CORTICOSTEROIDS IN PEDIATRICS

THESIS

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of the Master Degree of
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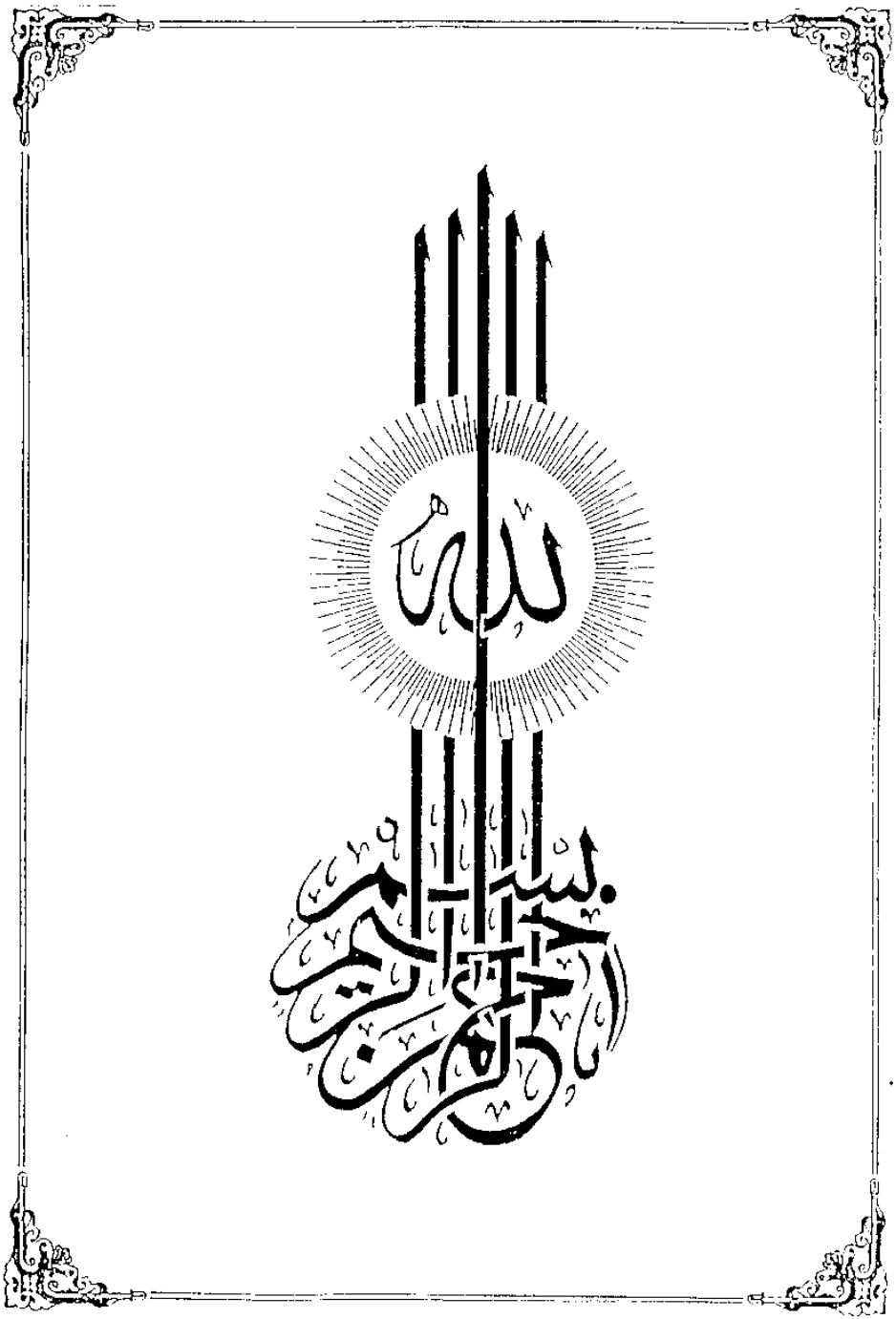

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INTRODUCTION :-

Corticosteroids are valuable agents in a great number of diseases in children.

Although they are a double weapon therapy, corticosteroids when carefully administered they form a magic therapy when indicated. (Avery, 1963).

Since the first revelation of its remarkable properties, corticosteroids have been tried for almost every group of ailments included in modern medical texts and have been to be effective in more than one hundred clinical syndromes. (Applezweig, 1962).

