STUDY OF THE PARACRINE ASPECT OF ISLET CELLS OF LANGERHANS OF THE PANCREAS IN FIRST DEGREE RELATIVES OF DIABETICS

Thesis
Submitted for partial fullfilment
of the Master Degree in
Endocrinology and Metabolism

By

Omneya Moguib Saleh Abdel - Rahman

M.B.B.CH

Supervisors

Prof. Dr.

Sayed Mohamed Raafat
Professor of Internal Medicine and Endocrinology
Faculty of Medicine
Ain shams University

Prof.Dr.

Mohamed Alaa El-Din Hamed
Professor of Internal Medicine and Endocrinology
Faculty of Medicine
Ain shams University

Dr.

Fadila Ahmed Gadallah
Ass. Prof. of Internal Medicine and Endocrinology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
1995

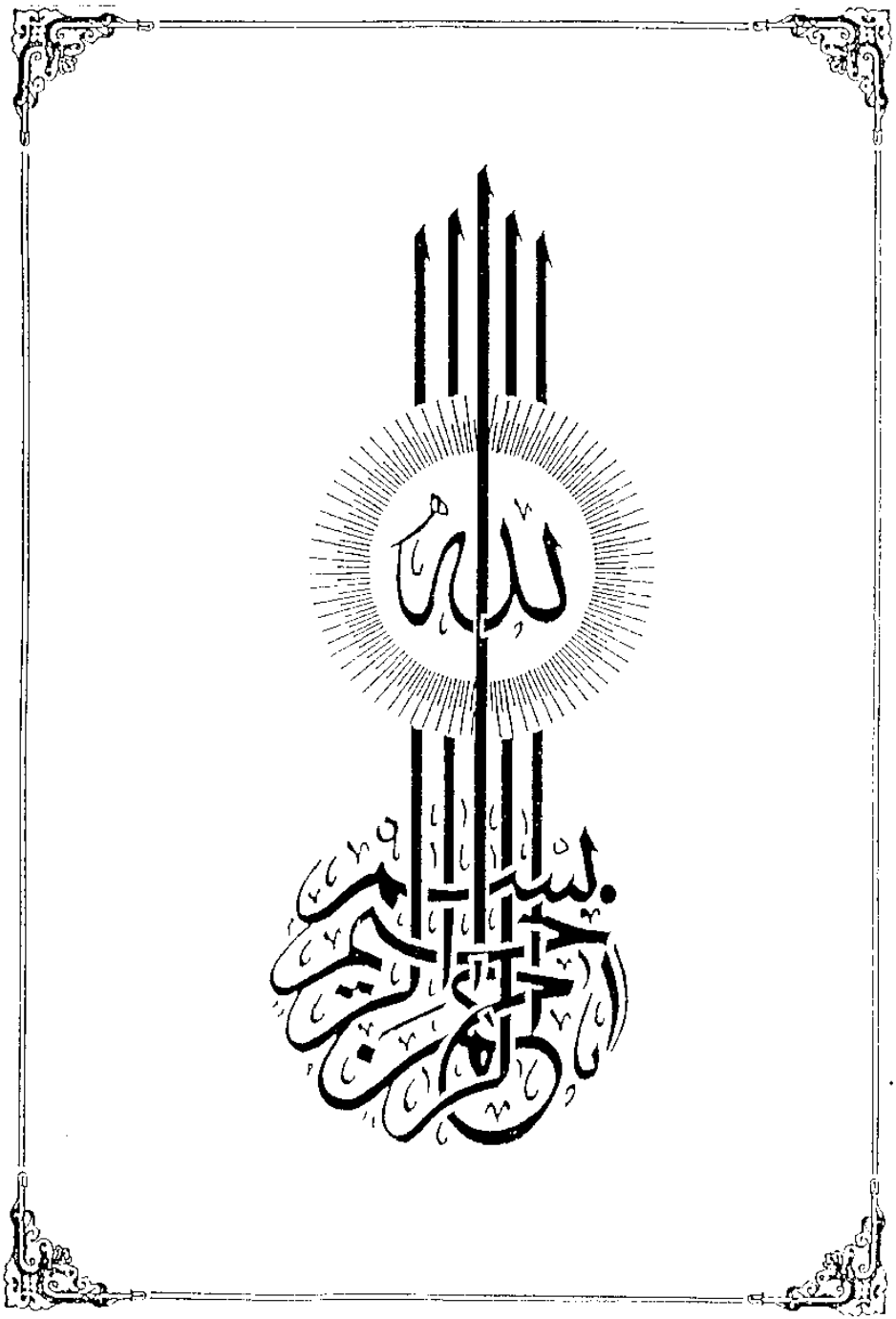
Above All And First of All Thanks to GOD

