C. Androgen Synthesis

- **Dehydroepiandrosterone (DHEA):** major androgen/androgen precursor produced by the adrenal cortex
  - Prehormone converted into androstenedione via $3\beta$-OHSD and $\Delta^{5,4}$-isomerase
- **Androstenedione:** also formed in the adrenal via conversion of 17-hydroxyprogrenolone via 17,20-lyase
  - Reduced at C17 position to form testosterone
- **Testosterone:** most potent androgen
  - Small amounts produced in the adrenal
  - Mainly produced in the testes
  - Most of the 17-hydroxyprogrenolone follows the glucocorticoid pathway
    - Some subjected to oxidative fission and removal of the 2-carbon side chain by 17,20-lyase
      - Dual-function protein
      - Important in both adrenals and gonads
      - Acts exclusively on 17α-hydroxy-containing molecules
  - ↑Adrenal androgen production: if glucocorticoid biosynthesis is impeded by the lack of one hydroxylase
    - Adrenogenital syndrome

D. Testicular Steroidogenesis

- **Interstitial cells of Leydig:** synthesize testicular androgens
- **Cholesterol:** immediate precursor of gonadal cells
- **Rate limiting step:** delivery of cholesterol to the inner mitochondrial membrane by the transport protein StAR
  - This conversion is similar in the adrenal, ovary, and testis. However, in the latter two tissues the process is promoted by LH rather than ACTH.
- Conversion of pregnenolone to testosterone requires five enzyme activities:
  - (1) 3β-OSHD and (2) $\Delta^{5,4}$-isomerase
  - (3) 17α-hydroxylase and (4) 17,20-lyase
  - (5) 17β-OSHD
- Pregnenolone can also be converted to testosterone by the dehydroepiandrosterone (or $\Delta^{5}$) pathway
  - Mostly used in the human testes
  - Metabolism of Testosterone

1. **Oxidation at the 17 position**
   - Occurs in many tissues, including the liver
   - Produces generally inactive or less active 17-ketosteroids
2. **Reduction of the A ring double bond and the 3-ketone**
   - Less efficient pathway
   - Occurs in target tissues
   - Produces potent DHT
- **DHT:** most significant metabolic product of testosterone
  - Active in prostate, external genitalia, and some areas of the skin
  - Plasma content in adult male: DHT (~400 μg) <<< Testosterone (5 mg)
    - about 50 to 100 μg of DHT: secreted by testes
    - Others: produced peripherally from testosterone in NADPH-dependent 5α-reductase

E. Ovarian Steroidogenesis

- **17β-Estradiol:** primary estrogen of ovarian origin
  - Estrogens are formed by the aromatization of androgens in three hydroxylation processes, each requires O2 and NADPH
  - Aromatase enzyme complex: include P450 monoxygenase
  - Forms of estrogen
    - **Estrone**
      - Synthesized in numerous tissues
      - More abundant
      - Formed from the aromatization of androstenedione
      - Major source of estrogens in postmenopausal women
    - **Estriol**
      - Produced more during pregnancy
    - **Estradiol**
      - Formed if the substrate of the enzyme complex is testosterone
  - Theca cells produce androstenedione and testosterone
    - These products are acted upon by aromatase enzyme in granulosa cells to form estrone and estradiol
  - **Progesterone**
    - Precursor for all steroid hormones
    - Produced and secreted by the corpus luteum as an end-product