Adrenal Steroids Mineralocorticoids & Glucocorticoids

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Adrenal Gland

Cortex

Mineralocorticoids

(Aldosterone)

Glucocorticoids

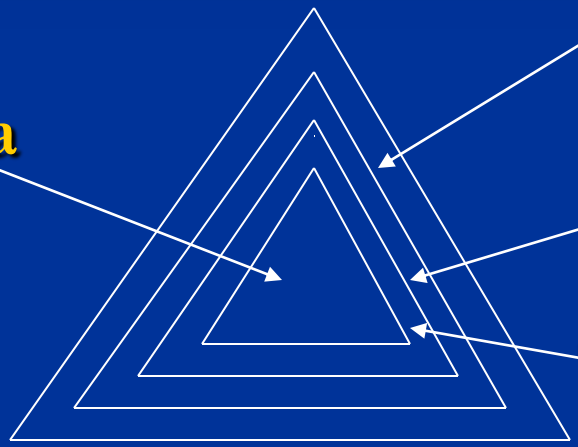
(Cortisol)

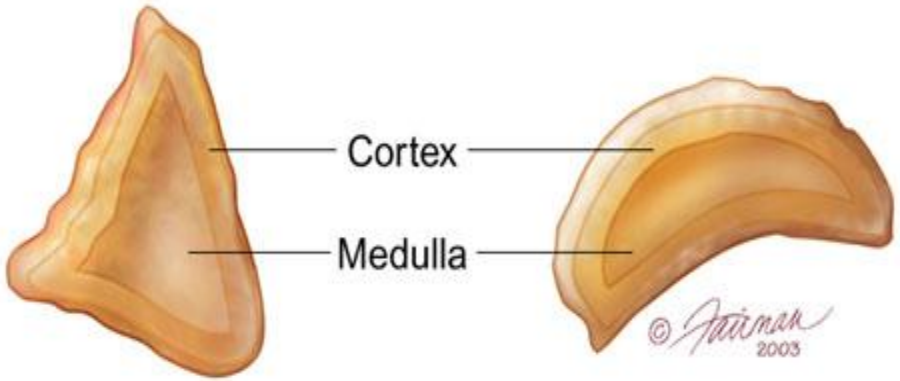
Sex hormones

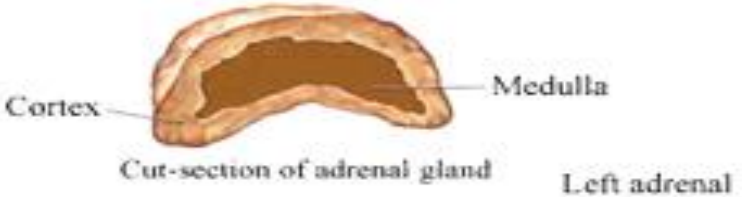
(Testosterone, Estrogen)