ACKNOWLEDGMENT

I would like to express my deep gratitude and appreciation to Prof. Dr. ***Sayed Mohamed Raafat****, professor of internal medicine, Endocrinology Department, Faculty of Medicine, Ain-Shams University and Dr.* ***Wassef Guirguis Nicola****, Assistant professor of internal medicine, Head of Endocrinology Unit of the National Research Center, for their sincere guidance, enthusiastic encouragement, valuable advices, kind supervision and constructive criticism. Their wisdom and vast experience are endless sources of help for all their students. I am much obliged to Dr. Wassef for suggesting the point of this work.*

I am very much grateful to Prof.Dr. ***Mohamed Alaa El-Din Hamed****, Professor of Internal Medicine and Dr.* ***Fadila Ahmed Gadallah****, Assistant Professor of internal Medicine, Endocrinology Department, Faculty of Medicine, Ain Shams University, for their kind supervision, valuable advices, encouragement and generous guidance.*

I wish to express my thanks to ***Dr. Baher Aly Massoud,*** *Lecturer of Internal Medicine, Endocrinology Department, Faculty of Medicine, Ain Shams University, for his great help and valuable advice in supervising this work.*

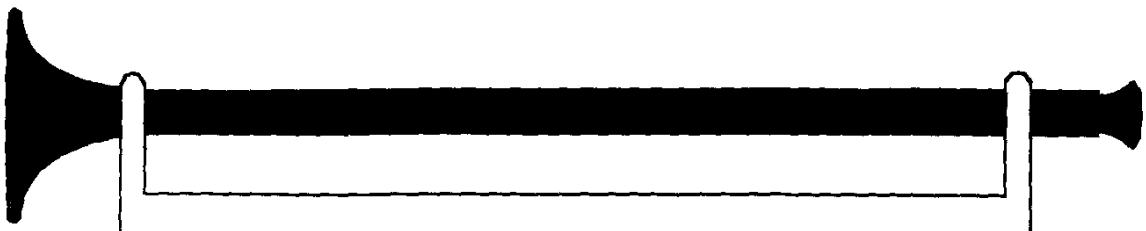


I wish to express my thanks to Dr. ***Zakaria Abdel Halim El-Khayat****, Lecturer of physiology, Basic Medical Science Department, National Research Center, for his cooperation, valuable assistance and great help especially regarding the extensive laboratory part of this work. He also helped me very much to get over many problems in this work.*

I am also grateful to Dr. ***Afaf Abdel Wahab****, Endocrinology Department, Faculty of Medicine, Ain Shams University for her encouragement and valuable advices.*