It soon becomes apparent that corticosteroid discovery had opened a treasure chest to the possibility for treatment of certian crippling and fatal diseases of unknown etiology, but simultaneously had opened a great box of anxieties for clinicians in the form of accidents resulting from undesirable side effects. However, high hopes for elimination of toxicity have not been fulfilled. For this reason, it can not be over-emphasized that the corticosteroids, in pharmacological doses, are powerful drugs with slow cumulative toxic effects on many tissues, which may be inapparent until made manifest by a catastrophe.

The net result of world-wide investigations has been an advance of the greatest magnitude in understanding of the physiology, pharmacology, and therapeutic usefulness of these unique double weapon drugs.

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AIM OF THE ESSAY

This essay aiming to study the physiology, pharmacology, clinical syndromes related to corticosteroids as well as their therapeutic indications in children.

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- Applezweig, N., Modified Corticoids, 1st ed., Mc Graw-Hill Book Company, p.103, 1962.

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CORTICOSTEROID SYNTHESIS

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Corticosteroid Synthesis

The adrenal cortex begins to form in the fetus at the 6th week of gestation from the mesoderm of coelomic epithelium and the adjacent mesenchymal cells. Gradually, the cortex differentiates into fetal zone(a broad zone next to the medulla) and adult zone(a thin subcapsular zone). After birth the adult zone gradually develops into the permanent adult cortex whereas the fetal zone rapidly degenerates (Symington, 1969).

The adult zone is differentiated into the three zones; glomerulosa, fasciculata and reticularis.

Accessory adrenal gland (usually cortex only) may be present near the kidneys or in the retroperitoneal area or in relation to organs of reproduction.

The adrenl gland have an abundant blood supply derived from the abdominal aorta, inferior phrenic and renal artries. No innervation of the cortex (Warwick and Williams, 1973).

Neither the placenta nor the fetus alone has all the enzymatic system necessary for the synthesis of the large quantity of oestrogen produced during pregnancy.

They complement each other by the transport of intermediate steroids between them.

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Cholesterol, derived from the mother, is converted by the placenta to pregnenolone which acts as a precursor for progesterone(formed by the placenta) and oestrogen precursor steroids(formed by the fetus).
Some of the progesterone,formed by the placenta,passes to the fetus where it is used by fetal adrenal gland to form cortisol and corticosterone (Diczfalusy,1969).

The fetal zone is deficient in enzyme 3B-hydroxydehydrogenase, so has no ability to convert pregnenolone to progesterone and consequently depends on placental progesterone.

The adult zone shows a gradual increase in 3B-hydroxydehydrogenase activity. So by the time of birth, the normal infant is capable of independent survival in that the entire synthetic pathways of cortisol, corticosterone and aldosterone are present (Job and Chaussain,1981).

It must be noted that cortisol can cross placenta to the fetus . So, fetal cortisol is partly fetal and partly maternal.

The difference of cortisol levels between mother and her fetus(lower in the fetus)may be easily explained by the

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lower blood level of CBG in the fetus (Seron-Ferre et al., 1978).