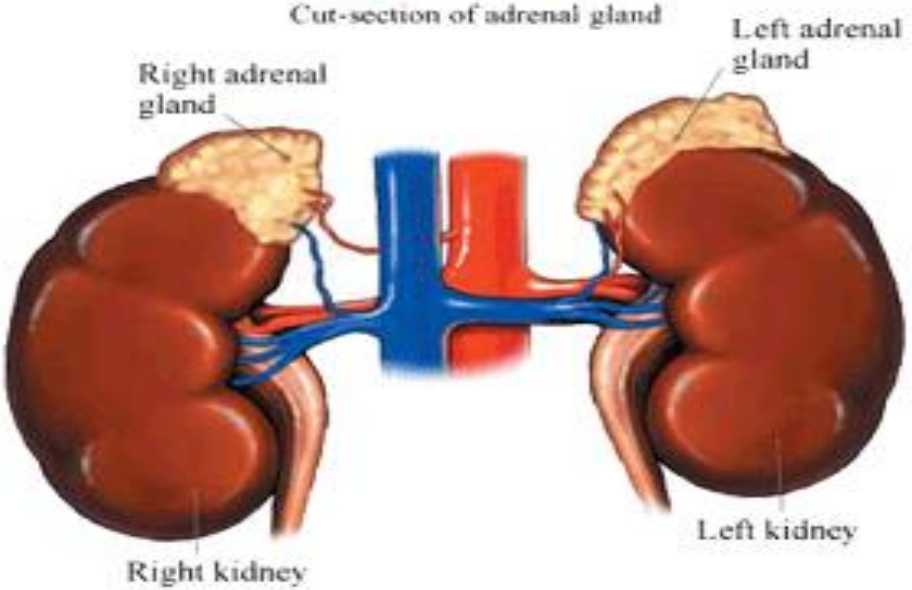
Medulla

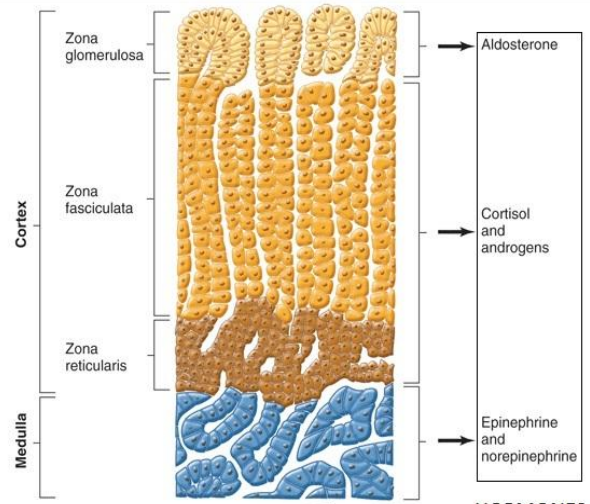
(E, NE)



