Adrenal Steroids
Mineralocorticoids & Glucocorticoids

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Adrenal Gland

Cortex

Mineralocorticoids

(Aldosterone)

Glucocorticoids

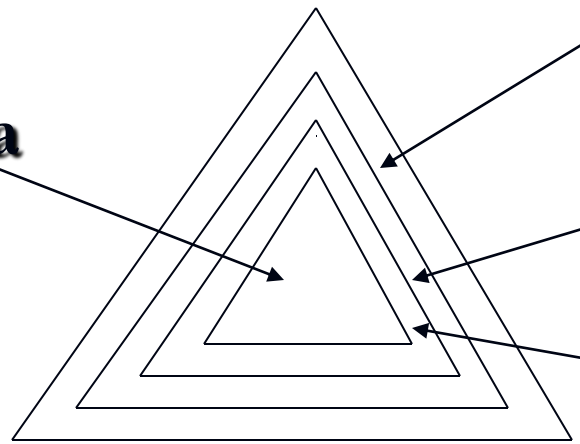
(Cortisol)

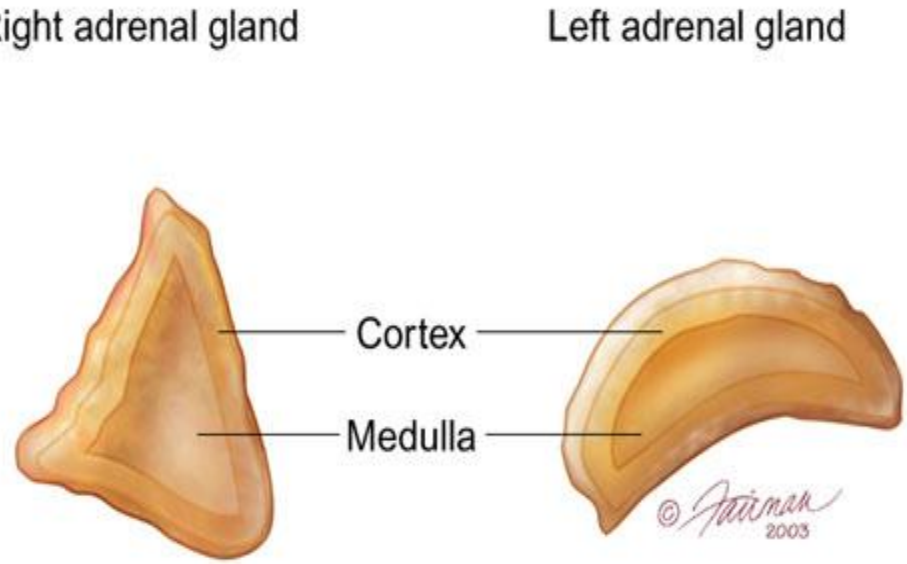
Sex hormones

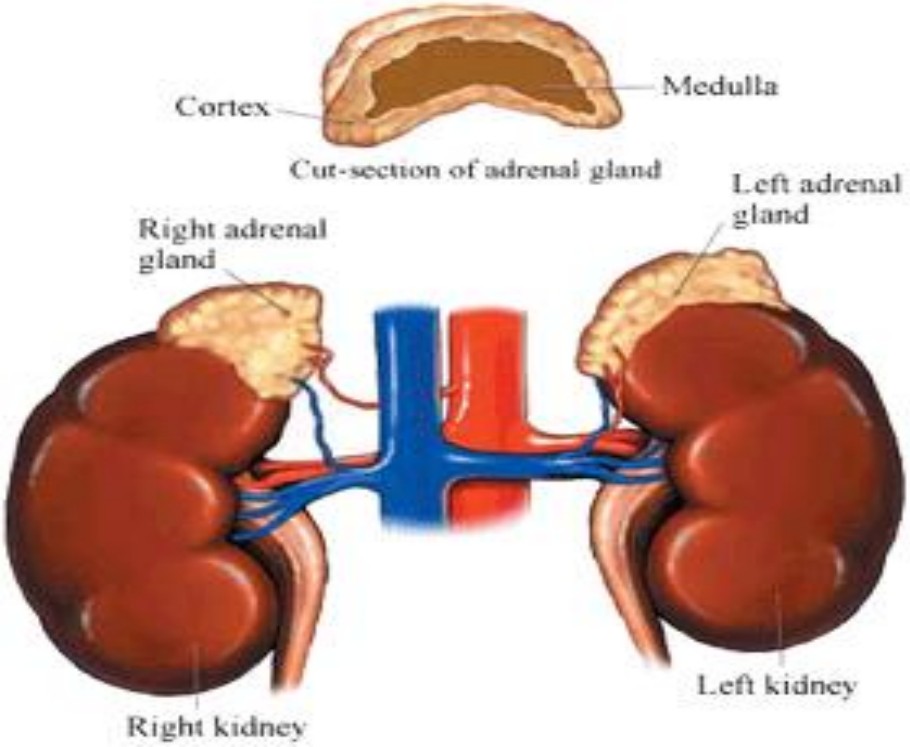
(Testosterone, E2, P)

