ADRENAL RESERVE
IN
SOME COMMON INFECTIOUS DISEASES

THESIS

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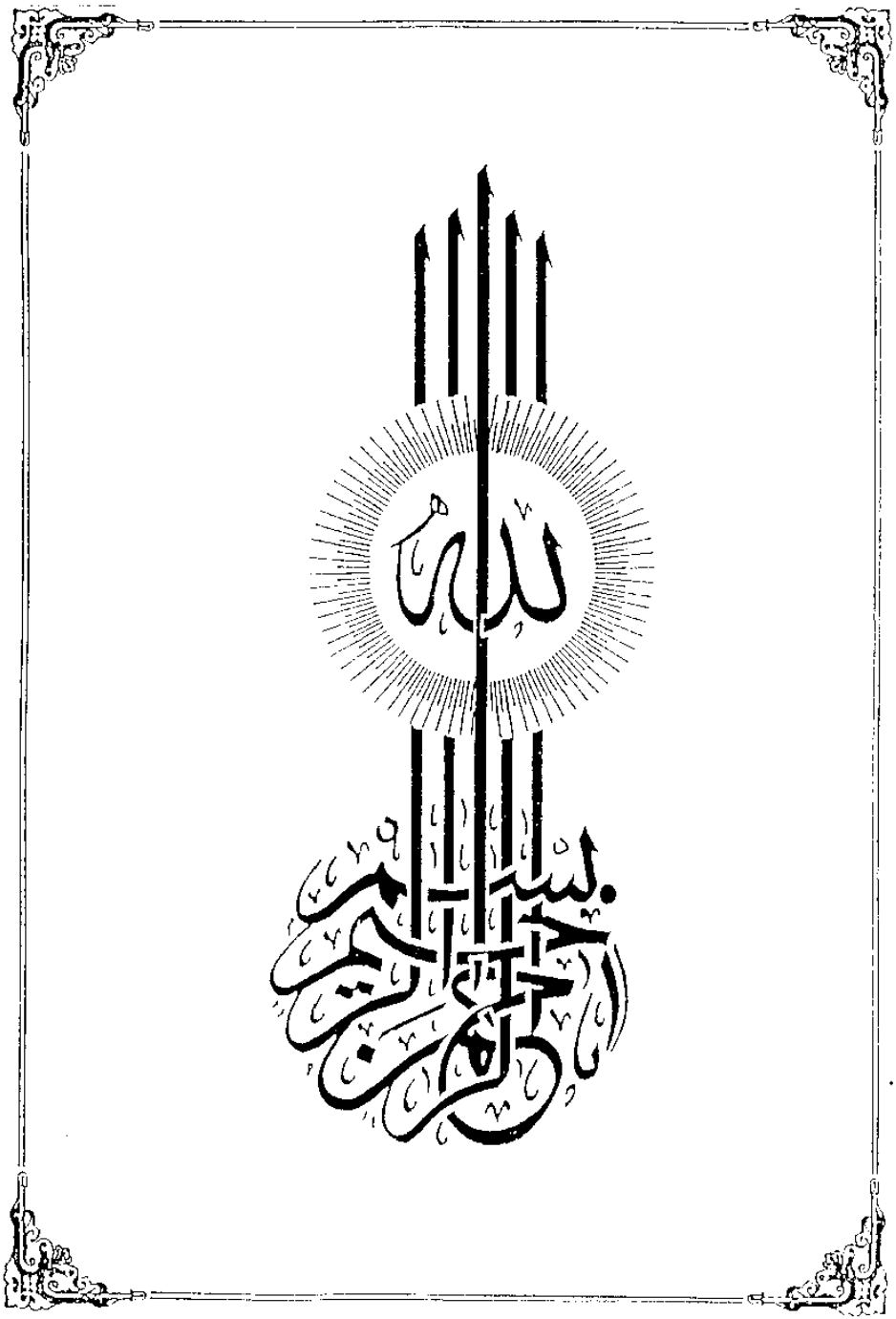

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The protective role of normal adrenocortical function in infectious illnesses is well known. Increased susceptibility to infections is the most common cause of crisis in patients with Addison's disease, on the other hand, infectious illnesses rank as major causes of death in patients with Cushing's disease. It is then concluded, that the human host does fare best, when his own pituitary-adrenal axis is normally responsive.