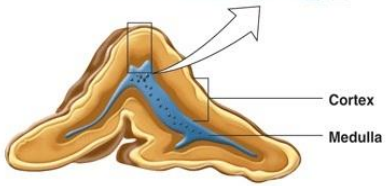


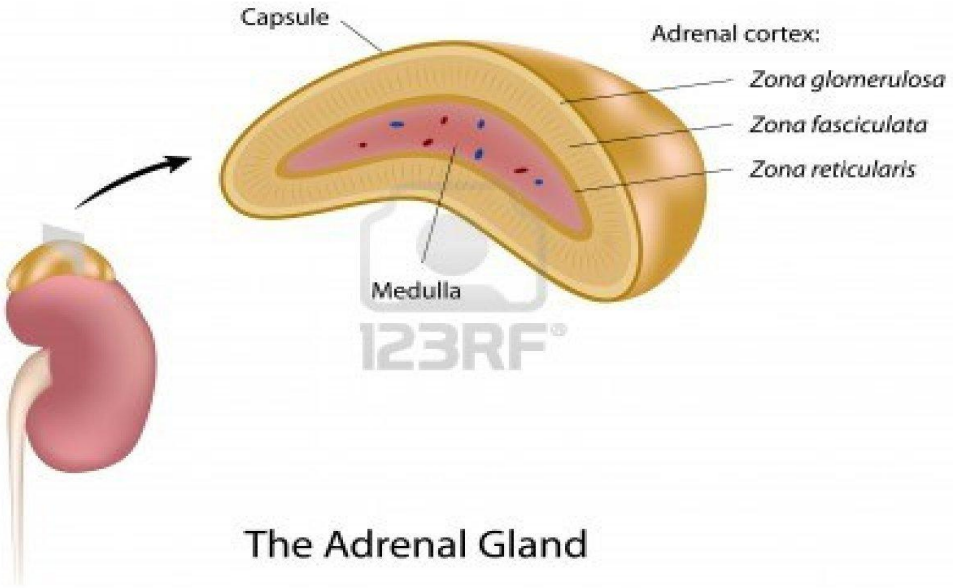






HORMONES



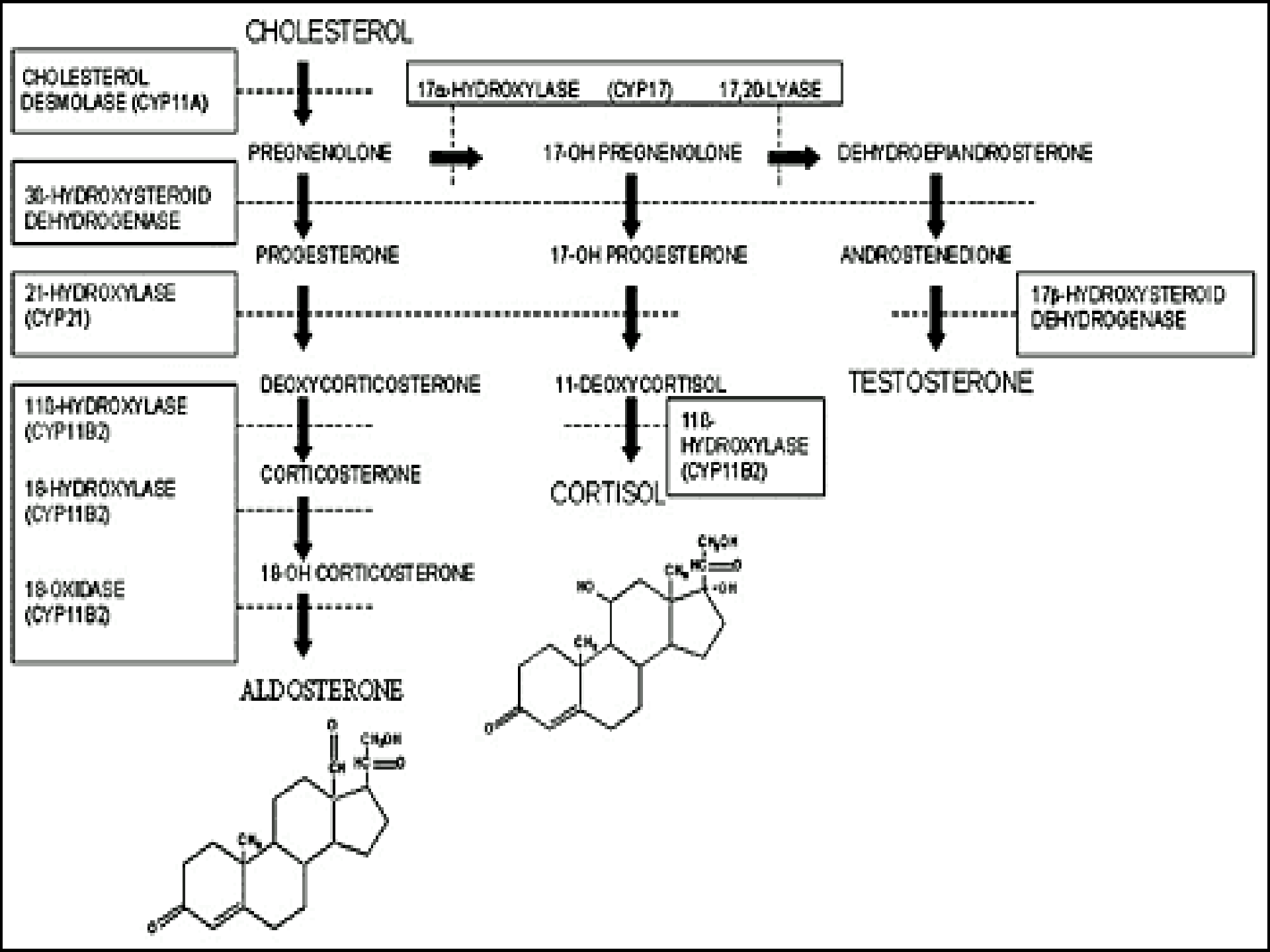


The Adrenal Gland

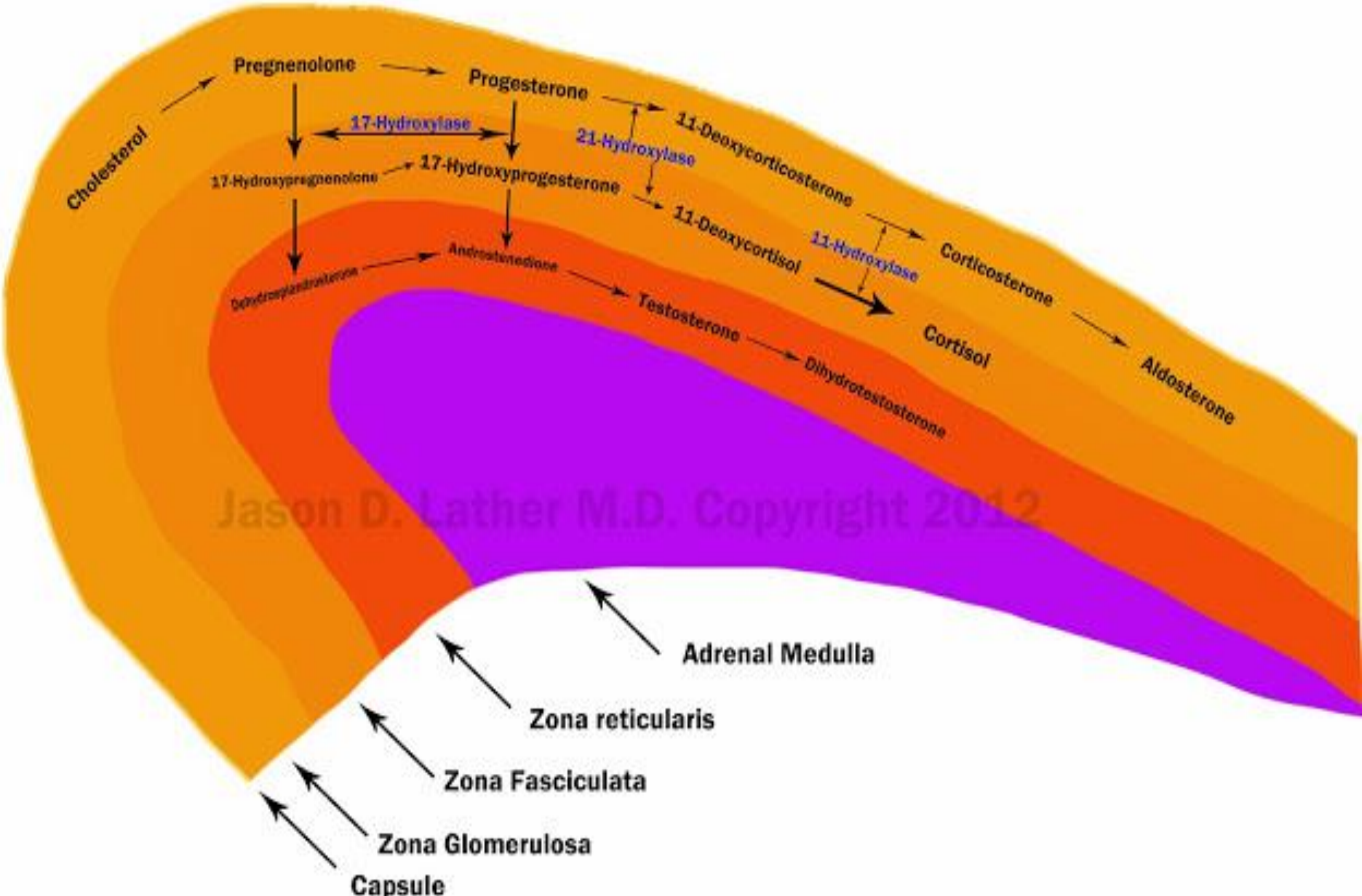
Mineralocorticoids (Aldosterone)

