# STUDY OF PLASMA GLUCAGON LEVEL IN NON DIABETIC PATIENTS WITH INFECTIOUS DISEASES

## THESIS

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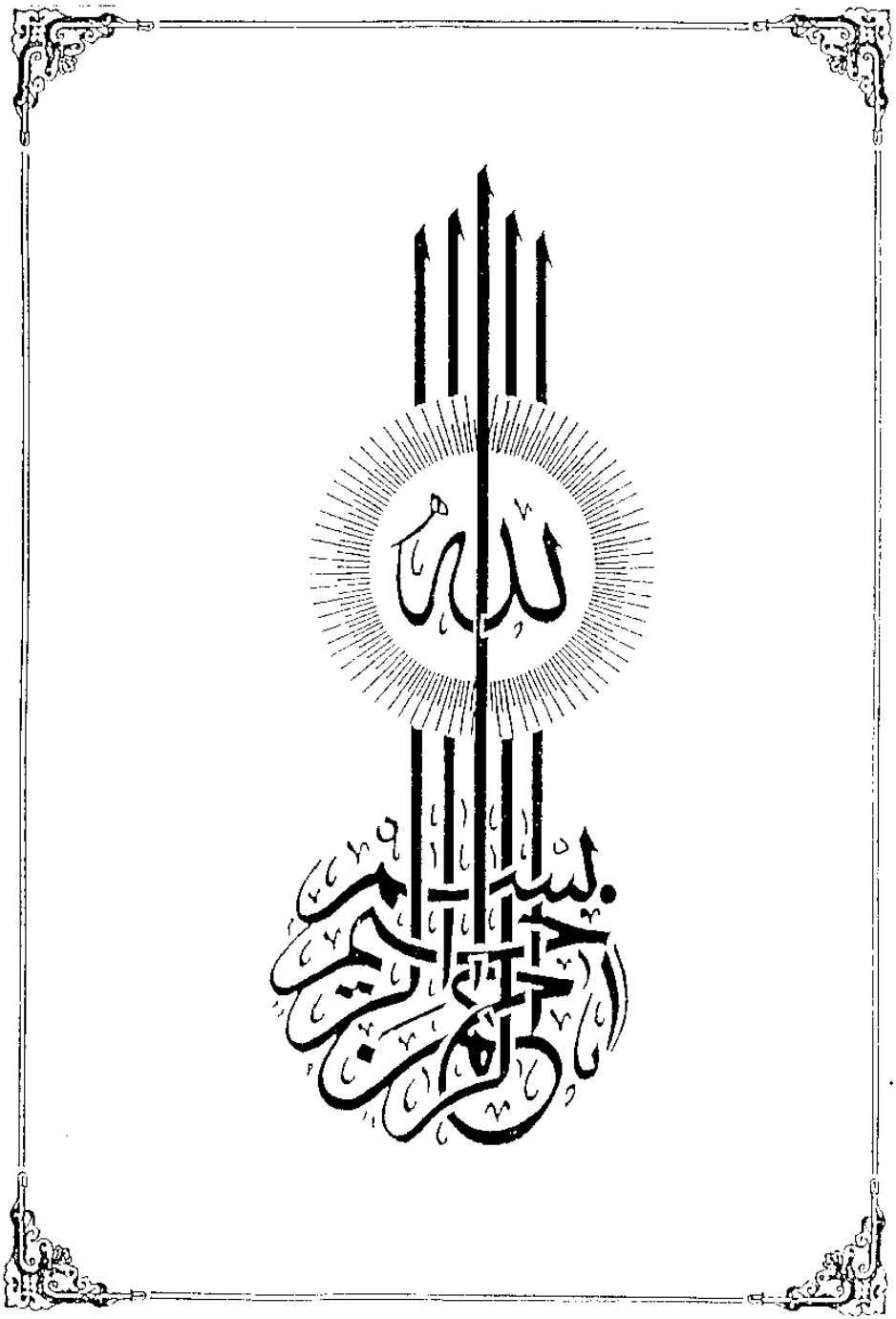

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# INTRODUCTION AND AIM OF THE WORK

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*Infection in humans is known to promote alteration in glucoregulatory hormone concentrations as well as in the carbohydrate metabolism of normal individuals or a worsening of the diabetic state (George etal 1974).*