The aim of this work, is to estimate some adrenocortical functions in some common infectious diseases, namely, acute meningococcal meningitis and typhoid fever.

REVIEW OF LITERATURE

THE NORMAL ADRENAL CORTEX

EMBRYOLOGY

During the 4th to 6th weeks of fetal life, cells from the coelomic mesoderm of the posterior abdominal wall near the mesonephros form a cluster between the root of the mesentery and the genital ridge to establish the fetal adrenal cortex. Five weeks later, small basophilic cells appear around the fetal cortex, these are the forerunners of the permanent adrenal cortex.

The adrenal glands are relatively large structures during fetal life and undergo rapid involution during the 1st few monthes of extra-uterine life (Villee, 1972).

The fetal cortex is ACTH-dependent and is relatively small in abscence of a functioning pituitary.

ANATOMY

The adrenal glands are paired, convoluted, somewhat pyramidal structures that are situated atop the kidneys. The outer portion or cortex is firm and golden yellow; the inner portion or medulla is soft and reddish brown in colour. Normally, each gland weighs about five grams. The adrenals

are supplied by numerous small arteries arising from the phrenic, the aorta and the renal arteries and occasionally by branches from the ovarian, spermatic or intercostal arteries as well. These vessels penetrate the gland along connective tissue trabeculae and break up into a network of sinusoidal capillaries that extend radially into large venous lacunae in the medulla. Venules collect into a large central vein that runs as an axis through the gland and empties on the left into the renal vein and on the right into the inferior vena cava. Anatomic variations are relatively common.

HISTOLOGY

The human adrenal has three zones; an outer zona glomerulosa, a middle zona fasciculata, and an inner zona reticularis. The narrow subcapsular zona glomerulosa consists of relatively small, compact cells grouped in ill-defined clusters. Electron microcopy reveals elongated mitochondria with transverse shelflike infoldings of the inner mitochondrial membrane (cristae). The wider zona fasciulata consists of larger lipid-laden cells radially arranged in parallel cords. Here the mitochondria are more nearly spherical, and the cristae appear as short tubular invaginations of the

inner membrane. The zona reticularis consists of anastomosing networks of cells that resemble those of the zona fasciculata except for the fact that they contain less lipid. Here the mitochondria are elongated and contain a mixture of tubular and flattened cristae. Differences in mitochondrial morphology are thought to be of aid in determining the origins of cells in adrenal neoplasms.

PHYSIOLOGY

Biological effects of glucocorticoids:-

Glucocorticoids are so termed because they have distinct effects on carbohydrate metabolism including promotion of gluconeogenesis, liver glycogen deposition and elevation of blood glucose concentrations. Of the naturally occuring steroids, cortisol is found to be the most potent as regards the glucocorticoid activity.

In addition to their action on carbohydrate metabolism, glucocorticoids also possess the following biologic properties:-

1. Protein-wasting activity:- Glucocorticoids accelerate the breakdown of proteins such as albumin. They inhibit amino acid uptake and protein synthesis by many extrahepatic tissues. Glucocorticoids accelerate the uptake of amino

acids by the liver, which utilizes some of them to synthesize albumin. But the liver also deaminates amino acids to form urea and substrates for energy metabolism, and this process is accelerated by glucocorticoids (gluconeogenesis).

2. ACTH-suppressing activity:- All glucocorticoids suppress the synthesis and secretion of ACTH. There is experimental evidence indicating that this action of the steroids is exerted, at least partially, at the level of the pituitary itself, but it is possible that glucocorticoids also act to suppress corticotropin-releasing factor (CRF).

3. Anti-inflammatory activity:- When present in supraphysiologic amounts, glucocorticoids inhibit inflammatory and allergic reactions. There are of course, many components to the inflammatory response to tissue injury, and glucocorticoids act to suppress the response at multiple points. Glucocorticoids have been shown to stabilize lysosomes; these are intracellular packages of proteolytic enzymes that, when released as a consequence of cellular injury, cause damage to neighboring cells. Glucocorticoids inhibit the diapedesis of leukocytes across capillary walls and their migration through tissues. They inhibit granuloma formation. As a consequence of these actions, glucocorticoids may interfere with host responses to bacterial

infection and suppress delayed sensitivity reactions. Closely related to their anti-inflammatory actions are the immunosuppressive actions of the glucocorticoids. These steroids are lympholytic. They cause decreases in circulating lymphocytes and diminish the size of lymph nodes, thymus, and spleen. Antibody production is decreased.

