T E S T O S T E R O N E

THESIS

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By

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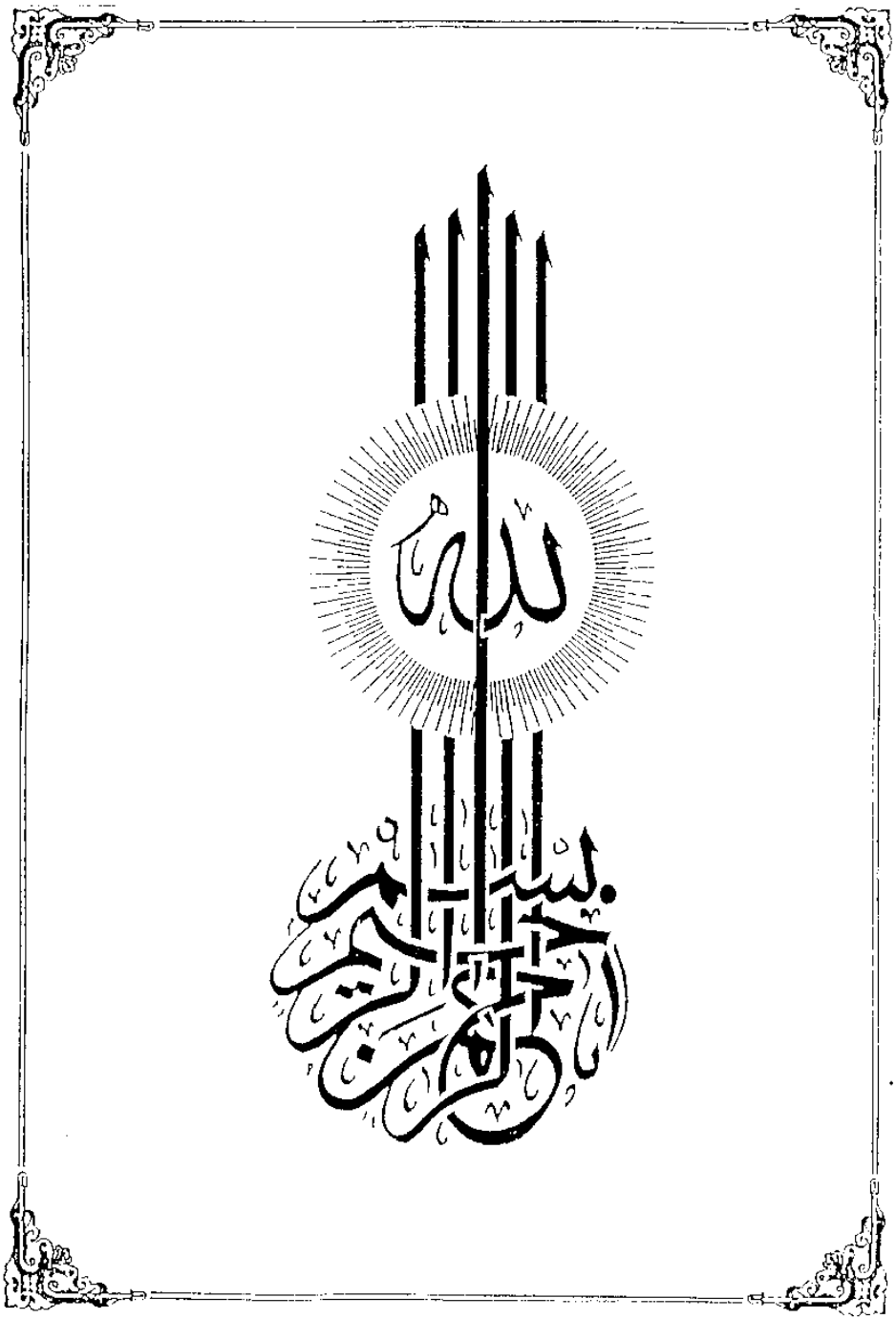

ABBREVIATIONS

ABP	: Androgen - binding protein
cAMP	: Cyclic adenosine monophosphate
ATP	: Adenosine triphosphate
C	: Carbon atom
Ca	: Calcium
DHEA	: Dehydroepiandrosterone
DHT	: Dihydrotestosterone
Dl.	: =100 ml
DNA	: Deoxyribonucleic acid
FSH	: Follicle-stimulating hormone
GnRH	: Gonadotropin-releasing hormone
HCG	: Human chorionic gonadotropin
HMG	: Human menopausal gonadotropin
LDL	: Low density lipoprotein
LH	: Luteinizing hormone
MCR	: Metabolic clearance rate.
McRT	: Metabolic clearance rate of testosterone
Mg	: Magnesium
NADP	: Nicotinamide adenine dinucleotide phosphate=CoII
ng	: Nanogram = 1/1000000 mg.
RNA	: Ribonucleic acid
mRNA	: Messenger ribonucleic acid
SHBG	: Sex hormone-binding globulin
	= TeBG: Testosterone-estradiol-binding globulin

