Sex Hormones
Biochemistry, Physiological Pathways, Methodology, And Clinical Disorders

Essay Submitted for Partial Fulfilment of Master Degree

In Clinical and Chemical Pathology

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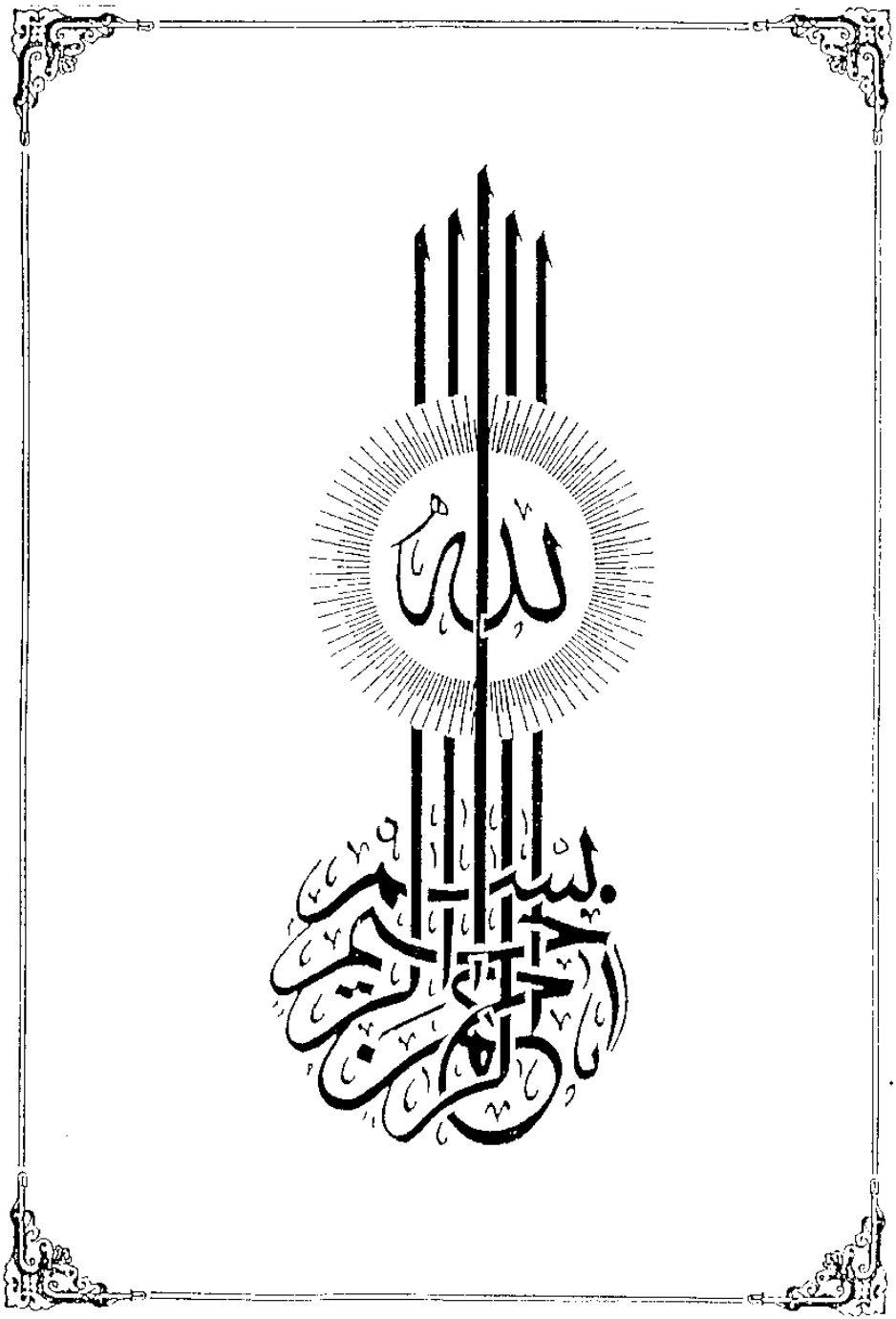
To My Parents
The First Teacher in My Life



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CONTENTS

INTRODUCTION

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In Both sexes, the gonads have a dual function: The production of germ cells (gametogensis) and the secretion of sex hormones. The testes secrete large amounts of androgens principally testosterone which induce secondary sex characteristics typical of the male.The ovaries secrete large amounts of estrogens which stimulate typical female secondary sex characteristics and as well growth and development of the female reproductive organs. progesterone is another steroid sex hormone secreted by the ovaries and has a special function in preparing the uterus for pregnancy.

