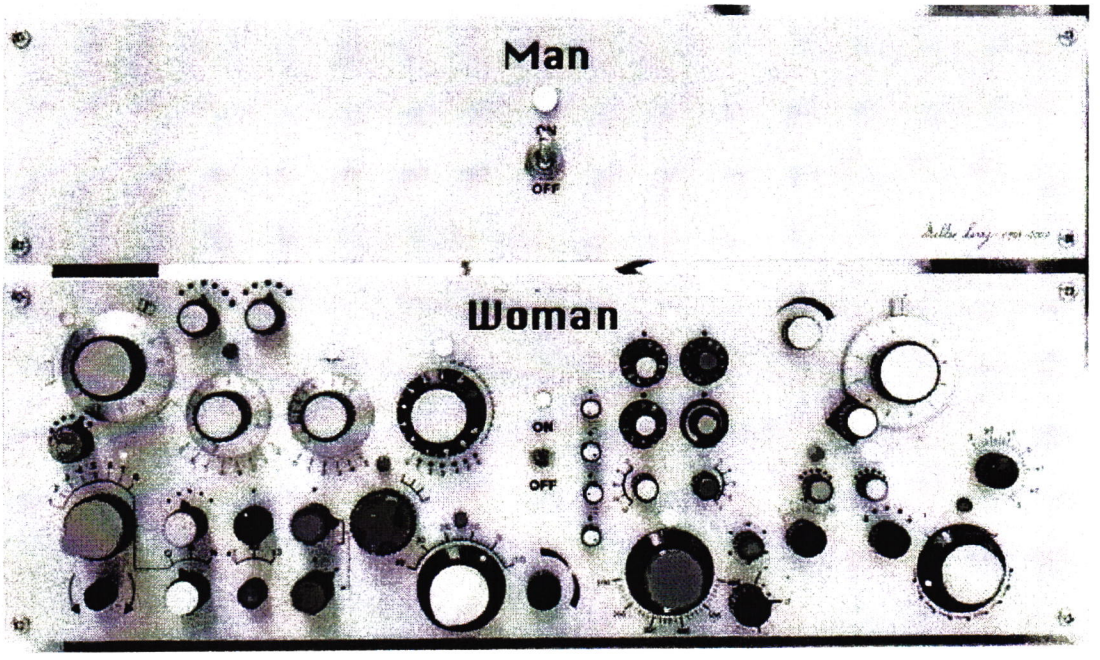
The major emphasis of this lecture is on male sex hormones. This will be followed by a discussion of female sex hormones. In order to prepare you for the difference between these two groups of hormones, the following illustration has been suggested.



I. Androgens -

A. The term androgen is not a specific hormone, it refers to a class of hormones. Some examples of androgens

1. testosterone
2. dihydrotestosterone (DHT),
3. dehydroepiandrosterone (DHEA)
4. androstenediol.

The chemical structures for these androgens are shown in Figure 45-3, page 854 in Kaplan.

B. Androgens are C-19 steroids - which are

1. primarily concerned with the development and maintenance of male sex characteristics.
   - **a.** commonly referred to as the male sex hormones.

2. **The principle and most biologically active androgen is testosterone.**
    a. **Testosterone is primarily produced in the Leydig cells of the adult testes.**
        1) **The testes have two main functions:**
            (a) spermatogenesis, the production of germ cells
            (b) steroidogenesis, the synthesis and subsequent secretion of the androgenic hormones.
    b. Testicular secretion accounts for about 95% of the circulating testosterone present in men.

C. **Androgens in females**

1. levels are 5-10% that of the male
2. Androgens serve as precursors for estrogens and have no other well-defined function in females.
3. An androgen deficiency in females has no known clinical significance other than leading to a decreased estrogen production.
4. Mild to moderate androgen excess disturbs the normal menstrual cycle and leads to excessive facial and body hair.

