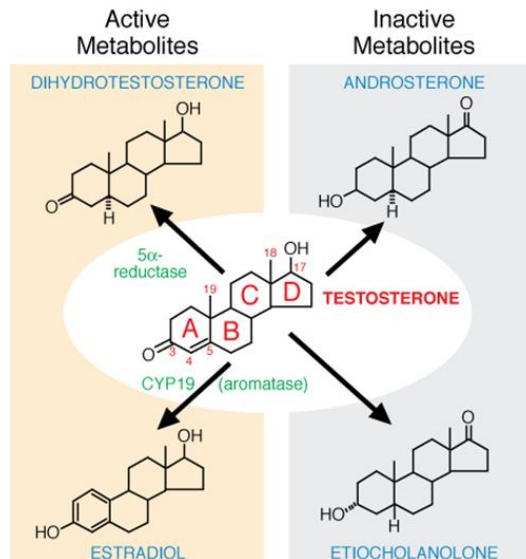




- **Testosterone is the principle androgen in both males and females, but:**
 - **In males:** it is synthesized by leydig cells.
 - **In females:** it is synthesized by corpus luteum and zona reticularis in the cortex of adrenal glands.
- **Synthesis of testosterone (this topic was discussed in previous problems and notes):**
 - **Cholesterol → pregnenolone → 17α OH-pregnenolone → dehydroepiandrosterone → androstendione → testosterone (which is then converted to the more potent form dihydrotestosterone by the enzyme 5α-reductase).**
 - **Notes:**
 - ✓ This process is stimulated by LH which is secreted by adenohypophysis under the stimulation from GnRH.
 - ✓ Testosterone has a negative feedback on the secretion of LH (direct) and GnRH (indirect).
 - ✓ Testosterone secretion is highest in the morning (at about 8 am) → this will diminish as age increases.
 - **Fate of testosterone:**



- **Androgen deficiency in females (especially at menopause) leads to:**
 - Low libido and fatigue.
 - Decreased sense of well-being.
 - Increased susceptibility to bone diseases.
- **What are the therapeutic uses of androgens?**
 - **Male hypogonadism.**
 - **Male senescence:**

Advantages	Disadvantages
<ul style="list-style-type: none"> • Increases bone mineral density. • Decreases fat mass. 	<ul style="list-style-type: none"> • Worsens benign prostatic hyperplasia. • Increases the incidence of prostate cancer.

- **Female hypogonadism.**
- **What are the uses of anabolic steroids?**
 - Chronic wasting conditions (e.g. muscle wasting).
 - Delayed puberty in boys.
 - Men with low levels of testosterone.
 - Elderly males: to increase their libido; protect them from losing their lean body mass and bone mass.



- Gender identity disorder (e.g. enhancing the appearance of secondary male characteristics).
- Growth failure (although the use of growth hormone is better!).
- **Abuse of anabolic steroids is represented by:**
 - Using them in sports!
 - Heterosexual men for cosmetic purposes.
 - Heterosexual women for masculinization.
- **Toxicity of anabolic steroids:**
 - Increased blood pressure (hypertension).
 - Dyslipidemia.
 - Acne.
 - Gynecomastia (development of breasts in males).
 - Liver damage (hepatotoxicity).
 - **Reduced sexual function (VERY IMPORTANT):**
 - ✓ Testicular atrophy.
 - ✓ Reduced sperm production (decreasing fertility!).
 - Stunted growth.
 - Increased risk for cardiovascular diseases.
 - Increased risk for cancers.
 - Psychiatric problems (androgens have an influence in making the person more violent!).
 - **Female-specific side effects are represented by:**
 - ✓ Increase in body hair.
 - ✓ Deepening of the voice.
 - ✓ Enlargement of the clitoris.
 - ✓ Decrease in menstrual cycles.
 - ✓ When taken during pregnancy:
 - ❖ Male features in the female fetus.
 - ❖ Female features in the male fetus (due to negative feedback = inhibition).

- **What are anti-androgens and their uses?**

Inhibitors of secretion	<ul style="list-style-type: none"> • Example: abarelix (it is a GnRH antagonist used in prostate cancer)
Receptor antagonists	<ul style="list-style-type: none"> • Flutamide: for prostate cancer and hirsutism • Spironolactone (aldosterone antagonist): for hirsutism • Cyproterone acetate: for hirsutism
5α-reductase inhibitors	<ul style="list-style-type: none"> • Finasteride: inhibits type-II of the enzyme • Dutasteride: inhibits type-I and type-II of the enzyme • These two drugs are used to treat: <ul style="list-style-type: none"> ✓ Prostatic hyperplasia. ✓ Male pattern baldness. ✓ Hirsutism.

- **Selective estrogen receptor modulators (SERMs):**

- **Pharmacological goals:**
 - ✓ Agonistic actions: bone.
 - ✓ Antagonistic actions: breast and endometrium.
- **Examples:**
 - ✓ Tamoxifen:
 - ❖ Inhibits the proliferation of human breast cancer cells.
 - ❖ Stimulates proliferation of endometrial cells.
 - ❖ Anti-resorptive effect on bone.
 - ✓ Raloxifen:
 - ❖ Anti-proliferative effect on ER-positive breast tumors.



- ❖ Does not cause proliferation or thickening of endometrium.
- ❖ Anti-resorptive effect on bone.

	Bone	Breast	Uterus
Tamoxifen	Agonist	Antagonist	Agonist
Raloxifen	Agonist	Antagonist	Antagonist

- **Therapeutic uses:**
 - ✓ Breast cancer.
 - ✓ Osteoporosis.
 - ✓ Infertility.
 - ✓ Menopausal hormone therapy.
 - ✓ Beneficial agonist actions (e.g. prevention of hot flashes and bone loss).
 - ✓ Blocks unwanted agonist action (e.g. breast and endometrium).