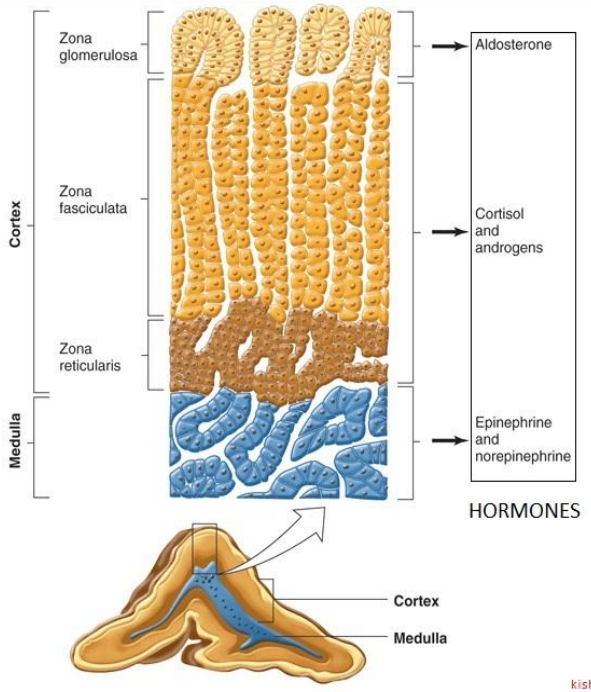
Medulla

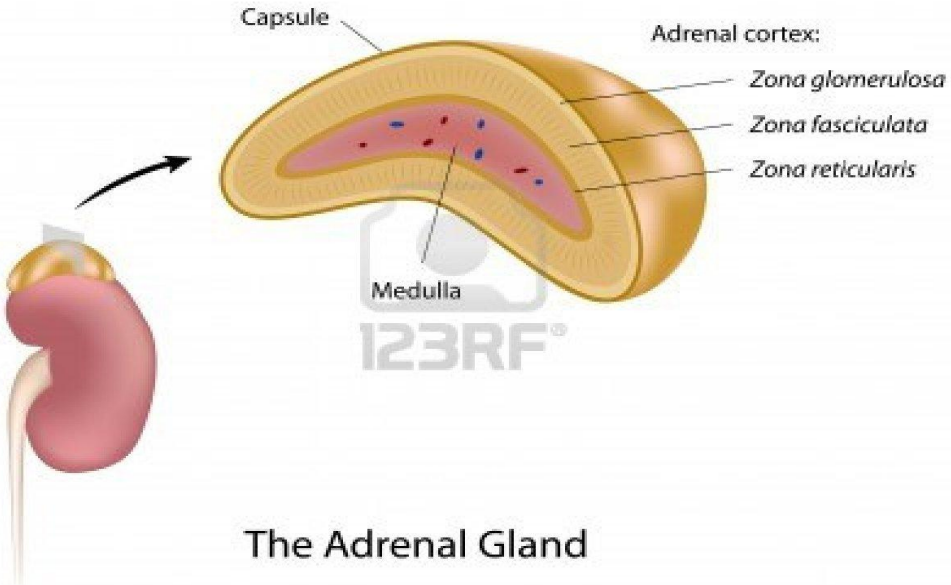
(E, NE)







