



# The Steroidogenic Pathways

THE KEY TO UNDERSTANDING HORMONES

BY

WILLIAM CLEARFIELD D.O.

# Objectives:

**Provide**

**Provide an Overview of the Steroidogenic Pathway**

**Review**

**Review Both Positive and Negative Influences on the Pathway**

**Provide**

**Understand the impact One Hormone Has on Others in the Pathway**

# Case History-R.R.

- ▶ 22 y/o male w hx of ADHD
  - ▶ Obese
  - ▶ Poor S.A.D. Diet
  - ▶ Poor Motivation, E.D.
  - ▶ Occupation: “Gamer?”
- ▶ VS
  - ▶ 73”, 382 pounds, BMI 50.40
  - ▶ BP 132/78, T 98.2, R 18, P 92, O2 Sat 95%
- ▶ PH
  - ▶ Infected cyst low back removed 4 years ago w continuous drainage.
    - ▶ 2 rounds of antibiotics when first developed without relief.
    - ▶ Drained by surgery q 6 mo. to year.
    - ▶ Mate dresses wound and expresses as much fluid out as possible
  - ▶ Lack of Energy, “Tired but Wired”, Insomnia
  - ▶ No Sex Drive
  - ▶ Loss of Muscle
  - ▶ Depressed
  - ▶ Poor Memory

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- ▶ **Cyst of skin** [ICD-10: L72.9]
- ▶ **Cellulitis of skin** [ICD-10: L03.90]
- ▶ **Morbid obesity [ICD-10: E66.01]**

## ▶ Plan

- ▶ Cleocin 300 MG Oral Capsule Take 1 capsules (600 mg) by mouth every 8 hours for 28 days

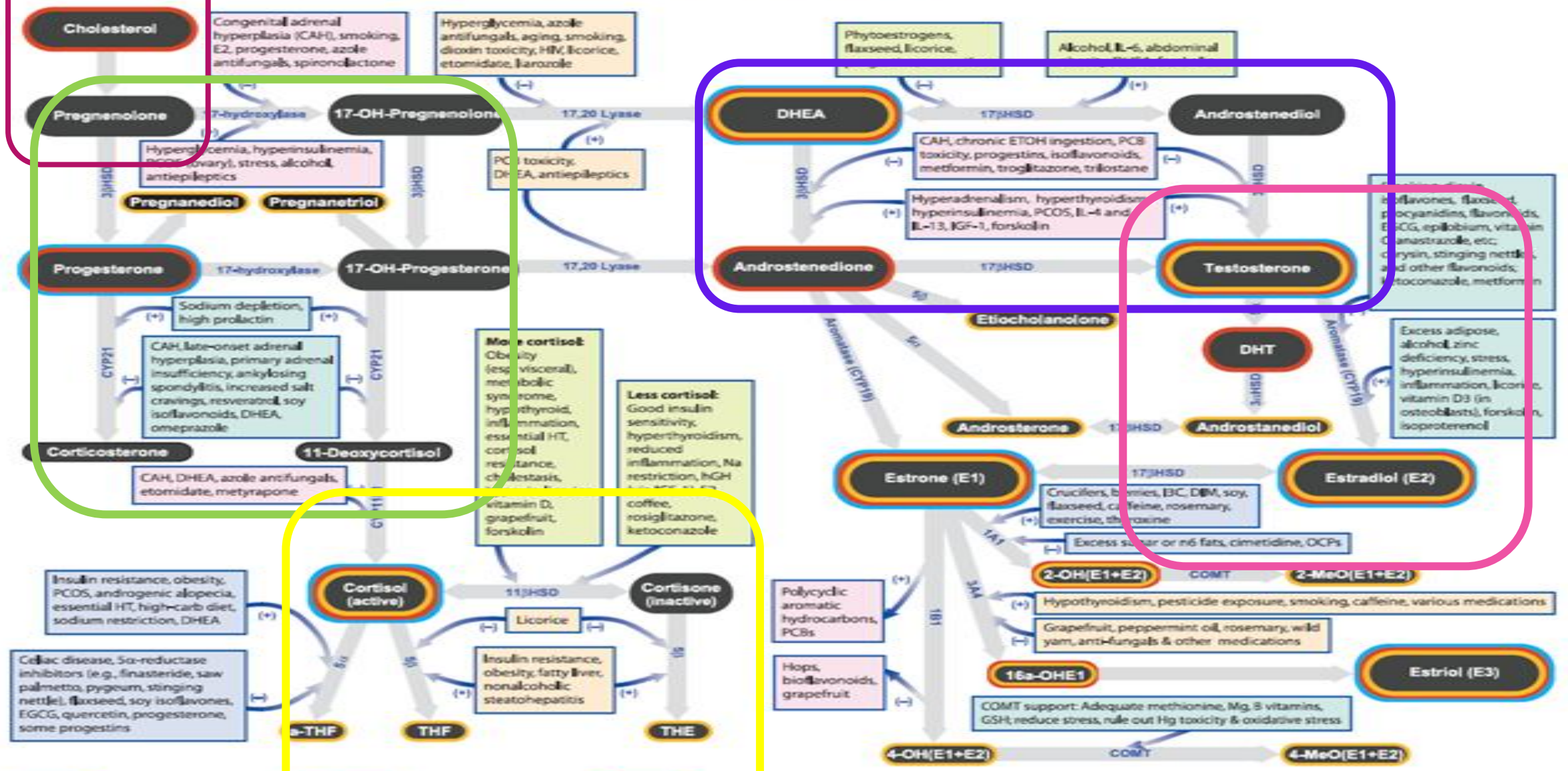
# R.R. Case Study

## ▶ Labs

▶ H/H	16.1./47.3
▶ FBS/Insulin/IR	79/11.2 (Range 2.6-24.9)/2.18 (normal <2.9)
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# R.R. Case Study - Affected Pathways?

## Steroidogenic Pathways





# Common Complaints: Hormonal Etiology

## *Teen Years*

- ▶ Acne
- ▶ PCOS
- ▶ Endometriosis
- ▶ Weight gain
- ▶ Irregular periods
- ▶ Menstrual cramps
- ▶ PMS

## *20's*

- ▶ PCOS
- ▶ Worsening PMS
- ▶ Infertility
- ▶ Hypothyroid
- ▶ Endometriosis
- ▶ Fibroids
- ▶ Heavy periods
- ▶ Painful periods
- ▶ Weight gain

# Common Complaints: Hormonal Etiology

**30's**

Acne

Infertility

PMS

PCOS

Fibroids

Endometriosis

Weight gain

Hair loss

Facial hair

Hypothyroid

Perimenopause

**40's**

Acne

Infertility

PMS

PCOS

Fibroids

Endometriosis

Weight gain

Hair loss

Facial hair

Hypothyroid

Perimenopause



# Common Complaints: Hormonal Etiology

**50's**

Hot flashes  
Night sweats  
Weight gain  
Depression  
Insomnia  
Vaginal dryness  
Low libido  
Hypothyroid

**60+**

Osteoporosis  
Decreased libido  
Sexual dysfunction  
Insomnia  
Migraine headaches  
Mood swings/anxiety  
Hair loss/Hair in places it shouldn't be  
Erectile dysfunction