CONTENTS

INTRODUCTION

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The testes secrete several male sex hormones, which are collectively called androgens, including testosterone, dihydrotestosterone, and androstenedione. However, testosterone is so much more abundant and potent than the others that one can consider it to be the significant hormone responsible for the male hormonal effects (Guyton, 1981). Crystalline testosterone, the physiologically important androgen secreted by the human testis, was isolated by David; et al., in 1935. In general testosterone is responsible for the distinguishing characteristics of the masculine body. It acts principally to promote the growth, differentiation, and function of the sex organs of reproduction, but significant effects are also exerted on a variety of other body tissues (Goodman, 1980).

The aim of this thesis is to review the literature of the subject of testosterone under the following items:

1. Chemistry and biosynthesis of testosterone
2. Secretion of testosterone.
3. Transport and metabolism of testosterone
4. Actions of testosterone.
5. Control of testosterone production.
6. Relation of testosterone to fertility.

CHAPTER I

CHEMISTRY AND BIOSYNTHESIS OF TESTOSTERONE

Chemistry and Biosynthesis of Testosterone

Chemistry of testosterone:

Testosterone, the principal hormone of the testes, is a steroid hormone (Ganong, 1977). The steroid hormones are generally lipid-soluble compounds. The half-lives of these hormones vary from 60 minutes for testosterone to 100 minutes for cortisol (Federman, 1981). Steroid hormones are lipid compounds. Cholesterol is a predominant sterol in animals, where it can be synthesized from acetate and stored in droplets or incorporated into cell membranes. A number of metabolites of cholesterol are utilized as hormones, including the endocrine secretions of the adrenal cortex, the testes, and the ovaries. The steroid hormones are chemically based on a structure called a cyclopentanophenanthrene nucleus (also called gonane or sterane), containing 4 carbon rings linked together to give a total of 17 carbon atoms. These carbons are numbered consecutively starting from the A-ring (Figure 1). This basic tetracyclic compound is initially synthesized as part of the cholesterol molecule, which has a side chain, containing eight additional

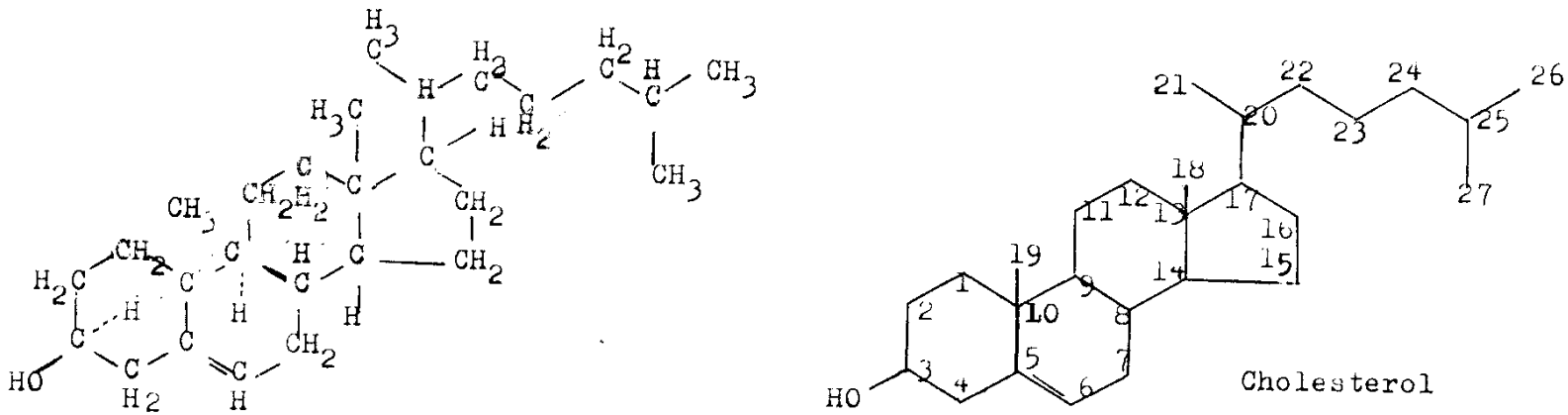

Fig. (1): Chemical structure of cholesterol and the conventional manner of numbering the carbon atoms (Bentley 1980)

carbons, attached at the 17-position. The steroid hormones are formed from the cholesterol by the cleavage of different sections of this side chain and substitution or insertion of various chemical groups at various positions. These modifications are mediated by specific enzymes which are present in the particular endocrine glands (Bentley, 1980).

