DIURNAL VARIATIONS IN PLASMA GLUCOSE LEVELS

T H E S I S

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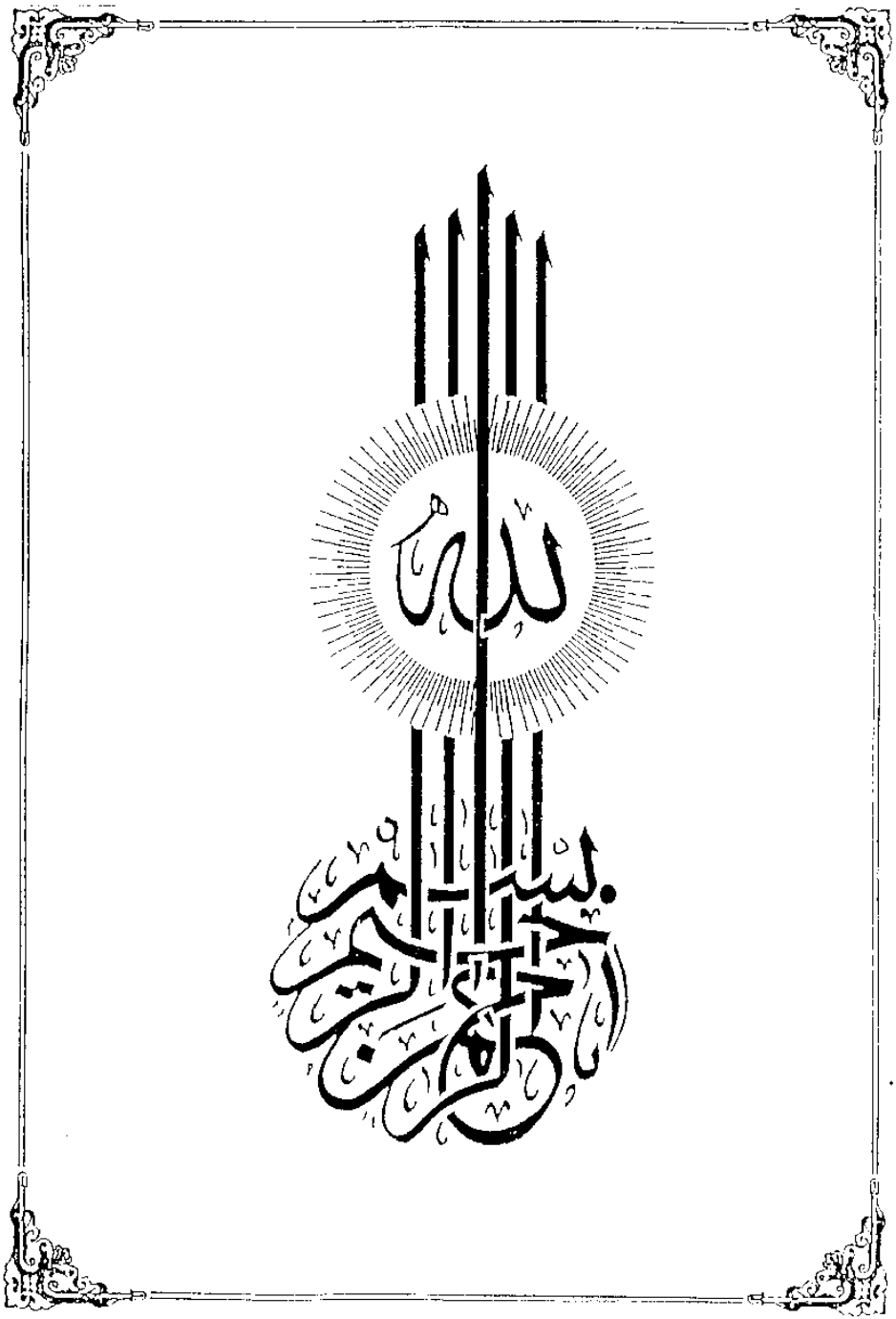

A C K N O W L E D G E M E N T S

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M. Mahhlouf

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C O N T E N T S

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INTRODUCTION

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

Diabetes mellitus remains an extremely difficult disease to diagnose, far more so than most internists recognize.

From a theoretical standpoint, diabetes can be defined simply as a genetic disorder of unknown cause characterized by :-

1) A relative or absolute decrease in insulin secretion, which ultimately results in hyperglycemia.

2) [illegible]

[illegible] measurement of plasma insulin, and for the quantification, [illegible], of [illegible] microangiopathy, from a practical standpoint the clinician must still rely mainly upon an elevation of blood glucose levels to establish the diagnosis of diabetes mellitus.

Moreover, since fasting hyperglycemia is now generally considered to represent a late manifestation of diabetes, the average physician will make the diagnosis of diabetes mellitus in a fasting euglycemic patient if he finds that the standard glucose tolerance test is abnormal.