D. **Androgens in males:**

1. Androgen excess is rarely seen.
2. Androgen deficiency leads to a decreased libido, potency, and infertility.
3. The male fetus has the Y-chromosome, and, as a result, down through the various genetic stages the production of testosterone in the male fetus occurs.
    a. This production of testosterone is necessary for the development of the male reproductive system.
4. In the early fetal period of the developing male, testosterone is produced.
5. As the gestation period continues, the production of testosterone decreases. During the pregnancy, testosterone in the developing male is produced primarily during the first trimester.
6. After this period, (once the male reproductive system has been developed), testosterone is produced in the male at very low levels until about 12 years of age.
    a. During this "dormant" period from -3 months up to 12 years of age, testosterone levels are kept very low due to a negative feedback system.

    b. This negative feedback system is quite complex.
        1) The hypothalamus releases gonadotropin-releasing hormone (GnRH),
        2) GnRH stimulates the adenohypophysis to release FSH (follicle stimulating hormone) and LH (luteinizing hormone).
            a) The primary effect of LH is to stimulate synthesis and secretion of testosterone by Leydig cells.
            b) FSH appears to enhance this by increasing the number of LH receptors on the Leydig cell.

3) Testosterone then exerts a negative feedback effect on LH. At the level of the hypothalamus, many believe that testosterone is converted to estradiol before the negative feedback effect occurs.
   a) The enzyme responsible for this is aromatase. There are known deficiencies of this enzyme; drugs will also inhibit this enzyme.

4) Testosterone does not suppress FSH at physiologic levels.
   a) Instead, the polypeptide inhibin specifically inhibits FSH.
      i. Inhibin is produced by Sertoli cells of the seminiferous tubules. When the seminiferous tubules fail to function, FSH levels rise in the male.

5) Under FSH stimulation, Sertoli cells produce androgen-binding protein (ABP).
   a) ABP maintains locally high concentrations of testosterone in the siminiferous tubules necessary for effective spermatogenesis.
   b) They also synthesize inhibin.

6) Inhibin is not under the direct control of FSH (as in the case in most negative feedback circuits).
   a) Instead, inhibin is dependent on the functional activity of the Sertoli cells, which is dependent upon testosterone.
   b) Only very minute amounts of testosterone and inhibin are necessary to stop the production of FSH and LH.

7. At approximately the age of 12, there is a change in the sensitivity of this negative feedback system in the hypothalamus.
   a. As a result, small amounts of inhibin and testosterone will no longer inhibit the production of FSH and LH, and an equilibrium will be re-established at a higher level for testosterone.
   b. At this point, sexual maturation of the male begins. Therefore, the initial change is not in the testes but in the central nervous system.

E. Testosterone synthesis - In the synthetic pathway for testosterone the conversion of cholesterol to pregnenolone is the rate limiting step.

1. Once testosterone is released into the blood stream, it has to be significantly bound to protein since it is so very lipid soluble. The primary proteins that bind testosterone include:
   a. sex hormone binding globulin (SHBG), - a β-globulin which binds approximately 60% of the testosterone in the blood stream
   b. albumin which binds almost 40%.
   c. Free testosterone - Approximately 2% of the testosterone in the blood stream remains free.
      1) As with other hormones, the free form of testosterone is the physiologically active form.

   d. Hormones and drugs that affect testosterone binding - are important

because they may lead to changes in free testosterone.

1) **When there is a decrease in SHBG,** an increased concentration of free hormone occurs, and an increase in the binding protein leads to a decrease in free hormone concentration.
2) **Excess thyroid hormones and growth hormone** decrease the concentration of SHBG and the concentration of androgens, whereas estrogens and hypothyroidism increase SHBG.
3) **Anticonvulsants** increase SHBG and decrease free testosterone levels.

F. **Testosterone metabolism** - Once testosterone enters the blood stream, it can be converted into two active metabolites as well as inactive metabolites. Refer to Fig. 45-3, page 854 in Kaplan. The formation of estradiol in the lefthand portion of the figure. This is the estradiol referred to earlier as possibly being involved in the negative feedback mechanism.

