Glucocorticoid pharmacology

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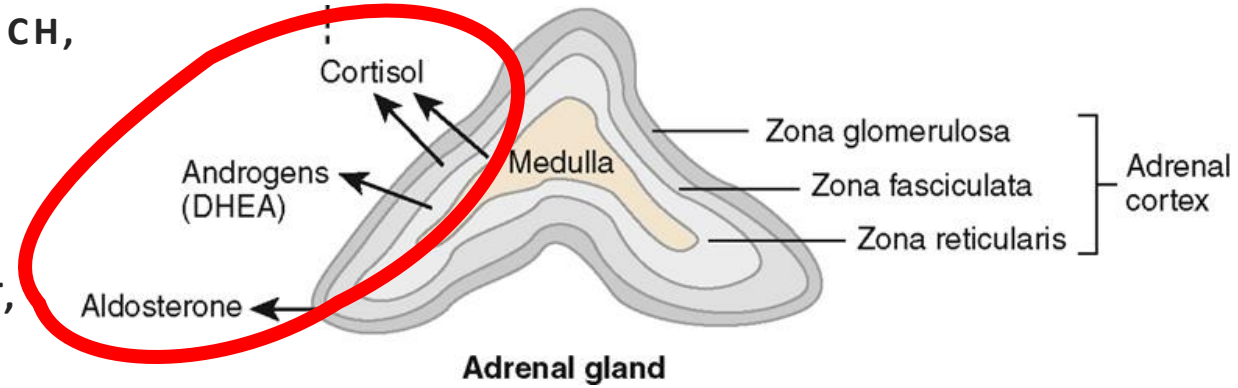

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Learning objectives:

- **By the end of this lecture, the student will be able to:**

- **Describe major pathways that regulate adrenal steroid hormone production.**
- **Describe main physiologic effects of adrenal steroids**
- **List & Compare between different semisynthetic steroid preparations.**
- **List main therapeutic indications of glucocorticoids.**
- **Describe major side effects of glucocorticoids.**

Lecture outline:

- Regulation of Adrenal Hormones
- Physiologic Effects of glucocorticoids
- Corticosteroid Drugs (classification)
- Corticosteroid Drugs (effects)
- Corticosteroid Drugs (indications)
- Corticosteroid Drugs (side effects)