4. Miscellaneous activities:- Glucocorticoids also have a multitude of other activities, including the induction of several enzymes, stimulation of hematopoiesis, promotion of fat deposition in faciocervicotrunkal areas, promotion of uric acid excretion, facilitation of free-water excretion, promotion of appetite, reduction of circulating eosinophils, and maintenance of muscular work capacity.

Cortisol synthesis:-

All adrenal steroids are derived from cholesterol, either synthesized within the adrenal from acetate, or extracted from arterial blood. The cholesterol side chain is cleaved, removing a 6-carbon fragment. The product of this reaction is 5-pregnenolone, a precursor of all further steroidogenesis. In the synthesis of cortisol, pregnenolone is hydroxylated to 17α-hydroxypregnenolone followed by dehydrogenation of the 3-hydroxyl group and isomerization to 4-5 unsaturation. 17α-hydroxyprogesterone is

then sequentially hydroxylated at the 21 and 11 β positions to form 11-deoxycortisol (compound S) and cortisol (Hydrocortisone or compound F)..(Saba and Hechter, 1955).
The sequence of these reactions is not constant, particularly with regard to dehydrogenation, which may occur before the 17α-hydroxylation reaction.

Cortisol transport:-

Cortisol is bound in plasma to corticosteroid-binding globulin (CBG), anα-globulin synthesized in the liver. Only a small fraction of circulating cortisol is free and biologically active. Increased estrogens enhance CBG synthesis which results in elevated levels of circulating cortisol. Free hormone levels are unchanged, however, and no metabolic abnormality ensues (Doe et al., 1960). Conversely, there are decreased CBG levels in liver disease and in the nephrotic syndrome, and while cortisol levels decrease,free (effective) hormone levels are normal (Musa et al., 1967).

Catabolism of cortisol:-

The half-life of cortisol is approximately 90 minutes. Binding to CBG serves to protect cortisol from more rapid metabolism. Catabolism occurs in the liver and a variety of metabolites have been described. Tetrahydrocortisone and tetrahydrocortisol are the most prevalent, but cortols ,

cortolones, 6 β-hydroxycortisol, and 17-ketosteroids are also formed. The tetrahydro derivatives are conjugated with glucuronic acid which allows for their rapid renal excretion (Peterson, 1971).

Control of cortisol secretion:-

Cortisol secretion is regulated by the central nervous system. Centers within the central nervous system control the elaboration of CRF by the hypothalamus. CRF is carried in the hypothamic-hypophyseal portal system to the anterior pituitary where it directly stimulates the release of adrenocorticotropic hormone (ACTH). ACTH, a polypeptide with 39 amino acids has its major physiologic effect in stimulating cortisol secretion and release by the zona fasciculata of the adrenal cortex. Like other protein hormones, ACTH binds to membrane receptors linked to adenyl cyclase, resulting in generation of intracellular cyclic AMP which acts as a second messenger (Boyd and Tazeciak, 1973). Upon exposure of adrenal cells to ACTH or cyclic AMP, cellular metabolism is increased, cholesterol is extracted from plasma, cortisol synthesis is enhanced, and cortisol is secreted into the systemic circulation

Diurnal variation:-

Daily cortisol secretion is characterized by increased activity in the early morning hours and inactivity in the late

evening hours (Krieger et al., 1971). The source of this diurnal variation is the central nervous system, and ACTH is also secreted in a diurnal fashion (Gallagher et al., 1973). Sudden changes in sleep-wake patterns do not affect the diurnal pattern, but a permanent change in daily sleeping habits will result in a gradual shift of the diurnal pattern (Orth et al., 1967).

Secretion of ACTH and cortisol is episodic. Hormonal release occurs in "puffs" and between times there is no release of hormone. Most of these "puffs" occur in the early morning hours, accounting for the usual diurnal pattern (Krieger et al., 1971 and Gallagher et al., 1973).

Cortisol feedback:-

Under normal circumstances, plasma cortisol levels play a major role in controlling the amount of CRF and ACTH released. Thus, adrenal failure and low circulating glucocorticoid levels result in marked elevations of ACTH secretion, while administration of exogenous cortisol will suppress pituitary secretion of ACTH (Bethune et al., 1957). Small doses of corticosteroids will suppress the morning diurnal rise in ACTH.