Diabetes:

Aetiology and Pathophysiology of Diabetes Mellitus.

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In the *Second report of the WHO Expert Committee on Diabetes Mellitus,* diabetes mellitus is defined as a state of chronic hyperglycaemia which may result from many environmental and genetic factors, often acting jointly. The major regulator of glucose concentration in the blood is insulin, a hormone synthesized in and secreted by the ß-cells of the Islets of Langerhans in the pancreas. Hyperglycaemia may be due to a lack of insulin or to an excess of factors that oppose its action. This imbalance leads to abnormalities of carbohydrate, protein and lipid metabolism. The major effects of diabetes include characteristic symptoms, ketoacidosis, the progressive development of disease of the capillaries of the kidney and retina, damage to the peripheral nerves, and excessive arteriosclerosis.

Aetiology

N. Freinkel's recent review on the aetiology of diabetes confirms that significant developments in the last few years have clearly indicated that *primary* or *idiopathic* diabetes represents a syndrome characterized by absolute or relative insulin insufficiency but mediated by a number of different causes. In the least, insulin-dependent diabetes mellitus, IDDM, (i.e., Type I, formerly designated as juvenile-onset or ketosis-prone diabetes) and non-insulin-dependent diabetes mellitus, NIDDM, (i.e., Type II, formerly designated as maturity-onset or ketosis-resistant diabetes) represent wholly different entities rather than simple quantitative gradations of insulinopenia.

The high concordance rates for NIDDM in monozygotic twins, even when they are geographically separated, suggests that intrinsic factors are of greatest aetiological significance in this population. Unfortunately, however, the site and nature of these intrinsic determinants have not yet been identified. The inborn defect(s) in NIDDM probably reside in some aspect of islet function.The variable patterns of insulin secretion in NIDDM are strongly suggestive of aetiological heterogeneity, and the differences between non obese and obese NIDDM are particularly noteworthy in this regard. Total secretion of insulin is most frequently attenuated in the lean, whereas the obese more often display exuberant insulin release. The delineation of a new subgroup of NIDDM with unique genetic properties, i.e., maturity-onset type of diabetes in young people (MODY), has provided some of the best evidence for aetiological heterogeneity. However, for the moment, it can only be concluded that environmental modifications may not appreciably modify the incidence of any type of NIDDM in view of the strong genetic overlay. Such manipulations should however, modify the severity, and perhaps even the time of appearance.

The less constant genetic pattern in IDDM than in NIDDM suggests that environmental factors may exert a greater aetiological impact. It seems probable that the correlations between HLA and IDDM reflect linkage disequilibria between genes determining vulnerabilities to IDDM and those coding for HLA antigens. As regards the environmental factor to which IDDM are genetically vulnerable, mounting evidence implicates virus in some instances, possibly variants related to Coxsackie virus B_4.

Chemicals may also be contributory, however, the impact of these may be mediated in a complex fashion. The underlying genetic vulnerability seems to reside in the manner in which the beta cell handles the environmental factor.

Genetic factors could determine the initiation of autoimmune processes spontaneously or in combination with the traumatizing variables cited above.

Pathogenesis

In J.S. Skyler et al's recent article on insulin update in Type I diabetes, one reads that current formulation of the pathogenesis of Type I or insulin - dependent diabetes mellitus (IDDM) is that a combination of genetic and environmental factors cause this condition. There appears to be a genetic predisposition conferred by a *diabetogenic* gene,

which resides on the short arm of chromosome 6 near the HLA region. The question of whether more than one diabetogenic gene exists or whether such genes might reside on other chromosomes is the subject of ongoing investigation. It appears that environmental triggers, in susceptible individuals, may initiate a pathogenetic sequence that results in pancreatic islet ß-cell damage. The most likely candidates as environmental triggers are viral infections and chemical toxins. The initial ß-cell damage appears to be perpetuated and sustained by an immune response, leading to further ß-cell destruction and consequent absolute insulinopenia. A period of partial remission, in which some ß-cell function recovers, may occur shortly after the onset of IDDM. Such remissions generally are of short duration. After the remission, absolute insulinopenia again emerges, although minimal endogenous residual insulin secretion can be demonstrated in some patients.