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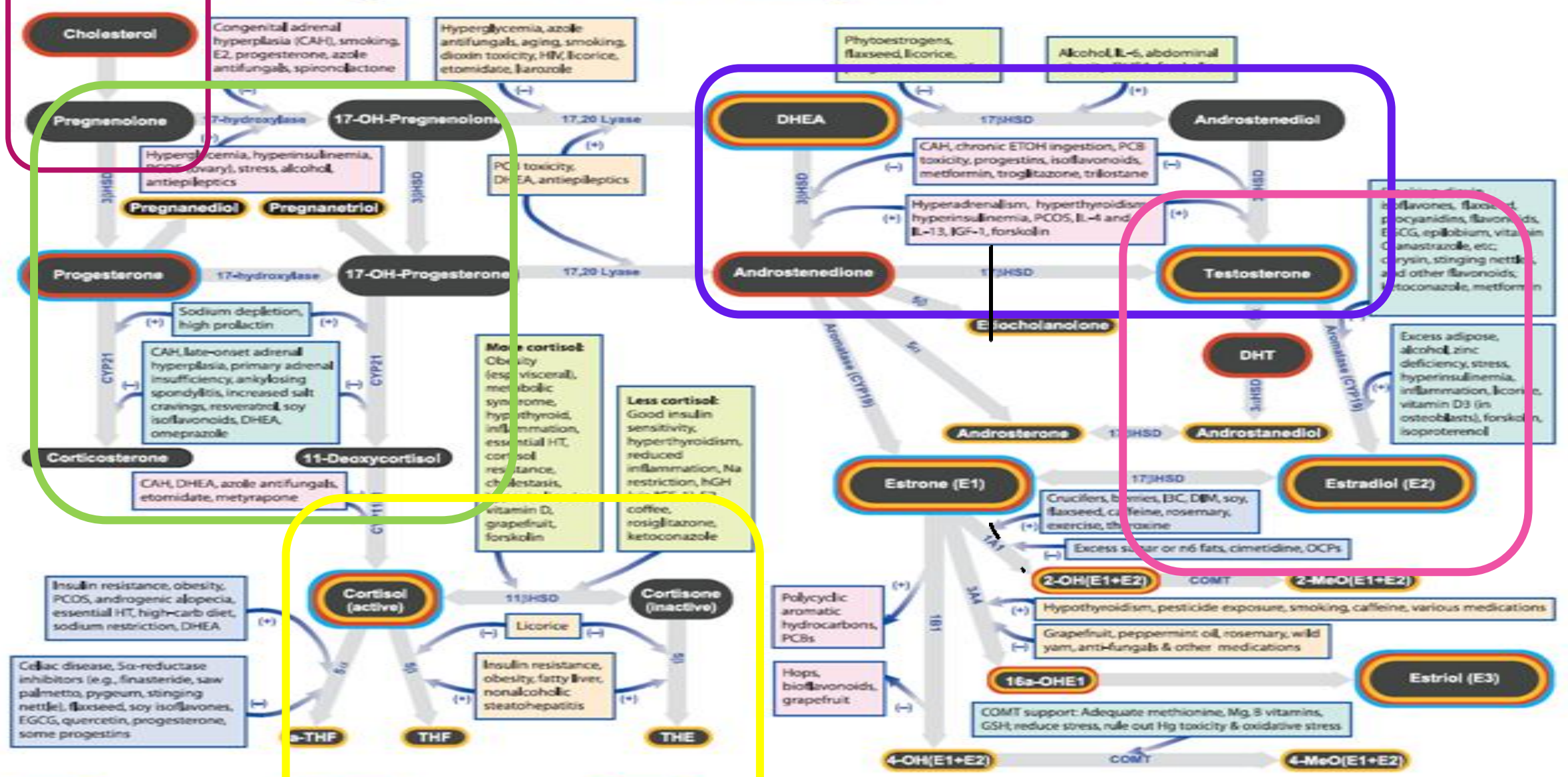
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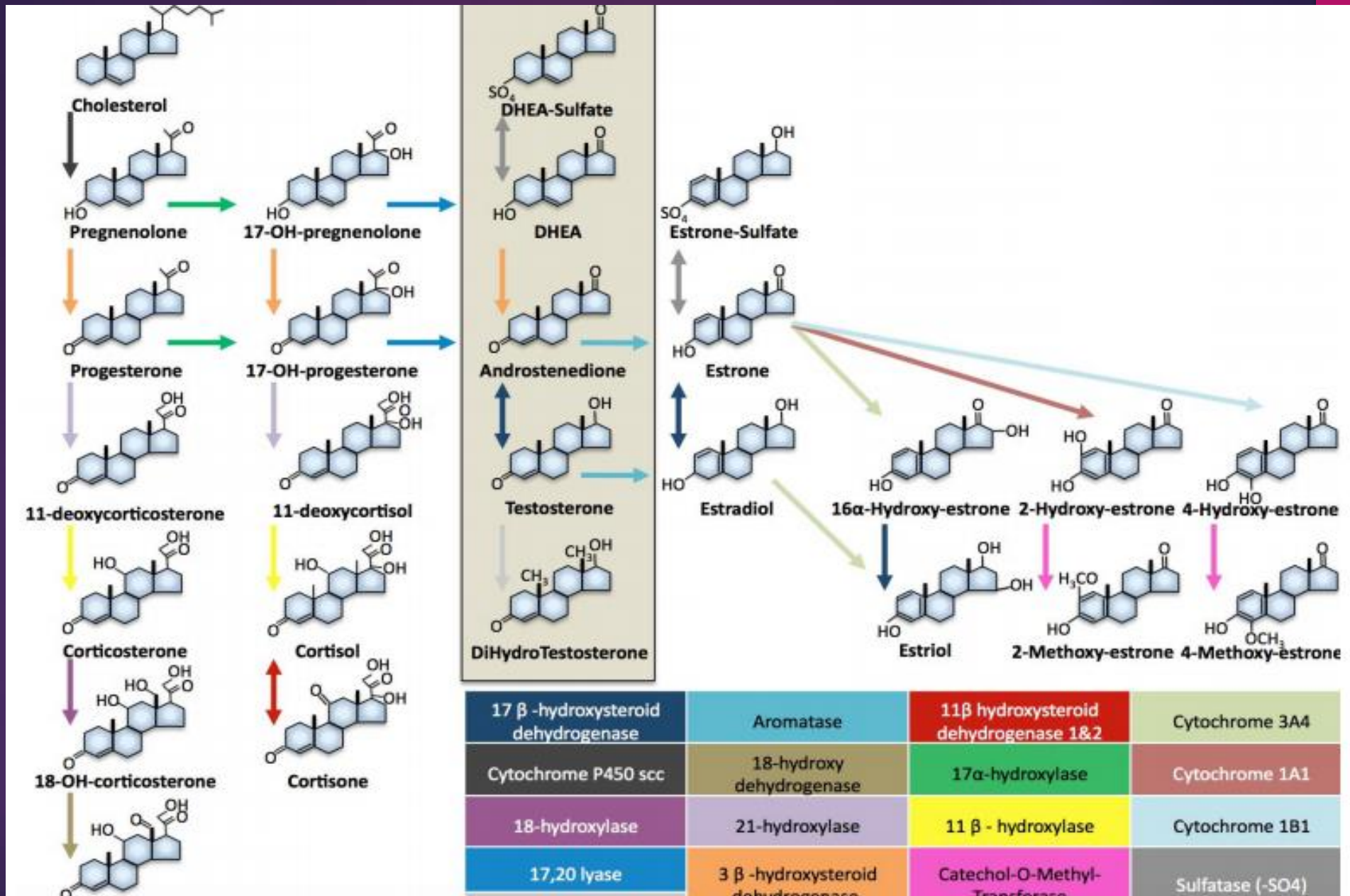
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# R.R. Case Study - Affected Pathways?

## Steroidogenic Pathways







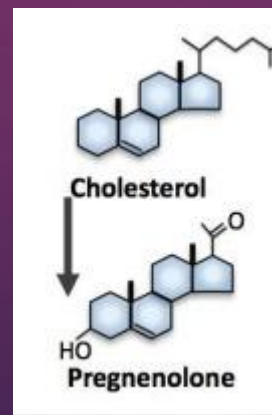


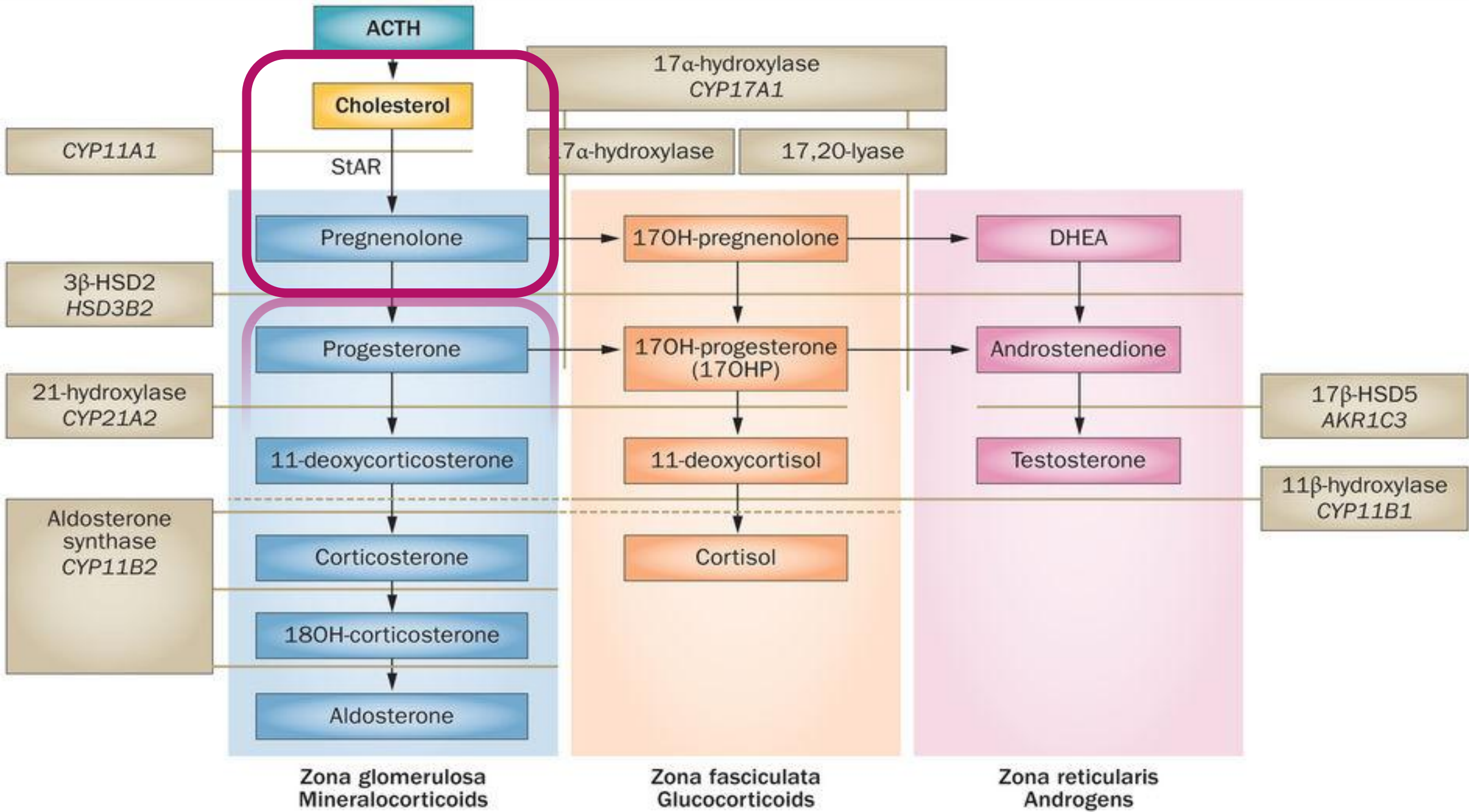
# Cholesterol is the Patriarch/Matriarch of the Steroidal Hormones

