# Hormone Biosynthesis and Metabolism

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# Introduction

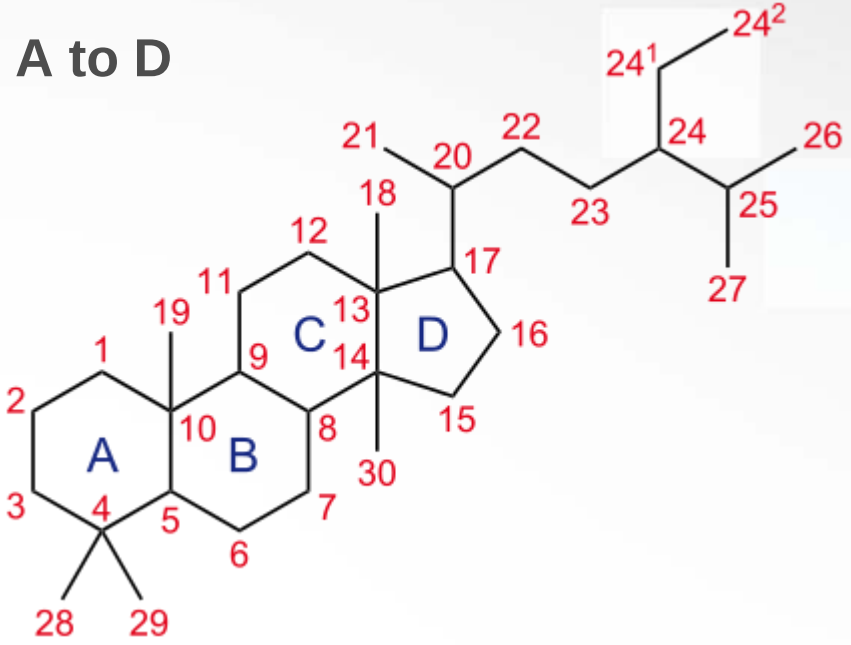
- "Hormones"
  - Substances that provide means of communication
  - Chemical regulatory and signaling agents
  - Local sites: cellular communication necessary
  - Paracrine
    - Intercellular communication, local diffusion
  - Autocrine
    - Intracellular communication, production of regulating substances
  - Intracrine
    - Intracellular communication, unsecreted substances bind to intracelllular receptors

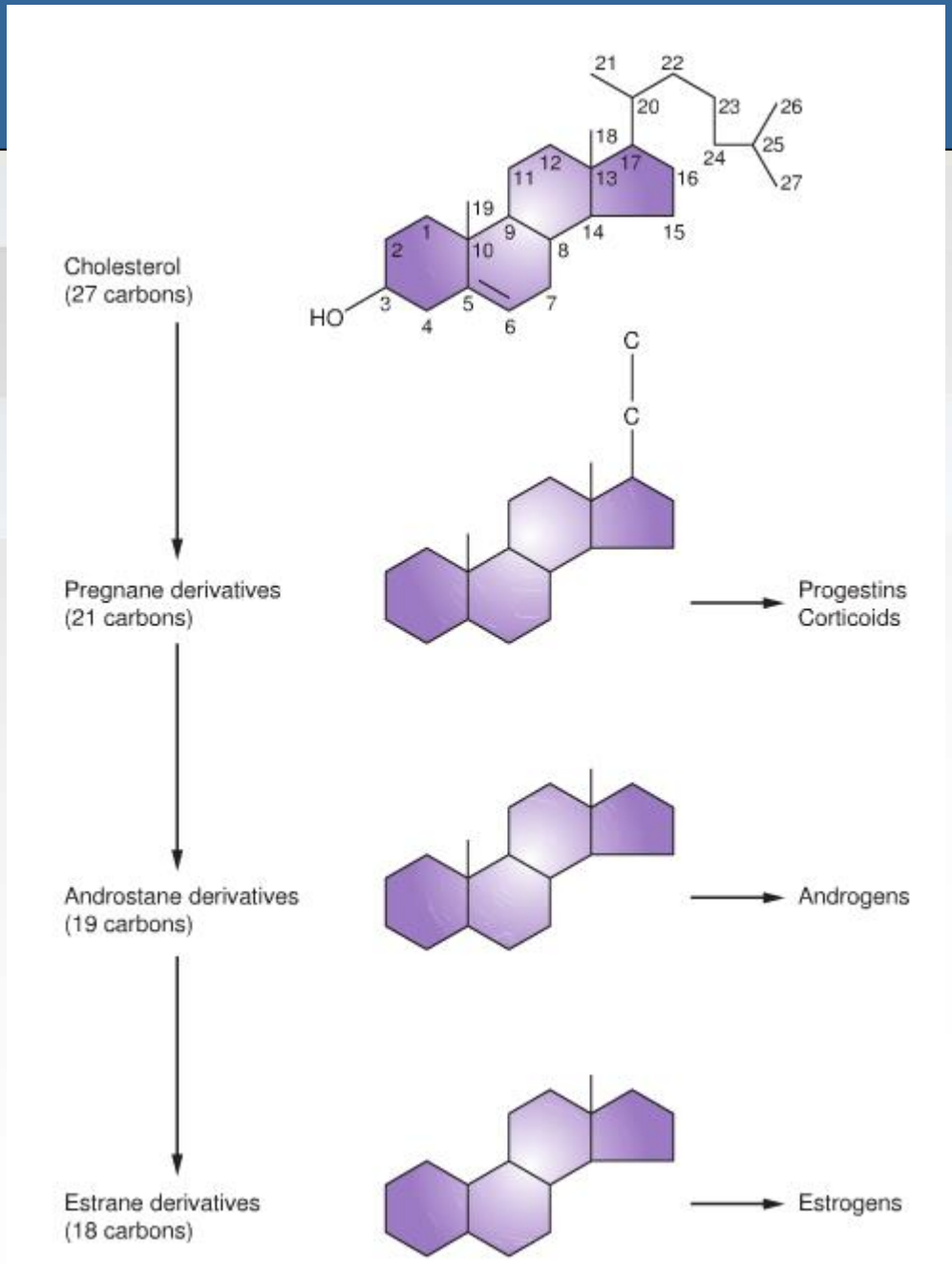
# Structure of Steroid Hormone

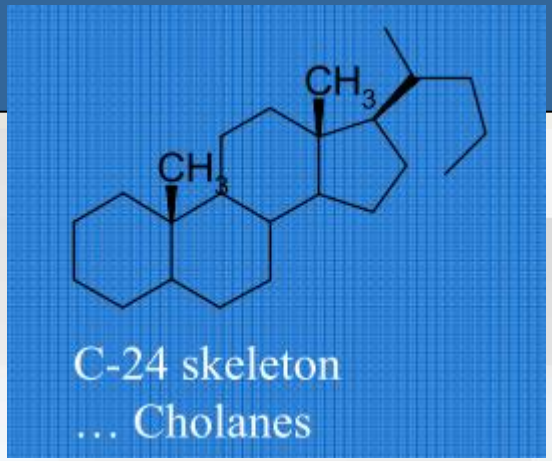
- Basically similar structure with relatively minor chemical differences
- Basic structure: per-hydro-cyclo-pentane-phenanthrene molecule
- Composed of 6-carbon rings and one 5-carbon ring
- One 6-carbon ring is benzene, two of the 6-carbon rings are naphthalene, and three 6-carbon rings are phenanthrene

# Structure of Steroid Hormone

- phenanthrene (three 6-carbon rings) + cyclopentane (5-carbon ring)
- Four rings named A,B,C and D
  - A,B,C : cyclohexanes (hexagon)
  - D: cyclopentane (pentagon)
  - Direction of numbering: from A to D





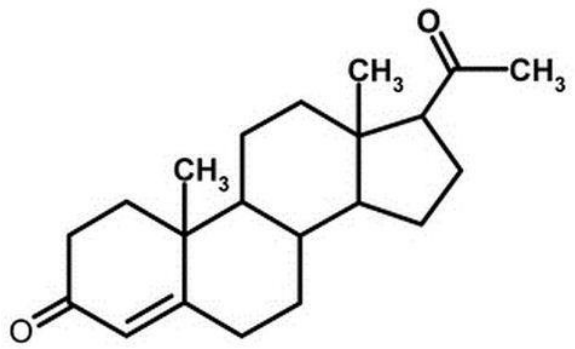

**21 Carbons - Pregnane**

**19 Carbons - Androstane**

**18 Carbons - Estrane**

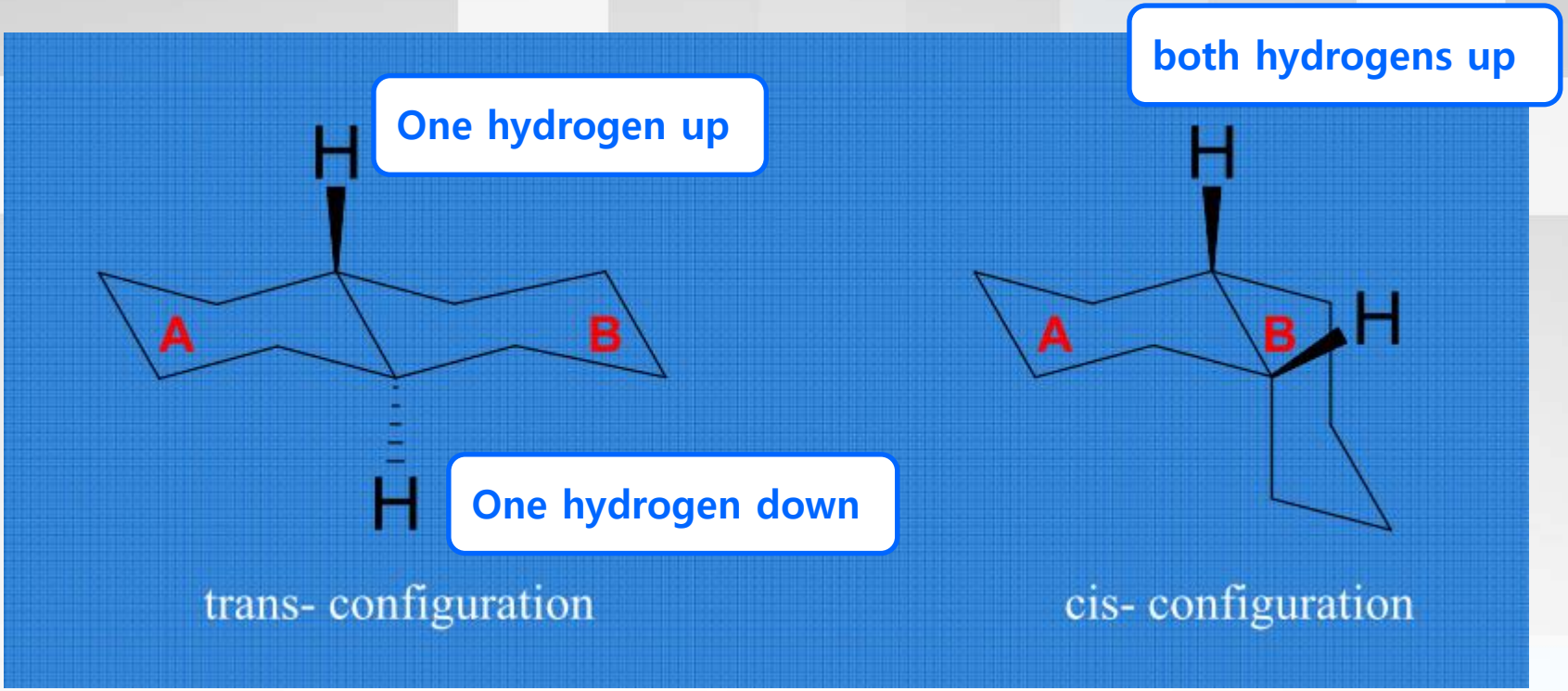
# Steroid Hormone Nomenclature

- Number of carbon atoms for basic name: pregnane, androstane or estrane
- Position indicated by number of carbon attachment
- Double bonds: -ene (1), -diene (2), -triene (3)
- Hydroxyl groups: -ol (1), -diol (2), -triol (3)
- Ketone groups: -one (1), -dione (2), -trione (3)
- Special designations
  - Elimination: dehydro (OH), deoxy (O2), nor (carbon)
  - Delta or ∆: location of double bond




