THE LIVER AND DIABETES MELLITUS

Thesis

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BY

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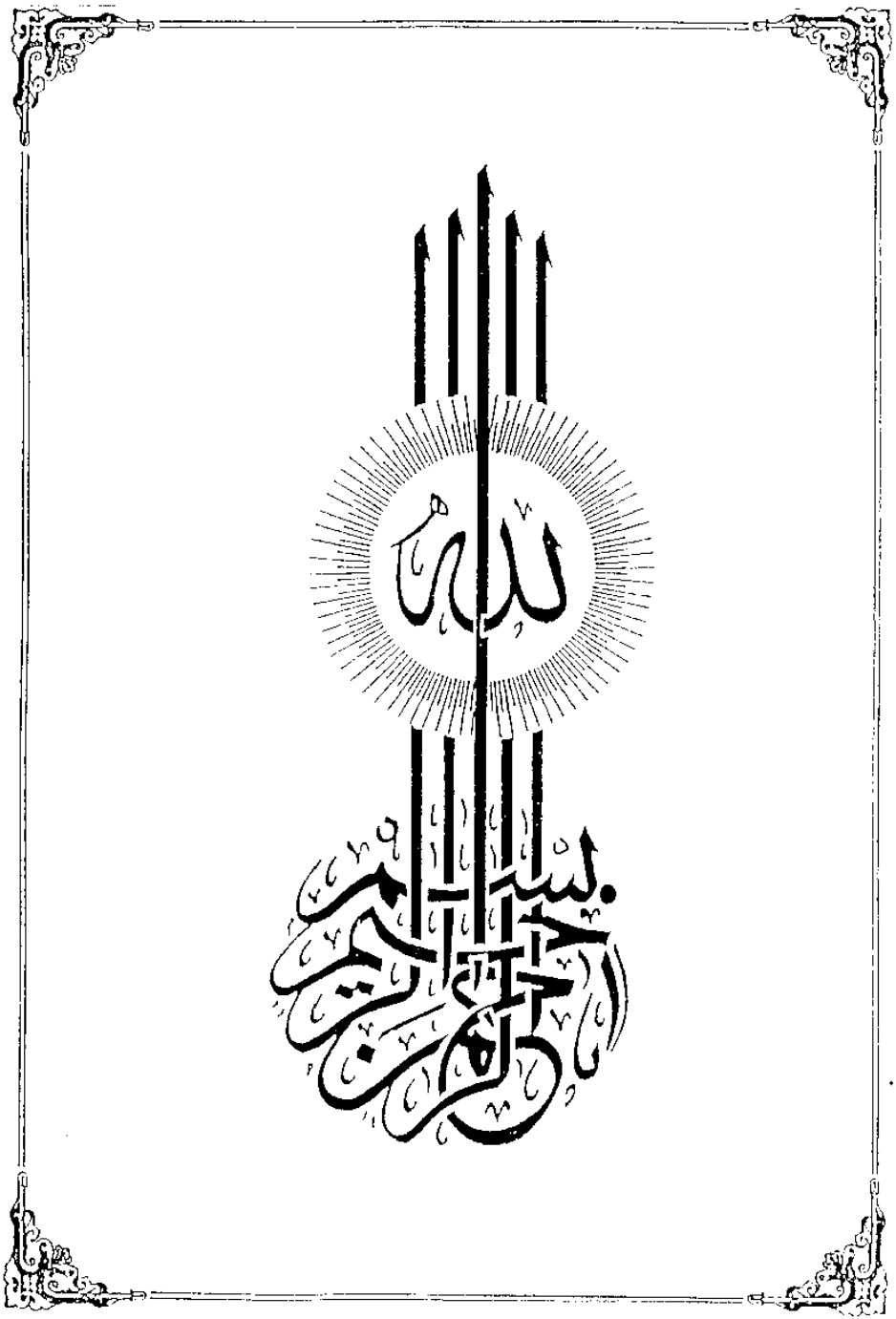
To the patients who cooperated freely to make this work possible I offer the results which may help to solve the problems of many other sufferers of the same diseases.

Gamal Y.S. Youssef



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CORRECTION

Page	Line	Wrong	Right
6	10	phosphorylation	dephosphorylation
24	5	acid	acids
27	12	maintain ng	maintaining
28	13	(Creutzfeldt,1970)	(Cruezfeldt,1973)
48	12	Tranquade	Tranquada
62	25	Davlos	Davalos

INTRODUCTION

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Diabetes Mellitus :

Definition :

Diabetes mellitus is not a disease in the classic sense, i.e., it has no distinct and definable pathogenesis, aetiology, invariable set of clinical findings , specific laboratory tests, and definitive and curative therapy . Rather, it should be viewed as a syndrome, i.e., a clinical entity which can involve any or all of a long list of symptoms and clinical laboratory findings which show a variable response to therapy . Because it has been easiest to measure and was the first discovered abnormality, the major focus has been to define the disease by glucose measurement. Four general areas are considered to be affected in the complete clinical syndrome and should be considered in making a clinical diagnosis.