Testosterone is a C_{19} steroid with a hydroxyl group in the 17 position (Figure 2). It is synthesized from cholesterol in the leydig cells. The biosynthetic pathways in all endocrine organs which form steroid hormones are similar, the organs differing from one another only in the enzyme systems they contain. In the Leydig cells, the 11- and 21- hydroxylases found in the adrenal cortex are absent but 17 α -hydroxylase is present (Ganong,1977).

Biosynthesis of testosterone:

The synthesis of testosterone (Figure 3), is conveniently discussed in three steps as follows:

I . Acetate ⟶ cholesterol
II . Cholesterol ⟶ pregnenolone
III. Pregnenolone ⟶ androgens

(Hall, 1979)

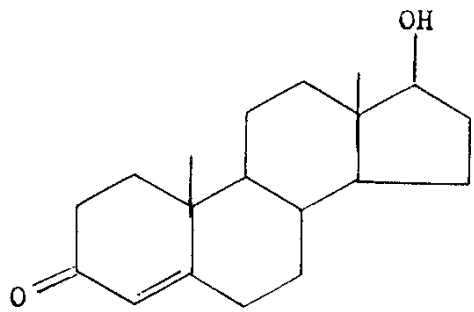

Fig. (2): Testosterone (Hall, et al., 1980)