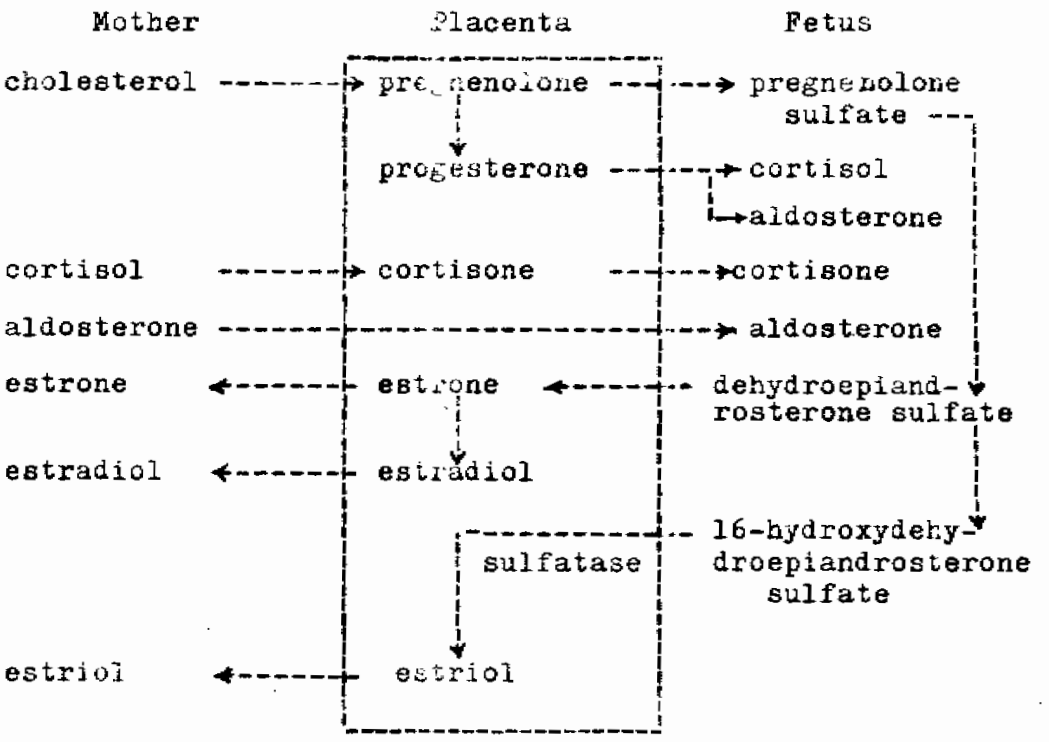

Figure 1:-

The main exchange of steroids among mother, placenta and fetus (Liggins, 1970).

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Corticosteroids in Cord Blood

In new-born infants the plasma transcortin (corticosteroid binding globulin) level is lower than older children and adults, even much lower than the level in the mother (about $\frac{1}{3}$ of maternal transcortin level) . However, free cortisol level is similar when expressed on the basis of surface area (Kenny et al., 1966). The plasma levels of transcortin from infants born vaginally are also higher than in those delivered by elective caesarean section, as vaginal delivary might be more stressful to the infant as well as to the mother and hence provokes a response from infant's adrenal gland plus cortisol transported to the infant via the placenta from stressed mother.

The cortisol:cortisone ratio in cord blood is about 0.7:1(persists for about 2 weeks after delivary), whereas in the maternal blood this ratio is 11:1.

The level of corticosterone in cord blood is also high (Forsyth, 1981).

Corticosteroid Synthesis:

Corticosteroids in the body are derived from cholesterol by a series of enzymatic reactions occuring in the adrenal cortex.

Cholesterol is synthesised directly from acetate, but

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cholesterol from other sources (e.g.from the liver) is also utilised.

The enzymatic reactions are shown in figure (2)