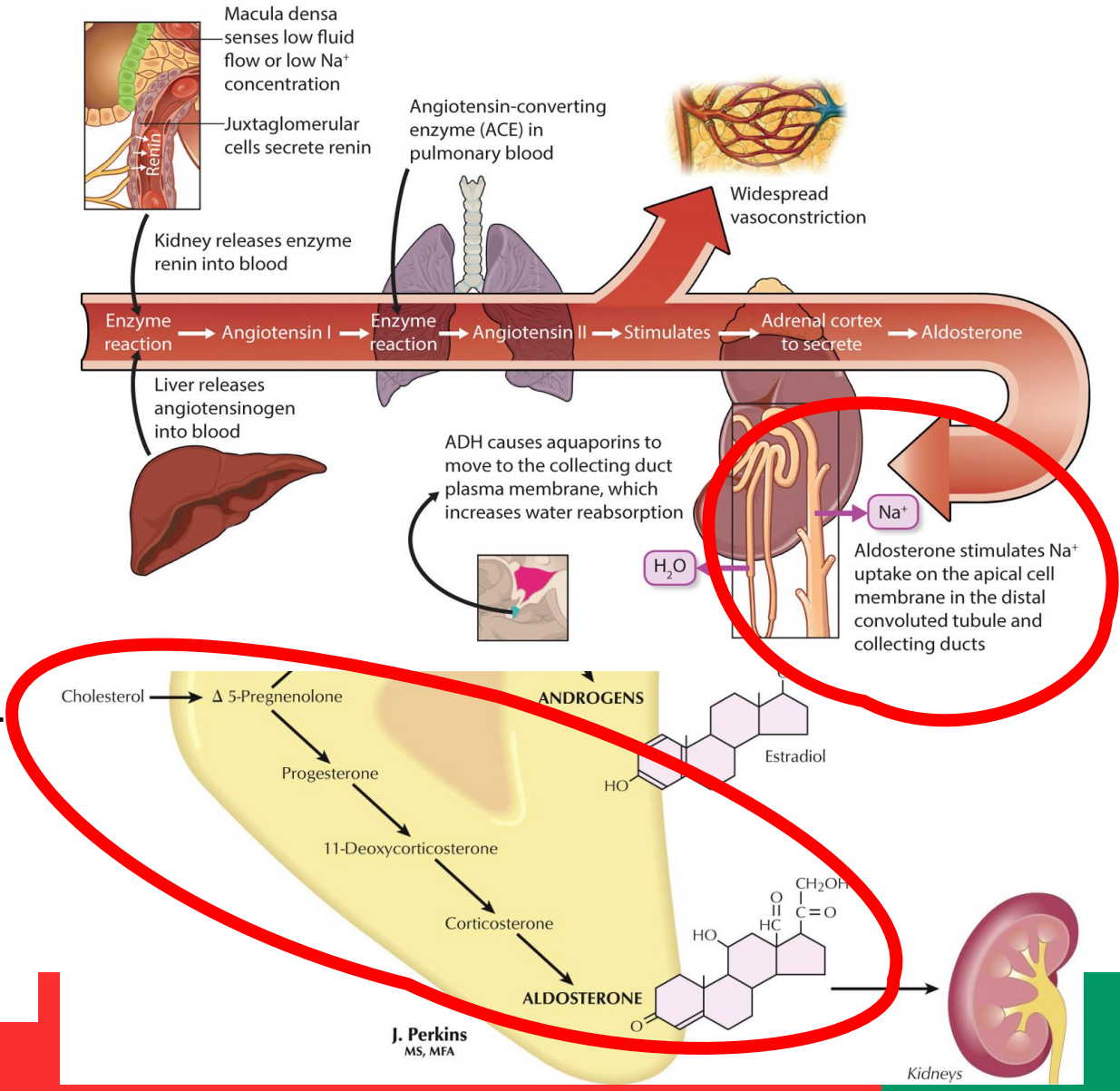
Regulation of Adrenal Hormones

The 2 adrenal glands are responsible for producing:

1. **Mineralocorticoids** (e.g., **aldosterone**) → which regulate fluid and electrolyte balance
2. **Glucocorticoids** (e.g., **cortisol**) → which are essential for carbohydrate metabolism and response to stress.

Aldosterone production is regulated by **the renin-Angiotensin system**.

