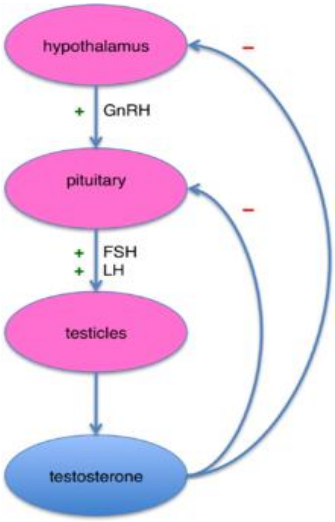
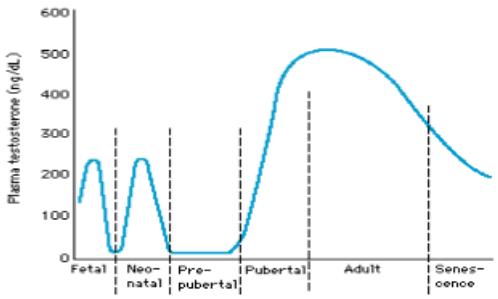
SITES OF ANDROGEN PRODUCTION:

Men	• Testes • Also adrenals release small amounts
Women	• Very small amounts of androgens derived from ovaries & adrenal glands • Role in skin (sebaceous gland), bone growth and sexual function

REGULATION OF ANDROGEN PRODUCTION:



CHANGES IN TESTOSTERONE SECRETION WITH AGE:



DIRECT AND INDIRECT ACTIONS OF TESTOSTERONE:

Estradiol ↑ Aromatase	• Termination of bone growth • Maintenance bone density • Gonadotropin regulation
Testosterone ↓ 5α-reductase	• Skeletal muscle mass/strength • Bone growth, density • Spermatogenesis • Sexual function
Dihydro-testosterone	• Hair follicles • Prostate • Skin

MECHANISMS OF ANDROGEN ACTION:

1. Once secreted by testes, testosterone is mainly protein bound (sex hormone binding globulin).
2. Free hormone enters the cell by diffusion. In some cells, it is converted to DHT.
3. Both testosterone and DHT bind to inactive androgen receptor (DHT with higher affinity), located in cytoplasm.
4. Binding results in dissociation of corepressor proteins, dimerization, translocation to nucleus and binding to androgen response element of androgen-regulated target genes.
5. Hormone-receptor complex interacts with coactivators to produce altered regulation of target genes

ANDROGEN ACTIONS IN MALES:

Sex organs	Development of male sex organs, prostate, seminal vesicles, spermatogenesis, sexual function
Voice	Larynx growth and voice deepening
Bone	Increases linear bone growth; also role in termination of bone growth and maintaining bone density
Muscles	Increases lean muscle strength and volume
Hair	Stimulates male-pattern hair growth
Skin	Increases skin thickness and oiliness
Brain	Increased libido, altered mood, behavioral effects
Kidney	Stimulates erythropoietin production

THERAPEUTIC USES:

ANDROGEN REPLACEMENT THERAPY IN TESTOSTERONE DEFICIENCY: 1° & 2° hypogonadism

- Induce/maintain pubertal development, including secondary sex characteristics
- Permit normal accumulation of bone mass & achieve optimal growth and final height (if pre-pubertal)
- To develop and/or maintain skin, muscle and sexual organ function
- When used in appropriate doses, not associated with adverse effects

AGE-ASSOCIATED DECREASE IN ANDROGEN PRODUCTION:

- Decreased testosterone production is a normal consequence of aging in men
- May contribute to decreased sexual function, muscle and bone mass, and other sx
- Sometimes described as **late onset hypogonadism, andropause or low T**
  - Clinical definition still not agreed on

TESTOSTERONE REPLACEMENT THERAPY:

- In men > 65 yrs with age-related low serum T, replacement therapy for 12 months produced a transient improvement in sexual function BUT no benefit in physical strength, vitality or cognition
- Emerging evidence of increased risk of CV events, particularly in pre-existing CVD
- Risk of prostate cancer not clear

OTHER USES OF ANDROGENS:

- To stimulate delayed growth and puberty in males
  - Due to true hypogonadism or constitutional delay of puberty
  - Usually used for relatively short periods (up to 3 months), then re-evaluated
- Catabolic or muscle-wasting conditions
  - In general, not particularly effective
  - However, AIDS is often associated with low serum T, treatment increases muscle mass and strength

TESTOSTERONE PREPARATIONS:

