RECENT TRENDS IN MANAGEMENT OF INSULIN DEPENDENT DIABETES MELLITUS (I D D M)

ESSAY

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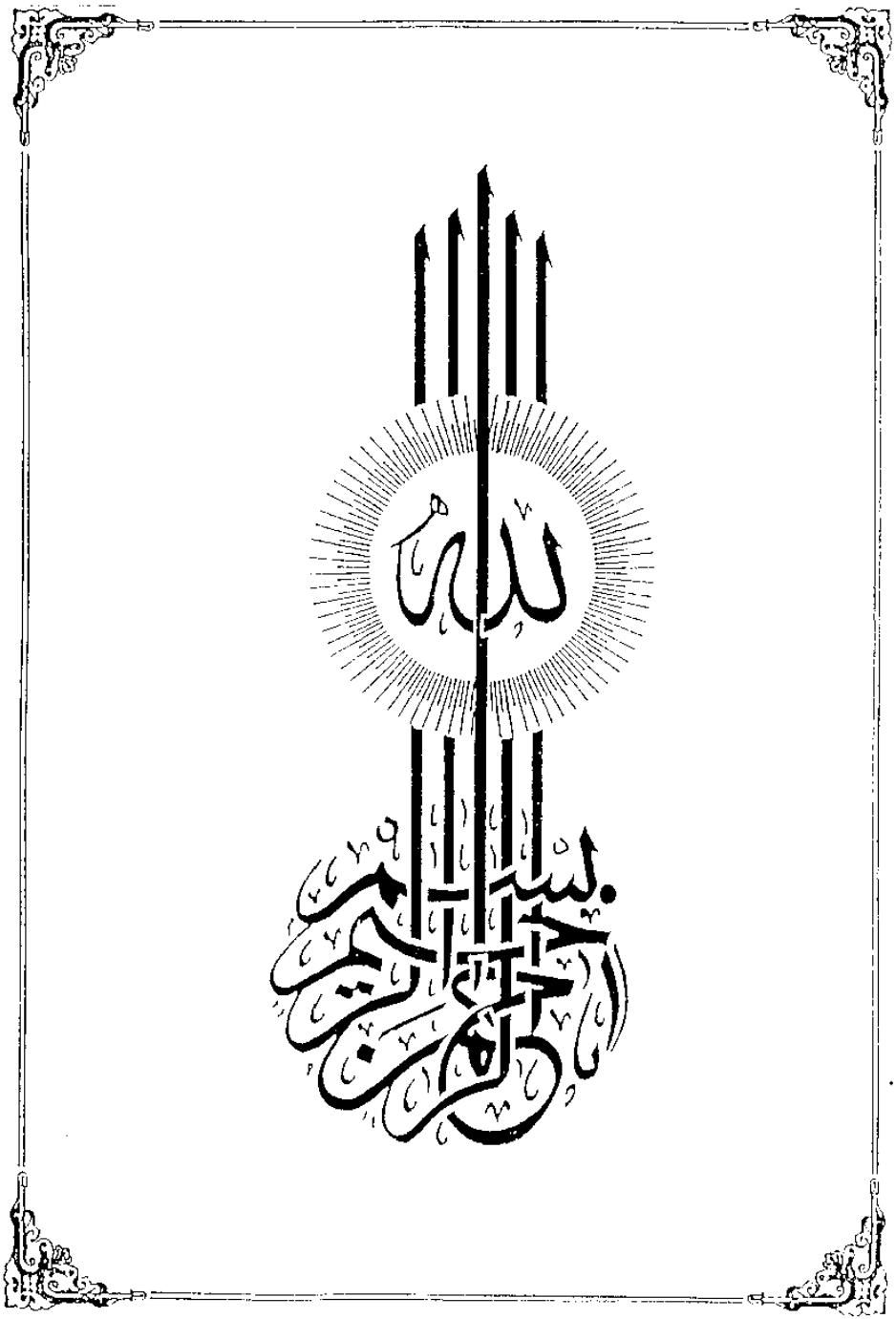
Dedicated To

