VIRAL ANTIBODIES IN JUVENILE ONSET INSULIN DEPENDENT DIABETES MELLITUS

THESIS

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By

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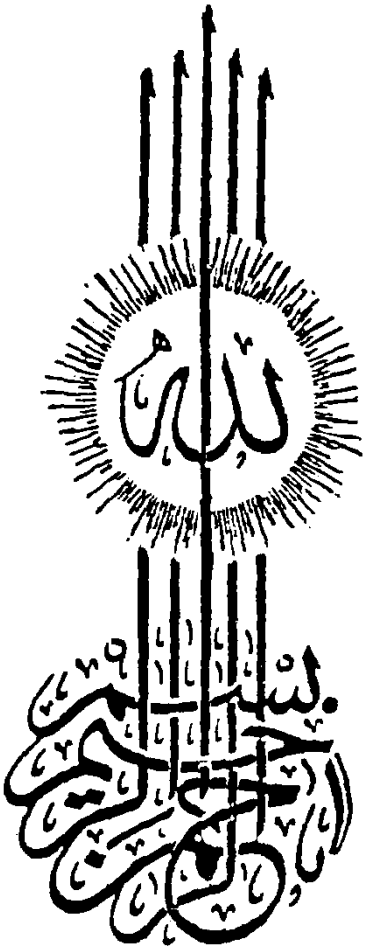

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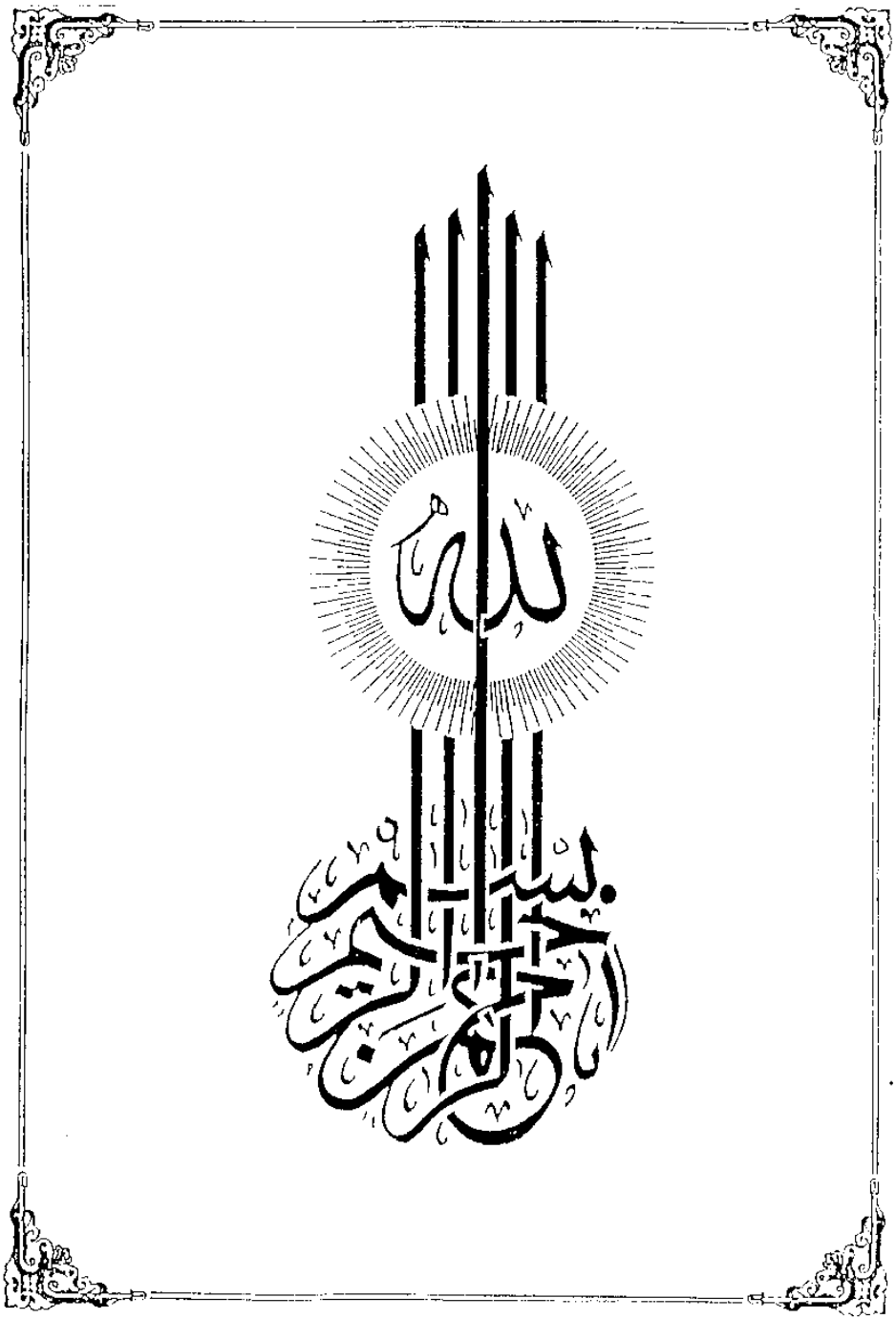

