Review

RECENT CONCEPTS ABOUT AETIOLOGY OF DIABETES MELLITUS

By

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Diabetes Mellitus has been known to afflict mankind for thousands of years. Diabetic surveys from various parts of the world indicate that on an average one to two per cent of population suffers from clinical or subclinical diabetes. Although tremendous progress has been made in its management, starting with dietary restrictions, the discovery of insulin in 1922 which transformed the outlook for life of diabetics and lately the oral hypoglycaemic agents have simplified the treatment in a fair proportion of diabetics. Our knowledge about this disease particularly the aetiology is far from complete. In the recent past some new concepts regarding the aetiology have been put forward and it is being realised more and more that diabetes is not the result of a single factor but a disease of varied aetiology.

The net physiological deficit in diabetes is lack of biologically active insulin irrespective of serum levels of insulin or insulin like activity being high, low or normal. The result is hyper-glycaemia, glycosuria, metabolic and structural changes. Greenberg (13) defines diabetes as a primary genetic disturbance where the major biochemical manifestations are hyperglycaemia and glycosuria and the complications mainly vascular and neurological are the major structural manifestations. As for the clinical course, it is generally believed that diabetes starts before birth although many decades may elapse before any loss of carbohydrate tolerance occurs. Camerini-Davlos *et al.* (10) have suggested that diabetes has four stages.

(a) Prediabetes :— is the period from conception to the first demonstrable abnormality in carbohydrate tolerance in subjects genetically predisposed to develop diabetes such as identical twins of diabetics or those with both parents diabetic.

(b) Latent chemical diabetes— Abnormal carbohydrate tolerance brought to light only in a state of metabolic stress as in pregnancy or after priming with corticosteroids.

(c) Chemical diabetes – Absence of clinical symptoms but carbohydrate tolerance is impaired.

(d) Overt diabetes— In addition to hyperglycaemia and glycosuria symptoms of diabetes are also present.

It is not essential for the disease to run only a progressive course. Regression is possible even without treatment or weight reduction.

GENETIC ASPECTS

Using the carbohydrate intolerance as the main criterion, a Mendelian 'recessive' basis has been suggested for the inheritance of diabetes mellitus. (Pincus and White (18), Steinberg (22).) Circumstantial evidence concerning the behaviour of the syndrome of overt carbohydrate intolerance suggests that if inheritance is involved, it is the liability to develop carbohydrate intolerance which is conferred by the appropriate genetotype and not the simple clinical disease (Vallance-Owen. 27). Vallance-Owen and Ashton (26) using the synalbumin insulin antagonism—i.e. the state of being synalbumin positive as a biochemical marker, suggest a Mendelian dominant inheritance. Yerganian (30) by his experiments on Chinese hamsters has shown that diabetic loci are highly mutable following hybridization and subsequent inbreeding and that unknown modifier genes are present which activate mutant loci.

DIABETES MELLITUS AND BLOOD GROUPS

In general the various reports in the literature are conflicting. Buckwalter (7) after studying the possible association between ABO, Rhesus and M N blood groups, salivary secretion of blood group antigens and diabetes mellitus found evidence of borderline significance in favour of an increased incidence of the disease in persons of group B as compared with those of group AB.

MICROANATOMY AND MICROPATHOLOGY

Studying the rat pancreas with electron microscopy Williamson *et al.* (29) reported that insulin stored as beta granules is liberated from beta cells by a simple process called "emiocytosis", the smooth sacs encasing the granules fuse with cell membrane and rupture liberating the granules into either the intercellular or pericapillary space, leaving behind microvilli which extend from the surface of beta cell into the intercellular or pericapillary space. The ultrastructure of beta granules in diabetics is probably similar to that of normal beta cell. Williamson (28) has shown that there is glycogen accummulation in beta cells in diabetes, the normal organelles are almost completely displaced and the nucleus appears encased in glycogen. This further aggravates the diabetic state by interfering with formation and release of insulin. Return to normoglycaemic state has been shown to result in disappearance of the accummulated glycogen.

AETIOLOGICAL CONCEPTS

Any hypothesis to explain the causation of diabetes mellitus has not only to explain the occurrence of lack of biologically active insulin but also occurrence of hyperglycaemia, obesity, high levels of insulin like activity (ILA) in the serum, thickening of capillary basement membrane and changes in the lipid metabolism like failure of insulin in normal physiological concentration to suppress nonesterified fatty acid (NEFA) release from the adipose tissue. All these facts need not co-exist or be observed in every diabetic.

(*a*) *Primary beta cell failure :* This is the oldest and classical concept of aetiology of diabetes. Why beta cell failure occurs still remains obscure and moreover, occurrence of insulin leak from failing beta cells can only explain hypoglycaemia and obesity. This has of course not been demonstrated so far.

