THE VIRAL AETIOLOGY OF TYPE I DIABETES MELLITUS, WITH SPECIAL REFERENCE TO HEPATITIS B VIRUS

THESIS

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BY

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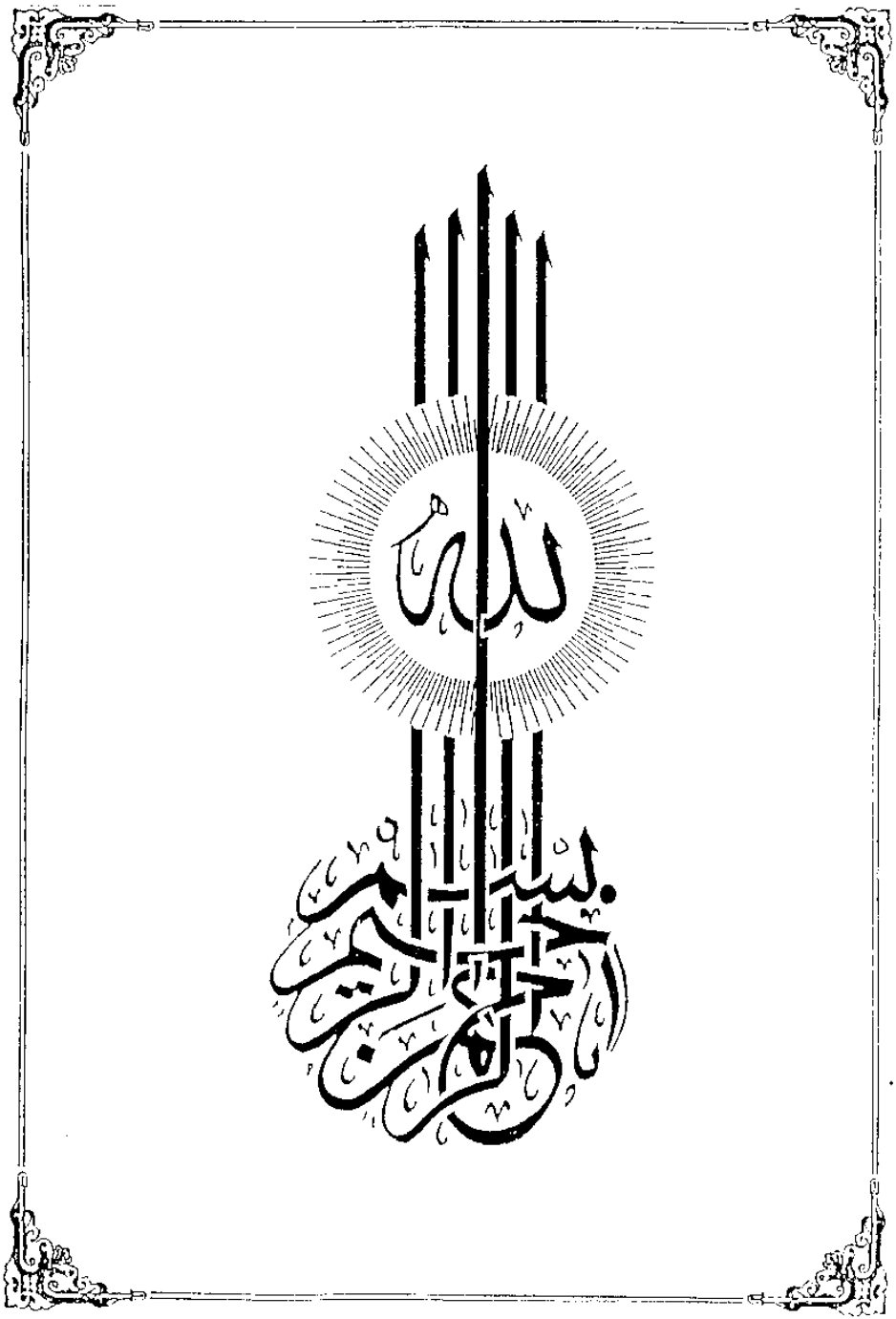

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FOREWORD AND AIM OF THE WORK

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Diabetes mellitus is a disorder best characterized as a state of chronic hyperglycemia of various aetiologies. The traditional classification of primary, or idiopathic, diabetes mellitus is based on the age of onset and recognizes "Juvenile-onset" and "maturity-onset" varieties. The terms "Juvenile" and "maturity" onset are now regarded as unsatisfactory and misleading. Some patients, mature in years, may develop diabetes that is insulin-dependent, and a further presentation of diabetes in the young has been described: "maturity-onset diabetes of young people" (MODY) (Tattersal and Fajans, 1975).