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C O N T E N T S

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INTRODUCTION AND AIM OF THE WORK

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The etiology of diabetes is not yet definitly known. It may be the result of a combination of hereditary and environmental factors.

Viruses have recently attracted increasing interest as possible etiological agents. Although their role has been clearly shown in experimental diabetes in animals, but their importance in the etiology of diabetes in man is still uncertain. (Craighead, 1968).

The fact that the incidence of juvenile onset diabetes varies with age season, year and geographical area (Bloom, 1975) suggest that environmental factors may be important.

Epidemilogical studies suggest a possible link between juvenile diabetes and mumps (Sultz, 1975) coxackie B_4 virus (Gamble, 1969), congeital rubella (Forrest, 1971).

Statistical studies also have suggested that diabetes may sometimes be associated with coxsackie B_4 infection. There is little direct evidence of the involvement of the islets of Langerhans in virus infection, but histological evidence of beta cell damage has been reported in coxsackie B and cytomegalo virus (Craighead, 1972).

This attracted our attention and stimulated us to do this study to investigate the possible role of such viruses in the etiology of juvenile onset diabetes mellitus.

REVIEW OF THE LITERATURE

Diabetes Mellitus

Definition:

Diabetes mellitus is a disturbance of energy metabolism which is due to a deficiency of insulin or its action. It is characterized by altered homeostasis of carbohydrate, protein, and fat. (Nelson, 1983).

It is characterized by failure to use glucose properly. This leads to hyperglycaemia, hyperosmolarity, glucosuria, polyuria, base loss and dehydration. Related abnormal fat metabolism produces ketonaemia and ketonuria, the ketones involved are acetone aceto-acetic acid and betahydroxy butyric acid. Proteins are consumed and muscles are wasted (Forfar, 1978).

It is the most common endocrine metabolic disorder of childhood that has important consequences on physical and emotional development.

Classification of diabetes mellitus:

It has become increasingly apparent that diabetes mellitus is not a single entity but rather a heterogenous group of disorders in which there are distinct genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance (Craighead, 1978).

In the last few years different classification of diabetes have been reported (Bottazo & Doniach, 1976); Irvine, 1977, Cudworth, 1981).

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, a new classification of the disease (National diabetes Data group 1979).

(A) Type I Diabetes.
(B) Type II Diabetes.
(C) Secondary Diabetes.

(A) Type I Diabetes (Juvenile-onset Diabetes):

This condition is characterized by severe insulinopenia and dependence on exogenous insulin to prevent ketosis and to preserve life. It is therefore also termed insulin dependent diabetes mellitus (IDDM). There may, on occasion

be preketotic, non-insulin dependent phases in the natural history of the disease. Although the onset occurs predominantly in childhood, it may come at any age.