Example> Progesterone
⇒ 4-Pregnene-3,20-dione

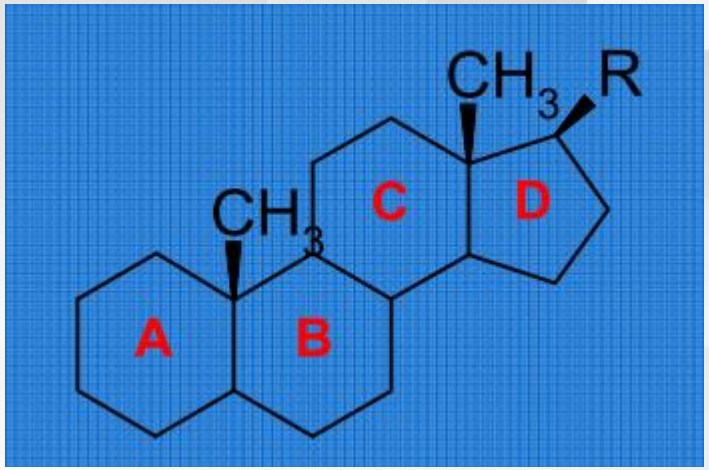
# Isomers of Sex Steroid

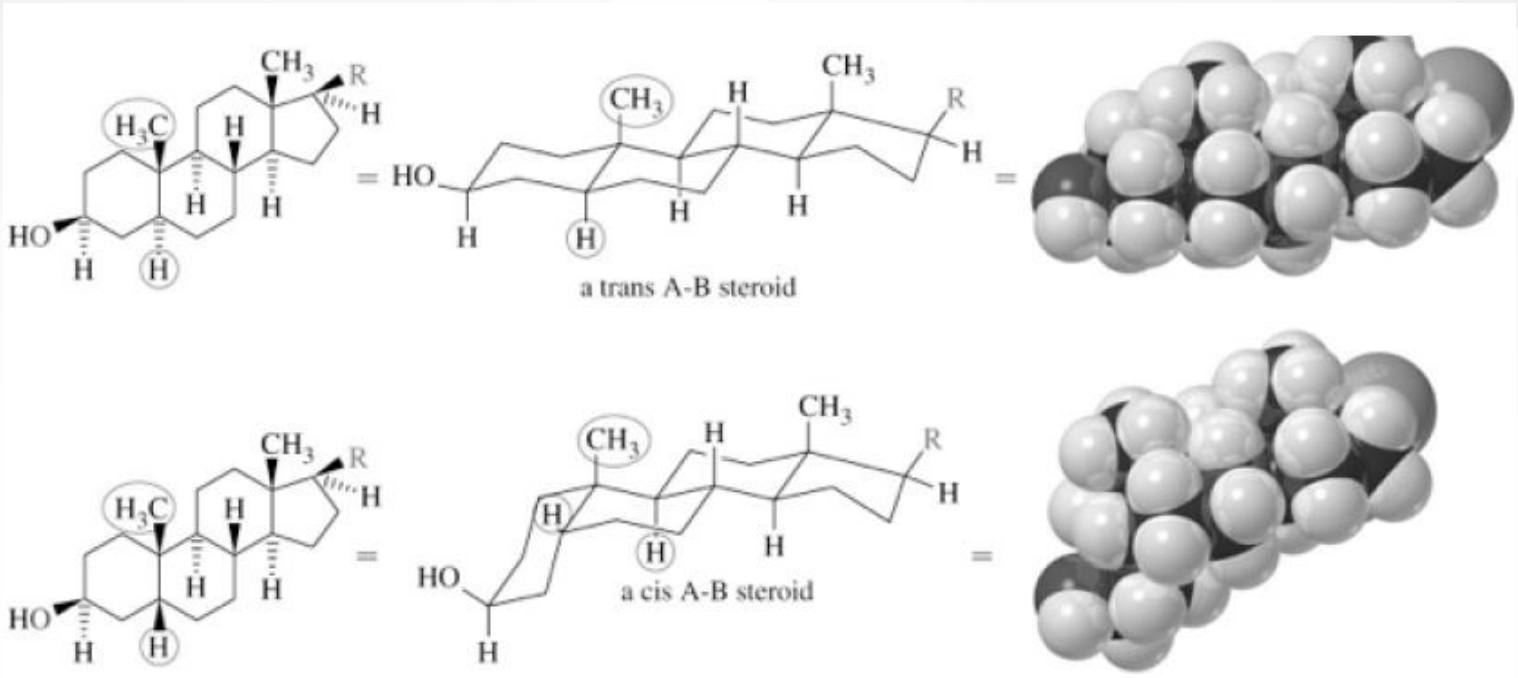



- Trans-fused cyclohexane rings are more stable than cis-fused

# Configurational Isomers of Steroids

- Fusion points between rings
  - 3 fusion points x 2= 6
  - $2^6$ isomers = 64



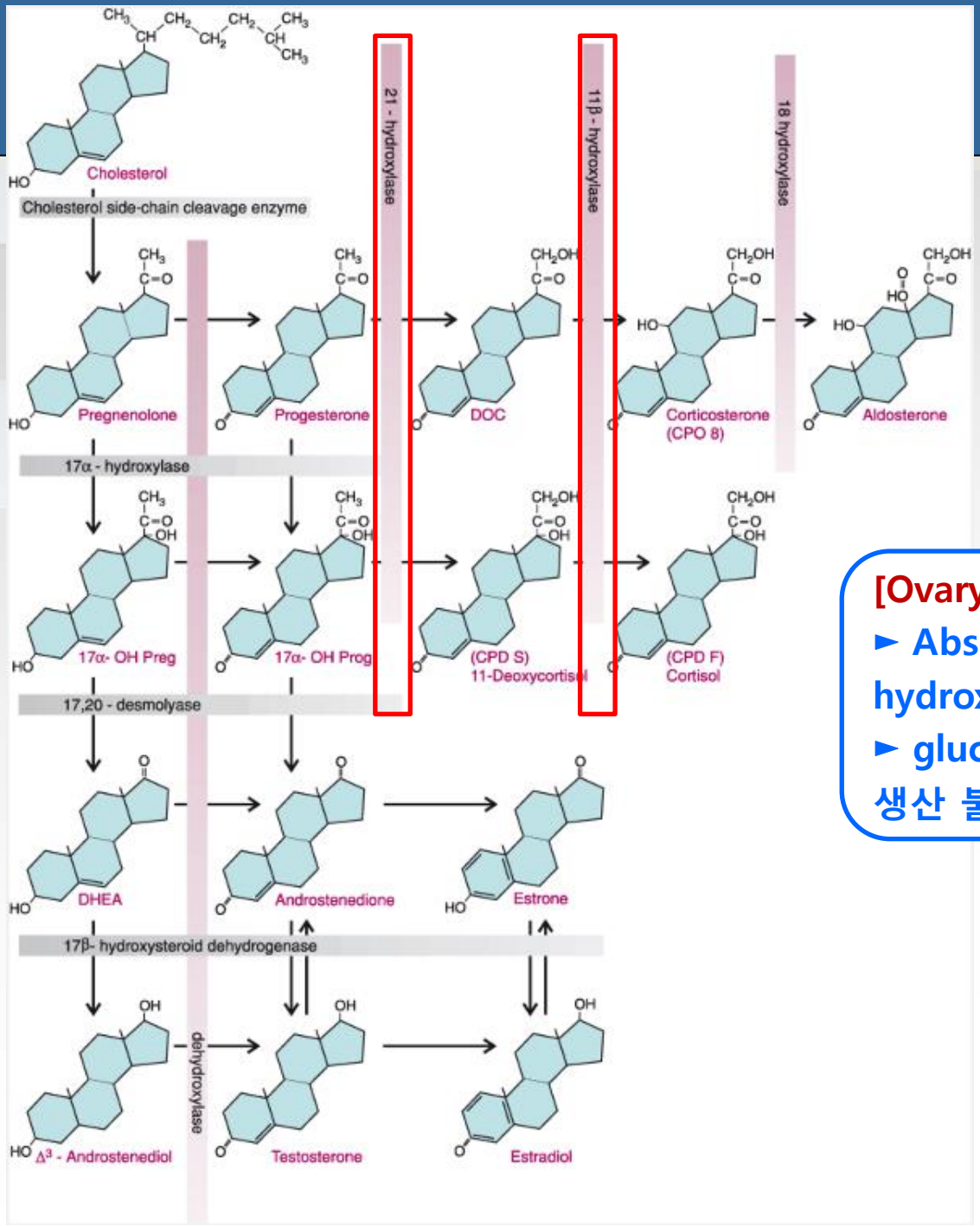
# Major sites of steroid hormone biosynthesis

- Adrenal cortex
  - Zona fascicularis and reticularis
    - Minor mineralocorticoids, Glucocorticoids, Adrenal androgens
  - Zona glomerulosa
    - Aldosterone
- Ovaries
  - Theca cells
    - DHEA
  - Granulosa cells and developing follicles
    - Estrogen
  - Corpus luteum
    - Progesterone

# Reactions during Steroidogenesis

| | |
|---|---|
| Cleavage of a side chain<br>(catalyze the formation or destruction of carbon-carbon bonds) | Desmolase rxn |
| Conversion of hydroxyl groups into ketones or ketones into hydroxyl groups | Dehydrogenase rxn |
| Addition of OH group | Hydroxylation rxn |
| Creation of double bonds | Removal of hydrogen |
| Addition of hydrogen to reduce double bonds | saturation |

| *Enzyme* | *Cellular Location* | *Reactions* |
|---|---|---|
| P450scc | Mitochondria | Cholesterol side chain cleavage |
| P450c11 | Mitochondria | 11-hydroxylase<br>18-hydroxylase<br>19-methyloxidase |
| P450c17 | Endoplasmic reticulum | 17-hydroxylase, 17,20-lyase |
| P450c21 | Endoplasmic reticulum | 21-hydroxylase |
| P450arom | CYPC19A1 ndoplasmic reticulum | Aromatase |