The secretory and gametogenic functions of the gonads are both controlled by the secretions of the anterior pituitary gonadotrophins FSH and LH. The sex hormones act as a feed back throughout the hypothalamus to inhibit gonadotrophin secretion *(Ganong 1977)*.

Any disturbance in the level of these hormones may result in many disease states in both sexes as infertility, hypogonadism, amenorrohea and hirsutism.

Thus the laboratory determination of sex hormones is essential to diagnose many different diseases *(Chattoraj et al 1986)*.

Aim of the Work:

I. The aim of this work is to write an essay on:

Biochemistry, physiological pathway, methodology and clinicopathological conditions on the following sex hormones.

1. Testosterone
2. Estrogens.
3. Progesterone.

II. To discuss the precision and accuracy of the clinical laboratory methodologies of the above mentioned sex hormones.

REVIEW OF LITERATURE

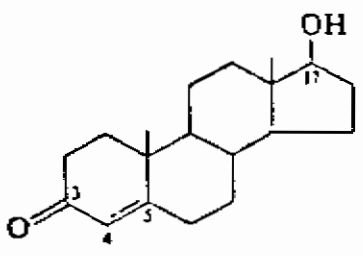
[A] ANDROGENS

1. *Chemistry and Types*

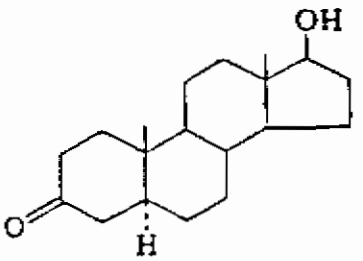
Androgens are a group of C_{19} steroids which exert profound influence on the male genital tract. They are concerned with the development and maintenance of secondary male characteristics, hence they are called male sex hormones. Testosterone is the principal member of androgens.

The structural characteristics of this steroid are unsaturated bound between C_4 and C_5, a ketone group at C_3 (Δ^4-3-keto), and a hydroxyl group in the β position at C_{17}. The hydroxyl group in the 17 β position as well as the oxygen atom in the C_3 position are essential for biological activity *(Chattoraj, 1976 & Roy, 1980)*. The formulas of testosterone and dihydrotestosterone are shown in Fig. (1) from *Chattoraj (1976)* .

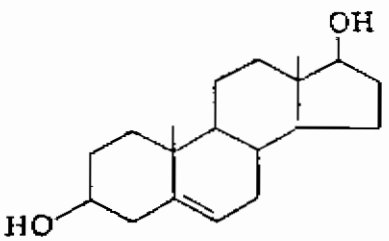
There are many different androgens, which have widely differing biological activities. They are to a considerable extent interconverted after secretion. Several structural modifications of the basic steroid nucleus are required to enhance androgenic activity *(Roy,. 1980)*. Testosterone is biologically the most active steroid, while andro-stenedione is considered as an intermediary metabolite which is likewise intermediate in potency between testosterone and androsterone *(Tatt and Horton, 1966)*.



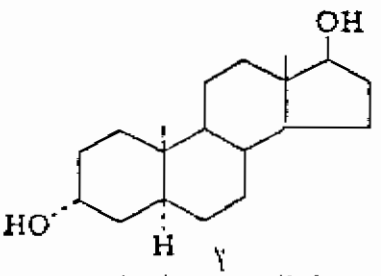
Testosterone
(17β-hydroxyandrost-4-en-3-one)



Dihydrotestosterone
(17β-hydroxy-5α-androstan-3-one)



Androstenediol
(3β,17β-dihydroxyandrost-5-ene)



Androstanediol
(3α,17β-dihydroxy-5α-androstane)

Fig. (1) Chemical structure of androgens

Dihydrotestosterone (DHT) is practically not secreted as such but originates from peripheral conversion of androstenedione and to a minor extent of testosterone *(Lto and Horton, 1971)*. It reflects therefore, an essential peripheral formation of androgens *(Vermeulen, 1980)*. This transformation occurs when the hormones enter the cells of most androgen sensitive tissues *(Mahoudean et al., 1971)*.

Dehydroepiandrosterone (DHEA) is secreted in large amounts (about 80%) from the adrenal cortex as sulphate ester and as free alcohol form *(Bird et al. 1978 & Vermeulen, 1980)*.

