SOME METABOLIC STUDIES IN PREDIABETES

M. D. THESIS

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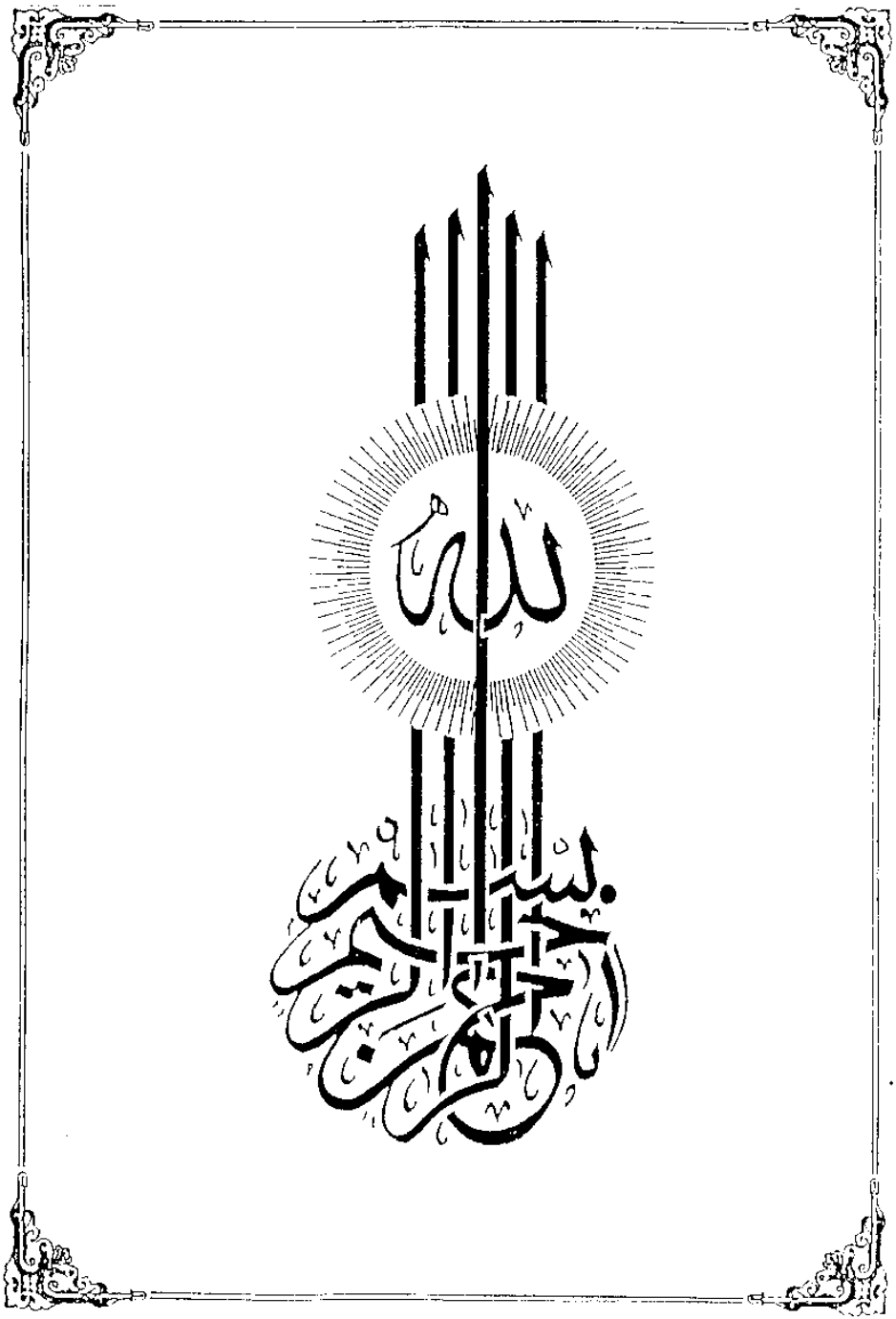

C O N T E N T S

CHAPTER I

INTRODUCTION

I N T R O D U C T I O N

It is well known that diabetes, as a disease can be delineated into two major types i.e. the juvenile and maturity onset. The first is different from the second in many aspects; although a genetic factor may lie behind both.

The maturity onset group is known to run with three phases, not well demarcated, but an international concepts of prediabetes followed by the chemical phase to end into the chemical or symptomatic diabetes.

In general, the aim of the physician, during therapy is to bring back the diabetic from the symptomatic phase into the prediabetic phase.

The aim of the thesis is to study with some detail, the prediabetic phase, since at this stage prophylactic measures may found to be of value to avoid risks and irreversable damage that results at the clinical phase.

In this context it is needed to mention disturbances in carbohydrate, fat and protein metabolism that occur in the diabetic phase. Since total pancreatomy in man results

in diabetes which needs not more than 30 units of insulin per day; while in diabetics one may need to a much higher dose in order to bring the patient to a normoglycemic phase; so it is highly important to discuss insulin secretion, release, degradation, agonists and autagonists.