(*b*) *Defective peripheral insulin clearance* : Butterfield (8) postulated that diabetics appeared to inherit a tendency to thicken the basement membrane of capillaries when they suffered hyperglycaemia from any cause and this might initiate a vicious circle by interfering with the entry of insulin and hence glucose from circulation into the tissues. By suggesting differential sensitivity of adipose tissue and muscles to circulating insulin, Butterfield (9) explains the occurrence of obesity in diabetics, adipose tissue needing less insulin for glucose deposition than muscles. As obesity supervenes, blood circulation to muscles diminishes with subsequent diminution in glucose uptake and more adipose tissue is formed. The occurrence of hyperglycaemia noted early in diabetes cannot be explained by this theory.

(*c*) *Abnormal glyceride metabolism* : Diabetes mellitus is considered primarily as deranged carbohydrate metabolism and the changes in fat metabolism are recognised as its sequelae. Randle *et al.* (19) and Hales & Randle (15) have observed that many disturbances in carbohydrate metabolism in pancreatic diabetes are caused by oxidation of fatty acids. These authors contested that changes in lipid metabolism such as raised serum nonesterified fatty acids (NEFA) being available for oxidation could be the cause rather than the result of impaired carbohydrate tolerance and insulin resistance, and that fatty acid metabolism is not dependent on glucose metabolism but there exists a reciprocal relationship between them. They described a glucose fatty acid cycle, the main features of which are (a) the release and oxidation of NEFA in adipose tissue and muscles is inhibited by glucose and insulin and (b) the released fatty acids from glyceride stores and their oxidation restricts the uptake and metabolism of glucose in muscle and perhaps also in the adipose tissue.

Adipose tissue is the biggest store for glycerides for muscles (and other tissues) with blood acting as carrier. Normally glucose and insulin control the release of a fatty acids from the fat depots but in essential diabetes insulin is no longer able to suppress effectively the release of fatty acids, the enhanced availability of fatty acids and their oxidation inhibit the uptake and metabolism of glucose by muscles and adipose tissue thus resulting in hyperglycaemia which overextends the insulin producing capacity of beta cells and causes their eventual failure. In early stages greater secretion of insulin from hypertrophied beta cells could suppress the NEFA release and thus result in hypoglycaemia and lipogenesis. The cause(s) of inheritance which primarily lead to these abnormalities in NEFA metabolism is hitherto unexplained.

It may also be pointed out here that hormones having antagonistic action to insulin such as growth hormone, corticesteroids and adrenaline have powerful fat mobilising property and this mechanism could well be one of the ways in which they oppose insulin.

(*d*) *Insulin Antagonists and Inhibitors* : The antagonistic action to insulin of certain hormones is well known but lately non-hormonal substances circulating in the serum have been described to have insulin inhibitory effect. Their exact role in aetiology of essential diabetes is uncertain although some workers have attributed primary role to some of them. In an attempt to avoid confusion prevailing in the literature Segal (21) has suggested that insulin antagonism be used for action(s) exerted by certain substances usually hormones which result in hyperglycaemia by enhancing entry of glucose into circulation without necessarily affecting its utilisation ; and insulin inhibition be referred to effects of substances (usually proteins) which may either compete with or destroy

insulin activity at or near its site of action. Although this differentiation is not absolute as some substances exert both effects directly or indirectly, it provides a good working classification.

1. INSULIN ANTAGONISM

(*i*) *Growth hormone* :—Secondary diabetes in acromegaly is well known and experiments of Houssay and those of Young have well established the diabetogenic effect of this hormone. It promotes hepatic gluconeogenesis. Reference has already been made to its fat mobilising property. Its effect on insulin inhibitors will be discussed later.

Prolactin, another hormone from anterior pituitary has similar but much weaker effects.

(*ii*) *Adrenaline* :—It promotes glycogenolysis in the liver and muscles. It is also lipolytic and inhibits glucose utilisation perhaps by increasing intracellular glucose-6-phosphate with consequent inhibition of glucokinase (Groen *et al*, 1958)

(*iii*) *Corticosteroids* :—These hormones also promote hepatic gluconeogenesis and are lipolytic.

(*iv*) *Glucagon* :—It promotes hepatic glycogenolysis. As yet excess of glucagon causing hyperglycaemia or glycosuria has not been reported.

(*v*) *Thyroid* :—Permanent diabetes in hyperthyroidism has not been described although glucosuria and impaired carbohydrate tolerance are described. There is rapid absorption of glucose.

2. INSULIN INHIBITION

(*i*) *Synalbumin inhibitor* :—Vallance-Owen (27) has put forward that diabetes may be due to the inheritance of some abnormal plasma proteins—which are insulin antagonists. Early studies on insulin requiring diabetics suggested that the patients needed insulin to overcome some antagonist in their plasma. Sufficient insulin was needed to neutralise this antagonist and to sustain the normal metabolic function. Vallance-Owen *et al.* (23) discovered that one antagonistic factor is associated with plasma albumin and hence named it synalbumin. It was found that essential diabetics, whether insulin requiring, obese or prediabetic have more synalbumin antagonist than normal subjects or pancreatic diabetics (25). Thus probably in idiopathic diabetes, there is increased synalbumin antagonism to insulin. This apparently is inherited on a Mendelian dominant basis (26). The clinical type of diabetes and the time of onset of carbohydrate intolerance will then depend on the degree of antagonism and on the resilience of the beta cells of the pancreas in withstanding this challenge (27). Thus carbohydrate intolerance may not develop in many constituted diabetics. It has been shown that plasma albumin fraction from hypophysectomised subjects whether diabetic or normol was devoid of insulin antagonism (23). Similar hormone dependence has been demonstrated in the case of adrenal corticoids (24). Thus as synalbumin antagonism is apparently mediated through the pituitary adrenal system, the antagonism is further increased during growth, pregnancy, infection, mental stress and administration of cortiocosteroids; states well known to aggravate diabetes. Lowy *et al* (16) have