Control of synthesis and release:

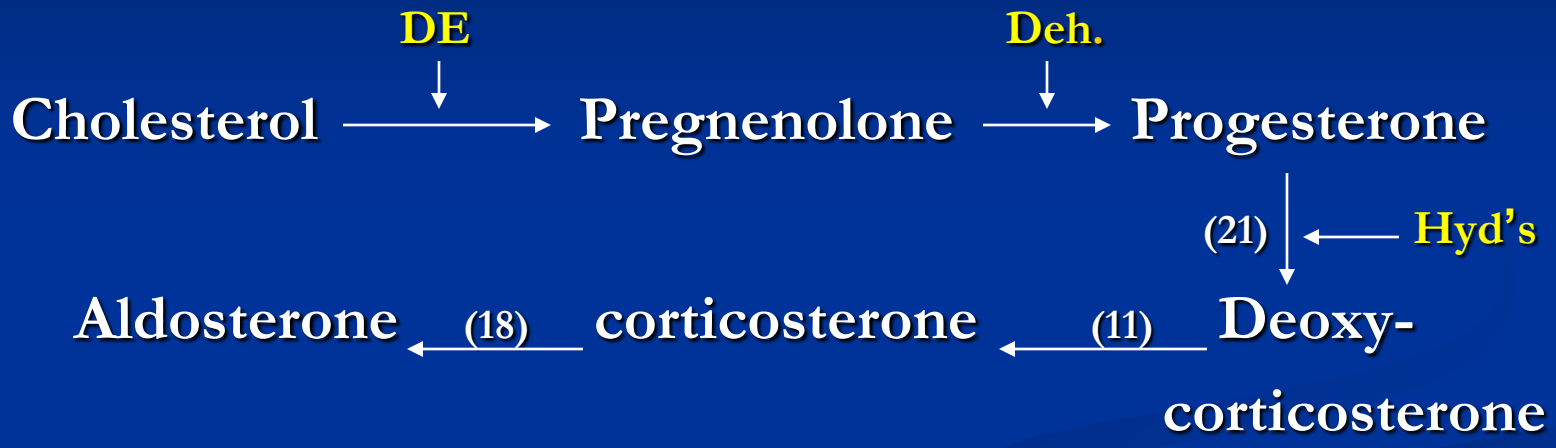
- ↑ Angiotensin III.
- ↑ Angiotensin II
- ↑ K^+ (the most sensitive stimulator of aldosterone)
- ACTH
- ↓ ECF or blood volume.
- Metabolic acidosis