In the renal tubules, aldosterone bind to and activate specific mineralocorticoid cytoplasmic receptors → **↑ Na+ and water reabsorption** & **↑ K+ excretion.**



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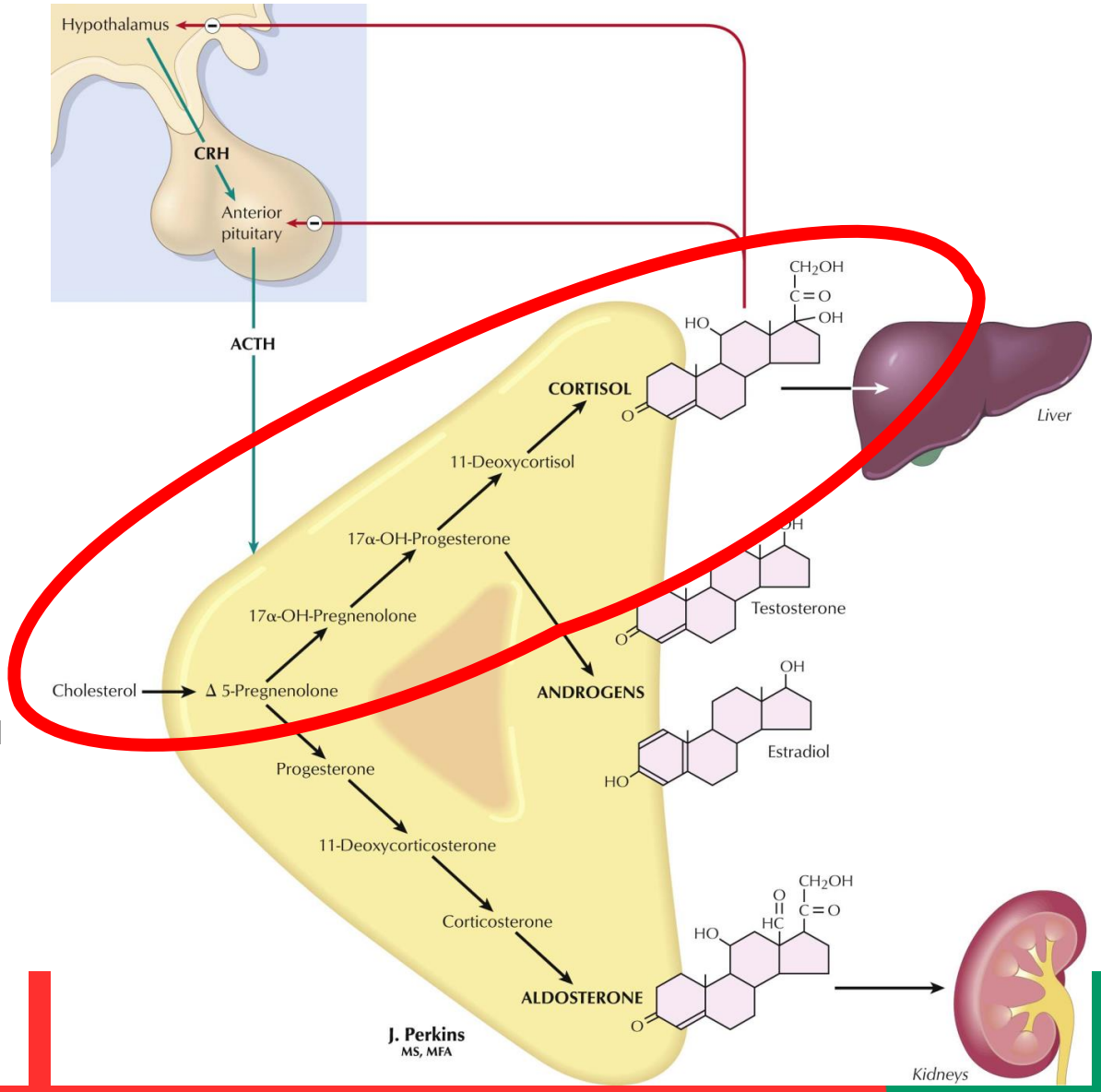
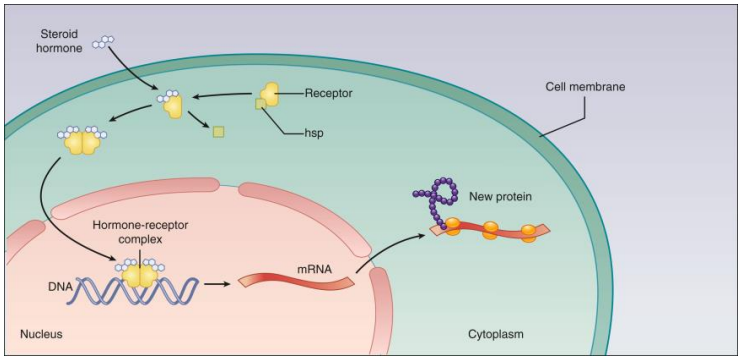
Cortisol production is regulated by **the hypothalamic-pituitary-adrenal (HPA) axis**.