*Glucagon is a catabolic hormone which main action is to increase the supply of glucose to the blood stream. It seemed likely therefore that glucagon would be necessary in situations where blood glucose tends to fall because of failure of carbohydrate supplies, as in starvation for example. However, glucagon might also be released in situations where it is advantageous,to have an elevated glucose level. Stress is such a condition (Bloom 1973).*

*Rocha etal (1973) described unusually high concentrations of glucagon in the plasma of non diabetic,patients with various bacterial infections, and the magnitude of glucagon increase appears to correlate well with the severity of illness in individual patients .*

*Furthermore, Rayfield etal (1973 a.) reported elevated plasma glucagon concentrations during viral illness in diabetic and non diabetic patients.*

*The present study is designed to evaluate plasma glucagon level in non diabetic patients with*

*infectious diseases so as to determine if whether infection is accompanied by hyperglucagonemia in non diabetic individuals.*

# REVIEW OF LITERATURE

# HORMONES AND INFECTION

*Many of the non specific generalized host metabolic responses to an infectious process are modulated,by hormonal actions. Alterations in the growth hormone responses following a glucose load have been observed in man during a viral illness (Rayfield etal 1973 a.) and in monkeys during bacterial infections (Rayfield etal 1973 b.).*

*Furthermore, during bacterial and viral illnesses, fasting hyperglycemia, glucose intolerance associated with hyperinsulinemia, hyperglucagonemia and elevated glucocorticoid concentrations have been documented in man (George etal 1974).*

*Beisel (1975) reported that individual endocrine,responses during infection are of variable duration and magnitude.*

** GLUCOCORTICOID RESPONSES:*

*Adrenal steroid changes were measured serially in groups of volunteers throughout the course of experimental infection with pasteurella tularensis. The urinary excretion of corticosteroids was increased during typical acute illness. With the onset of symptoms, 17-hydroxy corticosteroid (17-OHCS) excretion increased progressively to approximately double the control values. Within one day after initiation of streptomycin therapy and prior to the disappearance of*

fever and symptoms, urinary 17-OHCS excretion became normal. Increases in 17-Ketosteroids (17-KS) and pregnanetriol,excretion during illness were less consistent,and smaller in magnitude than those of 17-OHCS (Beisel etal 1967).

They have also observed that during the febrile period of typical tularemia, the normal afternoon diurnal fall in plasma 17-OHCS did not occur. Morning plasma values were, however, unchanged from preinfection concentrations. Furthermore, urinary aldosterone excretion began to rise in conjunction with early symptoms, but, unlike the other corticoids, showed a late peak followed by a gradual return to control values. The alterations in adrenal response were most prominent in volunteers with typical acute illness, and were minimal or absent in those with only mild symptoms (Beisel etal 1967).

The adrenocortical function has been studied in ten subjects suffering from acute infection with high fever. Measurements were performed during the acute stage and again after recovery. In all patients, cortisol secretion was higher during the acute period than after recovery. Urinary 17-ketogenic steroids were also significantly increased during the infection. However, the proportion of secreted cortisol converted into 11-oxy-17-ketogenic steroids was

*significantly lower during the acute stage than after recovery. This suggested that the catabolism of cortisol was modified during acute infection (Cornil etal 1968).*

*Furthermore, cortisol secretion rates have been shown to be above normal in patients with acute bacterial infections and virus encephalitis (Jacobs and Nabarro 1969).*

*However, Beisel and Rapoport (1969) reported that increased secretions of adrenal glucocorticoids begin shortly before the onset of fever. In addition cortisol production is increased during acute infection, but rarely to values greater than two to five times normal.Plasma cortisol measured during morning hours in an uncomplicated systemic infection usually maintains concentrations equal to or only slightly above the normal peak morning values. During acute illness, however, cortisol production appears to lose its circadian nadir, with the result that normal morning,values are maintained throughout the day (Beisel and Rapoport 1969).*

*Although markedly elevated plasma cortisol concentrations are rare during most acute infections, the onset of septic shock or hepatic dysfunction may lead to steadily increasing plasma cortisol concentrations because it is degraded less rapidly. On the*

other hand, glucocorticoid production may cease if an infection is complicated by hemorrhagic infarction of the adrenal cortex (Beisel 1975).