CARBOHYDRATE METABOLISM

Glucose is the final phase, after steps of digestion and absorption, available in the blood stream. As such it is useless, unless it captures phosphorus (phosphorylation), then it becomes useful or edible glucose. The process is enzymatically determined utilizing the hexokinase system and the result is a glucose-6- phosphate. From this stem 3 patways are ready:

(1) Storage as glycogen in liver and muscle.

(2) Glycolysis; by this is meant, breaking down of glucose; this may be:

a- Anaerobic, resulting in pyruvic acid (Embden Meyerhoff pathway.).

b- Aerobic (in the presence of oxygen)

Here carbon dioxide and energy are liberated through revolution of different acids (oxalacetic, citric, alphaketoglutaric etc..., coming from pyruvic) in the so-called citric acid of Kreb's Cycle.

(3) The pentose shunt or hexose monophosphate pathway (H.M.P.), triggered by glocose-6-phosphate dehydrogenase. This very important pathway, besides sypplying nucleic

acid, gives TP. NH (reduced triphosphopridine nucleotide which is essential for the process of lipogenesis (vide infra). Pyruvate is broken down to acetic acid which captures Coenzyme A. and thus rendered very active acetyl Co.A which is really the meeting point of carbohydrate, fat and protein; as acetyl Co A is the precursor of cholesterol, of k etone bodies and preceeds steps necessary for lipogenesis (storage of fat in fat depots).

The important enzyme, hexokinase is stimulated by insulin, deccelerated by thyroxine, growth hormone and adrenal stercids. Thus hyperglycemia can result from insulin insufficiency, excess growth hormone, adrenal steroids and thyroxine, the former being the more important and the commonest encountered in clinical practice as diabetes mellitus.

The liver cell is unique in two aspects. It is freely permeable to glucose unlike muscle or adipose tissue cell, it contains the enzyme glucose-6-phosphotase which is capable of producing glucose from glucose-6-phosphate. There is little hexokinase in the liver, but there is another important enzyme glucokinase, it phosphorylates glucose, its

action depends on the concentration of glucose in the liver cell, thus depending mainly on the supply of insulin; more glucose being poured out of the liver if there is deficiency of insulin. On the contrary, if insulin is available, glucokinase activity is enhanced, glucose is stored as glycogen.

LIPID METABOLISM

This is usually described as being altered in diabetes. Hypercholesterolaemia and increased triglyceride and free fatty acid levels are found in uncontrolled diabetes.

They are rough parameters of diabetic control as glycemia is.

Ingested fat is disposed of into three pathways:

1. Energy supply through fatty acids oxidation.
2. Stored by a process of lipogenesis and in this instance it needs well functioning two pathways:
   a- Anaerobic glycolysis which supplies phospho-glyceraldehyde since glycerol is needed for the storage of fat as triglyceride.
   b- The pentose shunt (hexose monophosphate pathway) which supplies T.P.N.H. necessary for lipolysis.

As previously mentioned (vide supra) both pathways require insulin which thus triggers lipogenesis rather than lipolysis.

3. Cholesterologenesis; this can be carried on even in the absence of exogenous fat through acetyl Co-A (endogenous cholesterol).

In juvenile diabetics lipolysis naturally exceeds lipogenesis due to insulin lack and this explains two events; the loss of weight and the tendency to ketosis.

Insulin corrects these defects, it promotes lipogenesis and gets off and can prevent ketosis.

In general lipolysis, on the other hand, is accelerated by catecholamines (epinephrine and nor epinephrine), glucagon, glucosteroids, thyroxine, growth hormone, vasopressin, placental lactogen and thyroid stimulating hormone.

The lipolytic actions of catecholamines are manifested through beta and (not alpha) adrenergic receptors, and through activation of inactive lipase. The actions of thyroxine and steroids is a permissible one.

Hypercholesterolemia may antedate diabetes and one is familiar with eye xanthomata in prediabetics.

PROTEIN METABOLISM

This is affected in diabetes in several ways. To start with, insulin is a potent anabolic hormone, since it is necessary for the process of incorporation of different aminoacids into polypeptide (protein) this process is indirect, insulin stimulates the transport of amino acid into the cell, it accelerates the incorporation of acetate or pyruvate into protein. As a source of energy to be supplied from oxidative phosphorylation, naturally insulin, triggers this process. It also stimulated the formation of R.N.A.

Amino acids may be synthetised in the body by complicated process of reductive amination, transamination, but 8 amino acids (essential) must be supplied in the diet. These are: -

Leucine, isoleucine, lysine, methionine, phenyl alanine, threonine, tryptophan and finally valine).

As mentioned previously all food stuffs meet, in the metabolic pool at the step of acetyl Co.A., for their final assimilation. In diabetes since there is a defect in carbohydrate metabolism, the body starts to use fat and finally

protein for its fuel. Gluconeogenesis(formation of glucose from protein) is the catabolic process which occurs in diabetes.

A common pathology of diabetes is thickening of the basement membrane due to laying down of P.A.S. positive material made up of protein + polysaccharide.