1. The hypothalamus releases **CRH** (corticotrophin-releasing hormone) in response to various stimuli.
2. CRH stimulates the anterior pituitary to release **ACTH (corticotrophin).**
3. ACTH then stimulates the adrenal cortex to produce **cortisol.**
4. As serum cortisol levels increase, synthesis and secretion of CRH and ACTH decrease via **a negative feedback loop.**

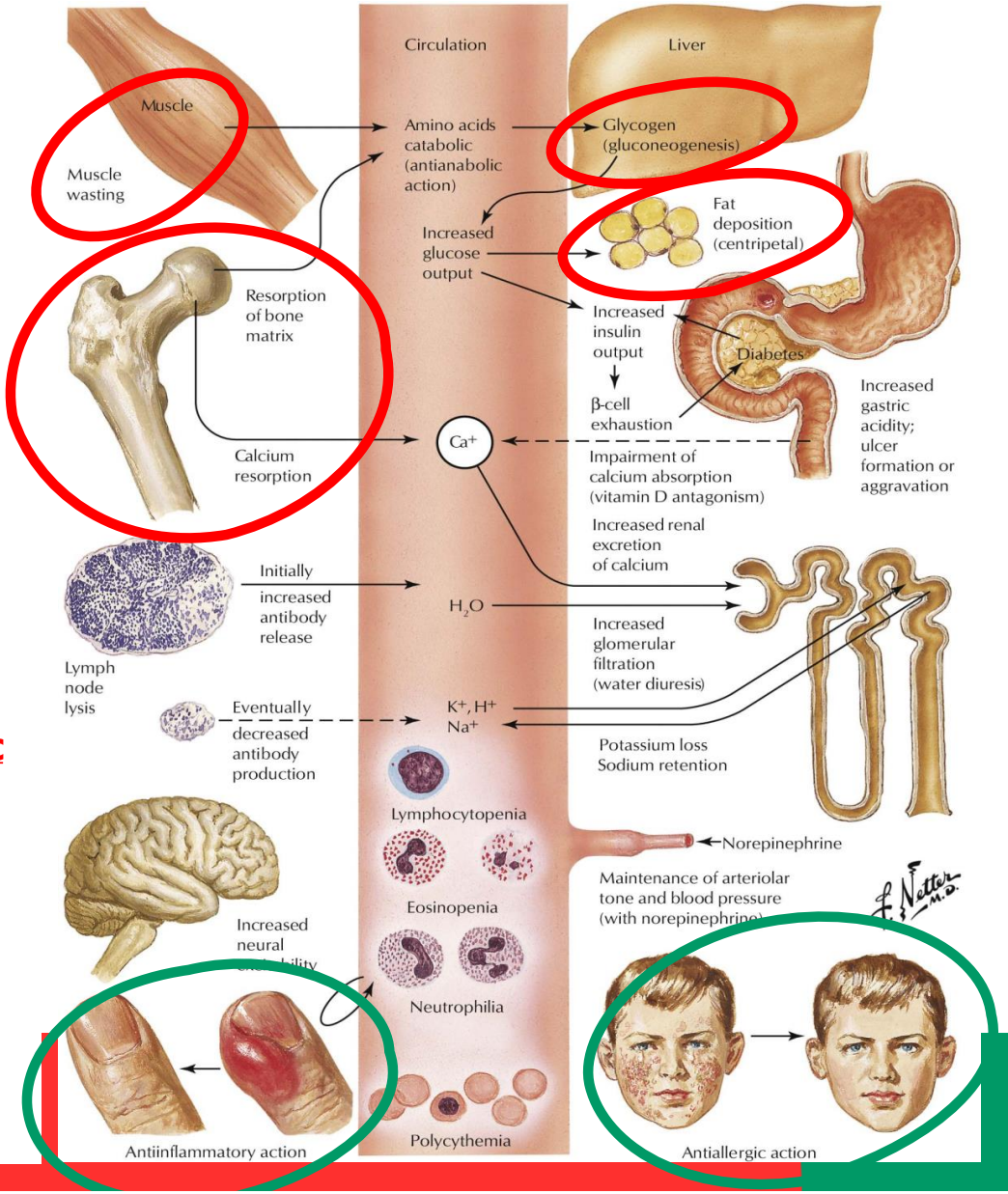


Physiologic Effects of glucocorticoids



Cortisol → bind to specific **cytoplasmic receptors** → translocated to the nucleus → **↑ or ↓ transcription of specific genes** → various **anti-inflammatory, anti-allergic and metabolic effects** of glucocorticoids:

1. ↑ **liver gluconeogenesis** (↑ formation of glucose from amino acids) → an anti-insulin effect.
2. ↑ **protein catabolism** → muscle and skin wasting & osteoporosis
3. ↑ **lipolysis** → abnormal fat distribution



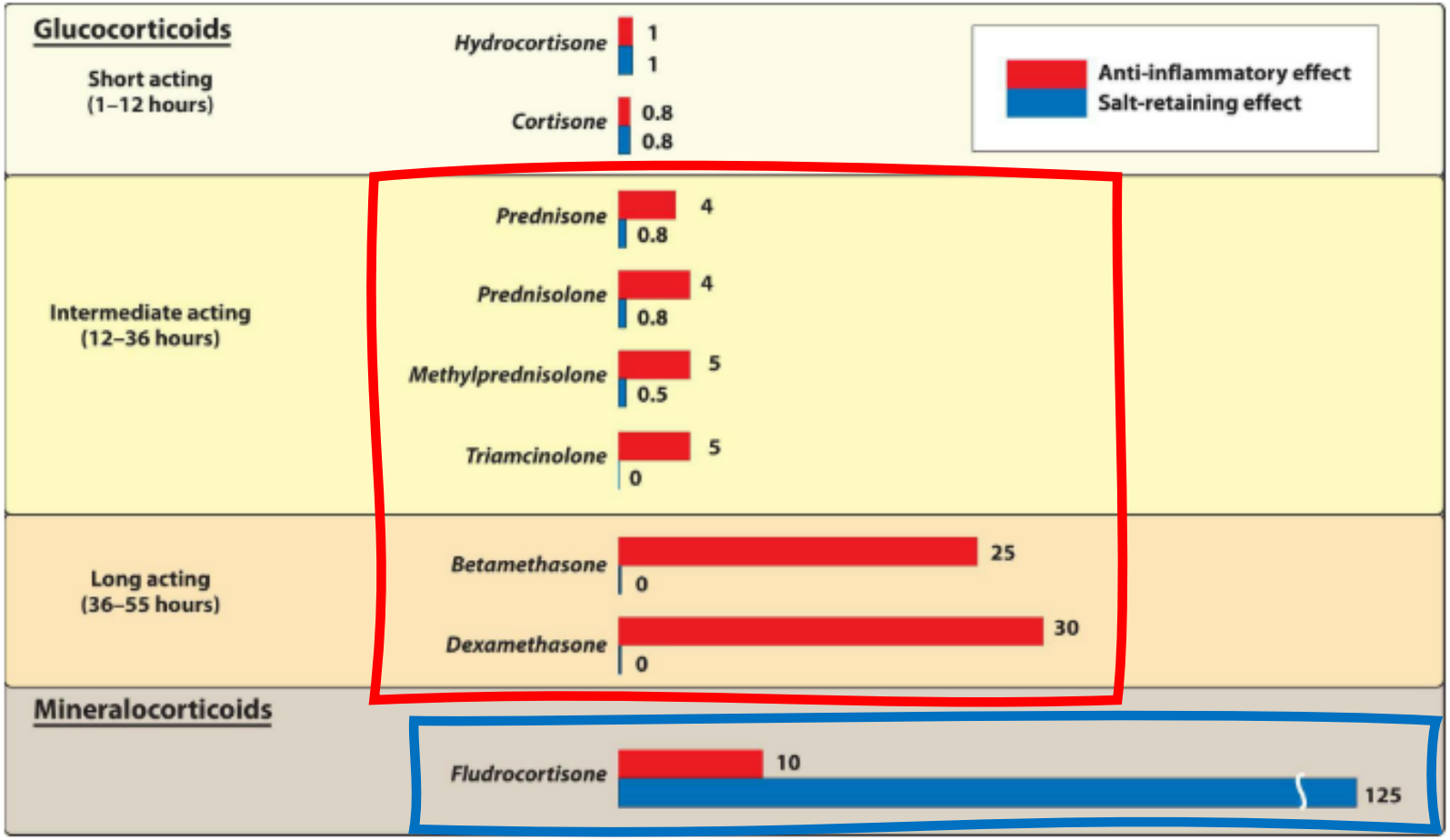
Corticosteroid Drugs (classification)