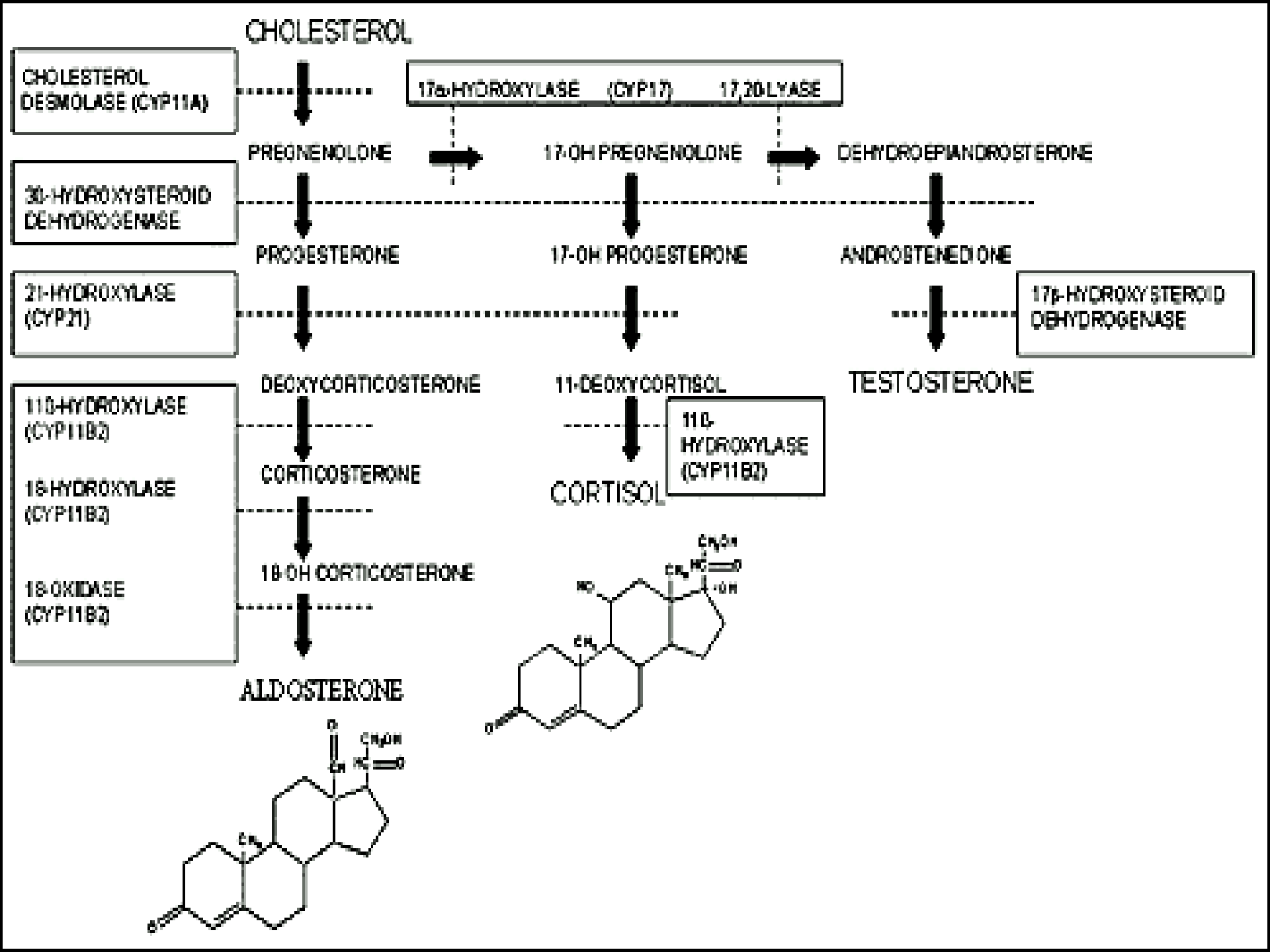




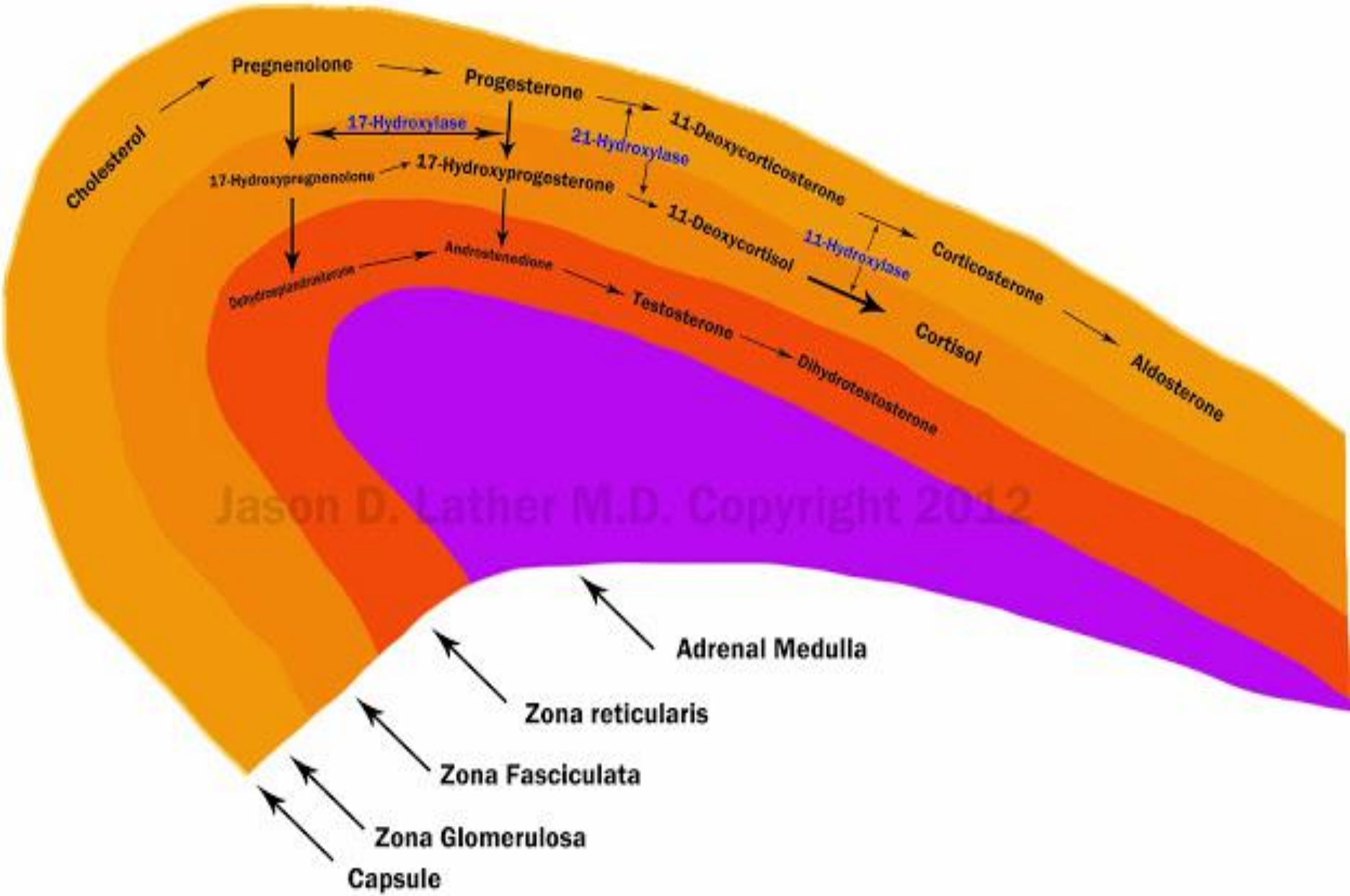