## *Cholesterol*

- ▶ Healthy fats and an adequate cholesterol levels to make hormones
- ▶ Very low cholesterol levels contribute to poor hormone production
- ▶ Statins, Red Yeast Rice, Binders, and genetically low cholesterol
  - ▶ Associated with increased risk for cancer, suicide, diabetes, memory concerns

Conversion of Cholesterol  
Modulated by  
To Pregnenolone  
Cytochrome P450



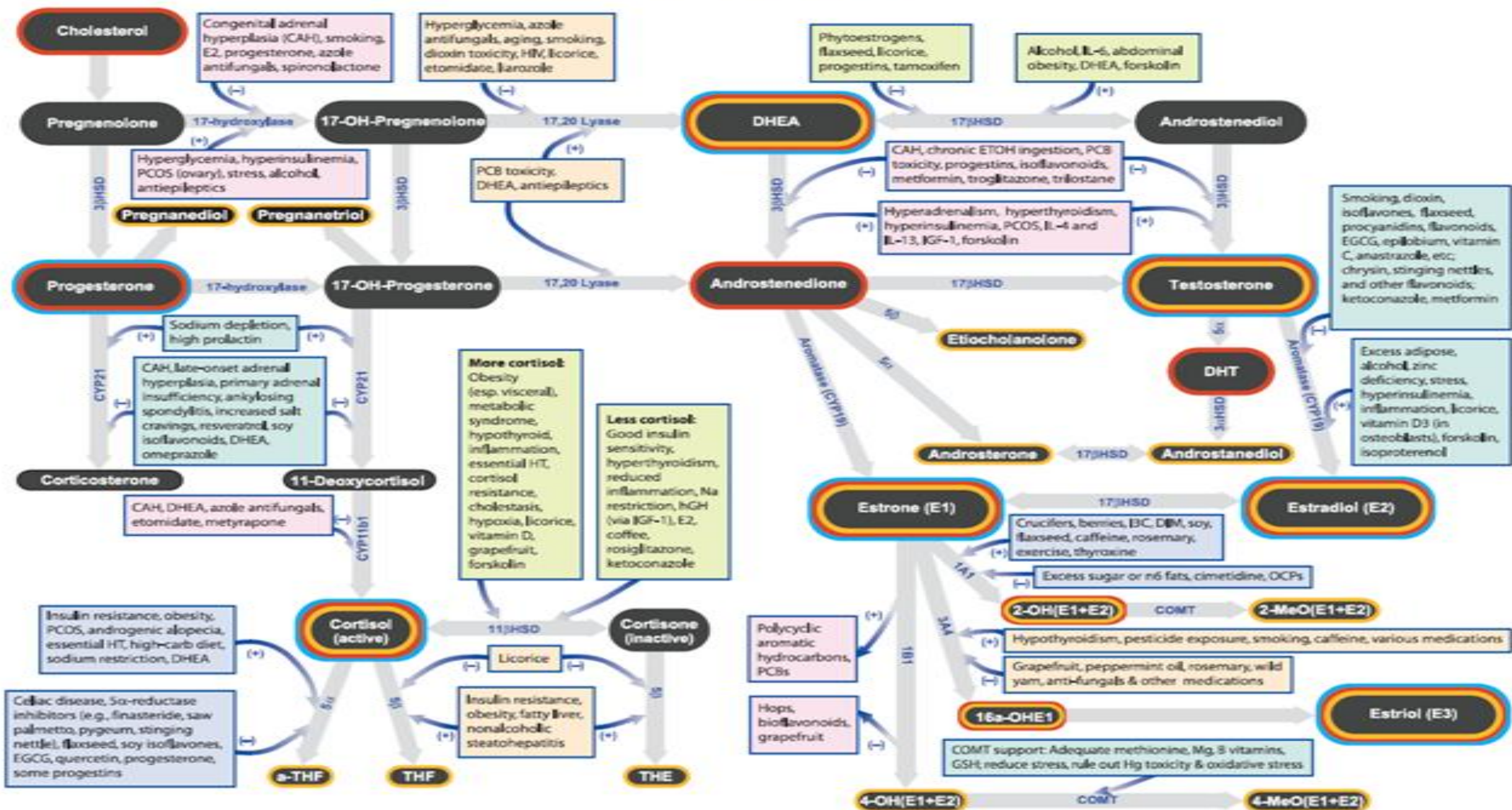


# Pregnenolone

- ▶ **Pregnenolone –**
  - ▶ **Manufactured primarily in adrenal glands**
  - ▶ **“Grandmother” Hormone**
    - ▶ **Decreases with Stress, Aging**
    - ▶ **Enhances memory and reduces stress-induced fatigue**
    - ▶ **Increases resistance to stress**
    - ▶ **Reduces PMS**
    - ▶ **Improves Immunity**
    - ▶ **Repairs myelin sheaths**