Natural

Semi-synthetic

Drug	Route of Administration	Duration of Action (Hours)	Mineralocorticoid (Salt-Retaining) Potency	Glucocorticoid (Anti-Inflammatory) Potency
Short-acting drugs				
Hydrocortisone (cortisol)	Oral, parenteral, or topical	8–12	++	+
Cortisone	Oral, parenteral, or topical		++	+
Fludrocortisone	Oral		+++++++	+++
Intermediate-acting drugs				
Methylprednisolone	Oral, parenteral, or topical	12–24	+	+++
Prednisone	Oral		+	++
Triamcinolone	Oral, parenteral, or topical		-	+++
Long-acting drugs				
Betamethasone	Oral, parenteral, or topical	24–72	-	+++++
Dexamethasone	Oral, parenteral, or topical		-	+++++

Corticosteroid Drugs (classification)



Corticosteroid Drugs

1. Fludrocortisone:

A mineralocorticoid → used **as replacement therapy in patients with primary adrenal insufficiency** (Addison disease).

2. Semisynthetic glucocorticoid drugs

Uses:

- Most commonly, used as **anti-inflammatory drugs** → for treatment of a wide range of inflammatory, allergic, autoimmune disorders.

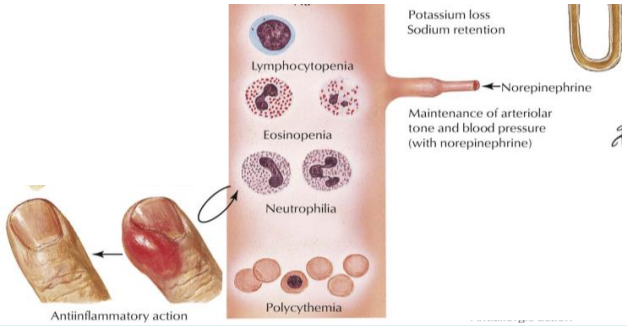
  Whenever possible, **topical or inhalational administration is preferred** because it avoids most systemic adverse effects

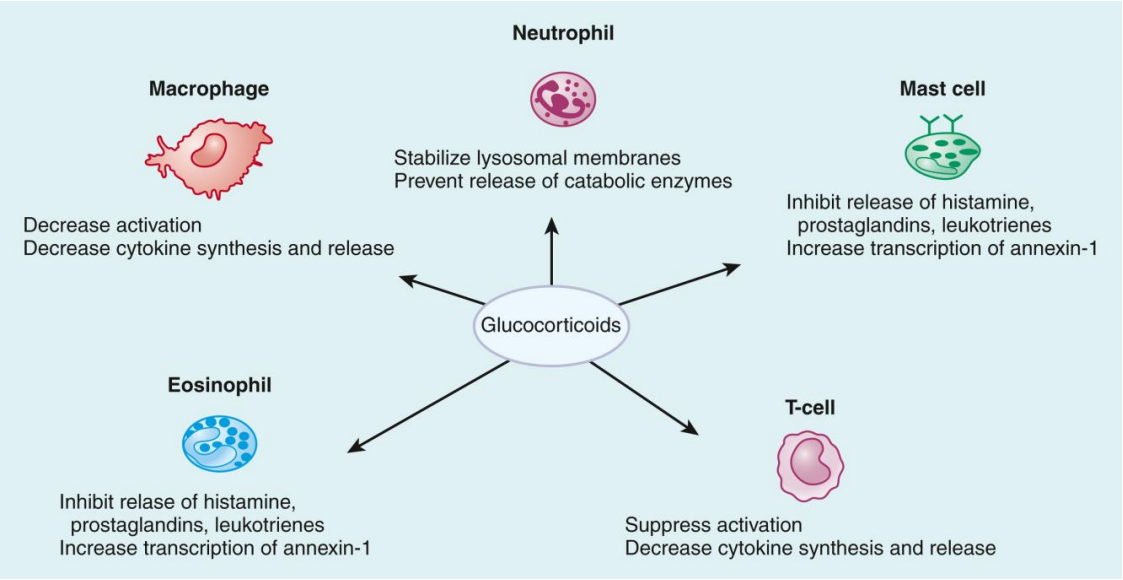
- Less commonly, used **as replacement therapy in the treatment of adrenal insufficiency** (e.g., cortisone & hydrocortisone)