Mineralocorticoids (Aldosterone)

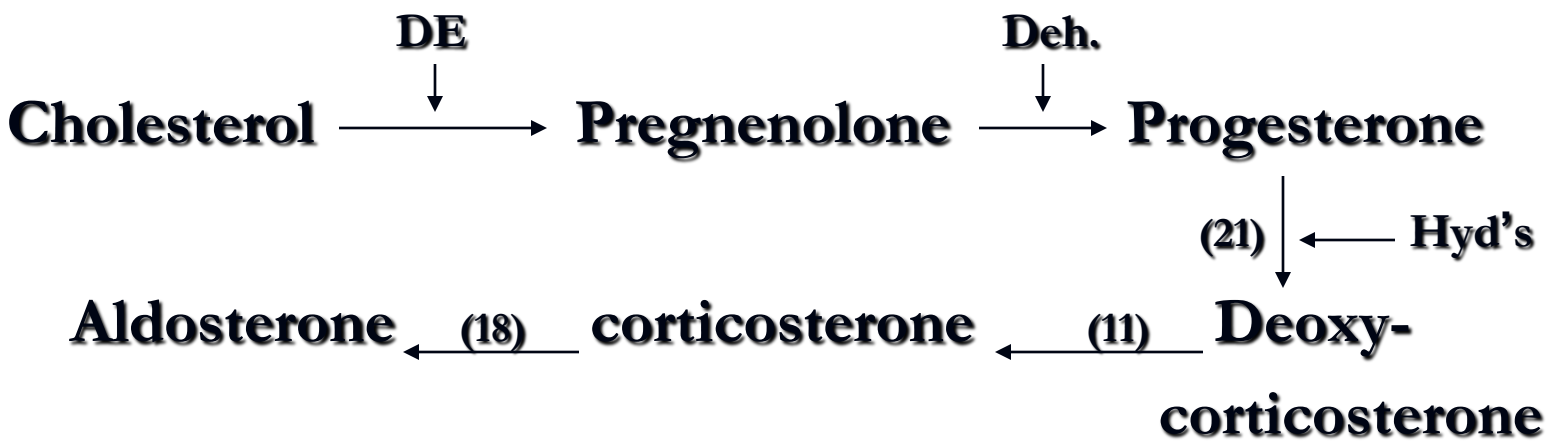
Control of synthesis and release:

- ↑ Angiotensin III.
- ↑ Angiotensin II
- ↑ K^+ (the most sensitive stimulator of aldosterone)
- ACTH
- ↓ ECF or blood volume.
- Metabolic acidosis


CHOLESTEROL
CHOLESTEROL DESMOLASE (CYP11A)
17α-HYDROXYLASE (CYP17)
17,20-LYASE
PREGNENOLONE
17-OH PREGNENOLONE
DEHYDROEPIANDROSTERONE
3β-HYDROXYSTEROID DEHYDROGENASE
PROGESTERONE
17-OH PROGESTERONE
ANDROSTENEDIONE
21-HYDROXYLASE (CYP21)
17β-HYDROXYSTEROID DEHYDROGENASE
DEOXYCORTICOSTERONE
11-DEOXYCORTISOL
TESTOSTERONE
11β-HYDROXYLASE (CYP11B2)
11β-HYDROXYLASE (CYP11B2)
CORTICOSTERONE
CORTISOL
18-HYDROXYLASE (CYP11B2)
18-OH CORTICOSTERONE
18-OXIDASE (CYP11B2)
ALDOSTERONE

General Adrenal Anatomy and Biochemistry





DE= debranching enzyme; side chain cleavage enzyme; desmolase

Deh.= 3β-hydroxysteroid dehydrogenase enzyme

Hyd's= Hydroxylases

Renin-angiotensin-aldosterone axis

Angiotensinogen

Renin →

↓

Angiotensin I

ACE →

↓

Angiotensin II

↓

Aldosterone

- **<u>Factors/drugs ↑ renin-angiotesin-aldosterone:</u>**
  - **Volume depletion (hemorrhage, low Na^+ intake, dehydration, overuse of diuretics…)**
  - **Upright posture**
  - **K^+**
  - **ACTH**
  - **Vasodilators**
  - **Adrenoreceptor antagonists**

- **Factors/drugs ↓ renin-angiotesin-aldosterone:**

- **Blood volume expansion**
- **Renin release inhibitors (also known as renin antagonists)**

Aliskiren, **Remikerin, Enalkiren, β_1-blockers**

- **ACE inhibitors**

Captopril, Enalapril, Benzopril, fosinopril, Lisinopril, Ramipril …

- **ARB's (Angiotensin II receptor blockers)**

Candesartan, Losartan, Irbesartan, telmesartan…

- **Aldosterone antagonists**

Spironolactone, Eplerenone

Effects of Aldosterone

Receptor-mediated

Acts on distal convoluted tubules in the kidney

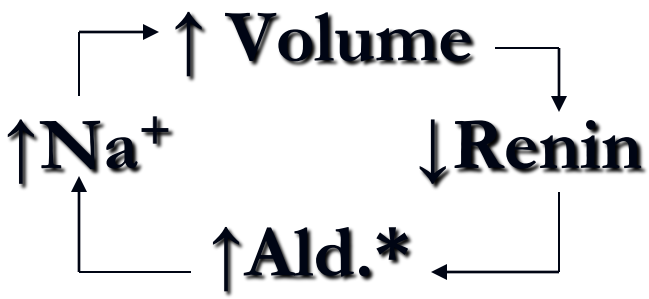
- **↑ reabsorption of Na^+ → hypertension**
- **↑ excretion of K^+ & H^+ → hypokalemia & metabolic alkalosis**
- **↑ EC volume**
- **↑ BP**

- **Disorders affecting aldosterone release:**

*** Hypoaldosteronism…rare**

*** Hyperaldosteronism**

1º



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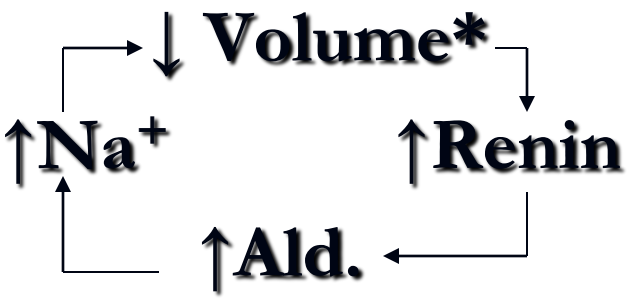
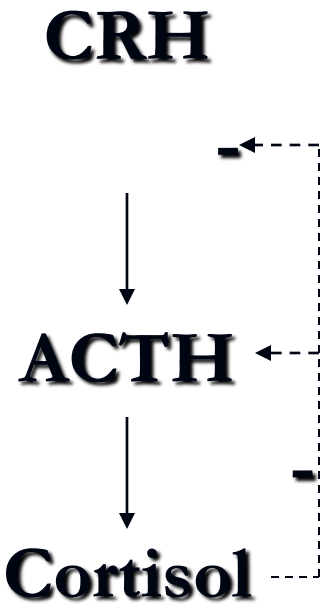