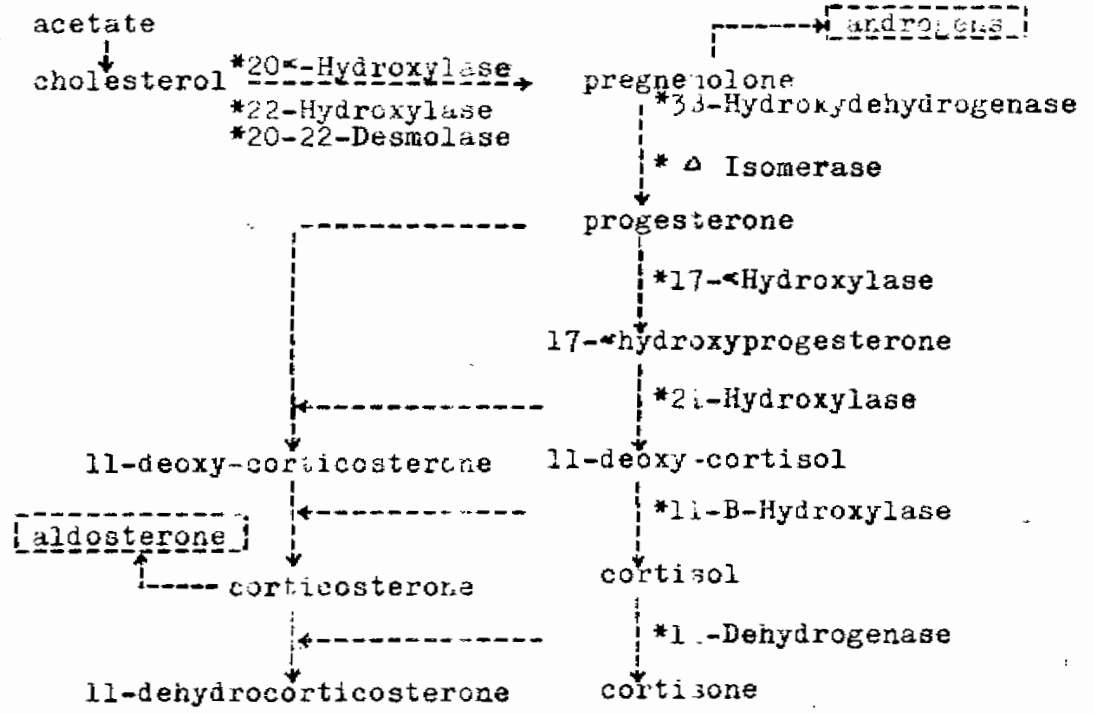

Figure 2: The enzymatic reactions involved in the synthesis of corticosteroids.

Great number of corticosteroids have been isolated from adrenal tissues, but the only corticosteroids normally secreted in significant amount are cortisol and corticosterone. Corticosterone has 1/3 time glucocorticoids activity of cortisol. Cortisol predominates in man(Grodsky,1977).

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Control of Corticosteroid Secretion:- (figure 3)

Nervous impulses from higher centres stimulate the median eminence of the hypothalamus to produce corticotrophin releasing factor (CRF), which is transported to anterior pituitary gland by a vascular connection.
The anterior pituitary gland secretes corticotrophin (ACTH), which is transported by blood stream to the adrenal cortex where ACTH stimulates the production of corticosteroids and adrenal androgens.
The level of cortisol production is involved in a feedback mechanism in that cortisol inhibits the hypothalamic release of CRF (Fleischer and Vale, 1968)

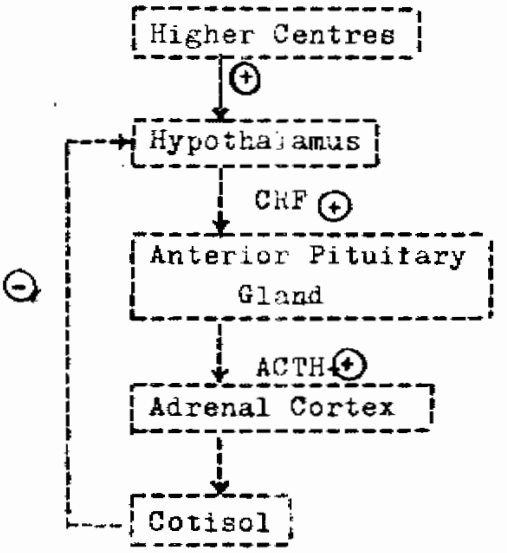

Figure 3; The control of corticosteroid secretion

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This mechanism maintains a normal level of cortisol secretion, but during stress there is increase in excitatory impulses from the hypothalamus leading to an increased cortisol secretion rate

The fetal hypothalamic-pituitary-adrenal axis (HPA-axis) is active from 3rd or 4th month of pregnancy. ACTH from fetal pituitary gland stimulates the adult zone and plays a less important role in the maintenance of the fetal zone.

It appears that ACTH alone, however, does not produce the total physiologic response observed in fetal adrenal growth and steroid secretion since it has been demonstrated that there is a continuous decrease in the concentration of ACTH in fetal plasma as human pregnancy advances (Winters et al.,1975).

ACTH production from fetal pituitary gland increases before birth leading to an increased cortisol secretion from adult zone, maternal ACTH does not cross the placenta to the fetus(Lanman.,1962).

As maternal cortisol may cross to the fetus we can suspect that administration of corticosteroids(only-

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Corticosteroids in The Blood and Distribution in The Body:-

Cortisol in blood is present eitner bounded to plasma protein(94%) or in th. free form (6%).
The free form is the active form and the bounded form is a reserve.The protei. which bound cortisol is called transcortin,a specific glycoprotein, but if the plasma cortisol level is elevated some cortisol will bound to albumin and furthur increase of cortisol will be free in the plasma(The biologically active form).

Transcortin could pass from the blood to the extracellular space allowing distribution of corticosteroids to various body compartment (Migeon,1968).

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