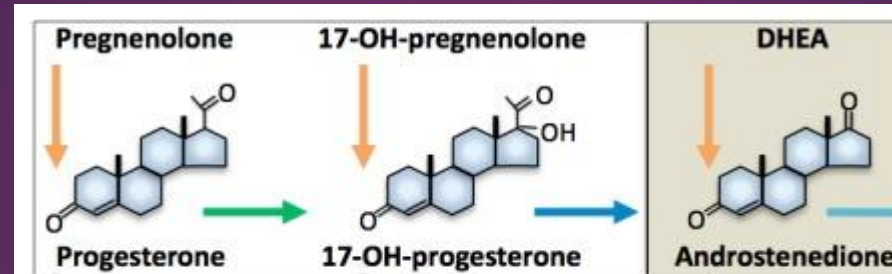


# Steroidogenic Pathways



# To Progesterone, Testosterone and Beyond!

## *3 $\beta$ -Hydroxysteroid Dehydrogenase (3 $\beta$ -HSD)*



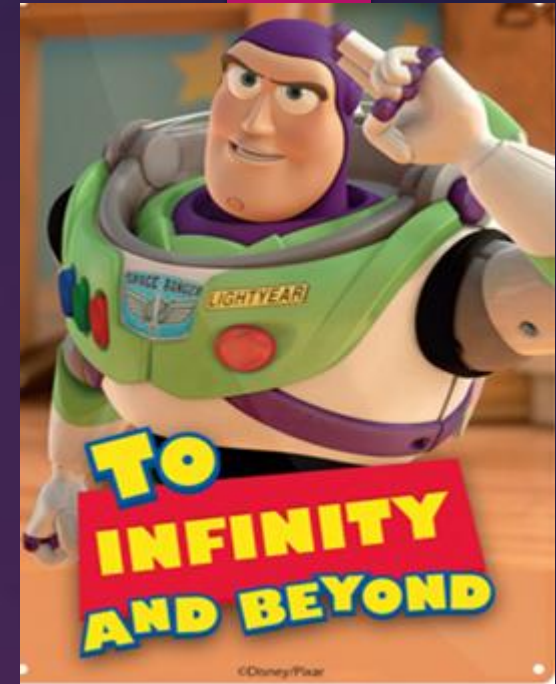
Converts Pregnenolone to Progesterone

Converts 17-OH Pregnenolone to 17-OH Progesterone

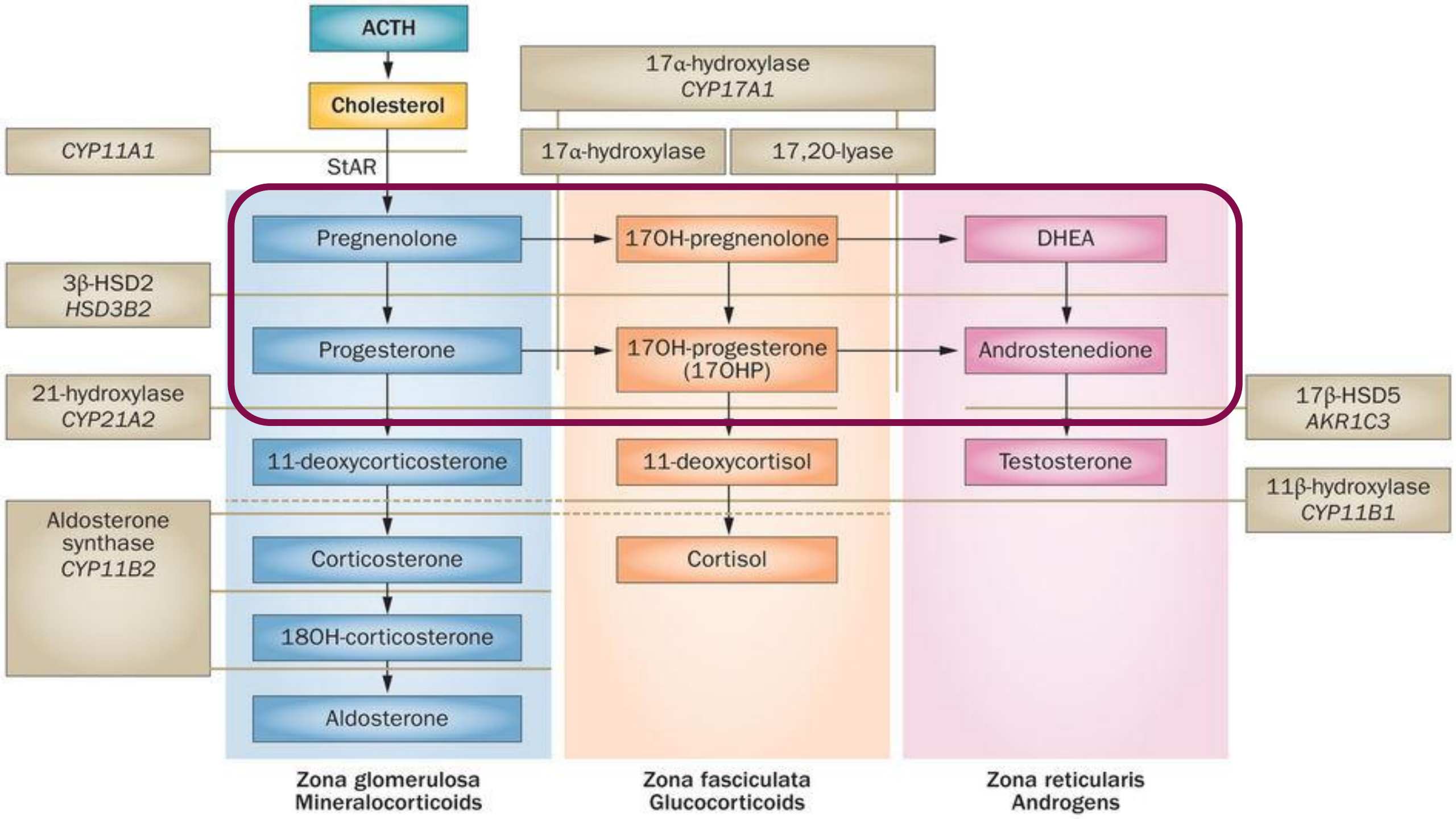
Converts DHEA to Androstenedione

Diminished with: Progestins, Metformin, Isoflavonoids, PCB's

Increased with: PCOS, Hyperinsulinemia, IL-4 and IL-13 (allergies),  
Hyperthyroidism – Forskolin







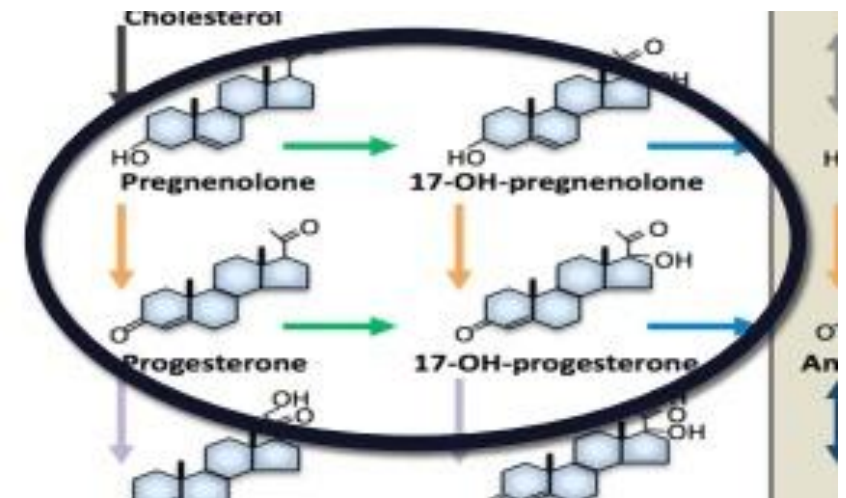


# Progesterone

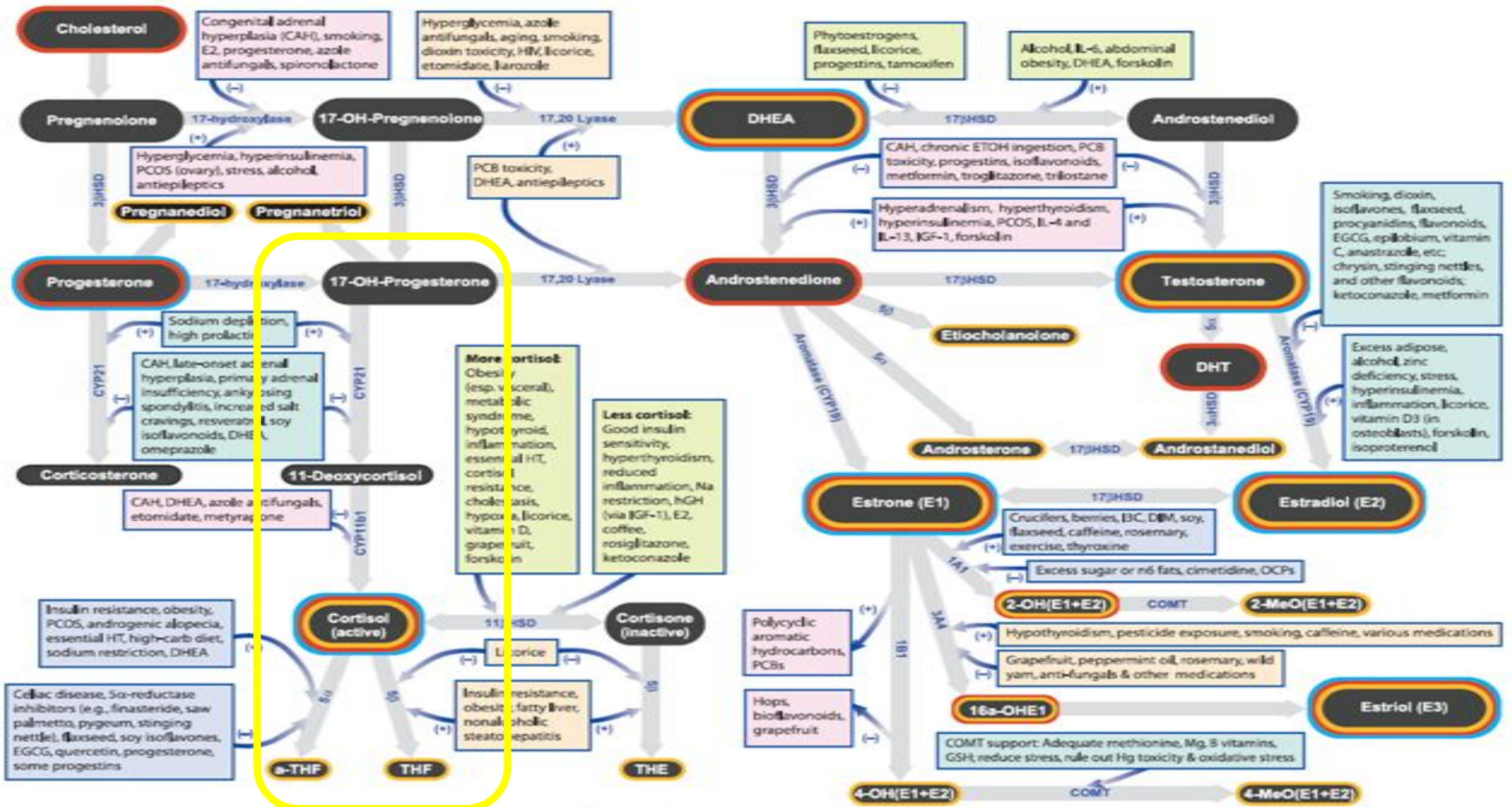
- ▶ **Originates mainly in the ovaries**
- ▶ **Increase in Progesterone:**
  - ▶ Pregnancy
  - ▶ Pregnenolone administration
  - ▶ Chaste Tree Berry (Vitex)
- ▶ **Decreased Progesterone:**
  - ▶ Progesterone based Birth control pills
  - ▶ Stress
  - ▶ Luteal phase defect/anovulation
  - ▶ Increased insulin
  - ▶ High prolactin
  - ▶ Underweight  
Hypothyroidism
  - ▶ Opioids
  - ▶ Underweight
  - ▶ Progestin releasing IUD (Mirena – releases low levels of progestins)

# 17 $\alpha$ -HYDROXYLASE

- ▶ Converts Pregnenolone to 17-OH Pregnenolone
- ▶ Converts Progesterone to 17-OH Progesterone
- ▶ Downregulated activity:
  - ▶ • Spironolactone
  - ▶ • Azole antifungals
  - ▶ • Congenital adrenal hyperplasia
- ▶ Upregulated activity:
  - ▶ • High insulin
  - ▶ • PCOS
  - ▶ • Hyperglycemia
  - ▶ • Stress
  - ▶ • Alcohol