1. Hyperglycaemia : There is an abnormality of carbohydrate metabolism resulting in hyperglycaemia and often associated with accelerated fat and protein catabolism. It may contribute to the other features but seems unlikly to be their sole cause.
2. Large vessel disease : There is accelerated atherosclerosis and medial calcification.
3. Microvascular disease : There is an abnormality of capillary basement membranes characterized by

thickness and abnormal function. These capillary-related lesions are often termed the microvascular or small vessel concomitants of diabetes.

4. Neuropathy : There are peripheral sensory- motor defects, segmental demyelination, and abnormalities of Schwann cells.

None of these findings is specific for diabetes, as each is also found in other diseases and syndromes. Since the primary defect in diabetes is unknown, a patient with any one or all of these abnormalities must be considered as a possible diabetic. The final decision is based on clinical and laboratory observations. Because plasma glucose can be measured simply and accurately, it remains the standard most often used parameter. (Williams, 1974).

Biochemistry :

Insulin is formed in the pancreatic islets on ribosomes on the surface of the rough endoplasmic reticulum of B-cells, as a single polypeptide chain, proinsulin, containing from 81 - 86 residues, depending on the species. The amino acids are so arranged that there is spontaneous folding of this molecule into a form in which the disulfide bonds characteristic of insulin are easily made. The conversion of proinsulin to insulin occurs by proteolytic cleavage, which reduces the

molecular weight of the protein from 9000 (proinsulin) to one of 6000 (insulin) and one of 3000 (C- peptide). This conversion occurs at the time of the transport of proinsulin to the Golgi complex, where it is apparently packaged into granules. Since the granules contain insulin and C- peptide in equimolar amounts it seems likly that the packaging occurs first and is followed by cleavage within the granule. Insulin is complexed with zinc and stored. The number of B- cell granules is a good indication of the amount of insulin present; however, it does not reflect the synthesis rate or release rate of insulin, but simply the balance between them at any one time.

Proinsulin synthesis and cleavage and insulin storage are not directly coupled to release; these processes appear to be separately regulated. Insulin synthesis is sensitive to glucose. An increase in synthesis due to glucose can be shown to occur in the absence of insulin secretion, for example, by incubation in a low- calcium medium (Steiner,1972). The conversion of proinsulin to insulin is known to be an energy dependent step. A trypsin - like enzyme is believed to be involved but has not been identified certainly. (Williams, 1974) .

The granules containing insulin are stored until a stimulus for its secretion is applied, such as glucose, glucagon, or tolbutamide. The early change in the release

process is a margination of the beta granules to the plasma membrane of the B- cell. The walls of these sacs fuse with the plasma membrane of the cell and rupture, and granules are then liberated into the extracellular space. They then rapidly disappear from the extracellular space, apparently undergoing rapid dissolution. Lacy , 1970, has called this process of granule ejection into the extracellular fluid emiocytosis.

Insulin is a powerful hormone with broad influences. Directly or indirectly, it affects the structure and function of every organ in the body- indeed, of every biochemical constituent.

The amount of insulin action depends at least on the (a) amount of insulin secretion, (b) insulin distribution, (c) type of tissue, (d) amount of insulin binding to its specific receptor, (e) types and amounts of nutrients inside and outside the cells, (f) types of ions and their concentrations, and (g) amount and types of other hormones.

Insulin's main functions are to stimulate anabolic reactions involving carbohydrates, fats, proteins, and nucleic acids. It catalyzes the formation of macro-molecules in cells which then are used in cell structure, energy stores, and regulation of many cell functions. Insulin stimulates the synthesis of protein from amino acids, nucleic acids from mononucleotides, poly -

saccharides from monosaccharides, and lipids from fatty acids.

The following are some of the specific actions of insulin. Insulin increases (a) plasma membrane transfer of glucose and certain other monosaccharides, some amino acids, some fatty acids, K^+ , and Mg^{++}; (b) Mg^{++}-activated ($Na^+ + K^+$) ATP ase activity; (c) glucose oxidation; (d) glycogenesis; (e) lipogenesis; (f) proteogenesis; and (g) formation of ATP, DNA, and RNA. Insulin decreases (a) glycogenolysis, (b) lipolysis, (c) proteolysis, (d) gluconeogenesis; (e) ureogenesis, and (f) ketogenesis. Some of the activities of insulin result from its inhibition of the supply of C.AMP, causing less activity of protein kinase. This is associated with less phosphorylation of enzymes, but an increase in activity of some non phosphorylated enzymes. The latter enzymes tend to promote anabolism : glycogenesis, proteogenesis, lipogenesis, increased levels of nucleic acids, and mitogenesis. Insulin does not stimulate glucose transport in red blood cells or in the brain, nor does it promote tubular reabsorption of glucose by the kidney or glucose absorption by the intestinal mucosa (Williams, 1974).