The studies of Melby and Spink have demonstrated that accelerated adrenal secretory activity exists in those patients with severe infection who survive and that even during such severe infection, the adrenal cortex is able to further augment cortisol production following stimulation with A.C.T.H (Melby and Spink 1958).

Patients with primary or secondary impairement, of adrenal cortical function may respond poorly to any acute illness, injury or surgical operations, and unless adequate steroid cover is given circulatory failure with severe hypotension may occur. It seems reasonable therefore to give intravenous steroids to any patient in shock as the result of an acute infectious illness provided suitable antibiotics are being given (Jacobs and Nabarro 1969).

It is reemphasized that patients with severe sepsis who are not responding adequately to standard therapy should be suspected of having adrenocortical insufficiency and treated accordingly (Sibbald etal 1977).

The high level of plasma cortisol in acute medical illnesses results presumably from hypothalamic

stimulation, A.C.T.H. release and increased cortisol secretion by the adrenal cortex (Jacobs and Nabarro 1969). In patients with chronic illnesses and in terminal states, defective hepatic metabolism of cortisol becomes increasingly important in the production of very high levels of plasma cortisol. In acute illnesses, however, pain may be one cause, tissue necrosis may be concerned, but fever is not necessarily associated with an increase of plasma cortisol (Jacobs and Nabarro 1969 ).

Drucker and Shandling (1985) reported that in acutely ill adults, elevated cortisol levels and increased, Cortisol release in response to A.C.T.H.administration,was associated with increased mortality, Survivors had lower mean, initial, and ACTH - induced cortisol levels.

Reported instances of low plasma cortisol levels have been seen most frequently in association with disseminated meningococcemia, probably related to hemorrhagic necrosis of the adrenal glands (Migeon etal 1967). Rarely, plasma cortisol levels have been found to be within the normal range in instances of severe infection and occasionally low (Sibbald etal 1977).

Furthermore, Baue etal (1984) found low normal cortisol levels initially in a population of

adult patients with severe, multiple system injuries, and patients with complications after major thoracic or abdominal surgery. The cortisol levels remained stable throughout the illness, whether the patients survived or not, possibly reflecting ablunted stress response.

Cortisol appears to be a particularly important mediator of stress hyperglycemia (Chernow etal 1982). Glucocorticoids derived from the adrenal gland are important mediators of the body's stress response. Peripheral effects of glucocorticoids include, enhanced hepatic gluconeogenesis, decreased insulin secretion, reduced peripheral glucose uptake, enhanced amino acid uptake by the liver, diminished immune and inflammatory response and improved myocardial, contractility and vascular response to exogenous catecholamines. Glucocorticoid - mediated responses to stress are usually adaptive. Indeed, the lack of an adequate glucocorticoid response to severe illness, such as meningococcal sepsis, may be harmful, resulting,in hypoglycemia, hypotension and other manifestations of Addisonian crisis (Weise and Zaritsky 1987).

* <u>GROWTH HORMONE RESPONSES</u>:

Arise in plasma human growth hormone, not suppressed by glucose infusion,has been shown to occur within two hours after the administration of bacterial

pyrogen to patients with intact anterior pituitary function (Kohler etal 1967).

Frohman etal (1967) demonstrated also that pseudomonas endotoxin (Piromen) Stimulated the secretion of growth hormone as well as ACTH in man. Since neither clinical symptoms nor elevations of plasma growth hormone concentration occur until 1 hour after piromen injection, they are probably the result of secondary metabolic changes rather than a direct effect of the pyrogen itself.

Furthermore HGH, in common with ACTH, undergoes, hypersecretion in response to infectious illness. The observation of a detectable increase several hours prior to the onset of any clinical symptoms or fever gives evidence that the response of HGH is not secondary to either fever per se or the presence of acute clinical illness. It is of interest that the first detectable increase in this hormone occurred prior to the onset of illness, at a time when heightened protein anabolism has been observed to occur. On the other hand the restoration of catabolic losses during the convalescent,period following the illness was not accompanied by adetectable increase in HGH (Beisel etal 1968).

As regards viral infections a glucose load in man during the febrile but not the incubation period of sand fly fever demonstrated the acute development of