In the last few years different classifications of diabetes have been reported (Bottazzo and Doniach, 1976; Cudworth and Woodrow, 1977; Irvine, 1977). A major problem at present is that no classification is satisfactory for both the clinician and the researcher. In 1979 the National Diabetes Data Group developed, together with the main Associations for the study of diabetes, a new classification of the disease. This classification divides primary diabetes according to insulin dependence. The term "type I" is used to describe all insulin-dependent patients, regardless of age. "Type II" diabetes includes those patients previously

classified as maturity-onset diabetes. The use of the terms type I and type II is recommended as there would appear to be no sufficiently concise descriptive name that adequately describes the two major diseases that constitute the syndrome of primary diabetes. However, the sole criterion of insulin dependence may be misleading because there are many non-insulin-dependent subjects that are treated with insulin for various reasons. Furthermore, among the non-insulin-dependent patients there is a small group that within a few months or years of diagnosis develop a clear insulin dependence. To overcome these and other limits the same group proposed a parallel classification for research purposes. The detection of islet-cell antibodies (ICA), the association with organ specific autoimmune disorders, HLA typing and the mode of inheritance are the main criteria used in this subclassification.

In type I diabetes, a genetic susceptibility seems to interact with environmental agents and immunological factors producing the typical clinical syndrome. Those patients whose diabetes appears to be predominantly autoimmune are subclassified as type Ia, and those whose diabetes appears to be unrelated to autoimmunity are subclassified as type Ic. The majority of cases, where an exogenous agent (such as a virus) and autoimmunity both operate, are subclassified as type Ib (Fig. 1).

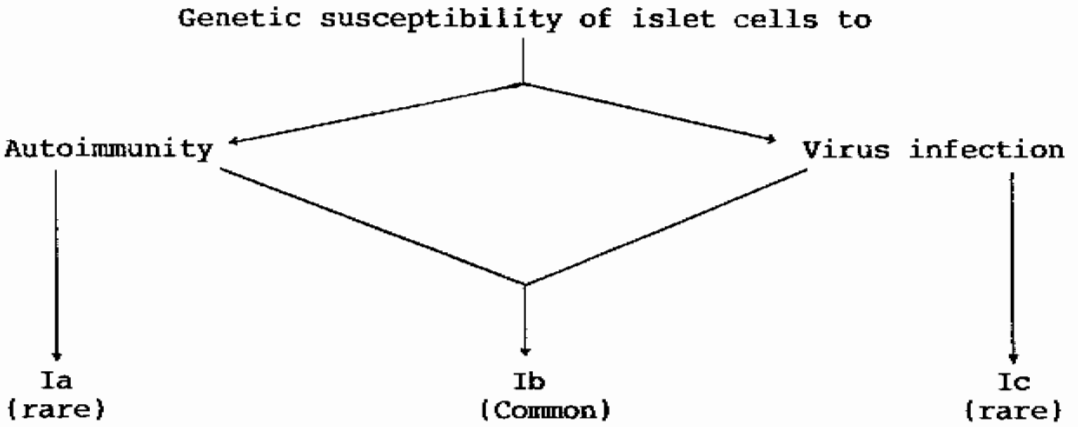

Fig. (1)

The concept of an interaction between islet-cell autoimmunity and viral infection in the pathogenesis of type I diabetes (From Irvine, 1977)

It does have to be strongly stressed that these subclasses of type I diabetes represent stages in a continuing spectrum and do not represent discrete subdivisions of type I diabetes.

The common characteristics of type I diabetes are a sudden clinical onset, severe hyperglycemia and the easy appearance of ketoacidosis, and severe insulin deficiency. The clinical onset is usually abrupt, but there is evidence of a long subclinical diabetic period in some individuals (Gorsuch, 1981). This latency is very short in the case of an acute and severe infection (type Ic) or long, up to many years, when a slow autoimmune reaction is the main

pathogenic factor (type Ia). In most cases (type Ib) an environmental factor triggers immunopathological phenomena in genetically predisposed individuals leading to islet-cell damage (Irvine, 1977).