Type I diabetes is clearly distinct by virtue of its association with certain HLA antigens histocompatibility loci antigens), auto immunity, and the presence of circulating antibodies to cytoplasmic and cell-surface components of islets cells. With few exceptions, diabetes in children is insulin dependent and fit the type I category.

(B) Type II Diabetes:

Persons in this subclass (formerly known as adult-onset diabetes, maturity onset diabetes (MOD) or stable diabetes) are not insluin dependent and only infrequently develop ketosis. Some may use insulin for correction of symptomatic hyperglycemia and ketosis may develop in some during severe infections or other stress.

Serum concentration of insulin may be normal or moderately depressed, but it is usually elevated. In the majority of instances the onset of non-insulin dependent diabetes mellitus occurs after age of 40, but it may occur at any age. It is rare in childhood, when it may be manifested as abnormal glucose tolerance, usually in obese individuals; there is adequate secretion of insulin but resistance to it. Weight reduction is indicated in these children.

Abnormal carbohydrate tolerance may also occur in children who have a strong family history of type II diabetes in a pattern suggestive of dominant inheritance; this pattern of diabetes has been termed MODY (maturity onset diabets of the young) and may require treatment with insulin. Of importance is that there is no association in this type of diabetes with HLA antigens, autoimmunity, and/or islet-cell-antibodies.

(C) Secondary Diabetes:

This subclass centains a variety of types of diabetes, fore some of which the etiologic relationship is known. Examples include diabetes secondary to exocrine pancreatic disease, such as cytic fibrosis; endocrine affection other than pancreatic disease, e.g. Cushing syndrome; and ingestion of certain drugs or poisons.

Certain genetic syndrome, including those with abnormalities of insulin receptors, also are included in this category. There is no association with HLA antigens, auto immunity, or islet cell antibodies among the entities in this subdivision (Nelson, 1983).

This classification divides primary diabetes according to insulin dependence. Nevertheless 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,

Table (1): Etiologic classification of Diabetes mellitus (National Diabetes Data group 1979; modified).

Class	Former Terminology	Etiology
Insulin-dependent Type (IDDM), Type I	Juvenile-onset diabetes Ketosis-prone diabetes	Genetic factors (increased frequency of certain HLA types), environmental or acquired factors, and abnormal immune responses seem to have an etiological role.
Non-insulin-dependent (NIDDM), Type II	Maturity-onset diabetes Ketosis-resistant diabetes	Heterogenous group with multiple etiologies. Genetic factors seem to have an important role in the etiology. Environmental factors superimposed on genetic susceptibility or probably involved. Obesity is suspected as an etiological factor and is recommended as a criterion for dividing NIDDM into subclasses.
Other Types, including diabetes mellitus associated with certain conditions and Syndromes	Secondary diabetes	In some of these type of diabetes the etiologic relationship is known, in others, an etiologic relationship is suspected because of a higher frequency of association of diabetes with a syndrome or conditions.

among the non insulin dependent diabetic patients, there is a small (group) that within 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 cells antibodies. The association with organ specific autoimmune disorders, HLA typing and the mode of inheritance are the main criteria (Irvine, 1977).

Type I Diabetes

The common characteristics of this form are sudden clinical onset, severe hyperglycaemia and the easy appearance of ketoacidosis, and severe insulin deficiency.

The clinical onset is usually abrupt but there is evidence of a long subclinical prediabetic period in some individuals (Gorsuch et al., 1981). It is still not clear which precipitating factors aggrevate and or reveal the insulin defecient states.

The prevalence of type I Diabetes is presumed to be around 0.1 - 0.5 % of the total population. It seems to be rare in many African and Asian population (Porte and Halter, 1981).

Its incidence in European studies (approximate at best) is around 10 per 100,000 (Bloom et al., 1975); (Christau et al., 1977).