My Wife, my Daughter Doaa, and my Parents

With All Affection and Respect



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LIST OF ABBREVIATIONS

ALS	Antilymphocyte Serum
ATp	Adenosine-5-triphosphate
BB rat	Biobreeding Worcester Rat
BB/W rat	Biobreeding Worcester Rat
BHI	Biosynthetic Human Insulin
BUN	Blood Urea Nitrogen
C-peptide	Connecting Peptide Molecule
CF-ICA	Complement Fixed-Islet Cell Antibody
CFT	Complement Fixation Test
CMV	Cytomegalovirus
CPI	Cardiac Pacemaker Inc.
CSII	Continuous Subcutaneous Insulin Infusion
Cy A	Cyclosporin A
ECG	Electrocardiogram
ELISA	Enzyme Linked Immuno-Sorbant Assay
GCIIS	Glucose Controlled Insulin Infusion System
GTI	Glucose Tolerance Test
HAT	Haemagglutination Inhibition Test
HbA_1C	Glycosylated Haemoglobin
HLA	Histocompatibility Loci Antigen
ICA	Islet Cell Antibody
ICSA	Islet Cell Surface Antibody
IDDM	Insulin-Dependent Diabetes Mellitus
IEC	Ion Exchange Chromatography
IgG	Immunoglobulin G
IGT	Impaired Glucose Tolerance
MDI	Multiple Daily Injection
MODY	Maturity-Onset Diabetes of Youth
NADpH	Nicotine Adenine Dinucleotide Phosphate (reduced form)
NDDG	National Diabetes Data Group
NEFA	Non-esterified Fatty Acids
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
NIDDY	Non-Insulin-Dependent Diabetes of Youth
NPH	Natural Protamine Hadrogen
OGTT	Oral Glucose Tolerance Test
PPI	Purified Pork Insulin
rDNA	Recombinant DNA
WHO	World Health Organization

AIM OF THE ESSAY

Insulin-dependent diabetes mellitus (IDDM) is a syndrome affecting mainly the children. It was reported that IDDM is the commonest endocrine disorder in childhood with frequent secondary complications.

The new techniques of diagnosis of recent cases and high risk groups give a good chance of better treatment.

The gratifying advances of activity regarding insulin and methods of its delivery, and the development of continuous subcutaneous infusion (CSII) pump have provided means of achieving prolonged near-normalization of the plasma glucose concentration.

The aim of this essay is to throw some light on recent trends in diagnosis and treatment of IDDM

INTRODUCTION

AND REVIEW OF LITERATURE

- **Historical Review**
- **Terminology**
- **Classification of Diabetes Mellitus**
- **Prevalence and Incidence of IDDM**
- **Aetiology of IDDM**

HISTORICAL REVIEW

Knowledge of diabetes dates back to centuries before Christ. The Egyptian Papyrus Ebers (1500 B.C.) described an illness associated with the passage of much urine *(George and Cahill, 1985)*.

The first accurate clinical description of the disease was made by Aretous of Cappadocia in the second century A.D., who stated "*Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine*", and gave it the name diabetes (a siphon) *(Lebowitz, 1984)*.

In the 3rd to 6th centuries A.D., scholars in China, Japan and India wrote of a condition with polyuria in which the urine was sweet and sticky. However, although it had been known for centuries that diabetic urine tasted sweet, it remained for Willis in 1674 to add the observation "*as if imbued with honey and sugar*". The name diabetes mellitus (mellitus = honey) was thus established. A century after Willis, Dobson demonstrated that the sweetness was, indeed, due to sugar.

The progress in the understanding of the disorder came slowly, till the middle of the 19th century. However, over these centuries gradually the course and complications of the disease were recognized. Gangrene had been described by Avicenna, an Arab physician, in about 1000 A.D. Its hereditary tendency was described "passed with the seed" as well as two general varieties; one with the classic acute symptoms (type I) or insulin dependent diabetes mellitus (IDDM) in today's terminology, and the other with "torpor, indolence, and corpulance" (type II or non-insulin dependent diabetes mellitus "NIDDM").

Within the past century, an association was established with a disturbance in the Beta-cells of the pancreas. These islets were first noted in fish by Brockman early in the 19th century, but they bear the name of Langerhans who described them in mammals in 1869. Soon after, the German scientists Von Mering and Minkowski found that surgical removal of the pancreas produced diabetes in the dog. At the turn of the century, an American scientist called Opie noted that beta cells in the islets were damaged in humans dying of the disease *(George and Cahill, 1985)*.

Throughout history, diabetes mellitus was thought to be a single disease, but rather a clinical syndrome characterized by inappropriately elevated fasting and/or post prandial glucose, and the development of long-term microvascular, macrovascular, and neuropathic changes is of very recent origin and stems from numerous investigations into the epidemiology, genetics, etiology, and pathogenesis of clinical diabetic states *(Lebowitz, 1984)*.