Aim of the Work:

The aim of the work is:

(1) to review the viral aetiology of type I diabetes mellitus.

(2) to study recently diagnosed patients with type I diabetes mellitus to detect a possible aetiologic relationship with type B viral hepatitis.

INTRODUCTION

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Pathoglogy of Pancreatic Islets in Juvenile-Onset Diabetes Mellitus:

The introduction of electron microscopy and immunocytochemistry into diabetes research has considerably enriched our knowledge of the cellular composition and the structural organization of the pancreatic islets (Gepts and LeCompte, 1981).

Despite the fact that heterogeneity of diabetes in man is becoming more and more evident, two clearcut entities emerge from pancreatic pathology. They roughly correspond to the conventional subdivision of idiopathic diabetes into a juvenile-onset and a maturity-onset type. This subdivision on the basis of age at onset has been criticized. Indeed, insulin-dependent diabetes may develop at any age, and some young diabetic subjects do not require insulin to achieve normoglycemia. However, in most maturity-onset diabetic subjects, including those with genuine insulin-dependent diabetes, the appearance of the pancreatic islets is distinctly different from that of subjects with diabetes of early onset, both quantitatively and qualitatively (Gepts and LeCompte, 1981).

Changes in the pancreas as a whole:

There are no specific gross changes in the pancreas of diabetic subjects. In insulin-dependent juvenile-onset diabetes the pancreas is often much smaller than normal. This reduction appears to result either from a secondary atrophy or from an arrest of growth because, at the onset of the disease, the weight of the organ is normal (Gepts, 1965).

Volume of islet tissue:

Precise evaluations of the amount of endocrine tissue in the pancreas of man are complicated by the fact that it is dispersed in a large exocrine gland of which it represents only 2 or 3 percent in volume. Nevertheless, numerous studies have been performed and have reached convergent conclusions: the number and size of the islets, and consequently the total volume of endocrine tissue, are reduced in the pancreas in diabetes. This reduction is more marked in cases of juvenile-onset diabetes (Maclean and Ogilvie, 1959).

General appearance of the islets:

In contradistinction to maturity-onset diabetics, the islet tissue of juvenile-onset diabetic subjects always shows distinctive and characteristic changes, even in

cases of recent onset. The majority of the islets are small and easily escape detection in routinely stained sections. These islets are composed of thin cords of small cells arranged in a more or less abundant fibrous stroma. They have classically been regarded as atrophic, but they are actually composed of cells actively producing hormones (Gepts and LeCompte, 1981).

Changes in the cellular composition of the islets:

Four types of cells are regular components of the pancreatic islets in man. They are the insulin-secreting B cells, the glucagon-secreting A cell, the somatostatin-secreting D cell and the "Pancreatic Polypeptide" - secreting PP cell. In addition to these four cell types, other much rarer types of cells have been detected in the human pancreas, e.g. the D_1 cell and the P cell. They are extremely rare and their secretion product has not been definitely identified. In the pancreas of juvenile-onset diabetic subjects the majority of islets are composed of narrow cords of small cells. In the past these islets have been regarded as atrophic, but with immunocytochemical methods they have been shown to consist of approximately two-thirds glucagon cells and the remaining third somatostatin cells (Gepts and DeMey, 1978).

In recent cases of juvenile-onset diabetes areas of islet hyperplasia and large islets occur, which are composed mainly of B cells showing signs of hyperactivity, such as degranulation and enlarged nuclei. Despite these areas of hyperplasia, the total number of B cells is greatly reduced, being less than 10 percent of the normal amount (Gepts and LeCompte, 1981).

Insulitis:

Insulitis is the name coined by Von Meyenburg (1940) to describe the inflammatory lesions which are present in the islets of Langerhans of some diabetics.

These lesions consist of cellular infiltration, usually predominantly lymphocytic, with or without cellular degeneration and with or without fibrosis.

Insulitis in diabetes should be distinguished from insulitis which occurs in some infants of diabetic mothers. In the latter the infiltration is composed mainly of polymorphonuclear cells among which are many eosinophils.