Metabolic Disturbances in Diabetes Mellitus:

Carbohydrates constitute the largest part of the total caloric intake. Much of this carbohydrate is either

ingested as glucose or transformed into it. A considerable amount of glucose can be utilized in the absence of insulin but it is necessary for the blood glucose level to rise significantly in order for this to happen. In normal persons the tissue threshold to glucose is approximately 70 - 90 mg / 100 ml., while in those with untreated diabetes it increases to 400 or more; sufficient insulin returns the threshold to normal.

The enzyme glucose -6- phosphatase, which is responsible of the phosphorylation of G-6- P permitting free glucose to enter the blood, is inhibited by insulin and stimulated by gluconeogenesis; thus, in diabetes, starvation, and hyperglucosteroidism, there is an increase in its activities leading to high blood glucose level.

Normally, the citric acid cycle supplies carbon atoms for various synthetic processes in the cell and the four carbon compounds so used are replaced by resynthesized oxaloacetate, produced by carbon dioxide fixation by phosphoenol pyruvate or via malate from pyruvate. The deficiency of these substrates in diabetes has been stated by some investigators to cause decreased oxaloacetate. Oxaloacetate is needed to combine with acetyl CoA to form citric acid, which is then oxidized in the citric acid cycle, contributing significant energy. Acetyl CoA tends to pile up when there is an

increased amount formed from lipolysis, decreased oxaloacetate to conjugate it for citric acid oxidation, and decreased lipogenesis. As acetyl CoA increases, it tends by mass action to promote normal or increased carbon dioxide production by the citric acid cycle. (Williams, 1974).

Winegrad, 1966,has reported an increase in the quantity of L-xylulose in diabetics. He concluded that increased production, as the result of hyperactivity of the glucuronic acid pathway, was the most likely cause of the increased L-xylulose. Insulin decreases the level of L-xylulose while growth hormone or epinephrine increases it. There probably are a number of other alterations in the glucuronic acid pathway in diabetics.

Untreated diabetics oxidize much more fat than do normal persons. In diabetes the decreased glucose uptake causes increased fat oxidation, and decreased lipogenesis results from the inadequate supply of TPNH. A deficiency of pyruvate and phosphoenol pyruvate causes decreased concentrations of oxaloacetate. This decrease tends to inhibit the citric acid cycle, but accumulation of excess acetyl CoA stimulates the citric acid cycle and also produces excess B-hydroxy - B-methyl glutaryl CoA (HMG CoA). Excess ketones and, under certain conditions, excess cholesterol are formed from HMG CoA. With a decrease in glucose utilization, as in starvation or

diabetes, an increase in plasma free fatty acids is found. When ketones are produced by the liver faster than the entire body can utilize them, ketoacidosis occurs. When glucose utilization is decreased even slightly, there is an excess plasma level of free fatty acids, triglycerides and other components.

Insulin deficiency also leads to decreased protein synthesis and increased protein catabolism. This defective protein metabolism is associated with impaired growth in young animals and with a negative nitrogen balance. It presumably also contributes to the delayed healing of wounds seen in diabetes.

Collagen is one of the most abundant glycoproteins in the body, and is a major component of basement membrane. Capillary basement membrane thickening constitutes one of the major pathologic changes in microangiopathies of diabetes. Synthesis of the carbohydrate component of glycoproteins from glucose is not under the influence of insulin, and since some cells do not require insulin for marked glucose utilization, with hyperglycaemia there are increases in sugar nucleotides and glycoproteins in glomeruli and other tissues of diabetics (Williams, 1974).

There is a manifold increase in plasma levels of valine, leucine, isoleucine, and alpha amino butyrate; the amino acids whose peripheral release is inhibited by

insulin. Moreover, leucine and isoleucine are ketogenic and therefore contribute to hepatic ketogenesis. However, there is a decrease in plasma alanine, glycine, threonine, and serine. Thus augmentation of gluconeogenesis occurs with insulin lack, yet there is a decrease in circulating glucogenic substrates. These observations suggest stimulation of hepatic uptake of glucose precursors in the absence of adequate insulin. The amount of alanine extracted by the livers of diabetics may be more than twice that extracted by non diabetics.

In normals, with feeding there is an increase in the rate of conversion of glucose to pyruvate (glycolysis), whereas with diabetes, fasting, exercise, protein feeding, or various stresses there is a reversal of substrate flow, with pyruvate going to glucose (gluconeogenesis). When there is excess glucosteroids, there is a tendency for decreased ketone production. (Williams, 1974).

Pathology :

.. Pancreas: The pathology of the pancreas varies greatly in diabetes. A decrease in the number of granules in B-cells is common and is accompanied by a decrease in insulin content (Wrenshall, 1956).

Among other pancreatic pathologic changes associated with diabetes, the most common is vacuolation of the B-cells. These vacuoles give a positive PAS reaction, suggesting glycogen within them. They are only found