Glucocorticoids
Anti-inflammatory Effects

Glucocorticoids have multiple actions on several types of leukocytes:

1. **Suppress activation** of T lymphocytes & macrophage
2. ↓ **production of cytokines** by activated T helper cells & macrophages.
3. ↓ **release of inflammatory chemical mediators** from mast cells and eosinophils e.g., histamine, prostaglandins & leukotrienes.
4. **Stabilize lysosomal membranes** of neutrophils and prevent the release of catabolic enzymes
5. Cause **vasoconstriction** and ↓ capillary permeability and inflammatory edema.
6. ↓ **number of circulating lymphocytes, eosinophils, basophils, and monocytes.**





7. ↑ **number of RBCs, platelets, and WBCs**.

Glucocorticoids

Other effects

1. ↓ **growth** in children.
2. ↑ development of **peptic ulcer**
3. Promote **fat redistribution**

Increase visceral, facial, and supraclavicular fat

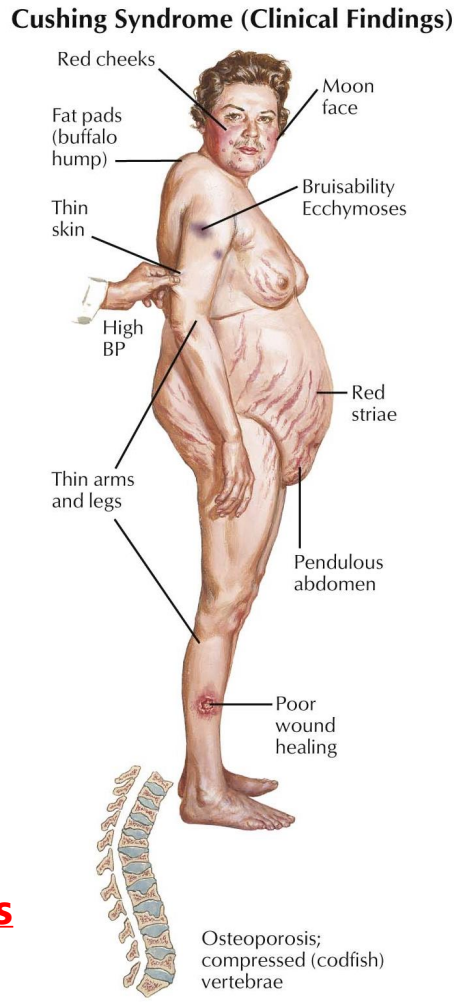
"moon face" and "buffalo hump"

4. **Antagonize Vitamin D** effect on calcium absorption
5. Stimulates structural/functional **development of fetal lungs**
6. Behavioral disturbances

Initially insomnia and euphoria followed by **depression or psychosis**

7. **Suppress pituitary release of ACTH (long-term use of glucocorticoids**

   → suppress the hypothalamic-pituitary-adrenal axis.



Glucocorticoids
indications

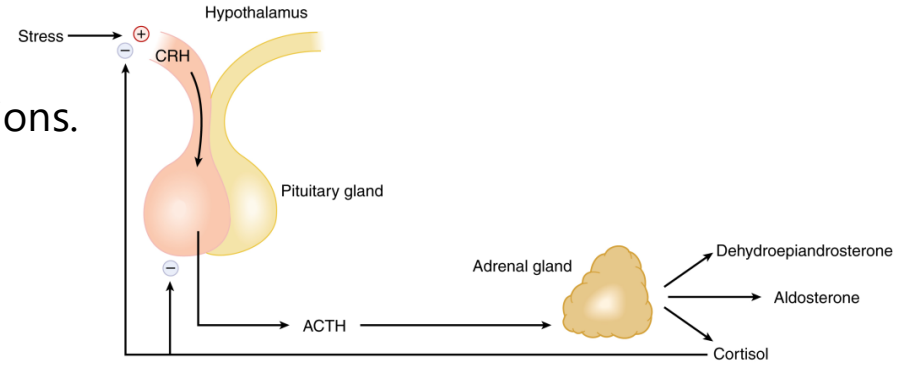
1. Treatment of Inflammatory, Allergic, and Autoimmune Disorders

Autoimmune disorders as: systemic lupus erythematosus, multiple sclerosis and ulcerative colitis.