*** Initial defect**

Glucocorticoids (Cortisol)

- **Feedback control**

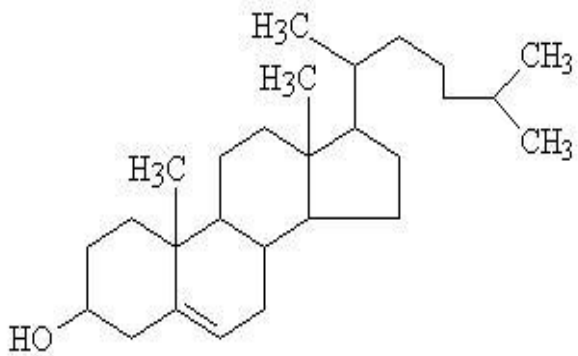


Glucocorticoids (Cortisol)

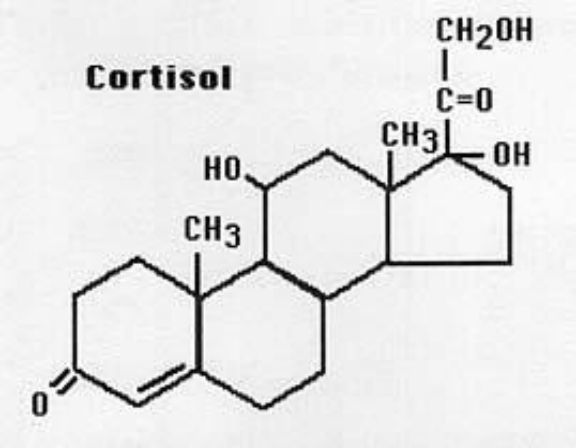
Circadian rhythm

Pt's on cortisol therapy…

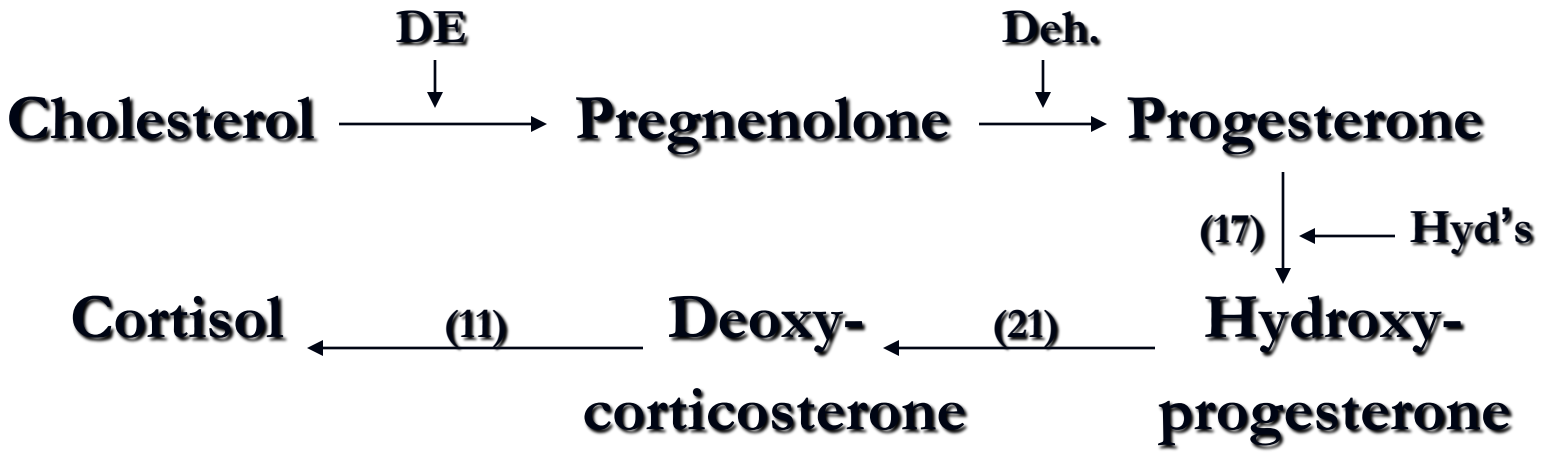
Cortisol synthesis (from cholesterol)



Cholesterol



Glucocorticoids (Cortisol)



DE= debranching enzyme; side chain cleavage enzyme; desmolase

Deh.= 3β-hydroxysteroid dehydrogenase enzyme

Hyd's= Hydroxylases

Steroid synthesis inhibitors

- o,p'-DDD (Mitotane)

Causes selective atrophy of Zona Fasciculata and Zona Reticularis

Useful in R_x of adrenal Ca when radiotherapy or surgery are not feasible and in certain cases of breast cancer

- Aminoglutethimide

Selective desmolase inhibitor and non selective aromatase inhibitor, same uses as mitotane

Steroid synthesis inhibitors:

- **Trilostane:**

Competitive inhibitor of 3β-hydroxysteroid dehydrogenase enzyme.

