" concept of the causation of the hyperglycaemia. "Under-utilization" and "over-production" are no longer rival theories, but are now together recognized as the immediate causes of hyperglycaemia in diabetes mellitus.

The effect of insulin in inhibiting gluconeogenesis can be observed in the correction by insulin of the negative nitrogen balance of the severe untreated diabetic, and in the restoration of growth in previously untreated or inadequately treated diabetic children; the latter is due also to the protein anabolic effect of insulin action referred to below.

In the absence of insulin action glycolysis is greatly reduced, and the availability of oxaloacetate decreased. In these circumstances the body can no longer derive the necessary energy directly from carbohydrate sources

and so turns to fat. Fatty acids are mobilized in excess of the catabolic capacity of the tissues, and the acetyl co-enzyme A which accumulates is converted into ketone bodies. It has recently been shown that fatty acids released from adipose tissue may be utilized directly by a number of tissues without prior conversion to acetoacetate or beta-hydroxybutyrate by the liver. The effect of insulin action in facilitating glycolysis restores the normal pathway of energy production and leads to the rapid disappearance of ketone bodies from the blood and urine.

4. It is now known that adipose tissue is normally capable of converting glucose to fatty acids and is probably the major site of this conversion. Experiments on rats with alloxan-induced diabetes have shown that insulin has a direct effect on the formation of fat from glucose. This is in line with the clinical observation that insulin therapy is often associated with an increase in body fat which may be so great that an undesirable degree of obesity results.

5. The anabolic effect of insulin action has been studied by Young (1937), Best *et al.* (1954), and many others, and there is now considerable evidence that insulin plays an important role in the process of protein anabolism and growth. Young showed that in the early stages of the production of experimental diabetes by anterior pituitary extract there is a phase of nitrogen retention and, in puppies, of excessive growth. This continues until hyperglycaemia develops and the animal becomes diabetic, when the nitrogen balance is reversed. It seems probable that the failure in insulin production is the result of exhaustion of the beta cells of the islets of Langerhans from overstimulation by growth hormone, and that nitrogen retention and growth continue only so long as the pancreas is capable of producing enough insulin. The response to adequate insulin therapy of the untreated diabetic child and often poorly controlled diabetic dwarf lends clinical support to an increasing volume of experimental evidence for this anabolic effect of insulin action.

Sulphonamide Hypoglycaemic Agents and Insulin*

In 1942, while investigating the chemotherapeutic action of the sulphonamide preparation I.P.T.D., Jambon *et al.* (1942) observed that it caused severe hypoglycaemia. The mechanism of this action was investigated by Loubatières (1955), but no attempt was made to apply it to the treatment of diabetes until 1955, when Franke and Fuchs (1955) recognized the hypoglycaemic action of the related compound N-(*p*-amino-benzene sulphonyl)-N₂-butylurea or carbutamide. Owing to the occurrence of toxic side-actions in a small number of diabetics treated with this drug its use has been abandoned in favour of tolbutamide, a chemically similar preparation with a CH₃ group in the *para* position in place of the NH₂ group of carbutamide.

The mode of action of tolbutamide, like that of insulin, is not fully understood; while both lower the blood sugar, it is not certain that they do so in the same way. Of the many theories put forward and possibilities investigated only three will be considered here:

1. *Inhibition of Some Contra-insulin Substance or Substances.*—Insulinase, glucagon, and adrenal and pituitary hormones all qualify for inclusion on the grounds that they destroy or are otherwise antagonistic to insulin, but there

is no convincing experimental evidence that their action is inhibited by tolbutamide.

2. *Increase in the Peripheral Utilization of Glucose.*—Although it might appear relatively easy to determine whether or not tolbutamide has this action, this has not proved to be the case, but the majority of reports to date do not support this hypothesis.

3. *Enhancement of the Action of Endogenous Insulin.*—This last view receives strong support from the generally accepted fact that, when all endogenous insulin is absent, either as a result of pancreatectomy or treatment with alloxan, tolbutamide exerts no hypoglycaemic action. Clinically the same is true in the severe forms of diabetes most often seen in young or relatively young patients characterized by ketosis and a low plasma insulin. If, however, tolbutamide acts by stimulating the beta cells of the islets of Langerhans and so increasing the amount of insulin reaching the liver via the portal vein, it is difficult to explain why it reduces the output of glucose from the liver while exogenous insulin has no such action. This discrepancy might possibly be accounted for by a difference between the actions of exogenous and endogenous insulin.

The therapeutic importance of these observations is that a good response to tolbutamide is only to be expected in those relatively mild diabetics who do not tend to pass ketone bodies in their urine, and whose daily requirement of insulin, if any, does not exceed about 30 units; such cases are often middle-aged or old and not infrequently obese.

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NOMENCLATURE OF BLOOD-CLOTTING FACTORS*

ACCEPTANCE BY THE INTERNATIONAL COMMITTEE ON NOMENCLATURE OF FOUR FACTORS, THEIR CHARACTERIZATION AND INTERNATIONAL NUMBER

Physicians often accuse basic scientists, chemists, and physicists in particular, of using a strange language which no one outside his own subject can understand, but at least the majority of physicists or chemists can understand what others in their own field are talking about. The field of blood coagulation is one in which medical men and biological scientists have created such chaos that they do not even understand what other workers in the field are talking about, far less the clinician or the medical student.

To improve international communications is a worthy object at any time: to do so in the field of clotting factors has proved a task of major difficulty. To bring together the *prima donnas* not only from different countries but from the same country, hold them together, and persuade them of the importance of a

*A separate article, to appear shortly, will be devoted to sulphonamide derivatives and other hypoglycaemic agents.

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