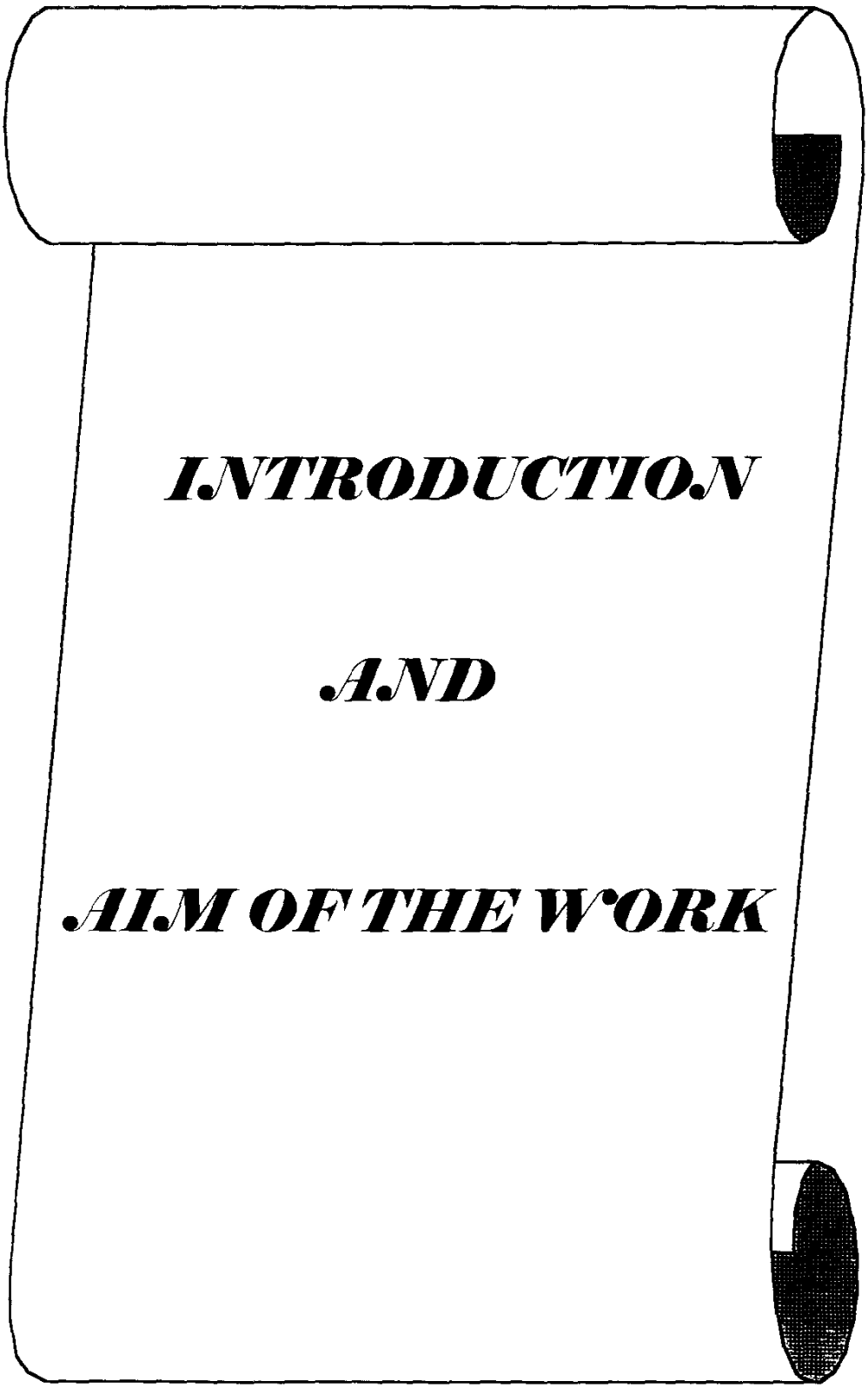
My deep and sincere thanks to my Father, Mother, brother Essam for their endless sacrifices.
I am very grateful to my cousin Eman for her help to accomplish this work.

Omneya Moguib Saleh Abdel - Rahman



STUDY OF THE

PARACRINE ASPECT OF ISLET CELLS OF LANGERHANS IN FIRST DEGREE RELATIVES OF DIABETICS



INTRODUCTION AND AIM OF THE WORK

Diabetes mellitus comprises a genetically heterogeneous group of diseases, and like other genetically determined diseases, diabetes mellitus is the outcome of the interplay of both genetic and environmental factors *(Bingley et al., 1989)*. Again, like other autoimmune diseases, diabetes mellitus may not be precipitated by an immunological event alone, but by some increased metabolic need for insulin which leads to the eventual succumb of the affected beta cells *(Gale, 1991)*.