It will be the major thesis of the following discussion that the use of the standard glucose tolerance test as a means for establishing the diagnosis of diabetes is fraught with error.

The purpose of this work is to review some of the factors that affect the plasma glucose levels, and the factors affecting the glucose tolerance. Of these factors, the diurnal variations of plasma glucose, is of particular importance, it sometimes a pitfall in the diagnosis of diabetes mellitus.

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REVIEW OF LITERATURE

CARBOHYDRATE METABOLISM

Dietary carbohydrates are for the most part polymers of hexoses, of which the most important are galactose, fructose and glucose. Most of the monosaccharides occuring in the body are the D-isomers. The principal product of carbohydrate digestion and the principal circulating sugar is glucose. The normal fasting level of glucose in peripheral venous blood, determined by the highly specific glucose oxidase method, is 60-80 mg/dl (3.4 - 4.5 mmol/L). (Lehmann, 1976) (Scally, R.E., 1978) (Young, D.S., 1975).

Substances other than glucose that cause similar reducing reaction are responsible for the higher values obtained with other methods. In arterial blood, the glucose level is 15-30 mg/dl higher than in venous blood.

Once it enters the cells, glucose is normally phosphorylated to form glucose-6-phosphate. The enzyme that catalyzes this reaction is hexokinase. In the liver, there is in addition an enzyme called glucokinase, which has a greater specificity for glucose and which, unlike hexokinase, is increased by insulin and decreased in starvation and diabetes. The glucose-6-phosphate is either

polymerised into glycogen or catabolized. The process of glycogen formation is called glycogenesis, and glycogen breakdown is called glycogenolysis. Glycogen, the storage form of glucose, is present in most body tissues, but the major supplies are in the liver and skeletal muscle. The breakdown of glucose to pyruvic acid or lactic acid (or both) is called glycolysis. Glucose catabolism proceeds in two ways: via cleavage to trioses, or via oxidation and decarboxylation to pentoses. The pathway to pyruvic acid through the trioses is the Embden-Meyerhof pathway, and the pathway through gluconic acid and the pentoses is the direct oxidative pathway, or hexosemonophosphate shunt. Pyruvic acid is converted to acetyl-CoA. Interconversions between carbohydrate, protein and fat include the conversion of the glycerol from fats to dihydroxyacetone phosphate and the conversion of a number of amino acids with carbon skeletons resembling intermediates in the Embden-Meyerhof pathway and citaic acid cycles to these intermediates by deamination. In this way, and by conversion of lactate to glucose, non-glucose molecules can be converted to glucose (gluconeogenesis). Glucose can be converted to fats through

acetyl CoA, but since the conversion of pyruvic acid to acetyl-CoA, unlike most of the reactions in glycolysis, is irreversible, fats are not converted to glucose via this pathway. There is therefore very little net conversion of fats to carbohydrate in the body because, except for the quantitatively unimportant production from glycerol, there is no pathway for conversion. (Ganong, W.F., 1979).

Citric Acid Cycle :

The citric acid cycle (Krebs cycle, tricarboxylic acid cycle) is a sequence of reactions in which acetyl-CoA is metabolised to CO_2 and H atoms. Acetyl-CoA is first condensed with a 4-carbon acid, oxaloacetic acid, to form citric acid and HS-CoA. In a series of seven subsequent reactions, two CO_2 molecules are split off, regenerating the oxaloacetic acid. Four pairs of H atoms are transferred to the flavoprotein-cytochrome chain, producing 12 ATP and four H_2O, of which two H_2O are used in the cycle. The citric acid cycle is the common pathway for oxidation to CO_2 and H_2O of carbohydrate, fat and some amino acids. The major entry into it is through acetyl-CoA, but pyruvic acid also

enters by taking up CO_2 to form oxaloacetic acid, and a number of amino acids can be converted to citric acid cycle intermediates by deamination. (Ganong, W.F., 1979).

PHYSIOLOGICAL REGULATION OF PLASMA GLUCOSE

Glucose, mainly in the form of its polymers starch and cellulose, is probably the most plentifull organic compound in the world. It is also the only carbohydrate that exists in the circulation of mammals in anything more than trace amounts. Other sugars such as fructose and galactose which either in their native form or as part of the disaccharides sucrose and lactose constitute about 15 - 13 percent respectively of the carbohydrate in the average well-balanced diet, these sugars are rapidly metabolised after ingestion. Consequently, except in a few extremely rare diseases, they occur only in minute quantities in the blood and other body fluids even after large doses by mouth.

However, glucose is virtually confined to the extracellular fluid (ECF) of the body, although this seldom contains more than 20 g at any one time, even following a large carbohydrate-containing meal. A small amount of