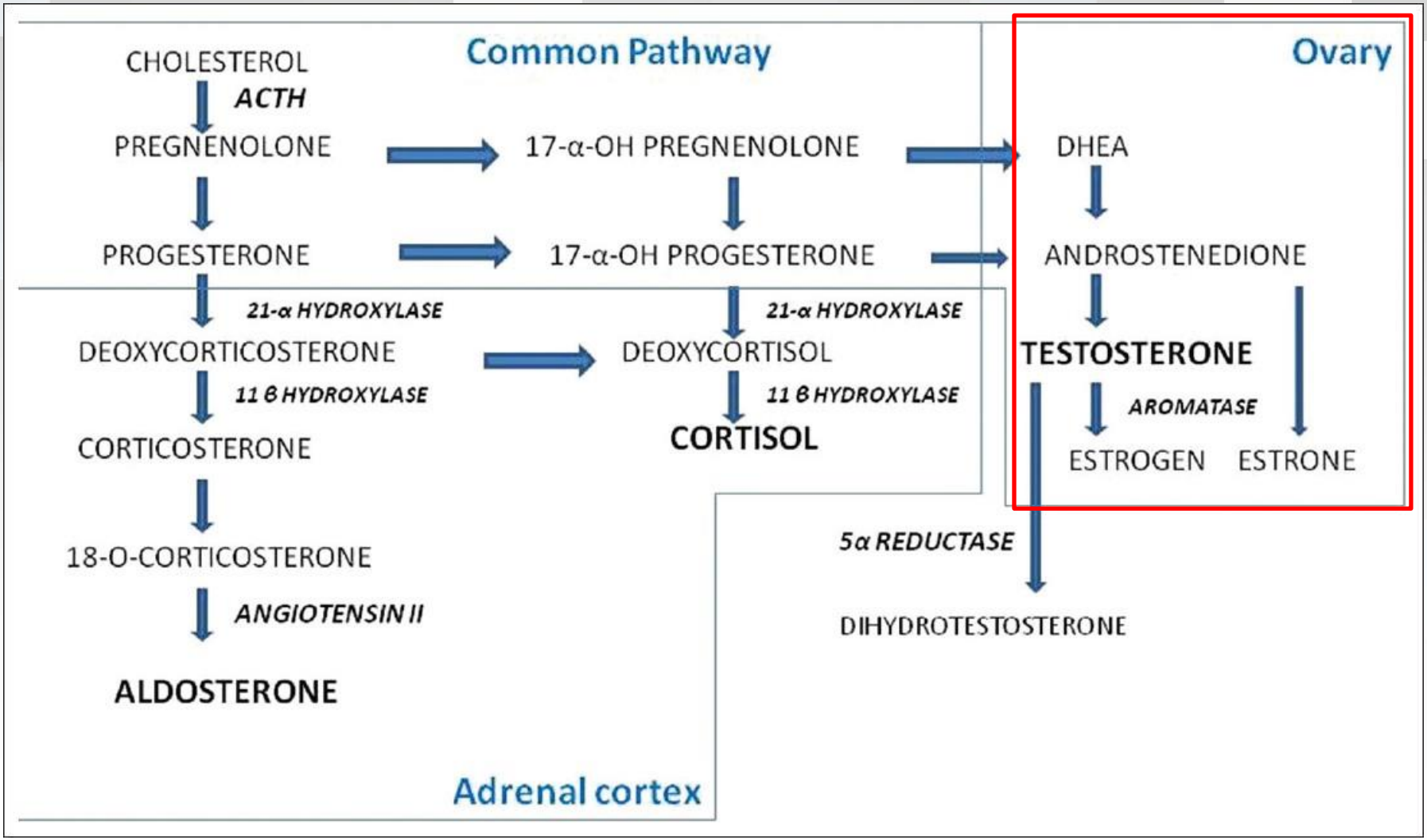



**[Ovary]**

► **Absence of 21-hydroxylase & 11β-hydroxylase**

► **glucocorticoid, mineralocorticoid 생산 불가**

# Steroidogenesis Pathway

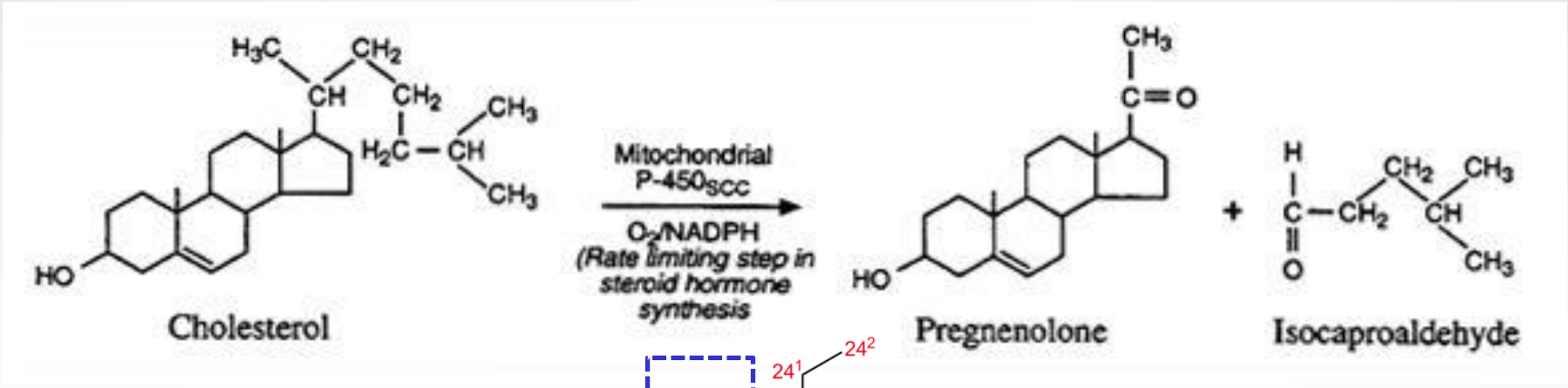


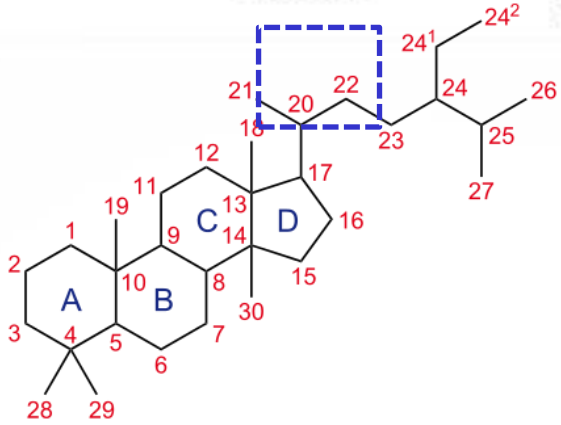
# CAH

- 21-hydroxylase def.
  - Simple virilizing, salt-wasting and late-onset (non-classic)
  - Markedly elevated level of 17-OHP
- 3β-HSD def.
  - Increased DHEA, DHEA-S
- 11-hydroxylase def.
  - Virilization, hypertension
  - Classic form: elevated DOC, DHEA, DHEA-S, ADD

# Cholesterol → Pregnenolone

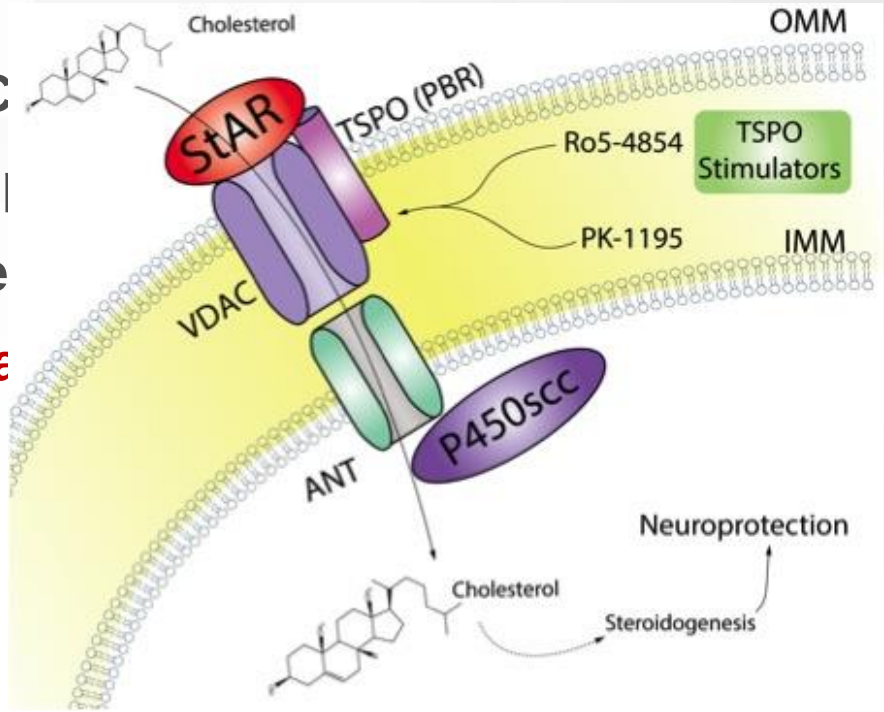
- P450scc in the mitochondria
  - by effect of tropic hormone stimulation by ant. Pituitary
  - Side chain cleavage at carbon 20 and 22 position
    = 20,22-desmolase



# Rate-limiting Step in Steroidogenesis

- Transfer of cholesterol from outer mitochondrial membrane to inner mitochondrial membrane
- Regulator proteins of acute intracellular cholesterol transfer
  - Sterol carrier protein 2 (SC
  - Steroidogenesis activator
  - Peripheral benzodiazepine
  - Steroidogenic acute regula



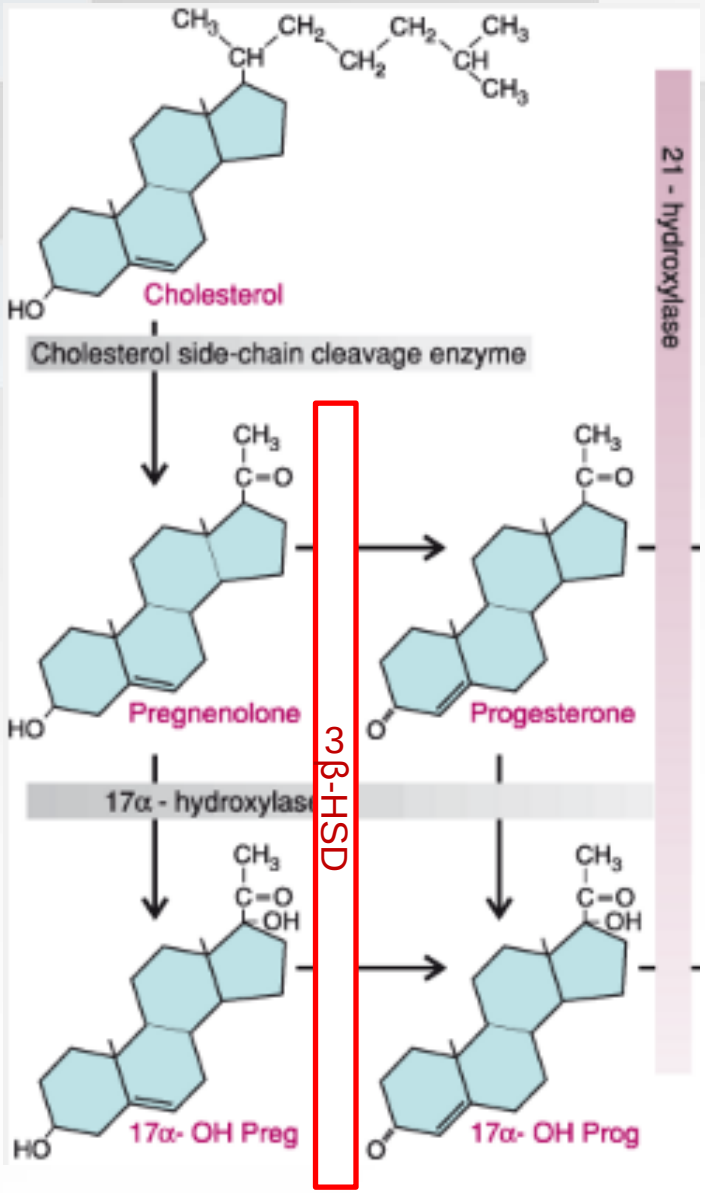
# Steroidogenic Acute Regulator (StAR) Protein