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 (CYP11B1)
11β-HYDROXYLASE (CYP11B2)
CORTICOSTERONE
CORTISOL
18-HYDROXYLASE (CYP11B2)
18-OH CORTICOSTERONE
18-OXIDASE (CYP11B2)
ALDOSTERONE

General Adrenal Anatomy and Biochemistry



Synthesis of Steroids

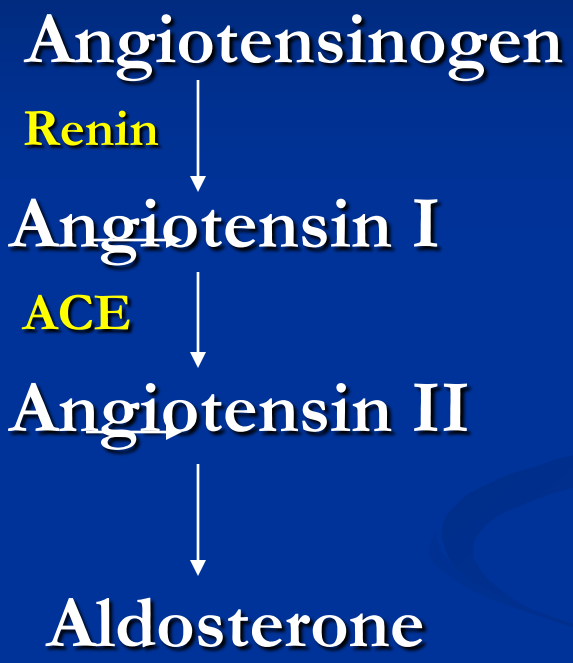


DE= debranching enzyme; side chain cleavage enzyme; desmolase

Deh.= 3β-hydroxysteroid dehydrogenase enzyme

Hyd's= Hydroxylases

Renin-angiotensin-aldosterone axis



Factors/drugs ↑ renin-angiotesin-aldosterone

- Volume depletion (hemorrhage, low Na^+ intake, dehydration, overuse of diuretics…)
- Upright posture
- K^+
- ACTH
- Vasodilators
- Beta Adrenoreceptor agonists

Factors/drugs ↓ renin-angiotesin-aldosterone:

- Blood volume expansion.
- Beta Adrenoreceptor antagonists
- Renin release inhibitors, also known as renin antagonists e.g. : Aliskiren, Remikerin, Enalkiren, β_1-blockers
- ACE inhibitors e.g. Captopril, Enalapril, Benazapril
- ARB's (Angiotensin II receptor blockers), e.g. Candesartan, Losartan, Irbesartan, Telmesartan.
- Aldosterone antagonists, e.g. 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

Glucocorticoids (Cortisol)

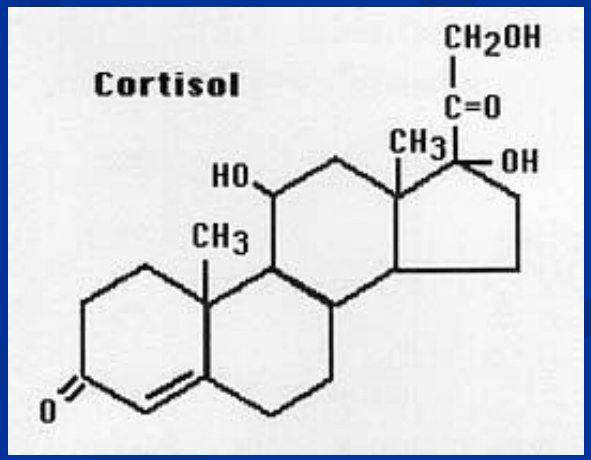
- Feedback control

Glucocorticoids (Cortisol)

