- **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 → pregnenalone → 17α OH-pregnenalone → 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:**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases bone mineral density.</td>
<td>Worsens benign prostatic hyperplasia.</td>
</tr>
<tr>
<td>Decreases fat mass.</td>
<td>Increases the incidence of prostate cancer.</td>
</tr>
</tbody>
</table>

- **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?**

<table>
<thead>
<tr>
<th>Inhibitors of secretion</th>
<th>Example: abarelix (it is a GnRH antagonist used in prostate cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor antagonists</td>
<td><strong>Flutamide:</strong> for prostate cancer and hirsutism</td>
</tr>
<tr>
<td></td>
<td><strong>Spironolactone (aldosterone antagonist):</strong> for hirsutism</td>
</tr>
<tr>
<td></td>
<td><strong>Cyproterone acetate:</strong> for hirsutism</td>
</tr>
<tr>
<td>5α-reductase inhibitors</td>
<td><strong>Finasteride:</strong> inhibits type-II of the enzyme</td>
</tr>
<tr>
<td></td>
<td><strong>Dutasteride:</strong> inhibits type-I and type-II of the enzyme</td>
</tr>
<tr>
<td></td>
<td>These two drugs are used to treat:</td>
</tr>
<tr>
<td></td>
<td>- Prostatic hyperplasia.</td>
</tr>
<tr>
<td></td>
<td>- Male pattern baldness.</td>
</tr>
<tr>
<td></td>
<td>- Hirsutism.</td>
</tr>
</tbody>
</table>

- **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.

<table>
<thead>
<tr>
<th></th>
<th>Bone</th>
<th>Breast</th>
<th>Uterus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>Agonist</td>
<td>Antagonist</td>
<td>Agonist</td>
</tr>
<tr>
<td>Raloxifen</td>
<td>Agonist</td>
<td>Antagonist</td>
<td>Antagonist</td>
</tr>
</tbody>
</table>

- **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).