- Increases steroid production
- Imported and localized in mitochondria

- Congenital Lipoid Adrenal Hyperplasia (AR disorder)
  - Mutation in StAR gene → premature stop codons
  - Failure in adrenal, gonadal steroidogenesis
  - Low level of steroidogenesis possible → feminization at puberty
  - Accumulation of intracellular lipid deposits → destroys steroidogenic capability

- StAR required for adrenal and gonadal steroidogenesis, necessary for normal male sexual differentiation

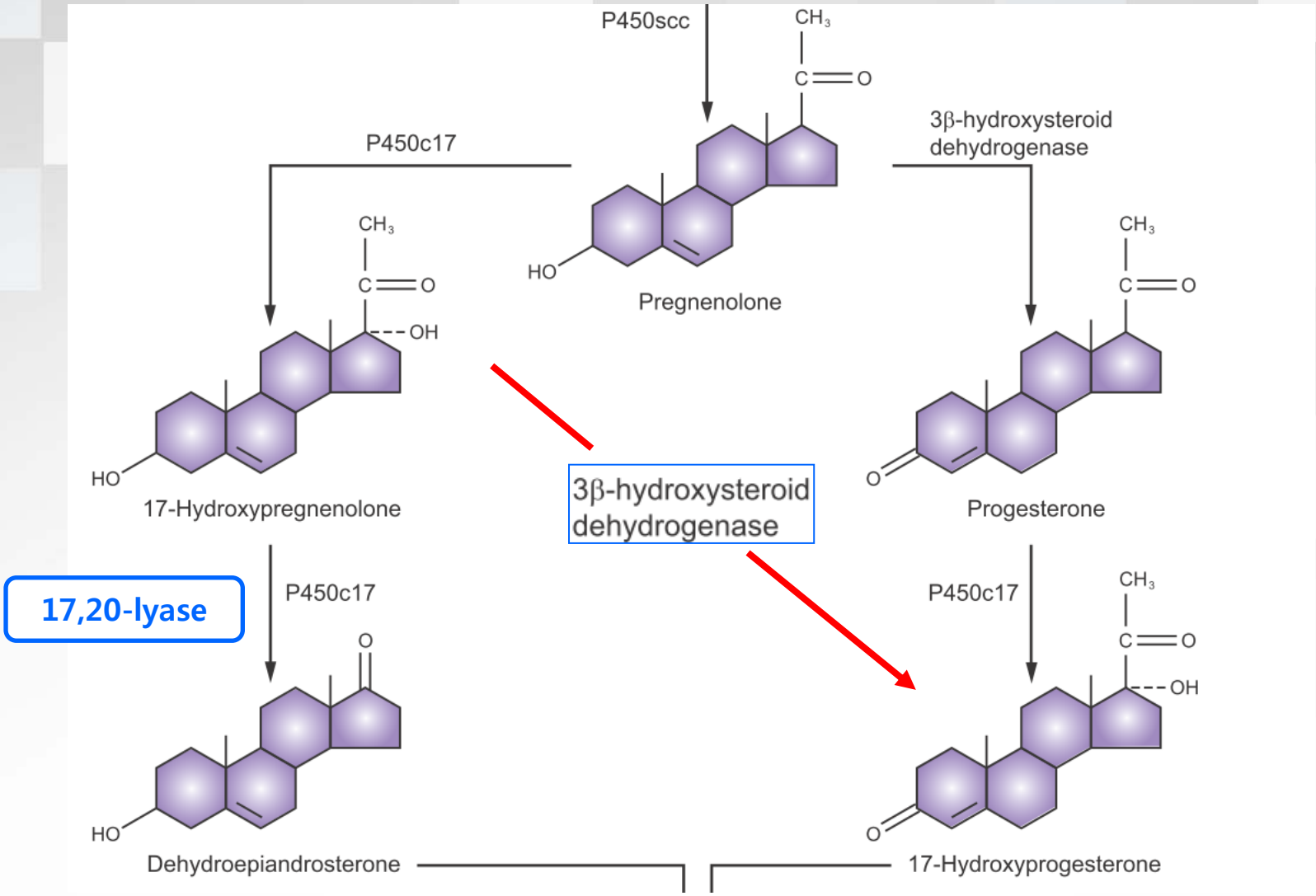
# Pregnenolone → Progesterone



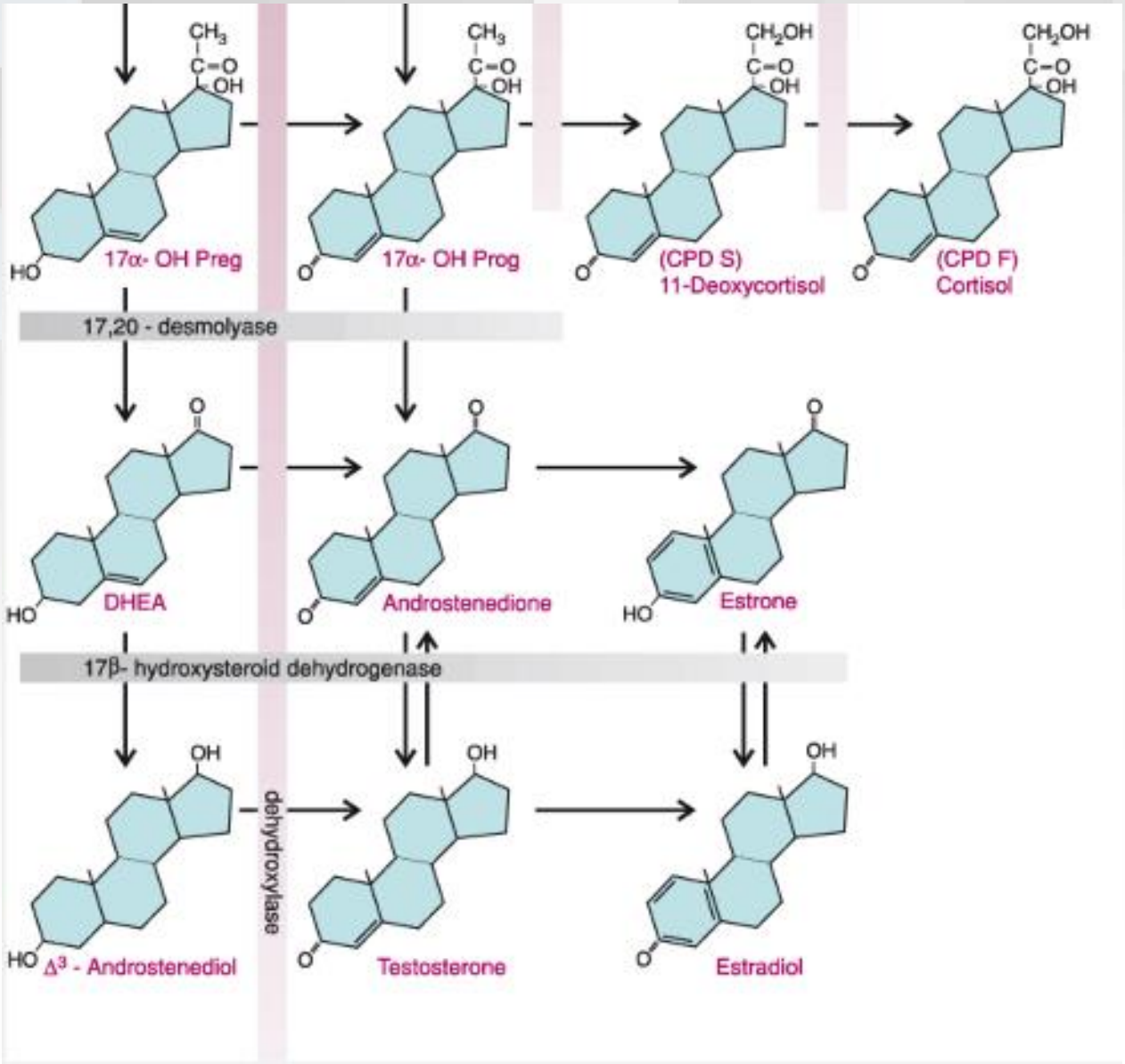

- **Pregnenolone → progesterone**

  **: two pathways!**

  - By 3β-hydroxysteroid dehydrogenase (HSD)
  - By $\Delta^{4\text{-}5}$ isomerase reaction

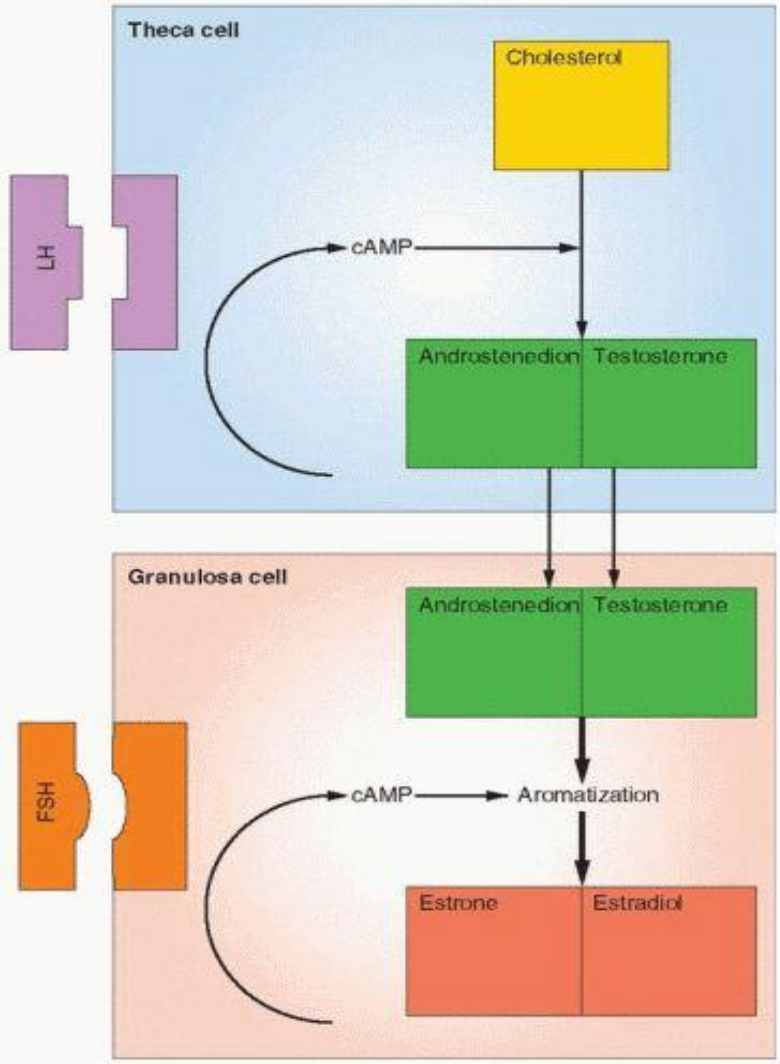

P450scc
CH3
C
O
HO
Pregnenolone
P450c17
3β-hydroxysteroid
dehydrogenase
CH3
C
O
OH
HO
17-Hydroxypregnenolone
3β-hydroxysteroid
dehydrogenase
CH3
C
O
O
Progesterone
17,20-lyase
P450c17
O
HO
Dehydroepiandrosterone
P450c17
CH3
C
O
OH
O
17-Hydroxyprogesterone

