MEASUREMENT OF ORAL GLUCOSE TOLERANCE AND Hb A_1c IN RELATIVES OF DIABETIC PATIENTS

A THESIS

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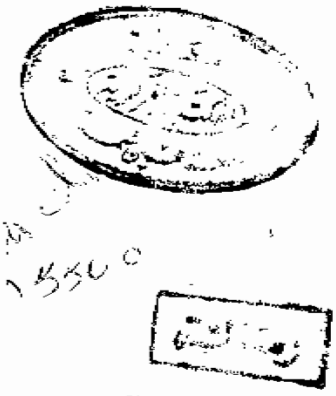

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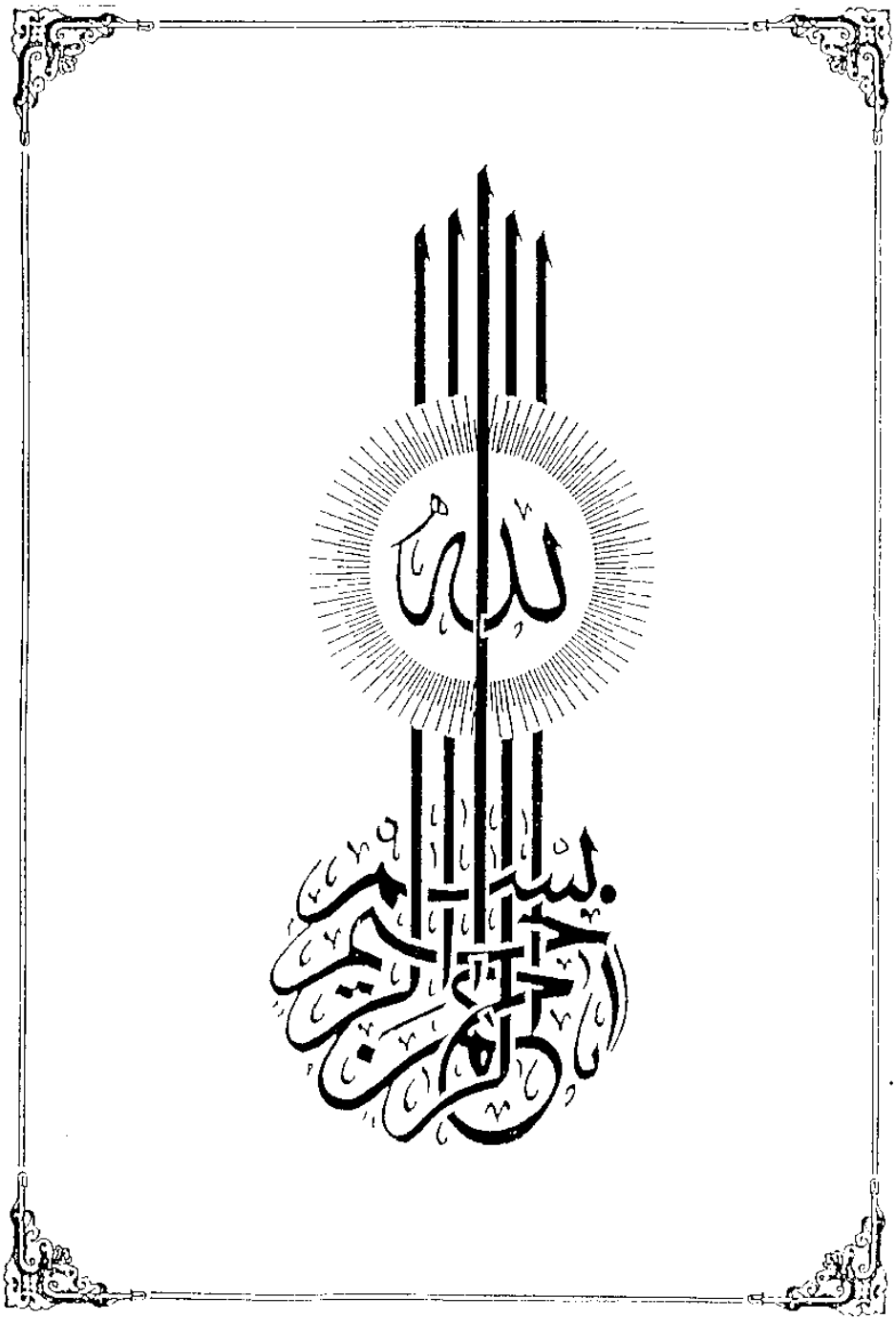

CONTENTS

AIM OF THE WORK

No doubts that predisposition to the development of diabetes mellitus is genetically transmitted. However the mode of inheritance of diabetes is poorly understood. It is described as either unknown multifactorial or transferred by recessive genes with variable penetrance.

Many attempts have been done to identify the person liable to develop diabetes. The finding of such method will through more light on the inheritance of diabetes. It also helps in searching for prophylactic methods against this disease.

The aim of this work is to measure O G T T and Hb A_1c in the families of diabetics as a method for early detection of carbohydrate intolerance.