Effective in Cushing's syndrome and breast cancer.

- **Ketoconazole:**

An antifungal agent

An inhibitor of different hydroxylases.

Inhibits steroidogenesis in adrenals and testes.

Effective in Cushing's syndrome and Ca of prostate.

Steroid synthesis inhibitors

- **Amphenone B**

An inhibitor of different hydroxylases but very toxic.

The therapeutic use of amphenone B is limited by its toxicity : antithyroid effect, **severe CNS depression, GIT upset and many skin disorders**

- **Metyrapone (Metopirone)**

11β-hydroxylase inhibitor

Effective as a diagnostic tool (metyrapone test) and in the management of Cushing's syndrome

Effects of Glucocorticoids

- **On proteins:**

↑ Catabolism ↓ anabolism

→ Osteoporosis; steroid myopathy; delayed wound healing; delayed peptic ulcer healing…

- **On CHO:**

Diabetogenic: gluconeogenesis; ↓ peripheral utilization of glucose)

Effects of Glucocorticoids

- **On lipids:**

↑ lipolysis

Fat redistribution

- **On electrolytes:**

Aldosterone-like effect

↓ Ca^{++} absorption from intestine

↑ Ca^{++} excretion by kidney

↑ Uric acid excretion

Effects of Glucocorticoids

- **Antiinflammatory effect:**

major mechanism:

Phospholipids

↓ ← **Pospholipase A2**

Arachidonic acid

Lipoxygenase | **Cyclooxygenase**

↓ ↓

Leukotreines (SRS-A) | **PG's**

Effects of Glucocorticoids

Other possible mechanisms:

- **Inhibition of neutrophil and macrophage function.**
- **Inhibition of platelet activation factor (PAF)**
- **Inhibition of tissue necrosis factor or receptor (TNF; TNR)**
- **Inhibition of nitric oxide reductase…**

Effects of Glucocorticoids

Immunosuppressant effect:

↓ initial processing of Ag

↓ Ab formation

↓ effectiveness of T-lymphocytes

↓ lymphocyte induction & proliferation

↓ lymphoid tissue including leukemic lymphocytes (antileukemic effect)

Effects of glucocorticoids

Antiallergic effect:

Supress allergic response

↓ histamine release

↓ eosinophils

CNS effects:

Euphoria

Psychosis

Glucocorticoids

- **Glucocorticoids dosage forms:**

Available in all dosage forms

Available in many preparations

- **Structure activity relationship:**
  Major objective: Good antiinflammatory effect, less or no aldosterone-like activity

- **Metabolism:**

In the liver by reduction and conjugation (90-95%); little hydroxylation reactions (5%)

Glucocorticoid preparations

Short-acting	Half-life	AIA	Ald.-like
Corisol	10	1	1
Cortisone	10	0.8	1
Corticosterone	10	0.3	30
Fludrocortisone	10	10	150

Glucocorticoid preparations

Intermediate-acting	Half-life	AIA	Ald.-like
Prednisone	20	4	0.8
Prednisolone	20	5	0.8
Methylprednisolone	20	6	-
Triamcinolone	20	6	-
Beclomethasone	20	6	-

Glucocorticoid preparations

Long-acting:	Half-life	AIA	Ald.-like
Betamethasone	50	25	-
Dexamethasone	50	30	-

** Plasma half-life; Nuclear half-life

Clinical uses to Glucocorticoids

- **Adrenal insufficiency (acute; chronic, Addisonian crisis, Addison's disease...)**

- **Inflammatory conditions (rheumatoid arthritis, SLE, arteritis, dermatomyositis, cerebral edema, ulcerative colitis, rheumatic carditis, active chronic hepatitis, proctitis, acute gout...)**

- **Allergic reactions (hay fever, eczema, dermatitis), bronchial asthma, status asthmaticus**

Clinical uses to Glucocorticoids

- **Immunosuppression: (organ transplantation, hemolytic anemia, leukemias, many tumors...)**