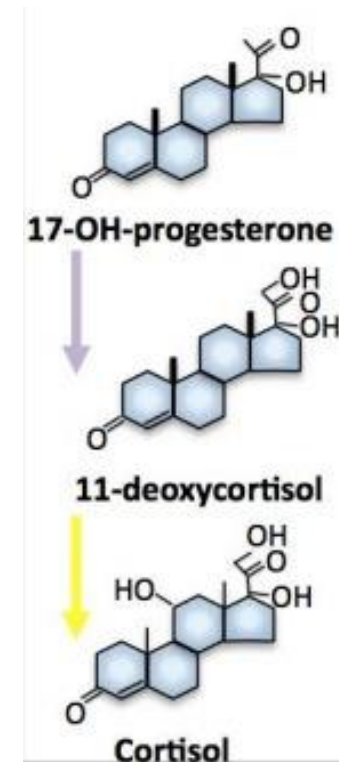
# Steroidogenic Pathways



# 21 Hydroxylase and 11 Hydroxylase

## ▶ Cortisol Production

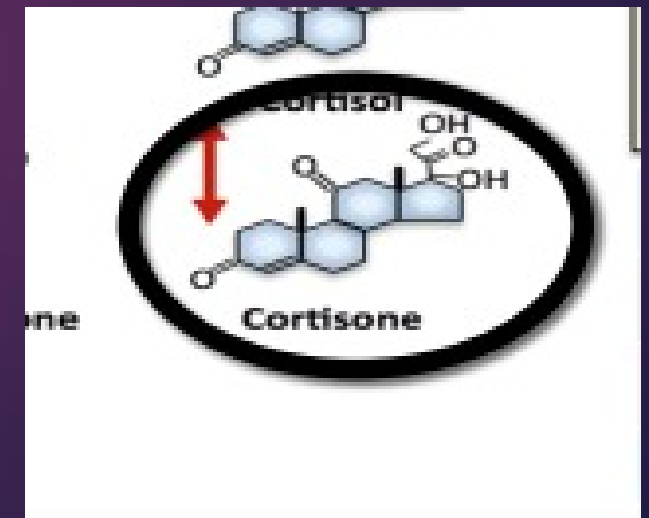
- ▶ • Made in the adrenal glands
- ▶ • Two enzyme reactions to convert from 17-OH-Progesterone
- ▶ • Increased conversion to cortisol seen in:
  - ▶ Sodium depletion
  - ▶ High prolactin
  - ▶ Stress
  - ▶ Inflammation
  - ▶ Cushing's
  - ▶ Obesity
- ▶ • Decreased cortisol:
  - ▶ Glucocorticoid use
  - ▶ Addison's Disease
  - ▶ Opioid use
  - ▶ Chronic marijuana use
  - ▶ Accutane





# 11 $\beta$ – Hydroxysteroid Dehydrogenase 1 & 2

- ▶ **Cortisol (active stress hormone ) vs Cortisone (inactive form)**
  - ▶ Via 11 $\beta$  hydroxysteroid dehydrogenase 1&2
  - ▶ **MORE CORTISOL**
    - ▶ Stress, inflammation Cushing's disease, obesity, hypothyroidism, licorice, grapefruit, high insulin, excess sodium, hypoxia, vitamin D, forskolin
  - ▶ **MORE CORTISONE**
    - ▶ Hyperthyroidism, estradiol, quality sleep, hGH (via IGF-1), good insulin sensitivity, reduced inflammation, Na restriction
- ▶ **Cortisol is metabolized by: 5 $\alpha$ -Reductase and 5 $\beta$ -Reductase (and 3 $\alpha$ -HSD) to a/b-THF & THE (cortisone metabolite) for excretion**
  - ▶ Increased in:
    - ▶ Obesity
    - ▶ High insulin
    - ▶ Hyperthyroid
  - ▶ Decreased in:
    - ▶ Hypothyroidism
    - ▶ Anorexia
    - ▶ Poor liver function

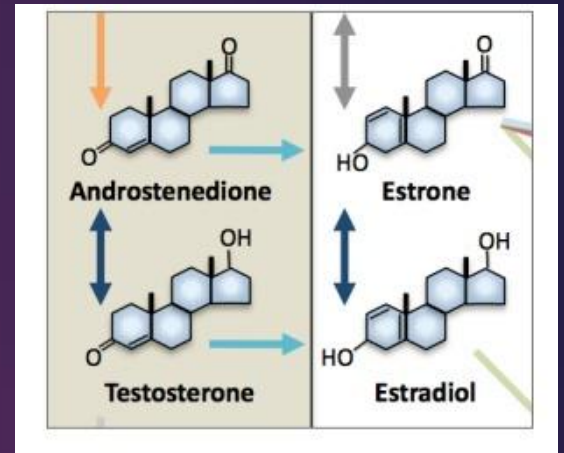






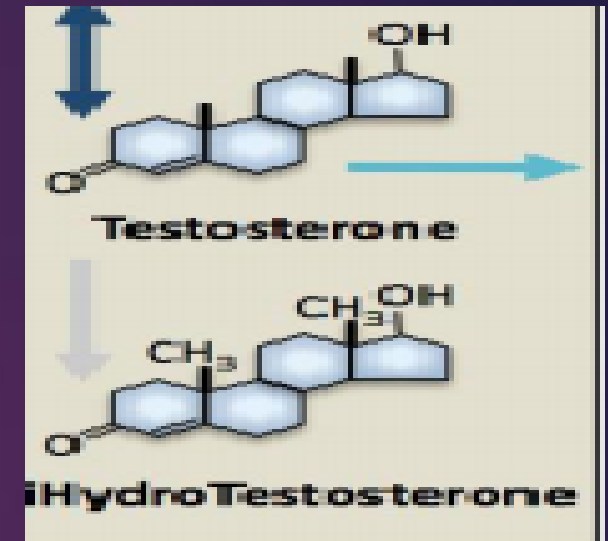
# Aromatase

- ▶ • Conversion of Androstenedione to Estrone (E1)
- ▶ • Conversion of Testosterone to Estradiol (E2)
  - ▶ Decreased aromatase activity:
    - ▶ Chrysin
    - ▶ Zinc
    - ▶ Flaxseed
    - ▶ Nettles
    - ▶ EGCG (green tea extract)
    - ▶ Anastrozole
  - ▶ Increased aromatase activity:
    - ▶ Inflammation
    - ▶ Excess adipose
    - ▶ High insulin
    - ▶ Alcohol
    - ▶ Mold/biotoxin illness (CIRS)



# 5 Alpha Reductase

- ▶ Makes androgens (testosterone) more potent •
- ▶ Activity:
  - ▶ Metabolizes progesterone into  $\alpha$ -Pregnanediol
  - ▶ Metabolizes cortisol into  $\alpha$ -THF (b-metabolites of both through  $5\beta$  activity)
- ▶ **Upregulated leads to high androgen symptoms:**
  - ▶ Men (thinning hair, prostate issues)
  - ▶ Women (PCOS, thinning hair, acne, facial hair growth)
- ▶ Increased enzyme activity:
  - ▶ High insulin and obesity
- ▶ Decreased enzyme activity:
  - ▶ Saw palmetto, nettles, EGCG, progesterone, zinc, finasteride



# A Word on 5 Alpha Reductase Inhibitors

## ▶ Finasteride and Dutasteride Cross BBB

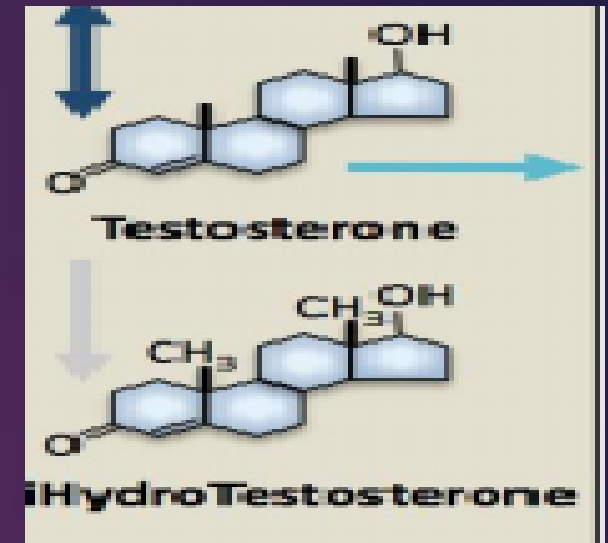


Blocks Enzyme Activity Centrally =

- ▶ Depression
- ▶ Fatigue
- ▶ Sexual dysfunction

## ▶ Preference for Peripherally Acting 5 AR

- ▶ Saw Palmetto, Pygeum, Zinc
- ▶ Nettles, Pumpkin Seed Extract
- ▶ EGCG, Pomegranate Juice
- ▶ Progesterone



▶ Gordon, M.; Traumatic Brain Injury; 2016 Millennium Health Centers Inc.. p.258

▶ Edinger KI: Testosterone's Analgesic, Anxiolytic and Cognitive Enhancing Effects May Be Due to action of 5 Alpha reductase metabolites in Hippocampus. Behavioral Science 2004 Dec:118(6):1352-64