THE GENETICS OF DIABETES MELLITUS

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Impressive advances have occurred in clinical and molecular genetics over the past few decades but the genetics of diabetes mellitus remains rife with controversy and speculation. This state of uncertainty prevails for three main reasons. First, although the familial clustering of diabetes has long been recognized a disease that "runs in families" may reflect a variety of shared environmental factors as well as common genetic components, in diabetes, the relative primacy of environment versus genotype is still an open question. Second, the variable age of onset, predominantly in and beyond middle age,i.e. abiotrophy, also complicates genetic studies. Thus pedigree analysis is rendered difficult when so many potential diabetics are yet to be recognized. Third, and most important, for accurate genetic typing, the specific variant gene and its product should be identifiable. Such genetic markers are lacking in diabetes. Indeed, the use of abnormal glucose tolerance as phenotypic marker takes us many steps away from the basic genotype. Even this criterion is variable so that glucose intolerance is said to be present on the basis of glycosuria alone, elevation of fasting blood sugar level, two hour postprandial blood sugar determination, or sequential blood

sugar determinations following glucose challenge. This demonstrates the ascending order of stringency that can be applied to the diagnosis of diabetes. Other markers have also been used such as capillary basement thickening, but these are presently controversial with respect to cause and effect. In short. Little progress has been made in unraveling the basic genetic defect(s).

Physiologic homeostasis is a result of interaction between an individual's genetic make-up and numerous factors in the environment Likewise, every human diseas-se, whether congenital or acquired, systemic or local, metabolic or degenerative, is also the result of an interplay between the genotype and the environment. Each individual not only finds himself in a personally specific environment but also represents a highly distinctive pack-age of genetic information. Thus approximately half the genes in each person exist in a form that differs from the one present in the majority,i.e. genetic polymorphism (Childs et al., 1968). This genetic individuality taken together with a cumulative environment that is specific for each person readily explains the normal range commo-nly observed in clinical practice. In other words each organism has a set of unique physiological limits which determine the capacity to maintain normal homeostasis or, conversely, to manifest disease. As an extreme example,

environmental factors imposed on a relatively "quiescent" genetic background can produce overt disease, e.g, inherited deficiency of glucose-6phosphate dehydrogenase which leads to hemolysis only following ingestion of certain drugs (Beutler, 1972). At the other extreme, the presence of a specific genetic mutation can be so assertive that it is expressed in virtually any environment at a predictable time and with a uniform clinical picture, e.g. Tay'Sachs disease (Sloan et al., 1972).

It must also be appreciated that two or more distinct mutations can produce a similar clinical picture. Thus, alternate forms of genes may exist at a single genetic locus not only as common polymorphisms but also as rare variants. On the other hand, a given clinical picture can emanate from mutations at different loci, is, genetic heterogeneity. It seems clear that the exact molecular basis of a given genetic trait plus the "background" genotype will determine the exact mode of transmission of diabetes. Moreover, the precise environmental history acting in conjunction with this unique genotype will simultaneously set the time of onset and shape the qualitative clinical picture in a given individual. In short, the unique genetic-environmental history of each person accounts for what we call the normal range in health and disease and, in turn, creates the limits of certainty in genetic counselling.

Possible Genetic-Biochemical Origins of Diabetes Mellitus

Diabetes is not a derangement of glucose metabolism alone, but also involves metabolism of proteins, lipids, nucleic acids, and complex derivatives of these major groups (Renold et al., 1972). If, for the moment, we simplify and define diabetes mellitus as inappropriate hyperglycemia caused by relative or absolute insulin deficiency, it seems clear that a number of factors operating either along or in combination could produce the final gross phenotype that we equate with diabetes mellitus. The range of possible sites of origin in diabetes is enormous and could involve one or more steps in the complex multitiered multiloop feedback system that regulates metabolic homeostasis (Goldstein, 1974,1978). Thus, diabetes could begin not only in pancreatic beta cells which secrete insulin but in other endocrine cells within and outside the pancreas, as well as in several kinds of peripheral "responder" cells. Without more specific genetic markers more closely linked to the underlying gene defect(s), the diagnostic precision in diabetes will remain crude.

Different Clinical Forms

It has long been evident that clinical diabetes mellitus can be subdivided into two major forms: the

less common juvenile-onset, insulin dependent, ketosis-prone form and the more common maturity-onset, usually insulin-independet, non-ketosis prone form. Much of the difficulty in earlier genetic analyses has resulted from the amalgamation of these two phenotypes when each very likely has a different pattern of genetic transmission. Thus, Falconer(1967) found the heritability index of diabetes to be 70 to 80 per cent among young diabetics and 30 to 40 per cent in diabetics over 55 years of age. Simpson made similar observations (Simpson, 1969) in finding that the heritability index decreased with the age of the proband. The increasing incidence of diabetes found in people of older age may simply relate to their progressively elevated blood glucose, and this may be an effect of aging per se (Andres, 1971).