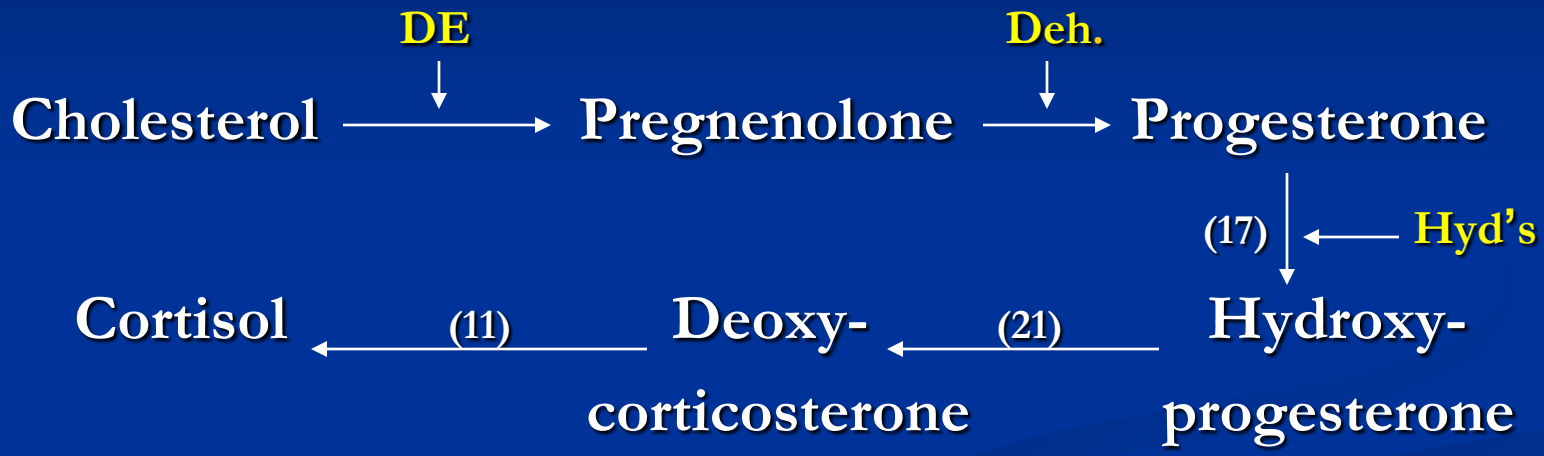
Secretion follows a circadian rhythm

Treatment with cortisol should mimic this rhythm.

Cortisol synthesis starts from cholesterol.



Glucocorticoids (Cortisol)



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Steroid synthesis inhibitors

- **o,p'-DDD (Mitotane):**

Causes selective atrophy of Zona Fasciculata and Zona Reticularis

Useful in 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:**

Antifungal agent

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.

Toxicity : antithyroid effect, severe CNS depression, GIT upset and many skin disorders

- **Metyrapone (Metopirone)**

11 β-hydroxylase inhibitor.

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

Actions of Glucocorticoids

- **On proteins:**

↑ Catabolism ↓ anabolism

This might result in osteoporosis; myopathy; delayed wound healing; delayed peptic ulcer healing…

- **On CHO:**

Diabetogenic: gluconeogenesis; ↓ peripheral utilization of glucose.

Actions of Glucocorticoids

- **On lipids:**

↑ lipolysis

This results in characterstic body fat redistribution.

- **On electrolytes:**

Aldosterone-like effect, lesser potency.