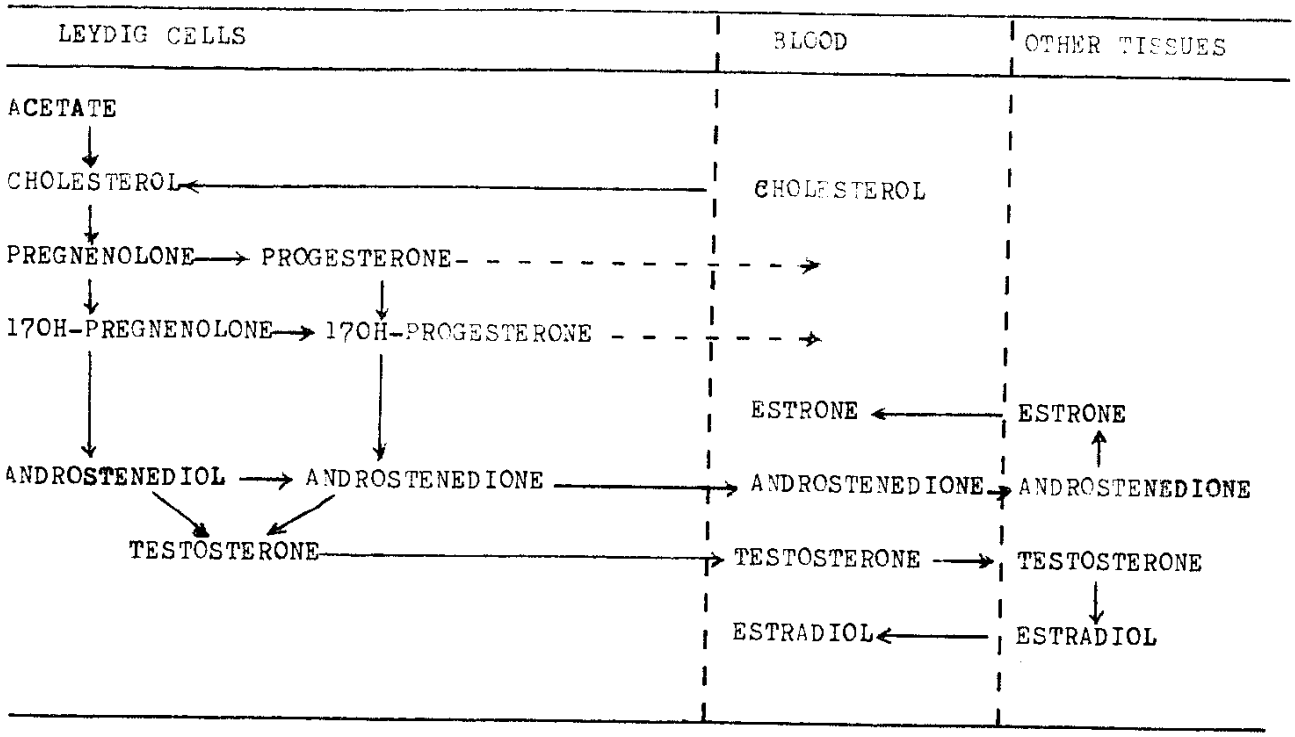

Fig.(3):(Androgen biosynthesis in Leydig cells and estrogen production in non glandular tissues) cholesterol is synthesized in Leydig cells from acetate and is derived from low density lipoprotein (LDL) following its uptake by specific LDL receptors. In man the major pathway of biosynthesis is via the delta-5 pathway, including pregnenolone, 17-hydroxy-pregnenolone, and androstenediol. In other species testosterone biosynthesis proceeds via the delta-4 pathway, including progesterone 17-hydroxyprogesterone, and androstenedione. Testosterone and androstenedione are secreted into the blood and are converted to estrone and estradiol, respectively, at extraglandular sites in multiple tissues. The direct secretion of estradiol by the testis counts for only a small portion of this estrogen which enters the blood (Bardin and Paulsen 1981).

I- Conversion of acetate to cholesterol:

The cholesterol is synthesized from acetate (Fig.4) through a long series of reactions involving acetyl co-enzyme A, mevelonic acid, squalene, lanosterol, symosterol, and desmosterol as some of the intermediates (Villee, 1972).

II- Conversion of cholesterol to pregnenolone:

The conversion of cholesterol to pregnenolone is catalyzed by an enzyme complex found in all tissues producing steroid hormones. The reactions depicted in (Fig.5) are unique to these tissues and occur in the mitochondria. The enzyme complex includes a cholesterol desmolase requiring NADPH, either Mg^{++} or Ca^{++}, and cytochrome P_{450} pregnenolone formed in this manner is the major steroidal precursor of all steroid hormones and exerts a feedback regulatory influence on steroidogenesis from cholesterol by inhibiting the initial hydroxylation of the side chain, which is a rate limiting process in steroid biosynthesis. (White, et al., 1978).

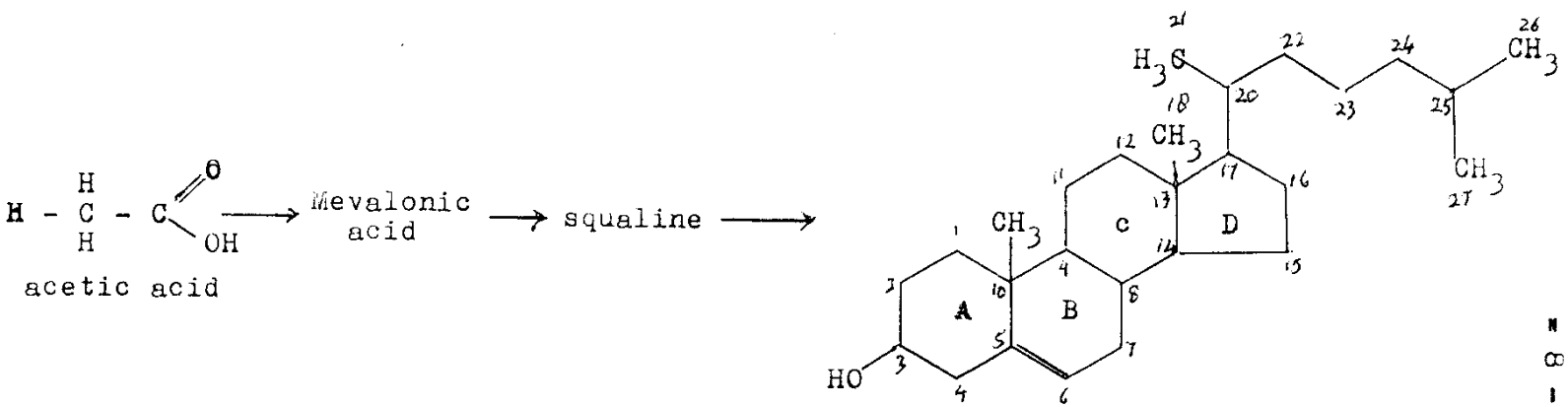

Fig. (4): Conversion of acetate to cholesterol (Bentley, 1980).