Maturity-onset Diabetes of Youth - A specific Genetic Form

Tattersall and Fajans have recently documented (Tattersall et al., 1975) a rare type of juvenile-onset diabetes distinctively different from classic juvenile-onset diabetes, the far more common form characterized by the usual abrupt clinical onset of severe symptoms, insulin-deficiency, and tendency to ketoacidosis. The newly recognized entity is maturity-onset type diabetes of youth, which is more akin to classical maturity-onset

diabetes of middle age. Symptoms are mild, stimulated insulin output is retained although delayed and diminished, but ketonuria and hyperglycemia can be controlled without insulin. Maturity-onset diabetes of youth was at first considered to be classical juvenile diabetes detected fortuitously at an early stage of progression. It now seems clear that although some cases may evolve to frank insulin-deficiency, most patients with maturity-onset diabetes of youth have little or no progression beyond two or even four decades of follow-up (Tattersall, 1976). A strong family history of diabetes always exists, and the clinical features comprise a nearly identical benign phenotype in all members of the family such that they can virtually all be managed successfully with oral hypoglycemic agents. Additionally, both microvascular and macrovascular complications seem rare. In the series of Tattersall and Fajans, an autosomal dominant mode of transmission seems most likely on the basis of three factors: (1) in 46 per cent of families, diabetes was directly transmitted through at least three successive generations; (2) eighty-five per cent of these diabetics had one diabetic parent; (3) fifty-three per cent of these diabetics had latent or overt diabetic siblings, i.e. close to a 1:1 ratio. On the other hand, in the families of juvenile-onset diabetics, three-generation inheritance was found in only 6 per cent, only 11 per cent had a diabetic

parent, and only 3 per cent of tested siblings were found to have latent diabetes. Additionally, the frequency of diabetes was no greater among the parents and grandparents of classical juvenile-onset diabetics, than in controls. Thus, juvenile-onset diabetes appears to be neither autosomal dominant nor autosomal recessive, but rather a complex multifactorial form of diabetes.

Ethnic Variation in Diabetes and Influence of Geographic Setting

It is well known that distinctive forms of diabetes occur in various ethnic groups. Moreover, alteration in the diabetic phenotype in the same ethnic groups after relocating to a different geographic setting is also clear. Much of this geographic effect can be traced to dietary factors and occupational differences, all of which are best subsumed by the increased incidence of a single parameter, obesity.

Classic examples of ethnic differences are the South African (Natal) Indian versus the South African black (Rimoin et al., 1971). Both ethnic groups have roughly similar diets with respect to fat and carbohydrate, but ketosis is rare in the Natal Indian and common in the black African. In contrast, the Indian has more frequent

vascular complications than the black (Walker et al., 1964). Similarly, the strikingly high incidence of diabetes in the modern American Indian (particularly those of the southwestern tribes, the Navajo and Pima) seems in great part related to greater dietary intake and increased adiposity of these previously hunting and gathering populations (Fulmer et al., 1963) (Bennett et al., 1971).

Genetic Disorders Associated with Diabetes Mellitus

An increasing number of syndromes are known to be associated with either overt glucose intolerance, insulin resistance or both (Goldstein, 1971, 1978) Table I. Although these syndromes are relatively rare, they comprise in aggregate a substantial proportion of total diabetes. Various genetic modes of transmission are found in this list. For example, both Werner's syndrome and ataxia telangiectasia have clear-cut autosomal recessive modes of transmission and feature an insulin-resistant non-ketosis prone form of diabetes (Epstein et al., 1965) (Schalch et al., 1970). But while individuals with Werner syndrome usually succumb to severe atherosclerotic complications, those with ataxia telangiectasia often fall prey to lymphomatous malignancy. Huntington's disease or hereditary chorea, an autosomal dominant disorder, is also associated with an insulin resistant maturity-onset form of diabetes (Podolsky et al., 1970,1972) perhaps related to growth

Table I : Genetic disorders Associated with glucose Intolerance and or insulin

Familial	Familial Continued
Alstrom syndrome	Optic atrophy and diabetes
Ataxia telangiectasia	Optic atrophy, diabetes
Cockayne syndrome	inspidus, and diabetes
Cystic fibrosis	mellitus
Fanconi anemia	Hereditary relapsing
Friedreich ataxia	pancreatitis
Glucose-6-phosphate dehydrogenase	Photomyoclonus, diabetes,
deficiency	deafness, nephropathy, and
Type 1 glycogen storage disease	cerebral dysfunction
Gout	Pineal hyperplasia and
Hemochromatosis	diabetes
Huntington disease	Acute intermittent prophyria
Hutchinson-Gilford (progeria)	Pheochromocytoma
syndrome	Prader-Willi syndrome
Hyperlipidemia, diabetes,	Refsum syndrome
hypogonadism&short stature	Retinitis pigmentosa, neuro-
syndrome	pathy, ataxia, and diabetes
Hyperlipoproteinemia III, IV,	Rothmund-Thomson syndrome
and V	Schmidt syndrome
Isolated growth hormone deficiency	Werner syndrome
Laurence-Moon Biedl syndrome	
Lipoatrophic diabetes	NONFAMILIAL
Muscular dystrophy	(Chromosomal)
Myolonic dystrophy	Down syndrome
Ocular hypertension induced by	Klinefelter syndrome
dexamethasone	Turner syndrome

Samuel Goldstein and Stephen Podolsky

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