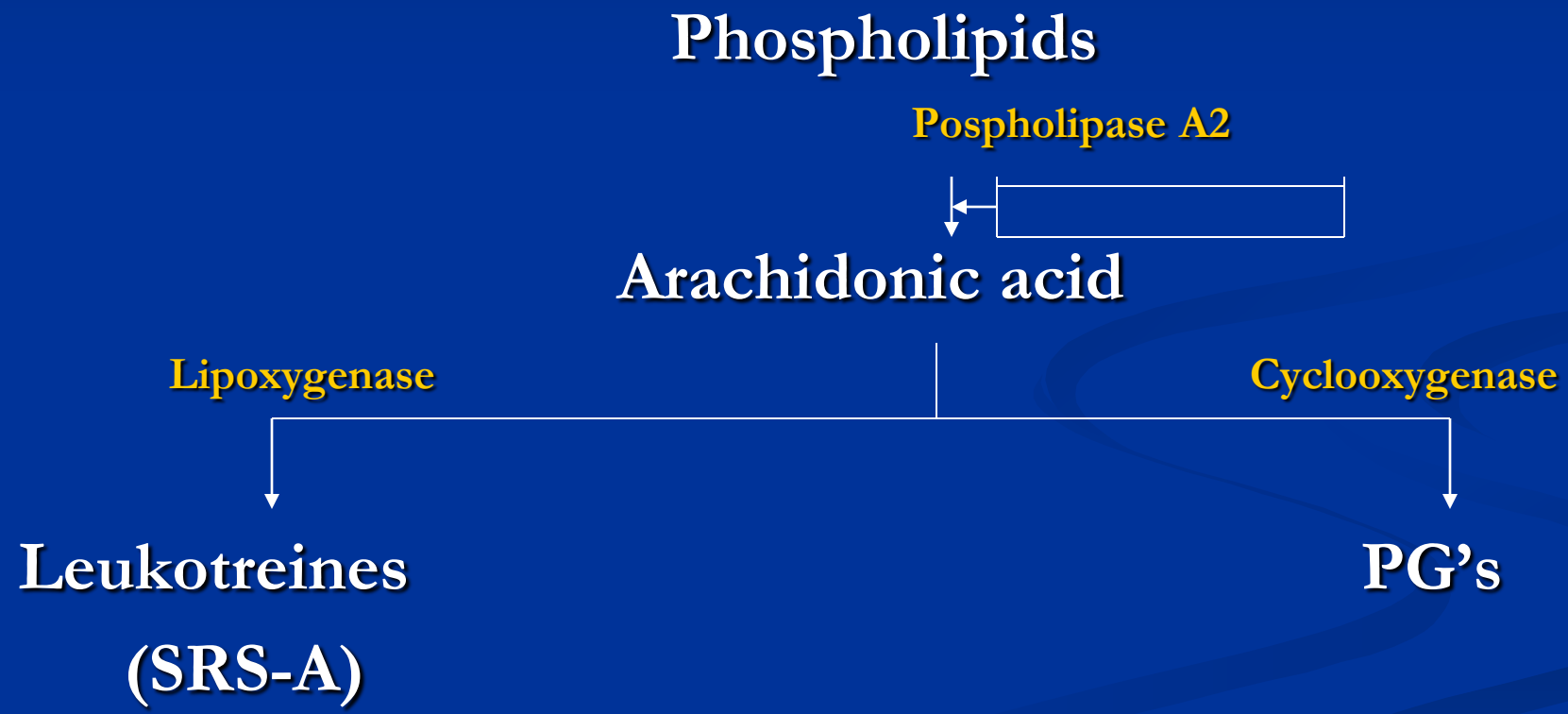
↓ Ca^{++} absorption from intestine

↑ Ca^{++} excretion by kidney

↑ Uric acid excretion

Actions of Glucocorticoids

- **Antiinflammatory effect:**



Actions of Glucocorticoids

Other possible antiinflammatory 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 antigens

↓ Antibody formation

↓ Effectiveness of T-lymphocytes

↓ Lymphocyte induction and 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	-

Clinical uses of Glucocorticoids

- **Adrenal insufficiency:** e.g. acute; chronic, Addisonian crisis, Addison's disease. Given in small physiological doses.

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

- **Allergic reactions:** e. g. hay fever, eczema, dermatitis, bronchial asthma, status asthmaticus