- P450c17
  - 17-hydroxylase and 17,20-lyase
  - Adrenal gland
    - Very little effect of 17,20-lyase
  - Theca cell and Leydig cell
    - Both activities
    - Principal pathway via DHEA
  - Corpus luteum
    - Principal pathway via progesterone


17α- OH Preg
17α- OH Prog
(CPD S)
11-Deoxycortisol
(CPD F)
Cortisol
17,20 - desmolyase
DHEA
Androstenedione
Estrone
17β- hydroxysteroid dehydrogenase
Δ3 - Androstenediol
Testosterone
Estradiol
dehydroxylase

# The Two-Cell System

- **First proposed by Falck in 1959**




1. FSH receptors are present on granulosa cells

2. FSH receptors are induced by FSH itself

3. LH receptors are present on theca cells and initially absent on granulosa cells → FSH induces appearance of LH receptors on granulosa cells with follicle growth

4. FSH induces aromatase enzyme activity in granulosa cells

# Primordial Follicle

- 1st visible sign of follicular development
  - Increase in the size of oocyte
  - Cuboidal granulosa cells rather than squamous

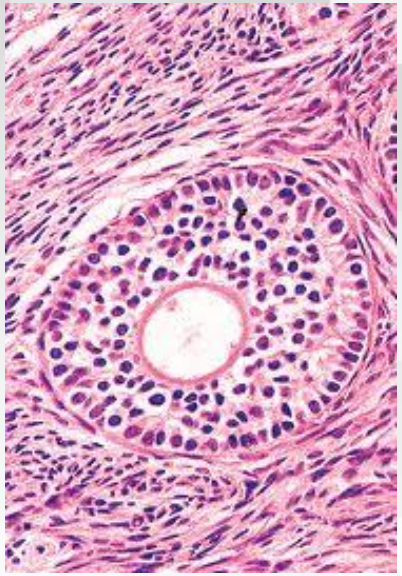

**Maturation rather than growth**

- Initiation of follicular growth: independent of FSH or LH
  - Primordial follicles in anencephalic fetus

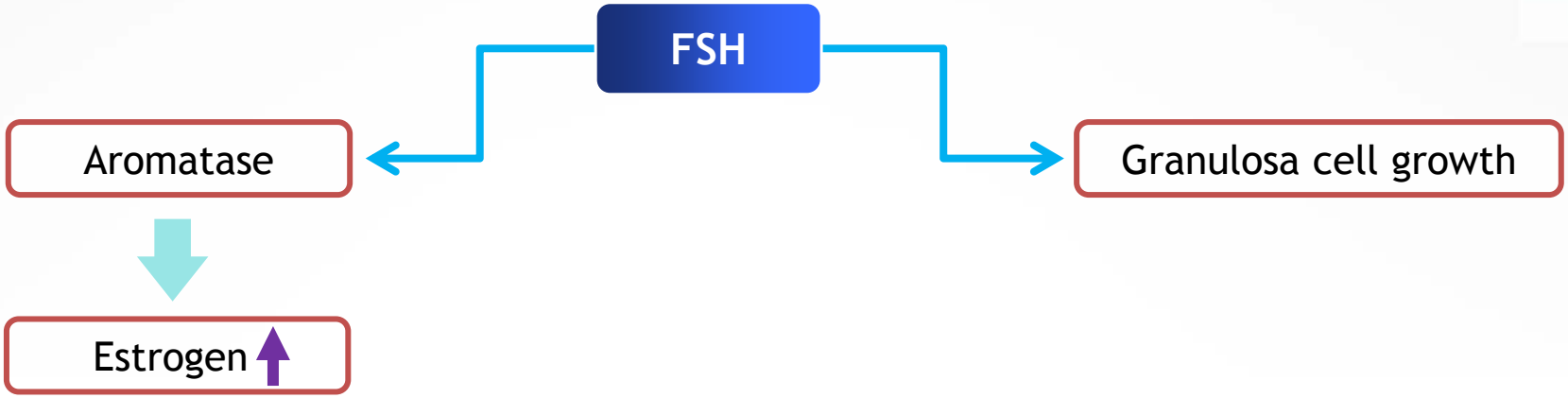
Baker & Scrimgeour. *J Reprod Fertil* 1980;60(1):193-9.

# Preantral Follicle

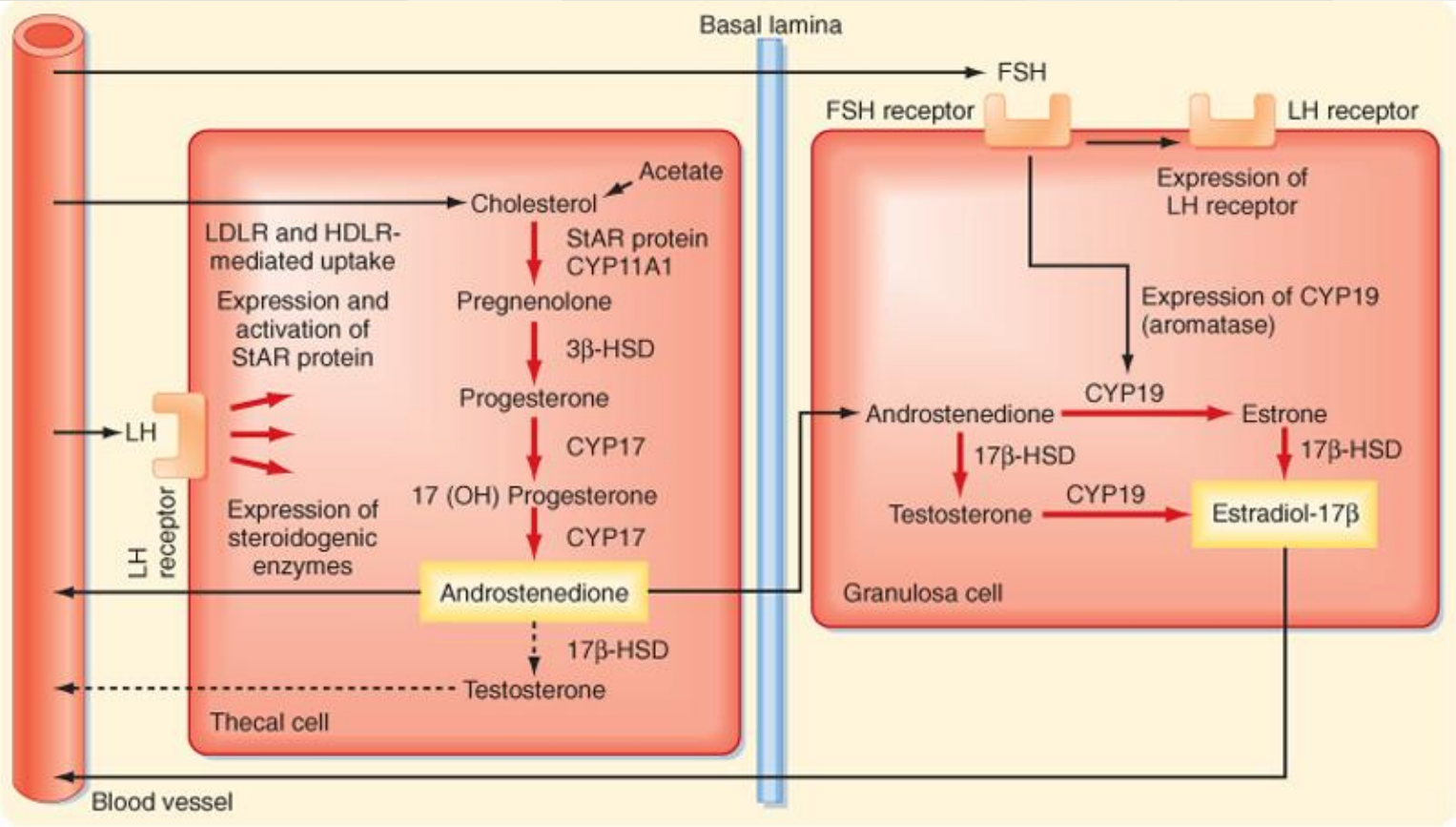
- Preantral follicle
  - Enlargement of oocyte
  - Surrounded by **zona pellucida**
  - Multilayer of G cells
    and organization of theca layer



  - **Dependent on gonadotropin**
  - Correlated with increasing production of estrogen



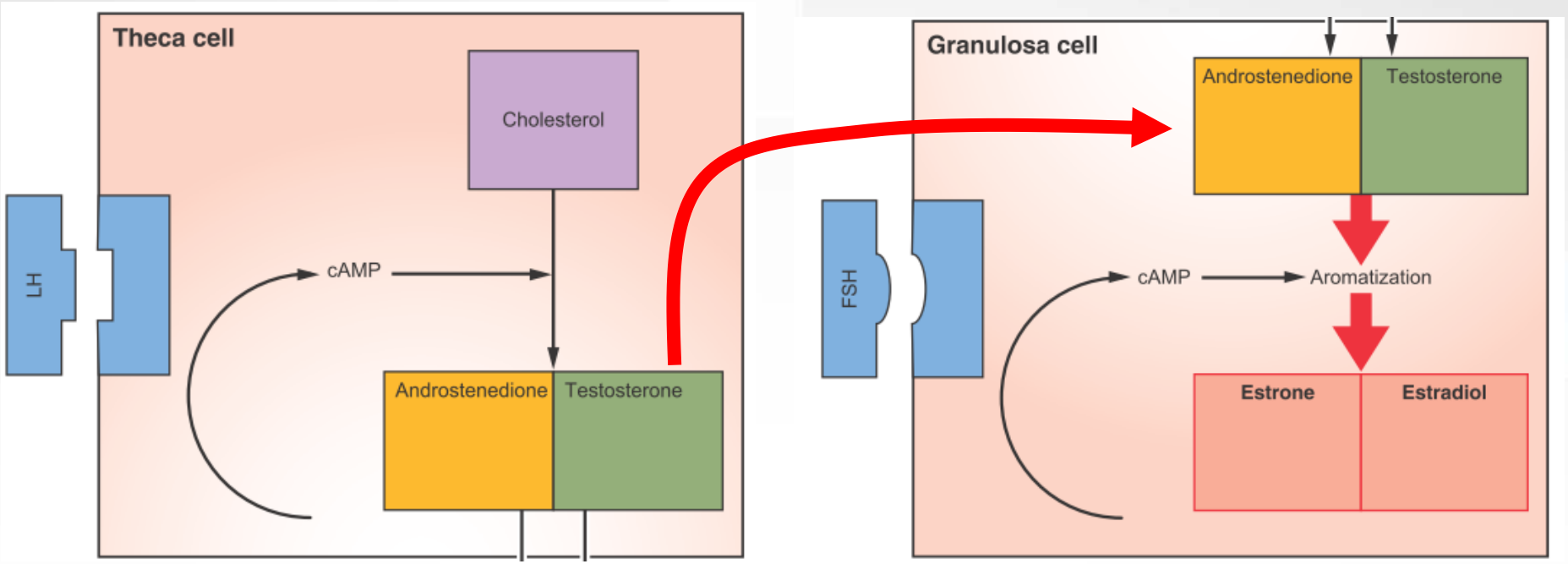
# Preantral Follicle




- **Estrogen production**
  - Limited by FSH Rc contents
  - FSH: raise the concentration of its own receptor on G cells
  - 1,500 receptors / G cell

# Two Cell, Two-Gonadotropin Theory

- **Preantral follicle & antral follicle**
  - LH receptors: only on the theca cells (20,000 Rc / cell)
  - FSH receptors: only on the granulosa cells