Several hormones have been thought to play a possible etiologic role in the development of the diabetes mellitus state. Of these hormones, insulin, glucagon and somatostatin are but examples *(Krans, 1987)*.

These hormones act as a paracrine autoregulatory mechanism. This is evident if we take into consideration the results of some workers who used antibodies directed selectively against individual islet cells functions. *Itoh et al. (1980)*, used anti somatostatin gamma globulin and found in vitro augmentation of both insulin and glucagon secretion. It seems that the islet cells function proceed as operational units rather than as mere collections of hormone secreting cells *(Mark et al., 1984)*.

Also it seems that, in diabetic patients, the paracrine autoregulatory mechanism is affected *(Mark et al., 1984)*.

****

Introduction

Aim of the Present Work:

The aim of our work is to study the behaviour of insulin, glucagon and somatostatin level, and insulin antibodies in close relatives of IDDM and NIDDM patients, before and after an oral glucose load to ascertain whether or not an early paracrine disturbance might underly the pathogenesis of the diseases. If this proves to be true, it may serve as an early marker for the detection of potentially diabetic relatives of known patients.

****

Introduction

REVIEW OF LITERATURE

Chapter I: Diabetes Mellitus.

Chapter II: Genetic Aspects of type I Diabetes

Chapter III: Genetic Aspects of type II Diabetes

Chapter IV: Immunologic Aspects of Diabetes Mellitus

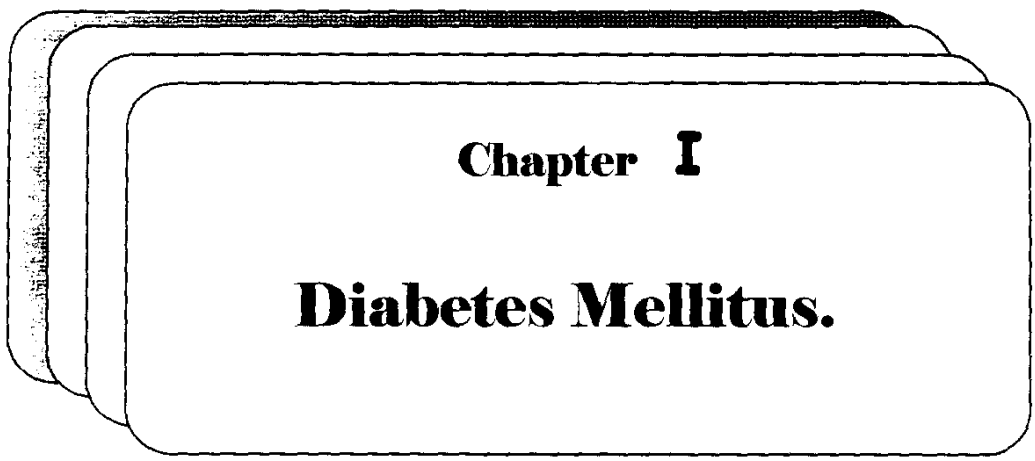
Chapter V: Islets of Langerhans

***Insulin.**

*** Glucagon.**

*** Somatostatin**

Chapter VI Interaction of Islet Cell Hormones .



Chapter I

Diabetes Mellitus.

Diabetes Mellitus

Definition:

Diabetes mellitus, which is characterized by chronic hyperglycemia, is considered as a heterogeneous group of disorders affecting carbohydrate, protein and fat metabolism, due to relative or absolute insulin insufficiency with specific microvascular complications and high incidence of macrovascular complications and neuropathies. Clinical features of diabetes mellitus include symptoms and signs primary related to the severity of the metabolic disturbance (Mykkanen et al- 1992).

Classification:

The WHO classification (1985) based on the U.S. National Diabetes Data Group recommendation is now generally accepted.

Individuals fall within a single class (defined by simple clinical and biochemical descriptions) at any one time, but their classification may change in the course of time.