II. **Androgen Functions in the Blood** - Once androgens enter the blood stream,

A. **The development and maintenance of primary and secondary male sex structures**.

B. **Androgens are anabolic agents,** which means they will promote protein synthesis resulting in increased mass of tissue.

1. The mechanism of action involves the entry of testosterone into the target cell.
2. It is then converted to dihydrotestosterone by the enzyme 5-α-reductase.
3. This dihydrotestosterone then binds with cytoplasmic protein receptors.
4. This complex migrates to the nucleus of the cell and produces the following changes:
   a. increases RNA polymerase activity
   b. increased RNA synthesis (messenger)
   c. increased protein synthesis
5. **As a result, there is an increased mass and primary sex structure growth**
   a. the male becomes sexually mature.
   b. In addition to this affect on the primary sexual structures, the production of testosterone causes the secondary sexual characteristics of the male to develop at the same time.

C. **Effects of testosterone on the males** at puberty

1. **The distribution of body hair.** The primary areas that are usually associated with androgens are on the face and usually on the chest.
   In addition, testosterone decreases the growth of hair on the top of the head.
   a. Theoretically, a man who does not have functional testes does not go bald. However, many men with actively functioning testes never go bald. This is because baldness is a result of two factors:
      1) a genetic background for the development of baldness
      2) superimposed on this genetic background, a large quantity of androgenic hormones
   b. A woman who has the appropriate genetic background and who develops a long-sustained androgenic tumor may also become bald.

2. **The voice.** - At puberty, when this testosterone is beginning to be secreted

again at higher levels, it causes hypertrophy of the laryngeal mucosa and enlargement of the larynx.

a. At first, these effects cause a crackling of the voice which is gradually followed by changes into the typical masculine base voice.

3. **The skin -** Testosterone increases the thickness of the skin over the entire body in addition to increasing the ruggedness of the subcutaneous tissue.
4. **Increases the rate of secretion by the sebaceous glands**. - When the male body first becomes exposed to this increase in testosterone levels, there is an excessive secretion by the sebaceous glands of the face.
    a. **This over- secretion can result in acne**. After several years of testosterone secretion, the skin usually adapts itself to the testosterone level in some way that allows it to overcome the acne.
5. **Testosterone also has an effect on muscle development,** - but there is a complicating factor with cortisol.
    a. **Cortisol stimulates protein catabolism (breakdown).**
    b. **Androgens compete with cortisol to stimulate anabolic activity on protein synthesis,** and therefore increase muscle mass. This increase in muscular development is one of the most important secondary male sexual characteristics developed after puberty.
        1) **Testosterone has often been considered to be a youth hormone** because of its effects on the musculature. It is used on occasion for the treatment of persons who have poorly developed muscles. It is also used illegally as an anabolic steroid.
6. **There are two other general effects of androgens.**
    a. **The first one is that androgens may result in the rearrangement of adipose tissue.** This may be antagonistic to the effects of glucocorticosteroids or cortisol, just as were the effects of androgens in muscle tissue.
    b. **The second general effect is on the bone.** Here androgens have two effects:
        1) increase bone growth
        2) promotes closure of the epiphyseal plates of long bones

D. **Androgen production** - Androgens are produced at normal levels in males up to 60-70 years of age and then their production usually starts decreasing due to a decreased blood flow to the testes.

1. **The production of androgens are not limited just to the testes.**
    a. **Androgens are also produced by the adrenal cortex**. The regulation of the androgens that are produced by the adrenal cortex is under the control of the anterior pituitary hormone ACTH.
    b. **Also, a small amount of androgens are produced by the ovaries.**
        1) In the female, most of the androgens and their precursors are converted to estrogens.
        2) In the ovary, the main androgen is androstenedione.

III. **Laboratory tests for Androgens -** , note that testosterone levels exhibit diurnal variation with concentration being highest between 6:00 and 9:00 am.

A. **There are three main laboratory tests used to evaluate testosterone levels.** These are:
   1. **Zimmerman reaction on a 24-hour urine looking for 17-ketosteroids**
   2. **RIA for testosterone**
   3. **Chemiluminescent assays for testosterone**