# Antral Follicle

- Dominant substance of FF in antral follicle
  - FSH & E2
- LH
  - Not normally present in FF until the midcycle
  - Premature elevation

Decreased mitotic activity in G cells
Degenerative change
Increased level of androgen

# Two Cell, Two-Gonadotropin Theory

- Interaction btw granulosa and theca cells
  - Not fully functional **until later in antral development**
- G cells in small antral follicle
  - Tendency to convert androgen to 5α-reduced form
- G cells in large antral follicle
  - Preferentially metabolize androgen to estrogen

# Two Cell, Two-Gonadotropin Theory

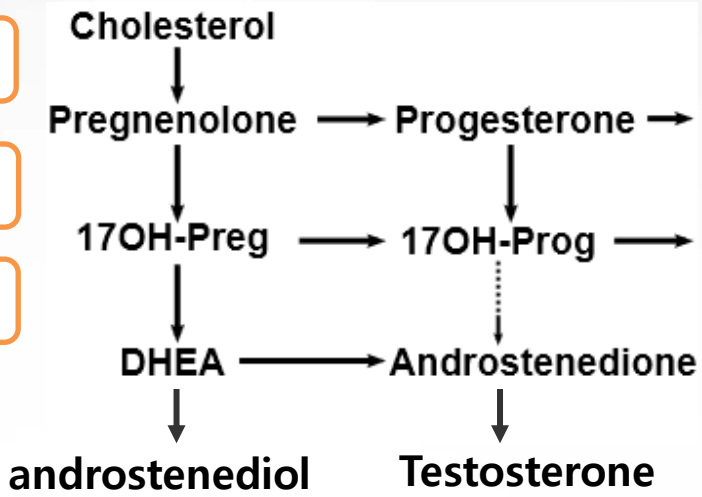
- P450c17
  - Expression in the theca cells
  - Conversion of 21-carbon substrate to androgens
  - 17α-hydroxylase / 17,20-lyase

P450c17 (theca)

P450scc

17α-hydroxylase

17,20-lyase




P450arom (G cell)

# Androgen in Preantral Follicle

- **Substrate for FSH-induced aromatization**

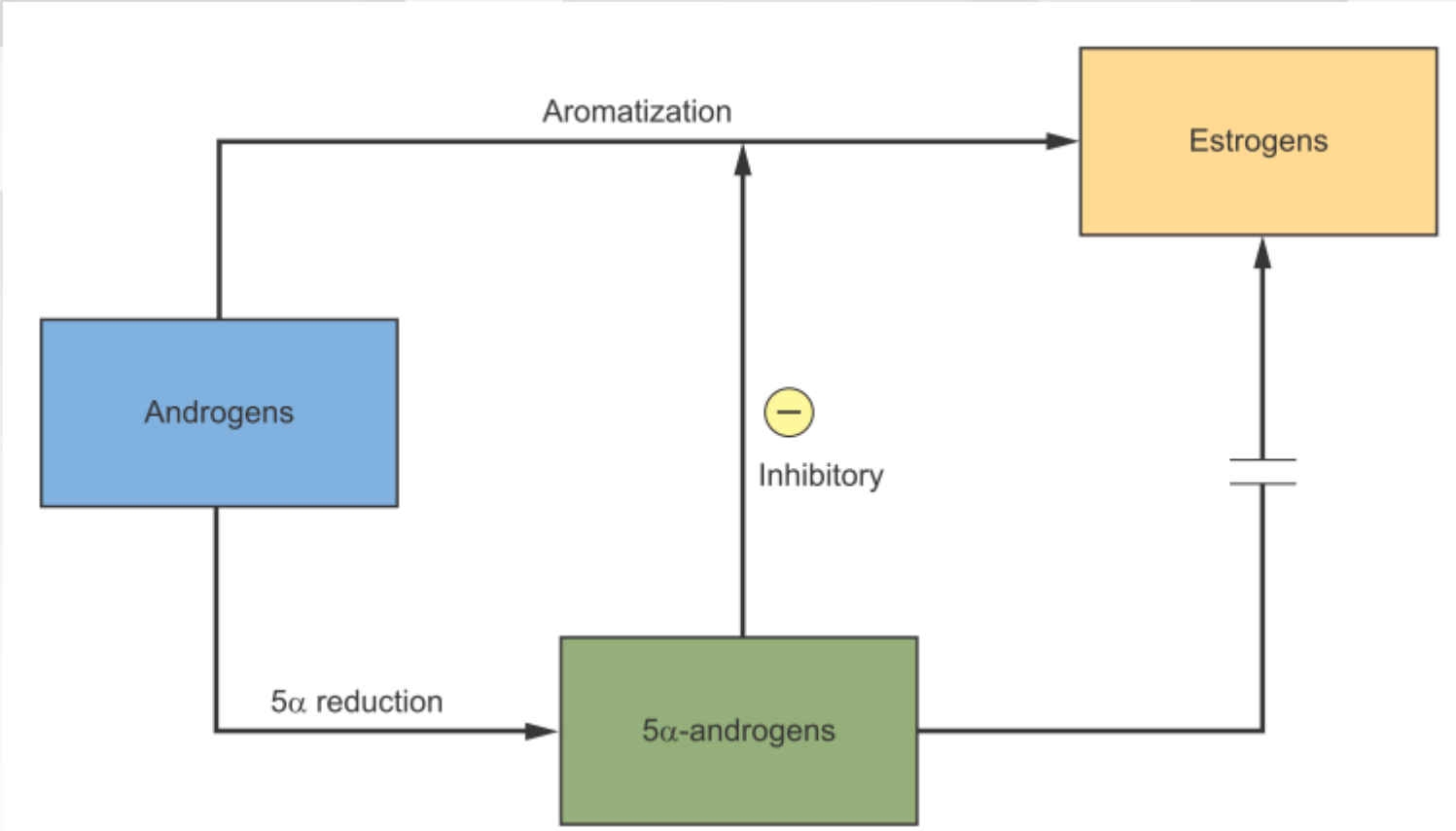
| Low conc. | High conc. |
| --- | --- |
| Enhance aromatase activity | Conversion to **more potent 5α- reduced androgens** rather than estrogen |

- Cannot be converted to estrogen
- Inhibition of aromatase activity

- Inhibition of FSH induction of LH Rc formation

**Androgen-rich follicle** ⇨ **Atresia**

# Androgen in Preantral Follicle




**Success of a follicle**

**androgen-dominated microenvironment**

**estrogen-dominated microenvironment**

# Blood Transport of Steroids

- Estradiol and testosterone circulating in blood
  - Mostly bound to a protein carrier, “SHBG”
  - 30% loosely bound to albumin
  - 1% unbound and free
  - Very small percentage bound to corticosteroid-binding globulin

- Hyperthyroidism, pregnancy, estrogen ⇒ SHBG ↑
- Corticoids, androgens, progestins, GH, insulin, IGF-1 ⇒ SHBG ↓

- Biologic effects of major sex steroids: determined by unbound portion
  “free hormone” “active hormone”
- Routine assays mostly determine ‘total’ hormone concentrations

# SHBG

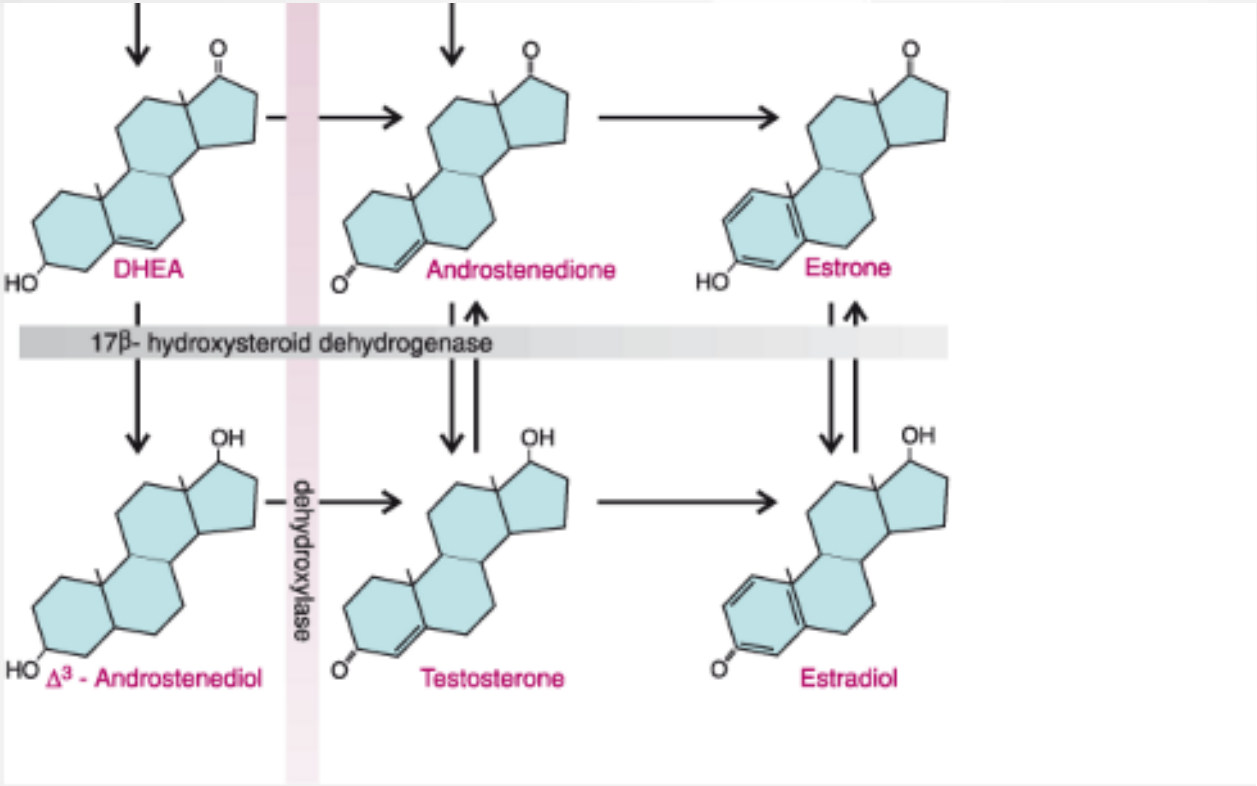
- localized to short arm (p12-13) of chromosome 17
- Circulating level of SHBG: inversely related to Bwt
  - Weight gain → SHBG ↓ → changes in unbound levels of sex steroids
- Insulin resistance, hyperinsulinemia → decreases SHBG levels
- Android fat (abdominal wall, visceral-mesenteric locations)