2. Biosynthesis of Androgens

Testosterone is the major androgen produced by the testis and its primary site of synthesis is the Leydig cells. Other sites of synthesis in the body are the adrenal glands, in addition to the ovaries in females.

a. Testicular androgens

i. Cytoarchitecture of the testis

Interstitium and seminiferous tubules. The interstitium contains blood vessels, lymph vessels, fibroblasting supporting cells, macrophages, mast cells, and Leydig cells. The interstitium occupies about 34% of the testicular volume of human testis, of which the Leydig cells

account for about 5-12% *(Christensen, 1975 and Kaler & Neaves, 1978)*.

According to *Kaler and Neaves (1978)* human Leydig cells at the light microscopic level appear as rounded or polygonal cytoplasmic profiles staining with the periodic acid-Schiff reaction and often containing a round nuclear profile with nucleolus, scattered individually or in clusters throughout the testicular interstitium. *Christensen (1975)* described the ultrastructure of the human Leydig cell as characterised by prominent mitochondria, abundant smooth endoplasmic reticulum, scattered patches of rough endoplasmic reticulum, and lipid droplets.

The seminefrous tubules contain germinal elements and supporting cells. The supporting cells include the sustentacular cells of the basement membrane as the sertoli cells. The germinal elements comprise a population of epithelial cells including a slowly dividing primitive stem cell population, the rapidly proliferating spermatogonia spermatocytes undergoing meiosis and the metamorphosing spermatids.

ii. Testicular androgen synthesis.

In Leydig cells, testosterone is synthesized from cholesterol or directly from active acetate acetyl co-enzyme A *(Guyton, 1981)*.

Cholesterol is probably synthesized from acetate rather than being derived from dietary cholesterol in the blood *(Dennick, 1972)*. The testicular biosynthesis of cholesterol from acetate occurs in the endoplasmic reticulum and involves the usual intermediates of cholesterol formation such as mevolate, squalene and lanosterol *(Dennick, 1972)*.

Normally, 95% or more of the cholesterol in the testis is present in an unesterified form *(Van der Molen et al., 1972)*. The newly formed cholesterol from acetate mixes with the pool of free cholesterol used for testosterone synthesis. Production of testosterone may also require hydrolysis of cholesterol esters under the influence of luteinizing hormone (LH) *(Pokel et al., 1972)*.

There are five enzymatic steps necessary for the conversion of cholesterol to testosterone. Three of these enzymes 20,22-desmolase, 3 β hydroxysteroid dehydrogenase and 17-hydroxylase, are common to the synthesis of adrenal hormones as well as androgens. The other two enzymes 17,20 desmolase and 17 β hydroxysteroid dehydrogenase are unique to the pathway of androgen synthesis *(Walsh and Amelar, 1977)*.

In the presence of the appropriate hydroxylating enzymes 20 α hydroxylase, 22 hydroxylase and 20,21 desmolase, the cholesterol is converted into 20 α hydroxy-cholesterol. It

is acted upon by 20-desmolase enzyme which causes side chain cleavage and formation of pregnenolone *(Bardin and Paulsen, 1981)*. The cholesterol side chain cleavage activity is probably located in the mitochondrial membrane *(Van der vusse et al., 1975)*, and requires nicotinamide adenine dinucleotide phosphate (NADP), molecular oxygen, an enzyme system containing cytochrome p450, a flavoprotein, and a non heme-iron protein *(Oshima et al., 1977)*. It is regulated by the luteinizing hormone (LH) which may act by enhancing the association between cholesterol side chain cleavage cytochrome p450 system in the mitochondria *(Mason et al., 1973)*.

The androgen biosynthesis now proceeds along two major pathways. One of them is the delta 4,3 ketosteroid (Δ4) pathway with the intermediates progesterone, 17-OH-progesterone, Δ4-androstenedione. The other one, along delta-5, 3 β hydroxy (Δ5) pathway, with the intermediates (17-OH-pregnenolone, dehydro-epiandrosterone androstenediol) *(Hall, 1979)*. In man, the major pathway of testosterone biosynthesis is via the Δ5 pathway, while in other species it proceeds via the Δ4 pathway *(Bardin and Paulsen, 1981)*.

In Δ5 pathway, pregnenolone is converted into 17-OH-prenenolone by the action of 17-hydroxylase enzyme, then in the presence of 17,20-desmolase enzyme, the side chain of C_{17} position of the last compound is cleaved off giving rise to