N.B. <u>beclomethasone</u> → an inhaled glucocorticoid → 1st-line therapy of bronchial asthma

<u>Mometasone</u> → topical in the nose for allergic rhinitis

<u>Topical steroids</u> → allergic & autoimmune dermatologic conditions.



2. Cancer

Treatment of lymphocytic leukemias and lymphomas

3. Respiratory Distress Syndrome in premature infants.

4. Replacement therapy in adrenocortical insufficiency

N.B. Most commonly, adrenal insufficiency results when **<u>steroid drugs are stopped suddenly</u>** after being used for a prolonged time.

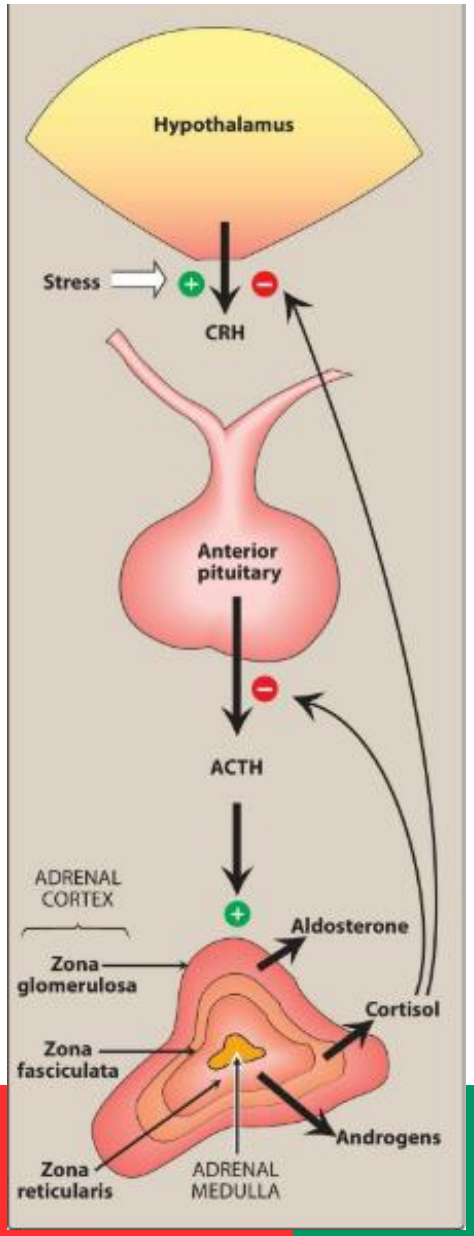
Glucocorticoids
indications

Replacement therapy in adrenocortical insufficiency

1. Replacement therapy for **primary adrenocortical insufficiency (Addison disease)** → is caused by adrenal cortex dysfunction
2. Replacement therapy for **secondary or tertiary adrenocortical insufficiency** → These disorders are caused by a defect in CRH production or in ACTH production.

Hydrocortisone is used for treatment of these deficiencies.

2/3 of the daily dosage of hydrocortisone is administered in the morning and 1/3 in the afternoon, mimicking the normal circadian variation in cortisol levels.



Glucocorticoids
Pharmacokinetics

1. Absorption:

Glucocorticoids are highly lipid soluble → **well absorbed** after oral administration.

2. Glucocorticoids are **highly bound** to corticosteroid-binding globulin and albumin.

3. Metabolism:

Glucocorticoids are **oxidized by cytochrome P450 enzymes** and **conjugated** with sulfate or glucuronide in the liver before undergoing renal excretion.