The impairment of insulin secretion in IDDM involves both meal-related incremental insulin secretion, responsible for utilization and storage of nutrients, and basal insulin secretion between meals, responsible for modulating hepatic glucose and metabolic homeostasis in the postabsorptive period.

The same author in an editorial on the improved understanding of Type II diabetes states that still not clearly defined is the fundamental defect or defects involved in the pathogenesis of Type II non-insulin dependent diabetes mellitus. Abnormalities in both insulin secretion and insulin action have been demonstrated, and there has been considerable debate as to which is the predominant lesion.

Impaired islet ß-cell function in Type II diabetes is manifested in at least three ways:

(1) absence of first phase insulin response to glucose, resulting in an overall *delayed* insulin secretory response to glucose; in most circumstances, however, second phase insulin response is sufficient to control postprandial glucose excursions, restoring plasma glucose to basal (preprandial) levels before the next meal, albeit prolonged postprandial glucose elevation;

(2) decreased sensitivity of insulin response to glucose, such that insulin response to glucose is attenuated, and that the islet ß-Cell shows a relative *blindness* to hyperglycaemia;

(3) decreased overall insulin secretory capacity, particularly in more severe Type II diabetes. It can be generalized, from various studies recently carried out, that patients with the most severe degree of Type II diabetes evidenced by significant fasting hyperglycaemia (i.e. fasting plasma glucose > 200 mg/dl), have the greatest impairment of islet ß-cell function and are relatively insulin deficient.

Impaired insulin action in Type II diabetes, i.e., insulin resistance, can be demonstrated in terms of both decreased insulin-mediated glucose disposal and subnormal suppression of hepatic glucose output. The insulin resistance in Type II diabetes is due to an impairment of insulin action at target cells. Although there is variability in the degree and nature of insulin resistance among different individuals and among different tissues within an individual, two categories of insulin resistance have been identified:

(1) decreased insulin binding to cellular receptors;

(2) defective insulin action as a consequence of defects in the effector system beyond the level of insulin binding to cellular receptors, collectively referred to as *postreceptor defects*.

In patients with impaired glucose tolerance or mild Type II diabetes, the degree of postreceptor defect is minimal, whereas in patients with more severe degrees of type II diabetes, evidenced by significant fasting hyperglycaemia (i.e., fasting plasma glucose>200mg/dl), the degree of postreceptor defect is marked, resulting in the greatest degree of insulin resistance.

R.S. Sherwin and P.H. Felig's account on the pathophysiology of diabetes further explains that inadequate insulin availability is the primary factor underlying the alterations in fuel homeostasis and counterregulatory hormone secretion which characterise the diabetic syndrome. With regards to fuel homeostasis the metabolic alterations observed in diabetes reflect the degree to which there is an absolute or relative deficiency of insulin. Viewed in the context of insulin as the major storage hormone, a minimal deficiency results in a diminished ability to increase effectively the storage reservoir of body fuels because of inadequate disposal of ingested food stuffs (e.g., glucose intolerance). With a major deficiency of insulin, not only is fuel accumulation hampered in the fed state, but excessive mobilization or production of endogenous metabolic fuels also occurs in the fasted condition (e.g., fasting hyperglycaemia, hyperaminoacidaemia, and elevated free fatty acids). In its most severe form (diabetic ketoacidosis), there is overproduction of glucose and marked acceleration of all catabolic processes (lipolysis proteolysis).

With regards to the role of insulin antagonistic hormones, glucagon contributes to the diabetic state primarily in circumstances of insulin deficiency. In diabetes suppression of glucagon by glucose is lost and protein-stimulated glucagon secretion is augmented. Glucagon hypersecretion may exaggerate the metabolic alterations accompanying insulin deficiency. However, relative or absolute insulin lack is the essential factor necessary for the changes in fuel mobilization and utilization which characterize diabetes. In contrast to glucagon, physiological elevations of cortisol or epinephrine markedly accentuate hyperglycaemia and hyperketonaemia in diabetics even in the face of insulin treatment.