Clinical uses of 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)**

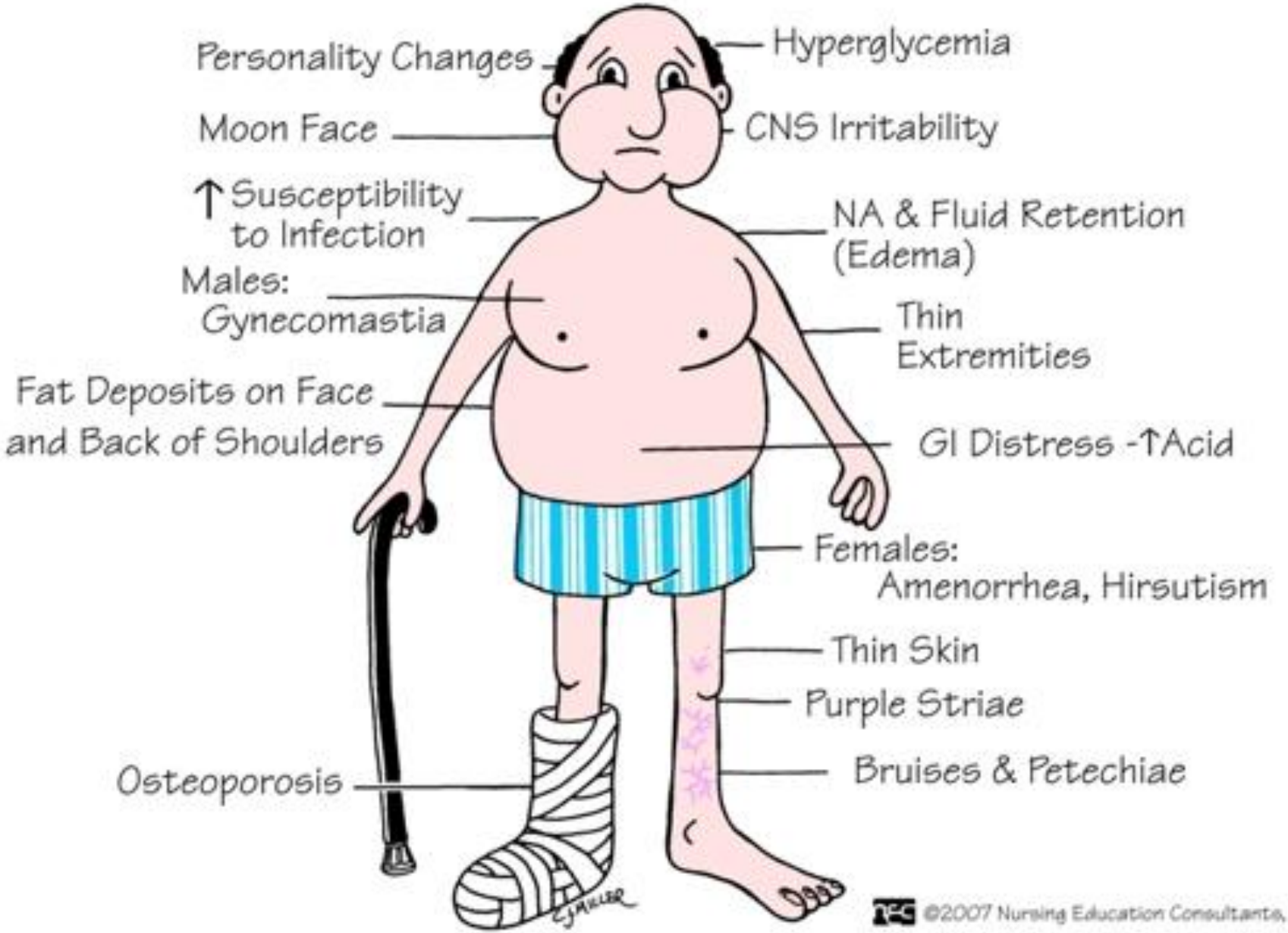
Side effects of Glucocorticoids

- **Suppression of hypothalamic-pituitary-adrenal axis:**
  - Major and most dangerous side effect.
  - If treatment extends more than two weeks:
    - Patient should be given supplementary therapy at times of stress.
    - Treatment should be tapered slowly.
  - If dosage is reduced rapidly:
    - Symptoms of the disorder reappear or increase in intensity.
    - Withdrawal syndrome appears: anorexia, N, V, weight loss, lethargy, headache, fever, joint and muscle pain, and postural hypotension.

Side effects of Glucocorticoids

- Cushing's syndrome
- Salt & water retention, edema, hypokalemia, ↑ HT, obesity
- Peptic ulcer disease and GIT ulcerations
- Osteoporosis
- Diabetes mellitus
- Viral and fungal infections
- Delayed wound healing, skin atrophy, and myopathy
- Suppression of growth in 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, less suppression of the hypothalamic-pituitary-adrenal axis, and fewer side effects