Androgenes and Antiandrogenes
Androgens

• The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females.

• **Testosterone** \([tess-TOSS-terone]\), the most important androgen in humans, is synthesized by Leydig cells in the testes and, in smaller amounts, by thecal cells in the ovaries and by the adrenal gland in both sexes.

• **Other androgens** secreted by the testes are 5α-dihydrotestosterone \((DHT)\), androstenedione, and dehydroepiandrosterone \((DHEA)\) in small amounts.

• In adult males, *testosterone* secretion by Leydig cells is controlled by gonadotropin-releasing hormone from the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH.
Figure 26.11
Regulation of secretion of testosterone.
DHT = 5α-dihydrotestosterone; LH = luteinizing hormone.
Testosterone or its active metabolite, DHT, inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates testosterone production.

The androgens are required for:
1) Normal maturation in the male.
2) Sperm production.
3) Increased synthesis of muscle proteins and hemoglobin.
4) Decreased bone resorption.

Synthetic modifications of the androgen structure modify solubility and susceptibility to enzymatic breakdown (thus prolonging the half-life of the hormone) and separate anabolic and androgenic effects.
Mechanism of action:

• Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell.

• Although testosterone itself is the active ligand in muscle and liver, in other tissues it must be metabolized to derivatives, such as DHT.

• For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis, and skin, testosterone is converted by 5α-reductase to DHT, which binds to the receptor.
Therapeutic uses

- Androgenic steroids are used for males with primary hypogonadism (caused by testicular dysfunction) or secondary hypogonadism (due to failure of the hypothalamus or pituitary).

- Anabolic steroids can be used to treat chronic wasting associated with human immunodeficiency virus or cancer.

- An unapproved use of anabolic steroids is to increase lean body mass, muscle strength, and endurance in athletes and body builders.
• **DHEA** (a precursor of *testosterone* and estrogen) has been touted as an **antiaging** hormone as well as a “**performance enhancer.”**

✓ There is no definitive evidence that it slows aging, however, or that it improves performance at normal therapeutic doses.

• **Danazol** [*DAH-nah-zole*], a weak androgen, *is used in the* treatment of endometriosis (ectopic growth of the endometrium) and fibrocystic breast disease.

• **Danazol** also possesses **antiestrogenic** activity.

• Weight gain, acne, decreased breast size, deepening voice, increased libido, and increased hair growth are among the adverse effects.
Pharmacokinetics

Testosterone:

- This agent is **ineffective orally** because of inactivation by first-pass metabolism.
- As with the other sex steroids, *testosterone is rapidly absorbed and is metabolized to relatively or completely inactive compounds that are excreted primarily in the urine.*
- **C17-esters of testosterone** *(for example, testosterone cypionate or enanthate)* are administered intramuscularly.
- The addition of the esterified lipid makes the hormone more lipid soluble, thereby increasing its duration of action.
- Transdermal patches, topical gels, and buccal tablets of *testosterone are* also available.
- *Testosterone and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity.*
Testosterone derivatives:

- Alkylation of the **17α** position of testosterone allows oral administration of the hormone.

- **Fluoxymesterone** [floo-ox-ee-MESS-teh-rone] have a longer half-life in the body than that of the naturally occurring androgen.

- Fluoxymesterone is effective when given **orally**, and it has a 1:2 androgenic-to-anabolic ratio.

- **Oxandrolone** [ox-AN-droe-lone] is another orally active testosterone derivative with anabolic activity 3 to 13 times that of testosterone.

- **Hepatic adverse effects** have been associated with the **17α**-alkylated androgens.
A Testosterone and Its esters

Fluoxymesterone
Methyltestosterone
Oxymetholone

Transdermal patch and cream

Metabolites appear in the urine

B

Serum testosterone (ng/dL)

Application of testosterone patch designed to deliver 5 mg/day

Injection of 200 mg of testosterone enanthate
Adverse effects:

- In females:
  - Androgens can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. Menstrual irregularities may also occur.
  - **Testosterone** should not be used by pregnant women because of possible virilization of the female fetus.

- In males:
  - Excess androgens can cause priapism, impotence, decreased spermatogenesis, and gynecomastia. Cosmetic changes such as those described for females may occur as well. Androgens can also stimulate growth of the prostate.

- In children:
  - Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.
General effects:

- Androgens can increase serum LDL and lower serum high-density lipoprotein levels.
- Whether these changes in the lipid profile predispose patients to heart disease is unknown.
- Androgens can also cause fluid retention, leading to edema.
In athletes:

- Use of anabolic steroids (for example, DHEA) by athletes can cause premature closing of the epiphysis of the long bones, which stunts growth and interrupts development.
- High doses taken by young athletes may result in reduction of testicular size, hepatic abnormalities, increased aggression ("roid rage"),
- major mood disorders, and other adverse effects described above.
Antiandrogens

- Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors.

- **Finasteride** \([\text{fin-AS-ter-ide}]\) and **dutasteride** \([\text{doo-TAS-ter-ride}]\) inhibit 5\(\alpha\)-reductase resulting in decreased formation of dihydrotestosterone.

- These agents are used for the treatment of benign prostatic hyperplasia.

- Antiandrogens, such as **flutamide** \([\text{FLOO-tah-mide}]\), **bicalutamide** \([\text{bye-ka-LOO-ta-mide}]\), **enzalutamide** \([\text{enz-a-LOO-tamid}]\), and **nilutamide** \([\text{nye-LOO-tamid}]\), act as **competitive inhibitors** of androgens at the target cell and are **effective orally** for the treatment of prostate cancer.