INSULIN-DEPENDENT DIABETES MELLITUS (IDDM)

Terminology

Insulin-dependent diabetes mellitus (IDDM) is a syndrome characterized by sudden clinical onset, severe hyperglycaemia, easy appearance of ketoacidosis, and severe insulin deficinecy *(Gorusch et al., 1981)*. It was reported that IDDM is the commonest endocrine disorder in childhood with frequent secondary complications *(Porte and Halter, 1981)*. IDDM defines a group of patients who are usually but not necessarily, under 30 years of age at the time of diagnosis. They usually present with an accelerating history of glucosuric symptoms for less than three months. they are thin and almost invariably exhibit weight loss. Only rarely are such patients discovered by testing for diabetes when they are asymptomatic; if so they may decompensate soon after *(Fajans et al., 1976)*. This defines their state of absolute insulin dependency *(Genuth, 1982)*.

Though a positive family history of diabetes, usually of this type, may be obtained, only 10 percent of such patients have either a diabetic parent or a diabetic sibling *(Fajans et al., 1978)*.

Fasting plasma insulin levels are low, and there is little or no response to challenge with glucose, amino acids, tolbutamide, glucagon, or other beta cell stimulants. Anatomically, the islets are small and devoid of beta cells, though hyperplasia of other islets cells that produce glucagon, somatostatin and pancreatic polypeptide is often seen *(Gepts et al., 1978)*. Ultimately, the beta cell function disappears as shown by low plasma levels of the

connecting peptide molecule (C-peptide) which is normally co-secreted with insulin *(Malmquist et al., 1982).*

A well defined subgroup of youthful-onset diabetics, sometimes known as MODY (maturity-onset diabetes of youth) or NIDDY (non-insulin-dependent diabetes of youth), may be diagnosed in their teens. Though these patients are usually treated with insulin, they are able to survive without it *(Fajans et al., 1978).*

Classification of Diabetes Mellitus

In the last few years different classifications of diabetes have been reported *(Bottazzo and Doniach, 1976; 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 (NDDG), developed together with the Main Associations for the Study of Diabetes, a new classification of the disease.

The classification of diabetes mellitus and associated states proposed by the National Diabetes Data Group, 1979 and provisionally endorsed by WHO (1980) is still the latest accepted classification *(Keen and Tang Fui, 1982; Genuth, 1982).*

Table (1) showing The Classification of Diabetes Mellitus *(From National Diabetes Data Group Report, 1979)*.

Class	Former Terminology	Aetiology
Insulin-dependent Type (IDDM), Type 1	Juvenile-onset diabetes, ketosis-prone diabetes.	Genetic factors (increased frequency of HLA Types), environmental or acquired factors, and abnormal immune responses seem to have an aetiological role.
Non-insulin-dependent Type (NIDDM), Type 2	maturity-onset diabetes, ketosis-resistant diabetes	Heterogeneous group with multiple aetiologies. Genetic factors seem to have an important role in the aetiology. Environmental factors superimposed on genetic susceptibility are probably involved. Obesity is suspected as an aetiological 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 types of diabetes, the aetiological relationship is suspected because of a higher frequency of association of diabetes with a syndrome or condition.

Table 2: **Showing clinical characteristics of the two major types of diabetes mellitus** *(From National Diabetes Data Group Report, 1979)*

Diabetes Data Group Terminology	Insulin-Dependent Diabetes Mellitus (IDDM)	Non-Insulin-dependent Diabetes Mellitus (NIDDM)
* **Clinical features:**		
- Age of onset	Usually less than 45 years Rare in newborn, but increase in frequency at preadolescence (10-14 years of age).	Usually over 30 years
- Onset	Often rapid	Insidious
- Weight	Non obese	Often obsesese
- Ketosis	Common	Rare
* **Epidemiolgy:**		
Prevalence	0.5%	2%
Sex	Slight male predominance	Female predominance
Seasonal variation	Present	?
Pathology:		
Islet mass	Severely reduced	Moderately reduced
Insulinitis at onest (Inflammation in the islet cells).	Present in 50-70%	?
Genetics:		
Concordance rate of identical twins.	< 50%	> 90%
Association with human leukocyte antigens (HLA)	Present	Absent
Immunology:		
Associated with other endocrinopathies	Frequent	Infrequent
Anti-islet cell immunity:		
Humoral	60-80% at onset	5-20%
Cell-mediated	35-50% at onset	5%