Administration:

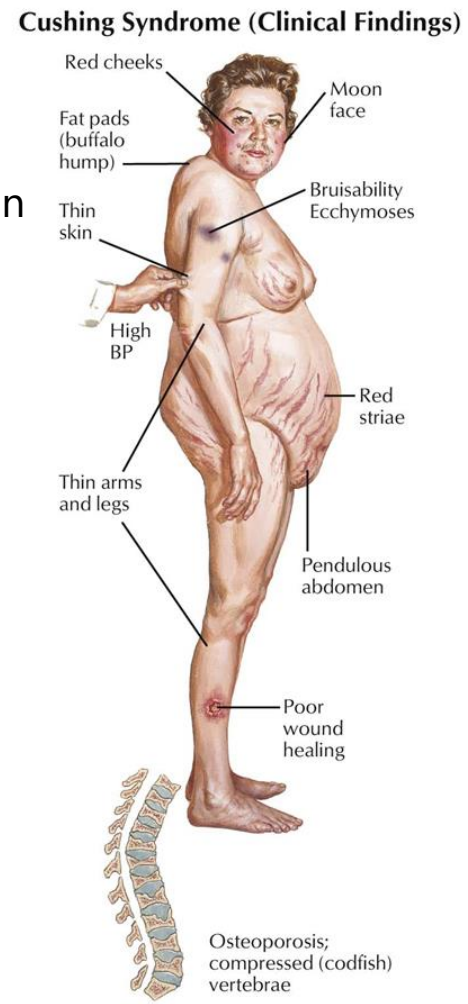
- *Orally* → to treat mild-moderate allergic conditions, autoimmune disorders and cancers.
- *Parenterally* (IV or IM) → to treat acute adrenal insufficiency, acute allergic reactions, and emergencies.

Glucocorticoids are often more effective when they are initially given in large doses then **gradually tapered over several days until treatment is discontinued.**

N.B. Alternate-day therapy, is a dosage schedule that appears to reduce adverse effects and produces less suppression of the hypothalamic-pituitary-adrenal axis by allowing more time for recovery between doses.

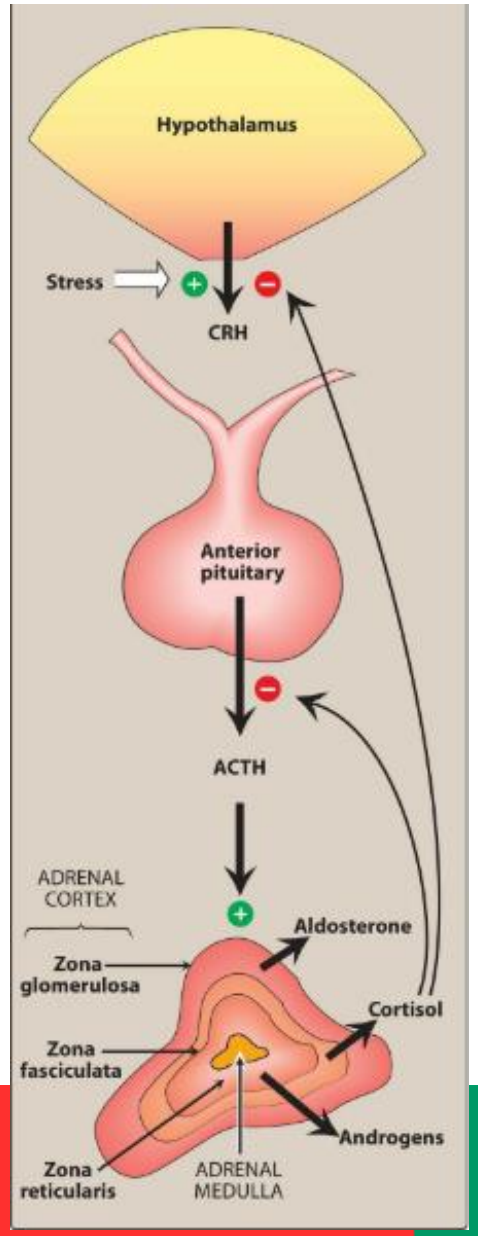
Glucocorticoids
Side effects

1. Administration of therapeutic doses of glucocorticoids > 2 weeks → results in Iatrogenic **"Cushing syndrome".**
   - Moon face & buffalo hump.
   - Increased hair growth (hirsutism)
   - Weight gain
   - Muscle wasting and weakness
   - Osteoporosis.
   - Dermatologic changes → acne (steroid acne), bruising, and thinning of the skin.
2. Metabolic changes → **hyperglycemia and hypertension**.
3. **Na^+ retention, K^+ loss**, and hypertension → more common with cortisone or hydrocortisone → have greater mineralocorticoid activity than other glucocorticoids.



Glucocorticoids
Side effects

4. Mood changes → **Euphoria or psychosis**.
5. **Exacerbate peptic ulcers**.
6. ↑ **susceptibility to infection**
7. Ophthalmic → **cataracts and glaucoma**
8. **Acute Adrenal suppression** due to negative feedback mechanisms
   - The degree of suppression is related to the dose and length of therapy.
   - When therapy is discontinued, **the dose must be gradually tapered.**



Q1

Give a brief overview of what you'll cover in your presentation.

Q2

Give a brief overview of what you'll cover in your presentation.

Refences:

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Thank you