# Estrogens

## E1 (Estrone)

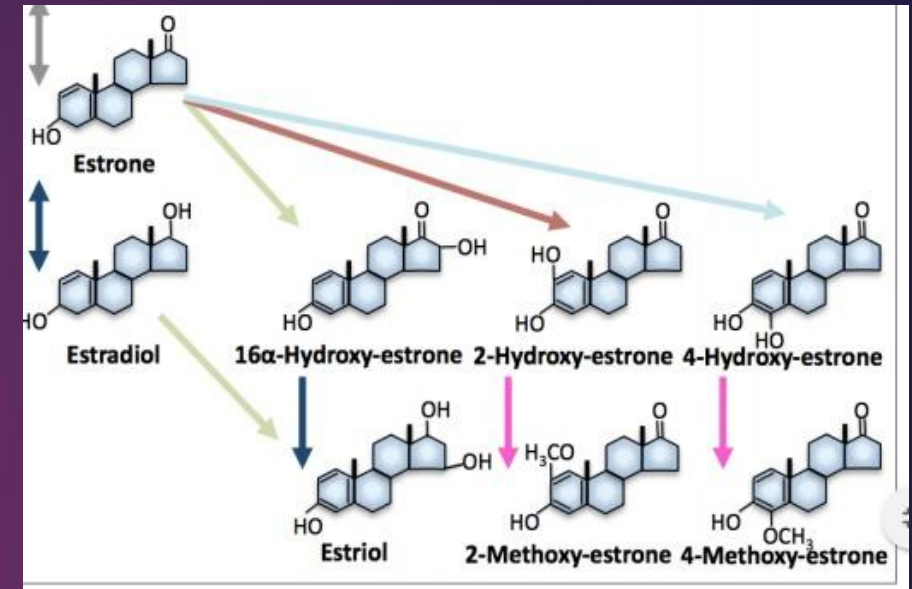
Main estrogen body makes postmenopausally.  
Increased levels may inc. breast ca. risk

## E2 (Estradiol)

Over 400 functions in body  
Most potent estrogen

## E3 (Estriol)

Least powerful, most beneficial  
Efficient metabolism results in predominance of 2-OH-E1 and 2-MeOE1  
Inefficient estrogen metabolism results in predominance of 16-OH-E1 and 4-OH-E1  
Acts negatively to allow oxidation  
Damages DNA (4-OH-E1)







# Estrogen

## Healthy metabolism:

Exercise

Cruciferous vegetables

Pesticide free diet

Weight loss

DIM/I3C

Less/no ETOH

Soy

High protein-anti-inflammatory diet

Flaxseed

Omega-3 fats

## Unhealthy metabolism:

Pesticides

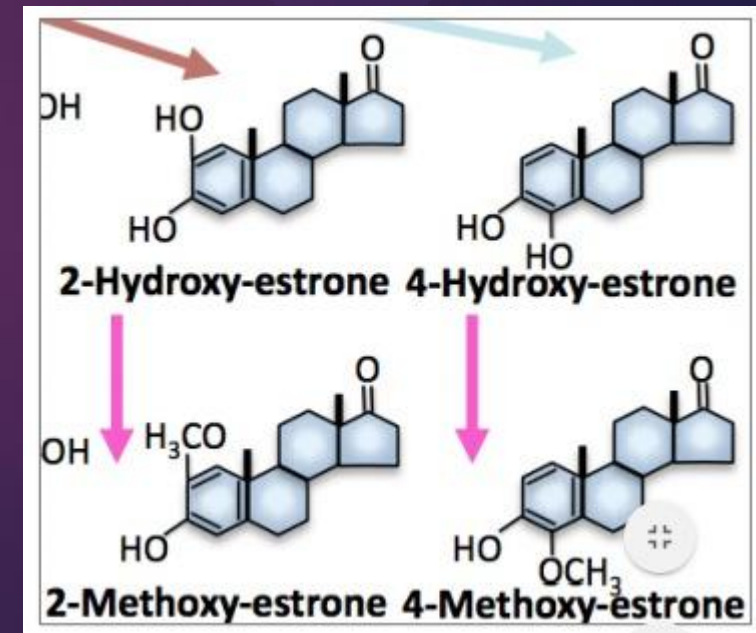
Smoking

Caffeine (conversion to 16OHE1)

Hypothyroidism

# COMT – Catechol-O-Methyltransferase

- ▶ One of several enzymes that degrade catecholamines:
  - ▶ Dopamine, Epinephrine, Norepinephrine
- ▶ Principal enzyme in the conjugation pathway for hydroxylated estrogens
  - ▶ Carcinogenic 4-hydroxy estrogens
- ▶ Methylation of 2-OH/4-OH estrogens is slowed in:
  - ▶ Genetic variants (SNPs) in MTHFR and COMT
- ▶ COMT is upregulated by:
  - ▶ Methyl donors
    - ▶ S<sub>Ado</sub>Me, B vitamins, TMG, choline, folate, and methionine





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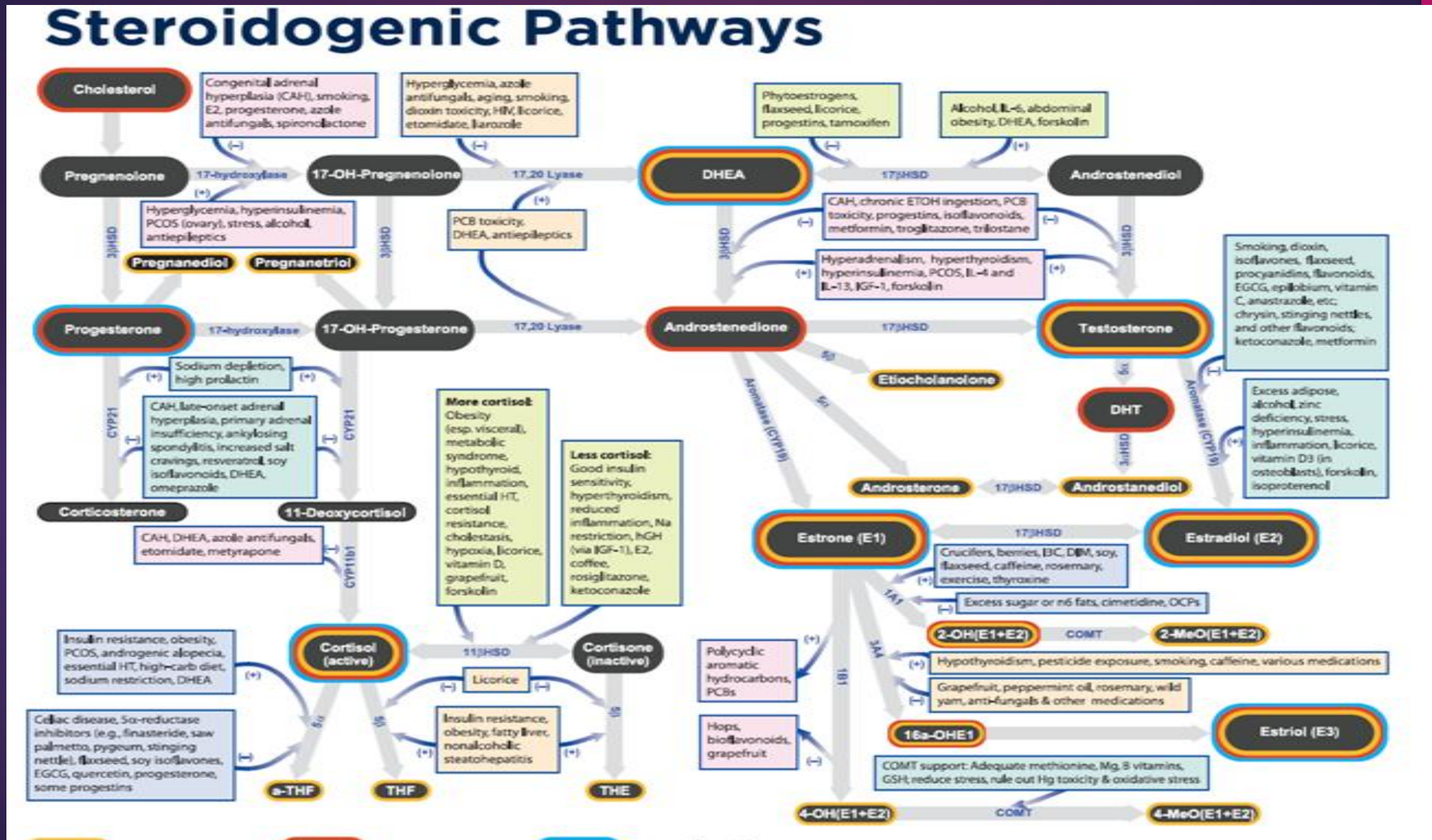
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# As Reflected in the Steroidogenic Pathway, What is Wrong?



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# Recommendations?