produced some evidence that this antagonism does not affect insulin action on adipose tissue and thus probably lipogenesis from carbohydrate sources is not affected. Hence the obese diabetics become obese because they are diabetic. Abbas and Tovey (1) have shown that albumin can pass through the placenta from the maternal to the foetal circulation. This may cause the characteristic hypertropy of the islets and through this macrosomia of the stillborn foetus of prediabetic mother.

This antagonist has not yet been isolated. It is probably a polypeptide of low molecular weight, less than 4000. Recent work by Ensinck and co-workers (12) has demonstrated that upon degradation of insulin into 'A' and 'B' chains, only the latter is bound to albumin. Ensinck and Vallance-Owen (12) have postulated that the 'B' chain of insulin may be identical with the synalbumin inhibitor. This suggests that synalbumin may be the consequence of insulin resistance and not the cause. The important question as to what is the state in vivo cannot be answered as yet.

(*ii*) Bornstein and Hyde (5) showed the presence in human pituitary of two fractions, HP_1 and HP_2 which had influence over the glucose uptake. While HP_1 was shown to have 'insulin-like' activity, HP_2 was shown to be a peptide which could inhibit the uptake of glucose in rat diaphragm. Further work (6) revealed that both these fractions are polypeptides and are probably insulin antagonists because their actions oppose those of insulin, although direct antagonism could only be shown in protein biosynthesis. It is possible that these substances may play some role in the fine control of biosynthetic phenomena.

The relation of the above polypeptides and their various fractions to the lipoprotein inhibitor as well as to the dialysable inhibitor (4) which was found to be raised in juvenile diabetics with vascular complications, is still not clear.

(*iii*) *Insulin antibodies* :—Berson *et al.* (3) have shown that in all persons treated with insulin for some weeks, circulating antibodies to insulin can be demonstrated, while in persons not so treated, antibodies have been shown to be responsible for insulin inhibition. The infrequency of insulin resistance of clinical significance is probably due to its being a weak antigen. The antibody acquired as a result of insulin therapy is a globulin which binds insulin. The rate of binding is proportional to the concentration of the antibody. Thus higher levels of antibodies will cause rapid and more complete binding. However, greater secretion of insulin can overcome this 'insulin resistant' state.

(*iv*) *Insulin binding* :—Antoniades *et al.* (2) have demonstrated that a portion of the insulin in blood circulates as a complex with protein and that the transport of insulin by protein may serve to provide for the storage of circulating insulin. Samaan *et al.* (20) have put forward a similar concept of typical and atypical insulin. They divided plasma insulin-like activity (ILA) into two parts (*a*) typical - resembling comercial or pancreatic insulin and (*b*) atypical—a larger molecule which the liver can make from typical insulin secreted by pancreas. Both atypical insulin and bound insulin (2) are effective on rat epididymal fat pad but not on the rat diaphragm while estimating the ILA. After a glucose load there is a fall in bound insulin-though less marked in diabetics than in normal subjects-but the atypical insulin rises in both. A malfunction of regulatory mechanism catalysing the binding of free insulin or dissociation of insulin complexes has been postulated in essential diabetes.

(*v*) *Insulinase* :—Mirsky (17) has reviewed the subject of excessive insulin inactivation being responsible for diabetes. Enzyme insulinase first described by his group in late forties is present in liver and kidney and also in other tissues. It is a proteolytic enzyme. It is yet to be demonstrated that excess insulinase activity can cause diabetes.

CONCLUSIONS

Diabetes mellitus can be regarded as a metabolic disorder of varied aetiology involving genetic, structural and biochemical factors. Insulin having been liberated from the beta cells reaches the liver in high concentration and is mixed through the pulmonary circulation. Its action upon the tissues depends upon *(a)* the time blood spends in passing through the capillaries, *(b)* presence of any binding protein, antibodies, inhibitors or antagonists, *(c)* permeability of basement membrane and *(d)* physico chemical or chemotropic factors in the tissues. Failure of any of these steps would result in ineffective insulin action and hyperglycemia which may lead to initially beta cell hypertrophy and ultimately exhaustion.

It may be concluded at this stage that exact aetiology of diabetes is still obscure. The various concepts put forward highlight one or the other biochemical and structural change(s) observed in established diabetes or its early stages.

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