[A] Clinical Classes:

I Diabetes Mellitus:

A] Type I: IDDM (insulin dependent diabetes mellitus):

IDDM identifies patients who cannot survive without insulin replacement.

It represents about 10-25% of whole diabetic population, the incidence of IDDM peaks at about 11-13 years of age (Williams et al - 1992).

Although insulin dependency means necessity of insulin to prevent ketosis, coma and death, careful study of the natural history of this disease and proper screening of population revealed an important fact that a stage may precede ketosis during which patients may be asymptomatic with normal or impaired glucose tolerance or mildly symptomatic with mild diabetes mellitus, the duration of this stage is variable but usually last few years (Chacra - 1988). Agroup of factors interplay in the pathogenesis of IDDM including genetic, autoimmune and environmental factors.

B] Type II: NIDDM (Non - insulin dependent diabetes mellitus):

Unlike type I, they are not insulin dependent, in the sense that they do not depend on insulin to survive but they may require insulin to achieve a good control, when diet and oral therapy fail, or temporarily during stress. NIDDM comprises about 75% of the diabetic population (Williams et al - 1992).

NIDDM is apparently due to a combination of impaired insulin secretion (especially in non - obese subjects) and insensitivity of the target tissues to insulin (especially in obese subjects) (Haffner et al - 1990).
Specific microvascular complictions are less common than in IDDM, where the onset is earlier and exposure to the disease generally longer. However, retinopathy, nephropathy and neuropathy, all occur. Also, there is a high risk of large - vessel atherosclerosis, commonly associated hypertension, hyperlipidemia and obesity may contribute. Myocardial infarction is also common and accounts for 60% of deaths (Ferrannini et al - 1991).

****

Type II diabetes represent a heterogeneous group of disorders in which many factors interplay, including genetic, pancreatic and target tissue defect.

Subtypes of type II:

1- Obese 60 - 90%.

2- Non obese 10 - 40%.

3- Other type as:

a- a)Maturity onset diabetes of the young (MODY) which is generally inherited as an autosomal dominant gene (Bell et al 1991).

b- b)Type II of early onset: which occurs between 25 - 40 years where epidemiologic studies suggested inheritance of a diabetogenic gene from both parents (Williams et al 1992).

c- c)Mutant insulins and proinsulins: (will be discussed later).

C] Malnutrition related diabetes mellitus:

This category was described by WHO Group in 1985, and was detected in tropical and under-developped countries. It is associated with nutritional deficiency and the absence of spontaneous ketosis.

D] Other type of diabetes mellitus associated with specific conditions and syndromes:

1- Pancreatic diseases:

as chronic pancreatitis (especially due to alcohol abuse), cystic fibrosis, haemochromatosis and totally pancreatectomized subjects (which

develop IDDM and are susceptible to ketoacidosis and to microvascular complications). (williams et al - 1992).

2- Endocrinopathies:

as acromegaly, hyperthyroidism, Addison's disease Cushing's syndrome, Conn's syndrome and phaeochromocytoma, rarely glucagonoma, somatostatinoma and VIP oma syndrome (Williams et al - 1992).

3- Drugs and toxins:

as: glucocorticoids and ACTH, most thiazide diuretics, diphenylhaydantoin, oral contraceptives, tricyclic antidepressants and rodenticides (Williams - 1992).

4- Certain genetic syndromes:

several syndromes of inherited insulin resistance are associated with diabetes, including:

Alstrom's,Laurance - Moom - Biedl, Prader - Willi, and Rabson - Mendenhall syndromes, also ataxia, telangectasia and dystrophia myotonica, also diabetes may affect Down's syndrome, Turner's syndrome and klinefelter's syndrome.

Impaired glucose tolerance and occaisionaly diabetes may complicate acute intermittent porphyria, coeliac disease (Williams et al - 1992).

E] Gestational diabetes mellitus:

This term should be applied to patients developing hyperglycemia during pregnancy, it occurs in about 2% of all pregnancies and a variable