## ▶ **Stress Reduction**

- ▶ Emotional/Mental – breathing exercises, prayer, meditation, yoga, etc
- ▶ Infection – antimicrobials/antifungals –
- ▶ Inflammation – dietary (low sugar/high protein) gluten free
  - ▶ Anti-inflammatories (omega-3 fatty acids, curcumin, etc)

## ▶ **Hormone Support**

- ▶ **Pregnenolone** 50 mg
- ▶ **DHEA** 25 mg – 50 mg
- ▶ **Testosterone** Yes or No?
- ▶ **Aromatase Inhibition**
  - ▶ Green Tea, Zinc citrate 50 mg/d, Flaxseed, Chrysin, Progesterone 2% Cream w gynecomastia
- ▶ **Adaptogenic** Herbs
  - ▶ Panax Ginseng, Rhodiola, Ashwagandha
- ▶ **Vitamin D3**
  - ▶ How much?, When?



# Follow Up

## ▶ 8 Weeks

- ▶ More strength, feels better, more energy
- ▶ Weight 365, following diet 80%, exercising 4 days/wk.
- ▶ Wound closed, no drainage for first time in 4 year
- ▶ Plan : D/C antibiotics, vitamin e oil for wound care
- ▶ Cont. Hormone Regimen 2 mo. then off a month

## ▶ 20 weeks

- ▶ Weight 344
- ▶ Testosterone 527, free 14.3
- ▶ Estradiol 27.4
- ▶ 25 OH Vitamin D 34.6
- ▶ Cortisol 19
- ▶ **ED Gone**

## ▶ 52 Weeks

- ▶ Weight 295
- ▶ Began Community College
- ▶ Wound healed
- ▶ Testosterone 874, free 17.1
- ▶ Estradiol 19.6
- ▶ 25 OH Vitamin D 49

## ▶ Regimen

- ▶ Gluten Free Diet 2000-2400 cal/d
- ▶ Tribulus/Tongkat ali combo for Testosterone Boost
- ▶ Continues Adrenal Regimen-No glandulars
- ▶ Vitamin D3 2000 IU @ bedtime

# T.G.-Case History

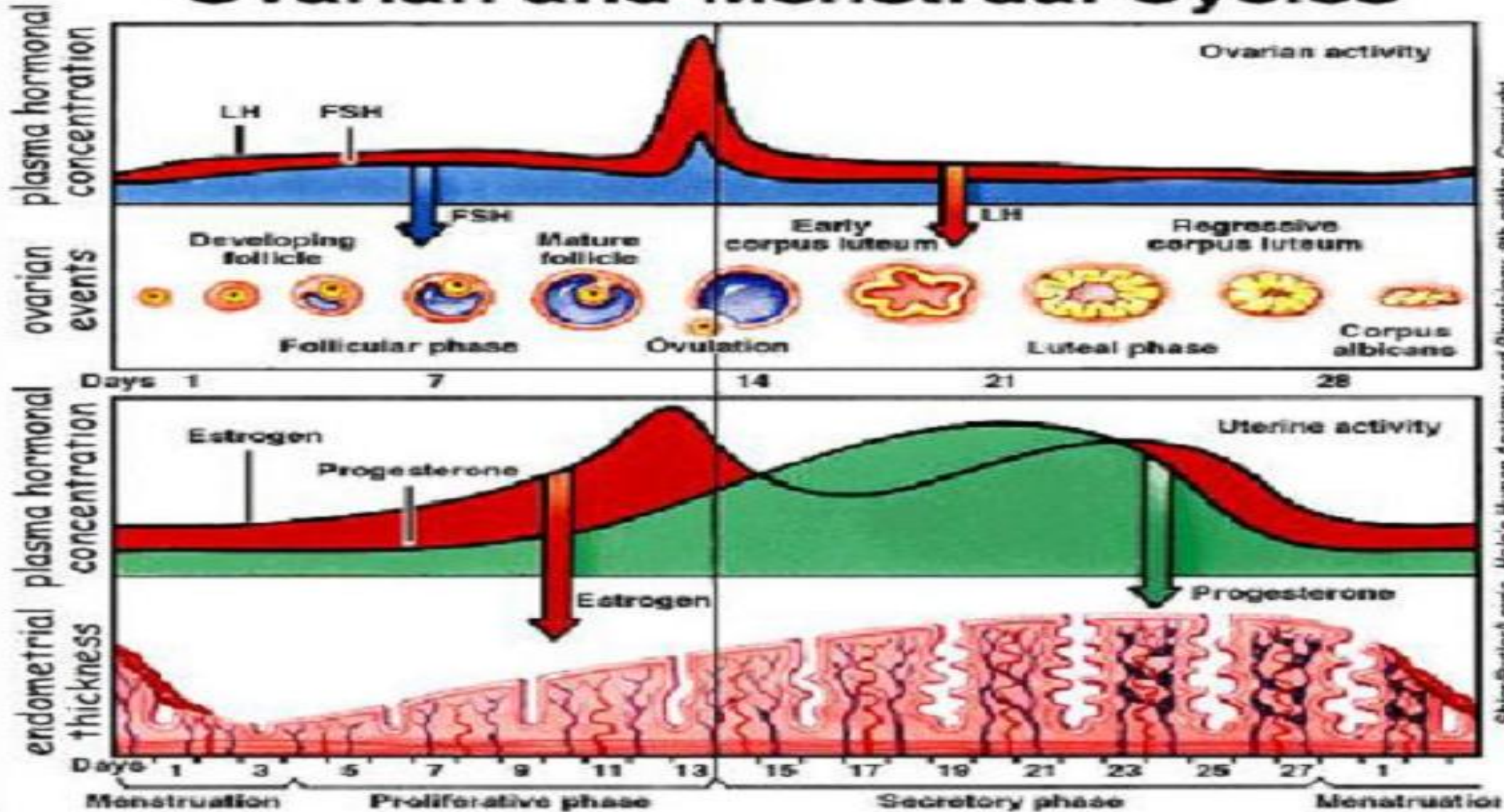
- ▶ **34 year old female with history of:**
  - ▶ Prolonged, painful menses, scanty flow at times
  - ▶ Hirsutism, Acne
  - ▶ Infertility
  - ▶ Overweight
  - ▶ Depression
  - ▶ Sensitive to sugar, needs to eat every 2-3 hours or becomes light headed, And. PAin 2 hours after eating
- ▶ **PE**
  - ▶ Ht: 61", Wt. 201#, BMI 37.98
  - ▶ BP 120/64, P82, R18, PO2 95%
  - ▶ Uterine Fibroid
  - ▶ Gallstones on Ultrasound

# T.G. Labs

- ▶ H/H/Ferritin 12.5/39.7, 70 (90-120)
- ▶ FBS/Insulin/IR/HbA1c 82/29.5 (Range 2.6-24.9)/5.97 (<2.9), 5.7
- ▶ cRP 27.3 (Range 0.0-4.9)
- ▶ Chol/Trig/HDL/LDL 232/1118/71/127
- ▶ Testosterone Total 66 (10-55), Free Testosterone 7.1 (0-4.2)
- ▶ DHEA 292 (55-345, goal 200-250)
- ▶ Estradiol 28 day saliva, Serum Day 19 of Cycle, 132
- ▶ Estrone Day 19 of Cycle 106
- ▶ Progesterone 28 day saliva, Serum Day 19 of Cycle, 0.6
- ▶ E/P Ratio, P/E Ratio 397, 4.55
- ▶ TSH/free T3/TPO/TAG/rT3 3.11, 3.5, 8, <1, 16
- ▶ 25 OH Vitamin D 27.9 (30-100)
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# Menstrual Cycle