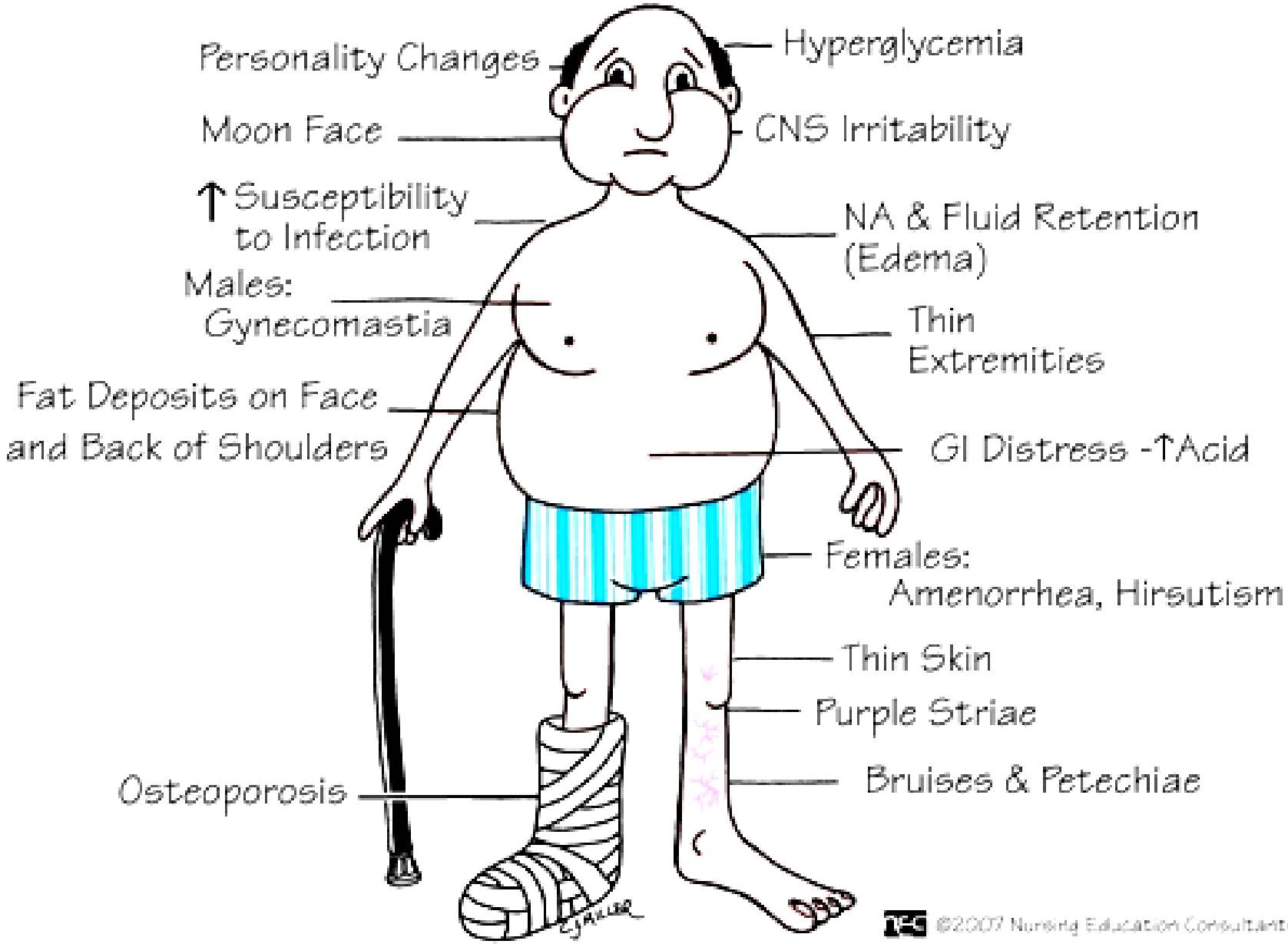
- **Hypercalcemia associated with Vit. D intoxication or sarcoidosis or hyperparathyroidism or cancer...)**

- **Many eye, ear, and skin diseases (allergic or inflammatory)**

Side effects of Glucocorticoids

- Suppression of hypothalamic-pituitary-adrenal axis (major and most dangerous side effect)
- Cushing's syndrome
- Salt & water retention, edema, ↑ BP, obesity
- Peptic ulcer disease and GIT ulcerations
- Osteoporosis
- Diabetes mellitus
- ↑ incidence of viral and fungal infections
- ↓ wound healing and skin atrophy and myopathy
- Suppression of growth of children
- Cataract…

CUSHING'S SYNDROME



Strategies in the use of Glucocorticoids

- **Use a short-acting steroid.**
- **Use the minimal possible dose.**
- **2/3rd of the dose in morning and 1/3rd in evening.**
- **Use alternate day therapy which is associated with less suppression to growth of children and to the hypothalamic-pituitary-adrenal axis and fewer side effects**