Testosterone esters	• Fatty acid esterified at 17β-hydroxy position
	  ○ Increased lipophilicity
	• Depot preparations administered IM every 2-4 weeks
	  ○ Slowly released from site of injection, hydrolyzed to testosterone	

Transdermal delivery systems	**Testosterone patch**	• Applied once/day
	Testosterone gel	• 1% testosterone applied • Single use packets or metered dose pump
	• Both delivery modes give testosterone levels in normal range • Potential for secondary exposure of women and children with gel	
17α-alkylated androgens	• Resistant to hepatic breakdown = effective on oral administration • Not recommended for clinical use due to risk of hepatotoxicity	

ANABOLIC STEROIDS:

- Attempt to separate effects of androgens on muscle & bone from other actions of androgens
- Only limited selectivity achieved = very limited clinical use; widely abused
- Most are 17α-alkylated androgens = orally active

ANDROGEN USE BY ATHLETES AND BODY BUILDERS:

- Reasons for use: to increase lean body mass, to decrease fat mass, to enhance performance, to sustain intensive training periods and to improve appearance
- Often used intermittently in very high doses (ex// stacking = using oral and injectable forms and increasing doses for 6-12 weeks at a time)
- Appear to increase muscle mass & strength, especially in combo with wt training but no evidence for improved indurance
- Mechanisms unclear but include hypertrophy of muscle fibers

ADVERSE EFFECTS OF ANDROGENS:
- Virilization of females (any age)
- Premature termination of bone growth and disturbances in sexual development and children
- 17α-alkylated androgens/anabolic steroids carry risk of hepatotoxicity
- Sodium retention leading to edema

ADVERSE EFFECTS OF VERY HIGH DOSES OF ANDROGENS/ ANABOLIC STEROIDS IN MEN:
- Suppression of spermatogenesis
- Testicular atrophy
- Decreased HDL, increased LDL
- Gynecomastia
- Psychological changes

ANDROGEN RECEPTOR ANTAGONISTS:

NON-STEROIDAL ANTI-ANDROGENS: Flutamide, bicalutamide, nilutamide, enzalutamide
- Competitive antagonists of the binding of androgens to nuclear receptors
- Block androgen actions in all target tissues, including hypothalamus/pituitary
  - Reduced negative feedback results in increased testosterone production

THERAPEUTIC USES:
- Treatment of advanced prostatic carcinoma
- Most commonly during first 2-4 weeks treatment with GnRH agonist
  - Counteracts symptom "flare" resulting from GnRH-agonist induced increase in testosterone production

ADVERSE EFFECTS:
- Hot flashes
- Decreased libido
- Erectile dysfunction
- Breast tenderness, gynecomastia

CYPROTERONE ACETATE:
- Competitive antagonist at androgen receptors
- Also has progesterone activity and blocks gonadotropin secretion

USES:
- Treatment of severe cystic **acne** as component of **Diane 35** (combination of ethinyl estradiol + cyproterone acetate)
  - Also has contraceptive effect BUT not approved for this use in Canada
  - Relatively higher risk of VTE than other oral contraceptives

5α-REDUCTASE (5AR) INHIBITORS:
- Types of 5α-reductase:
  - Type 1: found in prostate + other organs
  - Type 2: concentrated in male genitals and prostate
- 5α-reductase inhibitors:
  - Dutasteride inhibits Type 1 and 2 5α-reductase
  - Finasteride inhibits Type 2 5α-reductase only

USES:

BENIGN PROSTATE HYPERTROPHY:
- Decrease circulating DHT levels by 75-90%
  - Growth of prostate requires DHT
- Appear to be equally effective
- Used alone in men with enlarged prostate & obstructive sx
  - Decrease prostate size with improvement in urinary flow rate and symptoms
  - Decrease risk of long term complications by ~ 50%
  - Slow onset of action
- Combination therapy with α-blockers more effective than either alone in reducing the risk of progression

MALE PATTERN HAIR LOSS (ANDROGENETIC ALOPECIA):
- Delay hair loss and promote some re-growth of hair
- Better on vertex (top of head) than on frontal hair
- Slow onset, effective only as long as drug is given
- (approved use of finasteride only)

ADVERSE EFFECTS:
- Dose-dependent decreased libido, erectile dysfxn, gynecomastia
- Decreased PSA levels

EFFECT ON DEVELOPMENT OF PROSTATE CANCER:
- Both drugs have been shown to reduce detection of prostate cancers by 23-25% overall
- However, increased risk of detection of serious prostate CA
- Not considered to have favorable risk-benefit for prevention of prostate cancer