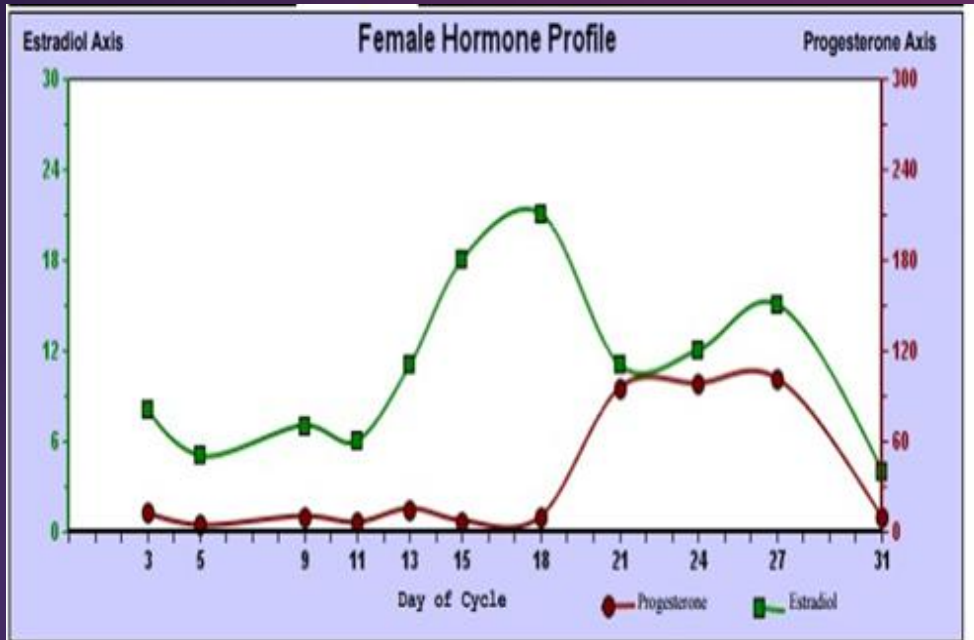
## Ovarian and Menstrual Cycles



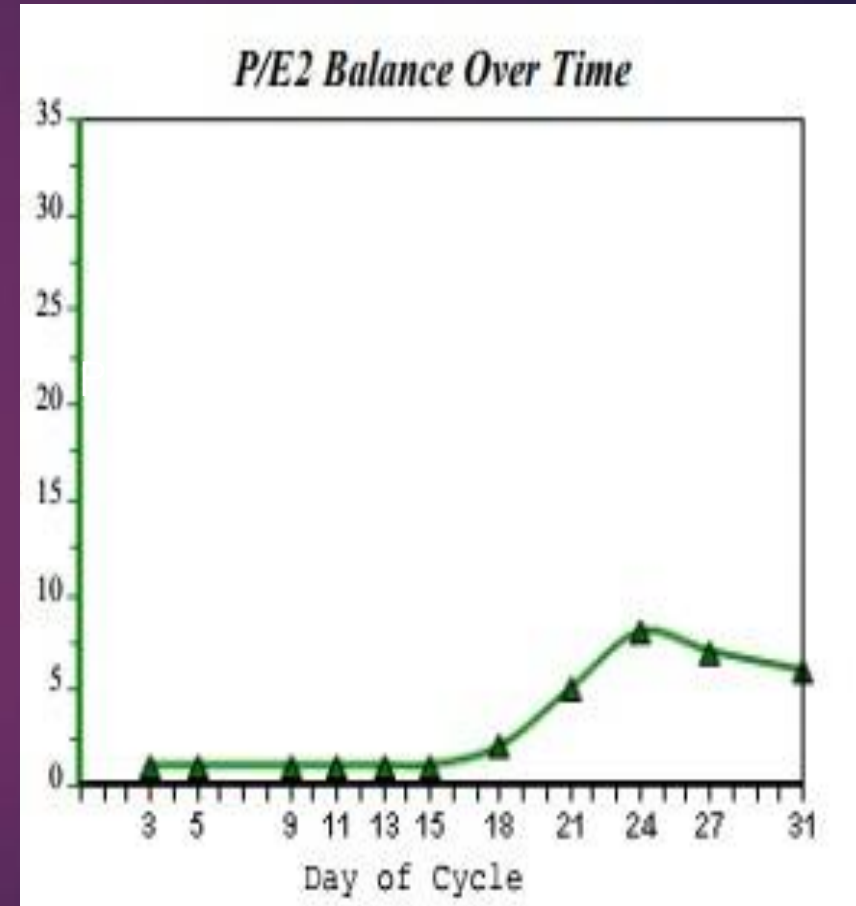
Sher/Butler/Lewis, *Hole's Human Anatomy and Physiology*, 8th edition, Copyright © 1990, The McGraw-Hill Companies, Inc. All rights reserved.



# 28 Day Saliva Evaluation



Description	Result	Ref Values
Dehydroepiandrosterone [DHEA + DHEA-S] (saliva) Pooled Value	3 Borderline	Adults (M/F): 3-10 ng/ml
Consider the ASI panel.		
Testosterone (saliva) Cycle Average	39 High	Adult Female Borderline: 6-9 pg/ml



**Luteal Phase P/E2 = 7**  
Goal 30-40

# 28 Day Saliva Test

## ***Estradiol Analysis:***

Total Cycle Estradiol Output:	118 pg	Range: 22 - 110 pg Borderline Low: 22 - 31 pg
Preovulatory Phase Estradiol Output:	76 pg	
Luteal Phase Estradiol Output:	42 pg	
Relative Luteal Phase Estradiol Output:	36 %	

## **I. Progesterone (P) Interpretation**

Luteal Surge of Progesterone Occurred Around Day 20  
Luteal Phase Deficit Type I, Shortened Phase, Less than 12 days

### ***Luteal Phase Progesterone Analysis:***

Net Output: 267 pg  
Total Output: 303 pg  
Relative Net: 88 %. Expected Minimum is 55%

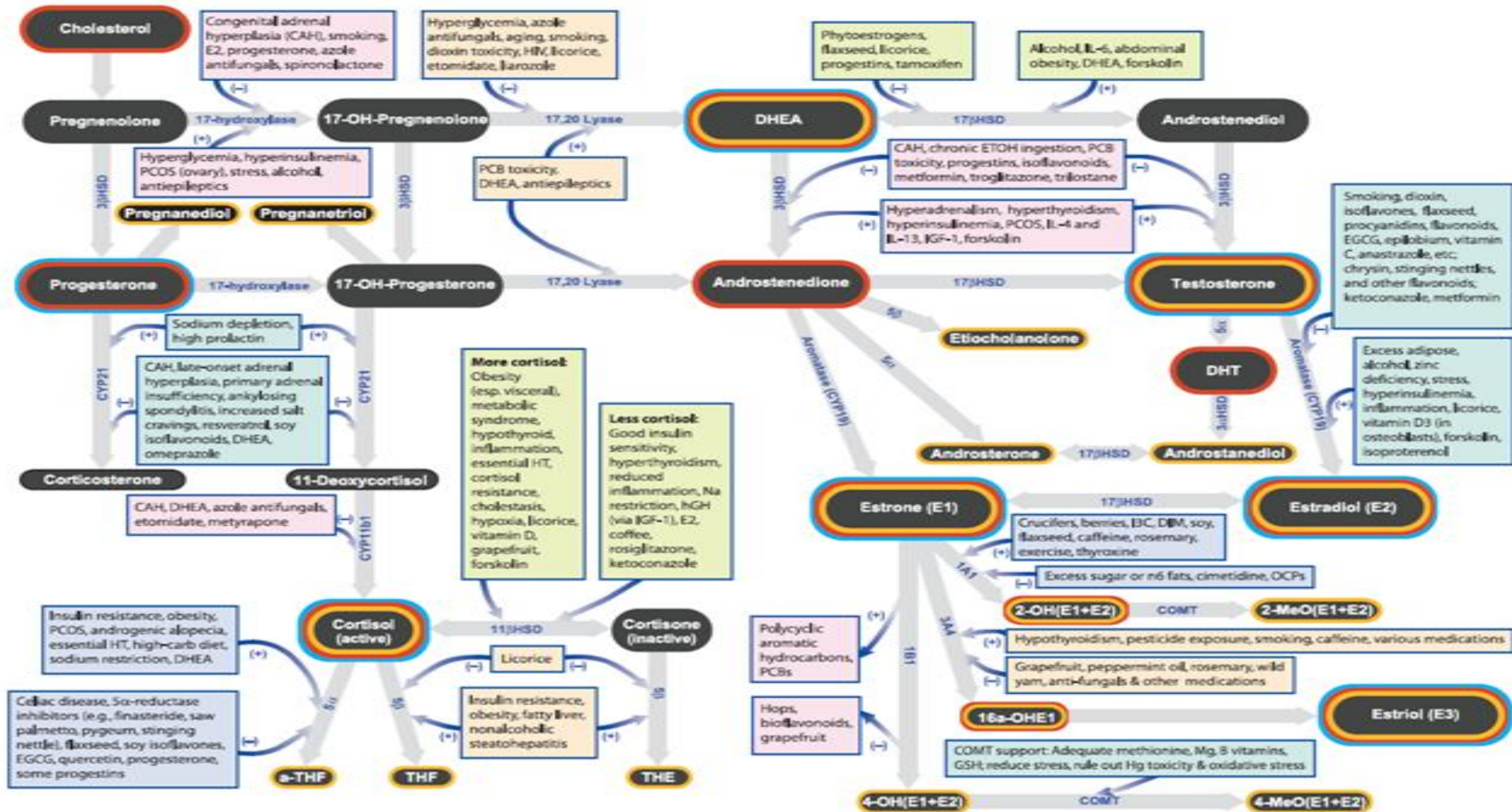
### ***Luteal P Output Distribution:***

Patient approached 90% of Progesterone Output by Day 26 of Period or by Day 6 of Luteal Phase.  
Luteal Phase Deficit Type III: Suboptimal Distribution of Progesterone Output over Luteal Phase.

- ▶ **Progesterone:** Low
- ▶ **Estrogen:** Production is normal.
- ▶ **DHEA:** Average DHEA-3 ng/ml.  
Reference Range: 3-10 ng/ml
- ▶ **Testosterone:** High. 39 pg/ml.
  - ▶ The borderline range is 6-9 pg/ml,  
Normal is 10-38 pg/ml.
- ▶ **Balance:** Favors estrogenic activity. Insufficient progesterone.
  - ▶ **Distinct estrogen dominance**

# What Relationships Do You See?

## Steroidogenic Pathways



# Fixing T.G.

H/H/ Ferritin

Glucose Metabolism

cRP

Lipids

Sex Hormones

Thyroid

Vitamin D

Low Dose Elemental Iron

Insulin Sensitization, Low GI Diet

Organic Anti-inflammatories

Statins, Heyna or No?

Decrease Testosterone

Decrease Estradiol, Increase Prog.

Normal or Not? reverse T3, significance

“Optimal” vs. “Normal.”

Time of day to administer?