  → asso. with hyperinsulinemia, hyperandrogenism, decreased SHBG

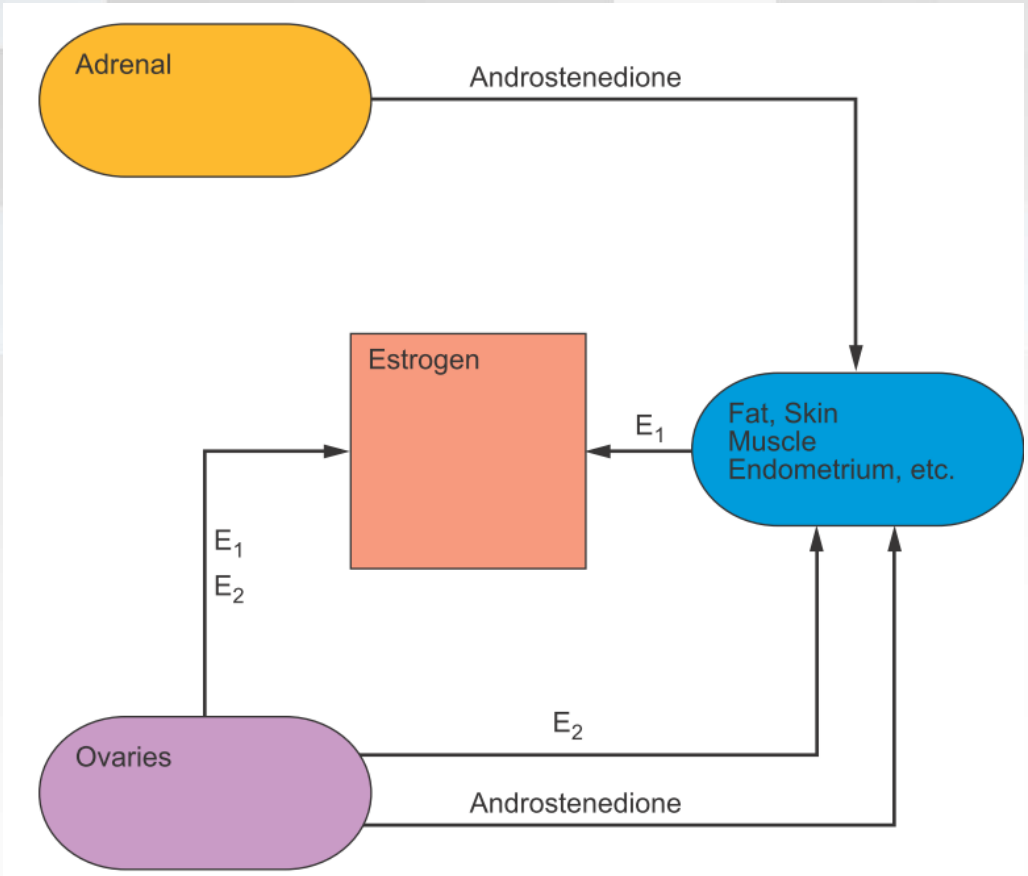
- SHBG conc. ⇒ marker for hyperinsulinemic insulin resistance
- Low SHBG ⇒ predictor for type 2 DM

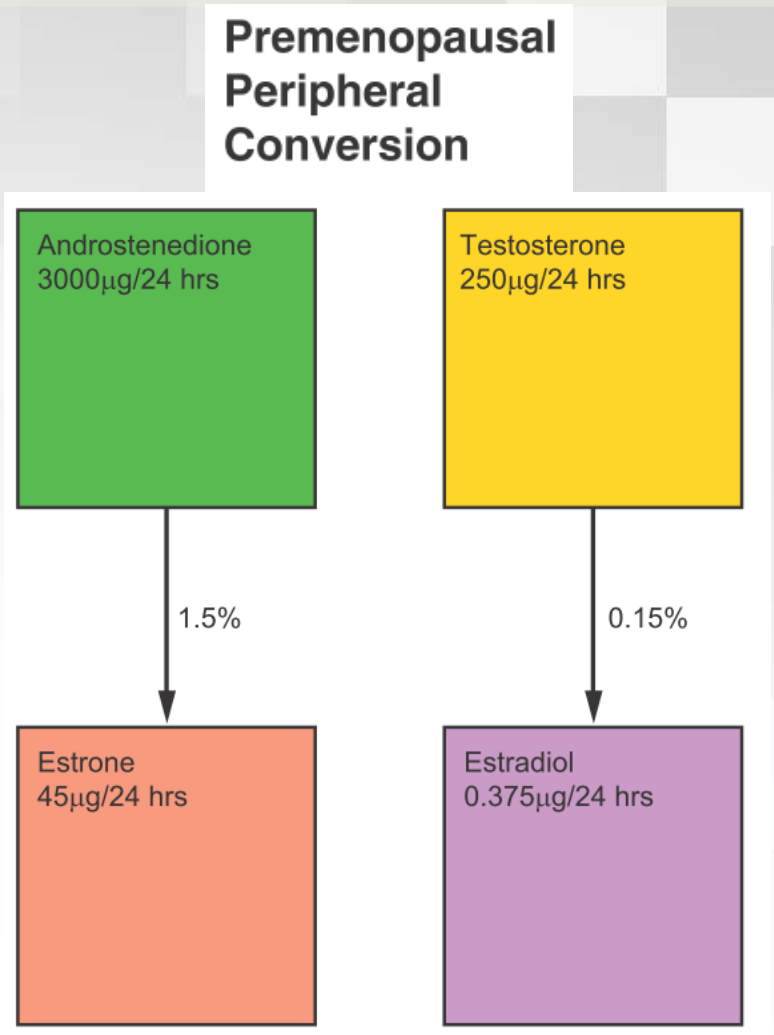
# Estrogen Metabolism

- **Estradiol: major estrogen product of ovary, two pathways**
  - Testosterone → (P450 AROM) → Estradiol
  - Androstenedione → via estrone (secreted in significant amounts) → Estradiol



# Estrogen Metabolism




- E2 production: 100-300ug/day
- ADD production: 3 mg/ day

Significant contribution

# Progesterone Metabolism

- Progesterone production rate
  - No Pph. conversion
  - Combination of secretion from adrenal gland and ovaries
  - Luteal phase: 20-30mg/day
  - 10-20% excreted as pregnanediol

- Blood levels of progesterone
  - After ovulation: 3~15ng/mL
  - CAH
    - serum progesterone: as high as 50 times above normal
    - Serum 17-OHP: 10-400 times normal

# Androgen Metabolism

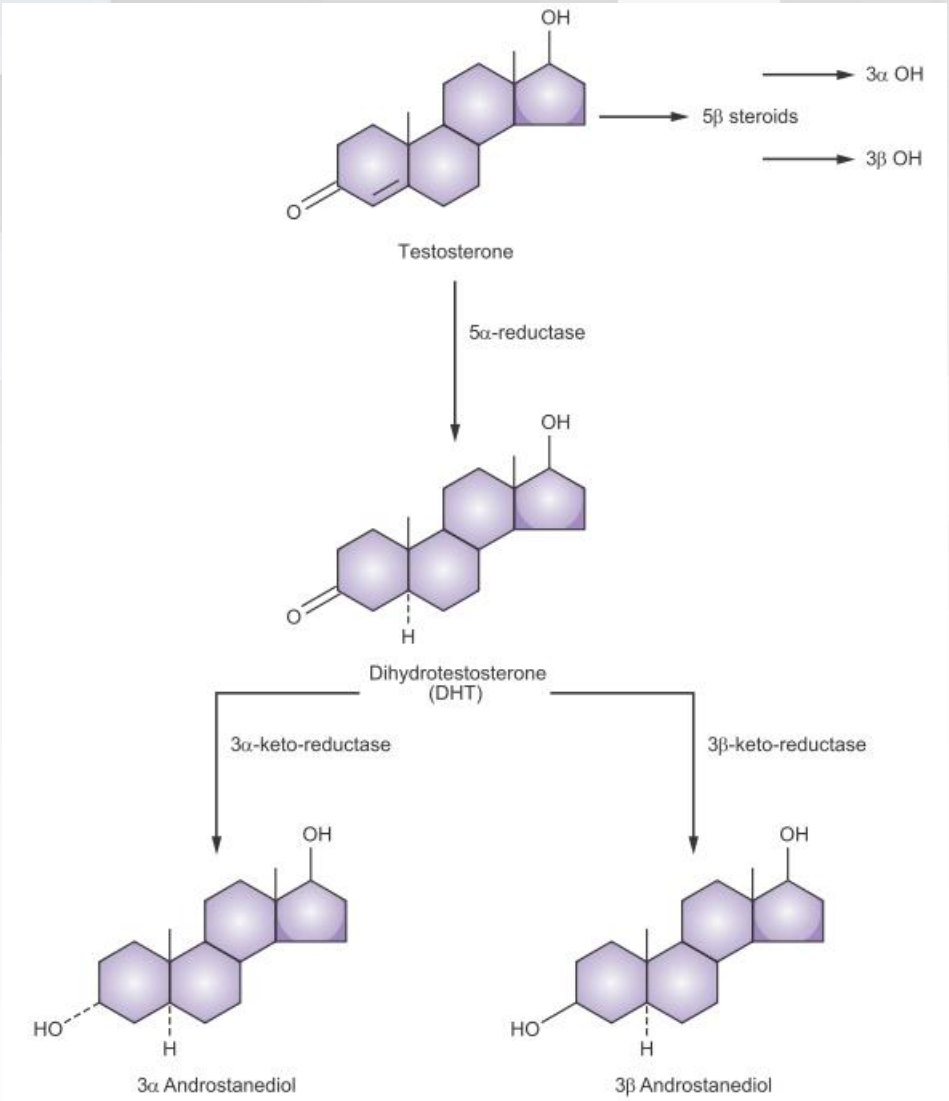
- Origin of circulating androgens in female
  - ADD
    - Adrenal (50%), ovary (50%)
  - DHEA
    - Adrenal (50%), ovary (25%), pph. Conversion (25%)
  - Testosterone
    - Adrenal (25%), ovary (25%), pph. Conversion (50%)

# Androgen Metabolism

- In men..
  - Majority of circulating DHT is derived from testosterone , converted by 5α reductase to DHT
- In women..
  - Production rate: ADD > T
  - Blood DHT **primarily derived from ADD** and partly from DHEA-S

- DHT
  - Intracrine hormone (formed and act within target tissues)
  - Blood DHT only about one-tenth the level of circulating testosterone

# Androgen Metabolism



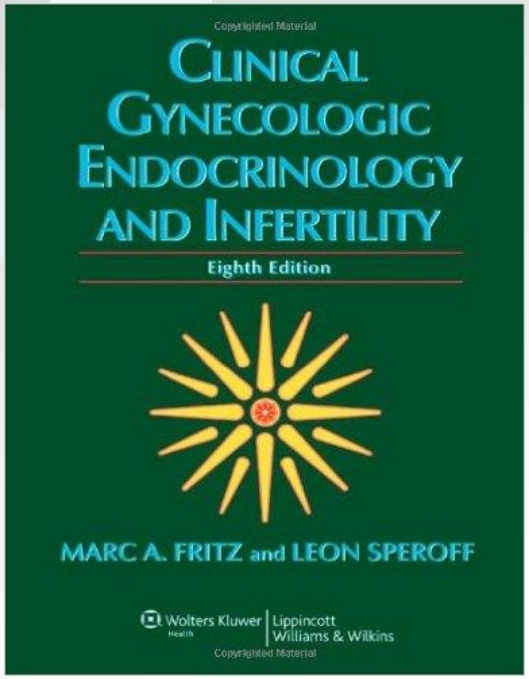

Testosterone converted to DHT by 5 α-reductase

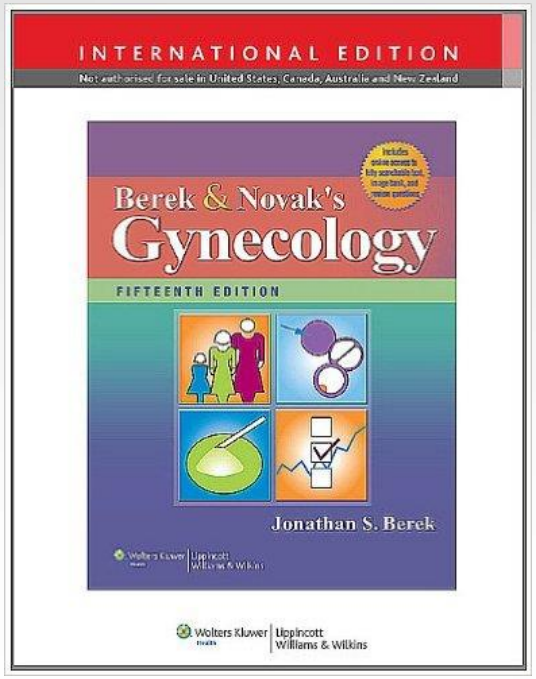
DHT further reduced to androstenediol (inactive) by 3 α-keto-reductase

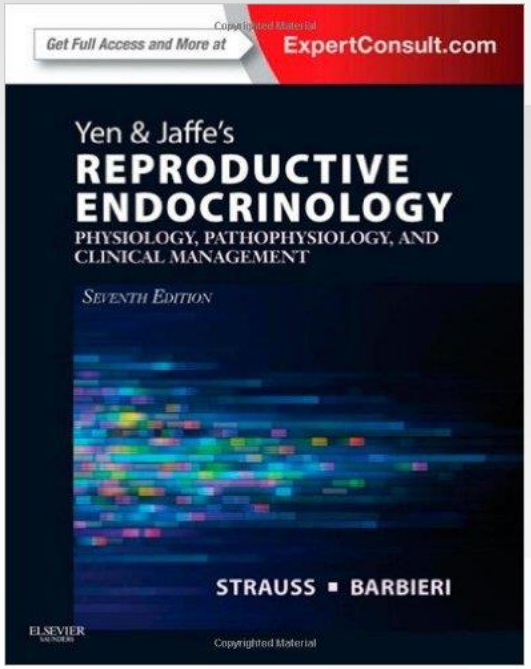
Wolffian duct structures
- epididymis, vas deference, seminal vesicle
- Dependent on testosterone

Urogenital sinus /tubercle
- Male external genitalia, urethra, prostate
- Requires conversion to DHT

# Recommended Readings




Thank You
for Your Attention!
서울대학교병원

# Testosterone and SHBG

## Mass Input for TT

**Data Entry**

| | | |
|---|---|---|
| Total Testosterone: | | ng/dL |
| SHBG: | | nmol/L |
| Albumin (default = 43): | | g/L |

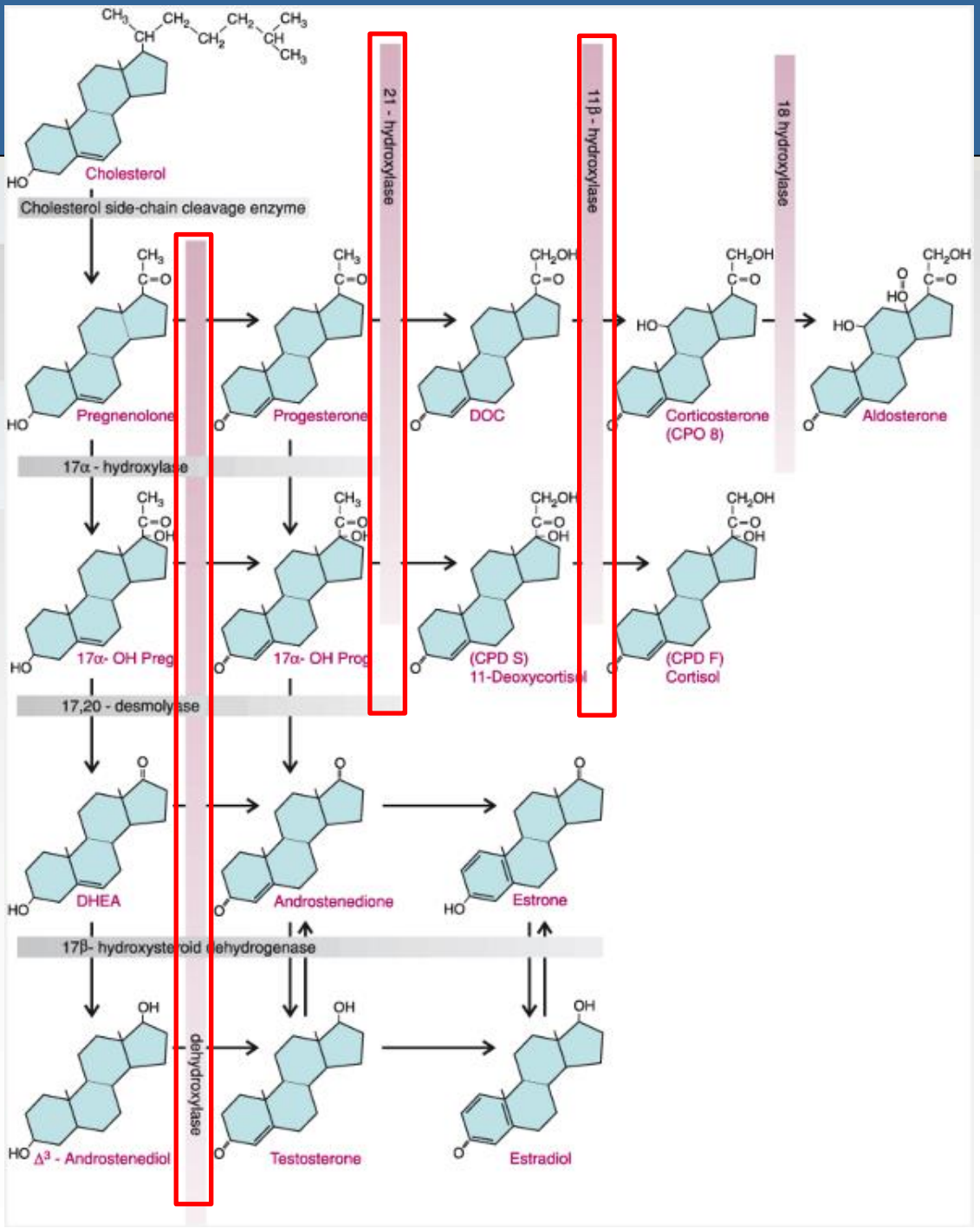
calculate reset print

**Data Results**

| | | | | |
|---|---|---|---|---|
| Free Androgen Index: | | | | |
| Free Testosterone* (cFT): | | pg/mL | | % of Total |
| Bioavailable Testosterone: | | ng/dL | | % of Total |

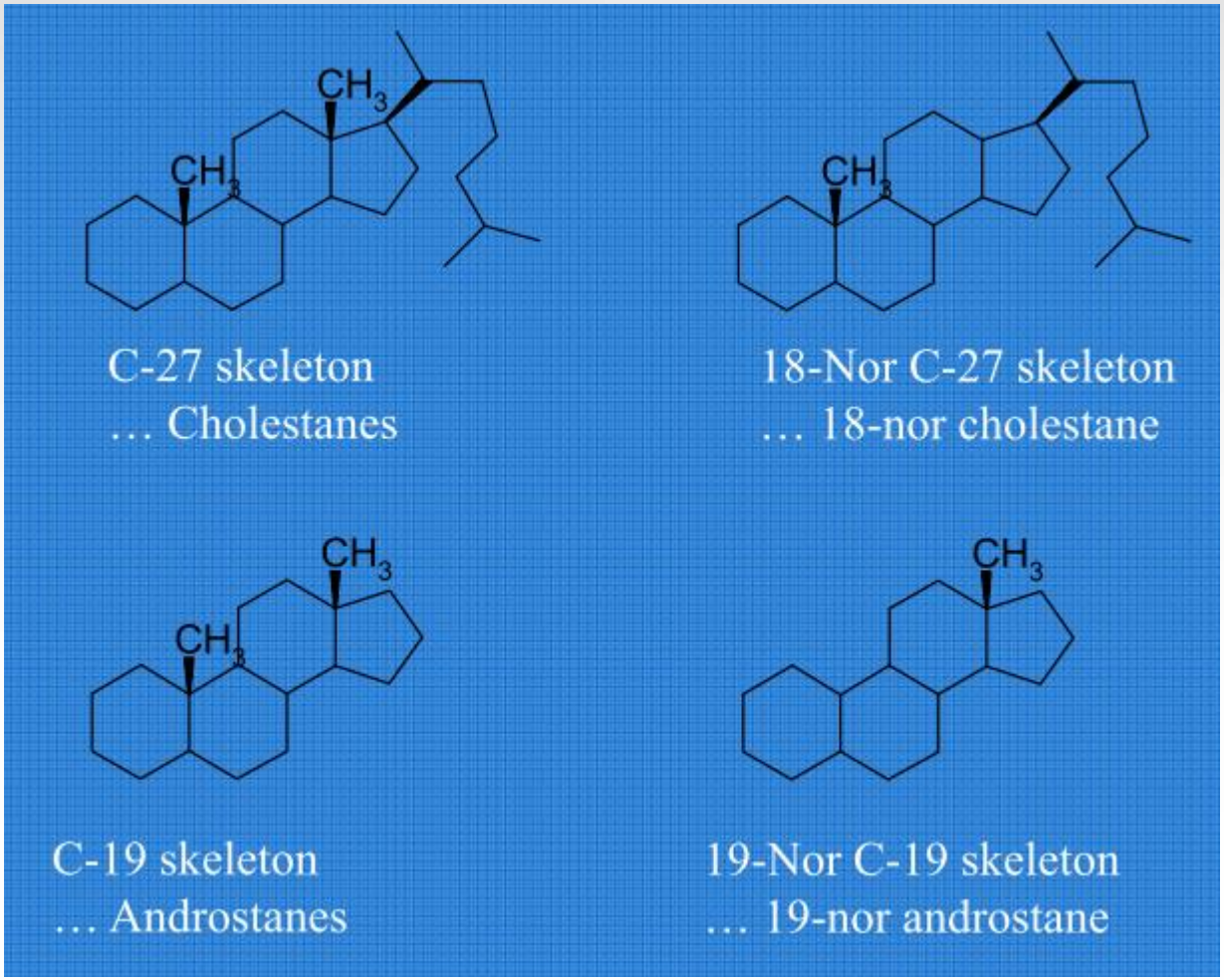
* This software is intended to facilitate calculation of 'free' and 'bioavailable' testosterone estimates, yielding results in accord with Vermeulen et al., JCEM 1999;84:3666, and with the ISSAM calculator. Siemens Healthcare Diagnostics (SHD) makes no claims as to the clinical utility or relative value of these derived measures. Results obtained with this software are intended for use only by qualified healthcare professionals, taking into account all relevant patient data in accordance with best medical practices. The use of this calculator is subject to the license on the distribution CD, cat. no. ZS1383CD.

# CAH


Cholesterol
Cholesterol side-chain cleavage enzyme
Pregnenolone
Progesterone
DOC
Corticosterone (CPO 8)
Aldosterone
17α - hydroxylase
17α- OH Preg
17α- OH Prog
(CPD S) 11-Deoxycortisol
(CPD F) Cortisol
17,20 - desmolyase
DHEA
Androstenedione
Estrone
17β- hydroxysteroid dehydrogenase
Δ3 - Androstenediol
Testosterone
Estradiol
21 - hydroxylase
11β - hydroxylase
18 hydroxylase
dehydroxylase

# Steroid Hormone Nomenclature

- **Usage of ‘Nor’ terminology**



# Preantral Follicle

- Synergistic effect of FSH and estrogen
  - Rapid accumulation of FSH Rc
  - Follicular response to relatively low conc. of FSH
  - Autocrine function for E2 within the follicle