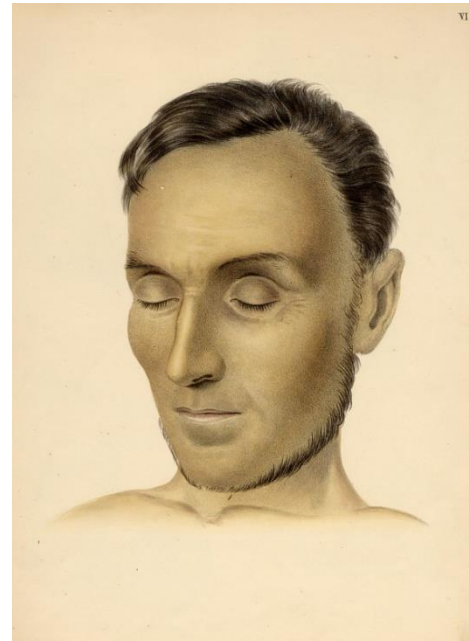
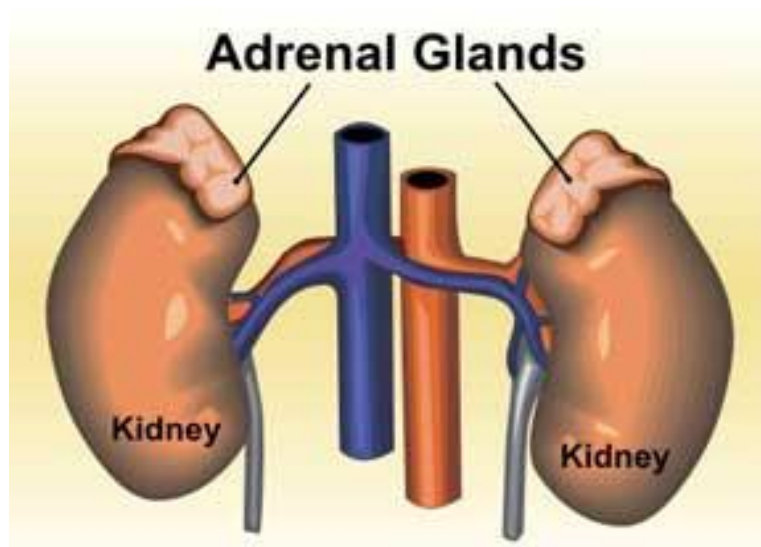
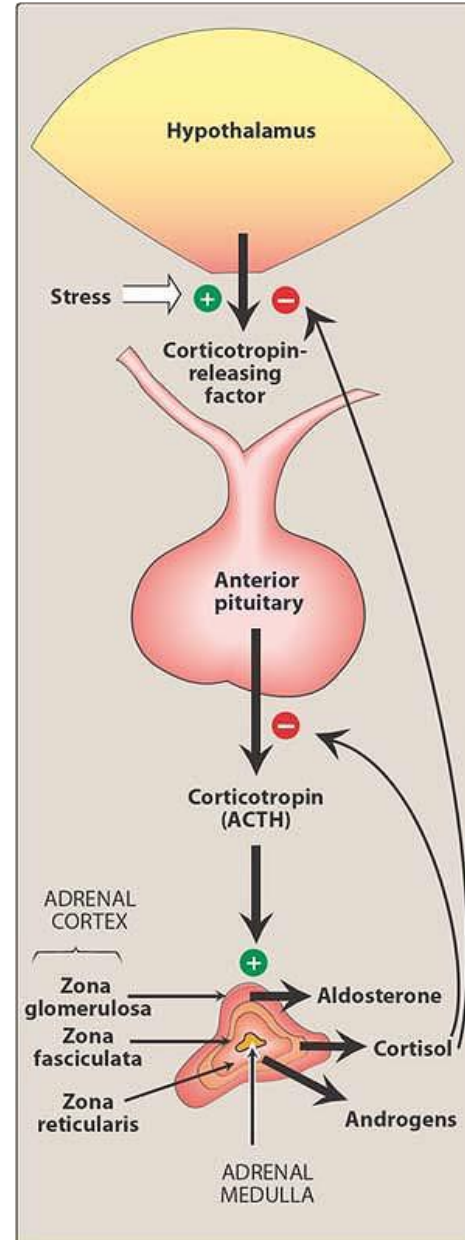


Adrenal Hormones



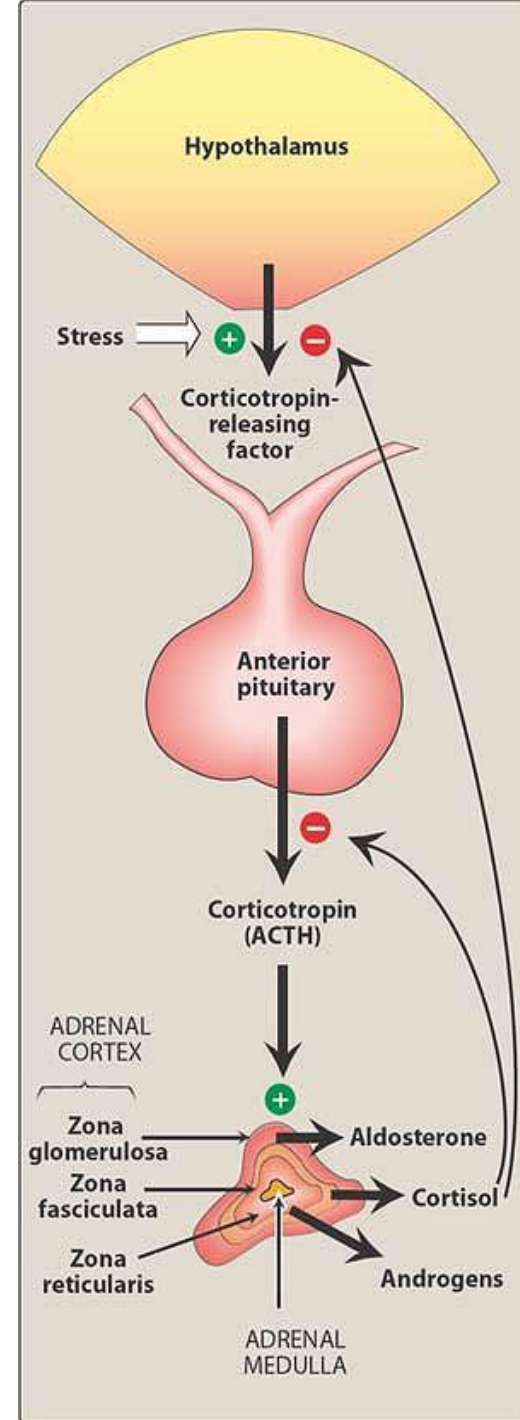
Adrenal Hormones

- The adrenal gland consists of:
 1. Cortex >>> secretes **adrenocorticosteroids** and **adrenal androgens**.
 2. Medulla >>> secretes **epinephrine**.
- The adrenal cortex is divided into **three zones** that synthesize various steroids from cholesterol and then secrete them:
 1. The outer layer of adrenal cortex: produces **mineralocorticoids** (for example, aldosterone).
 2. The middle layer synthesizes **glucocorticoids** (for example, cortisol).
 3. The inner layer secretes **adrenal androgens** (for example, dehydroepiandrosterone).



Adrenal Hormones

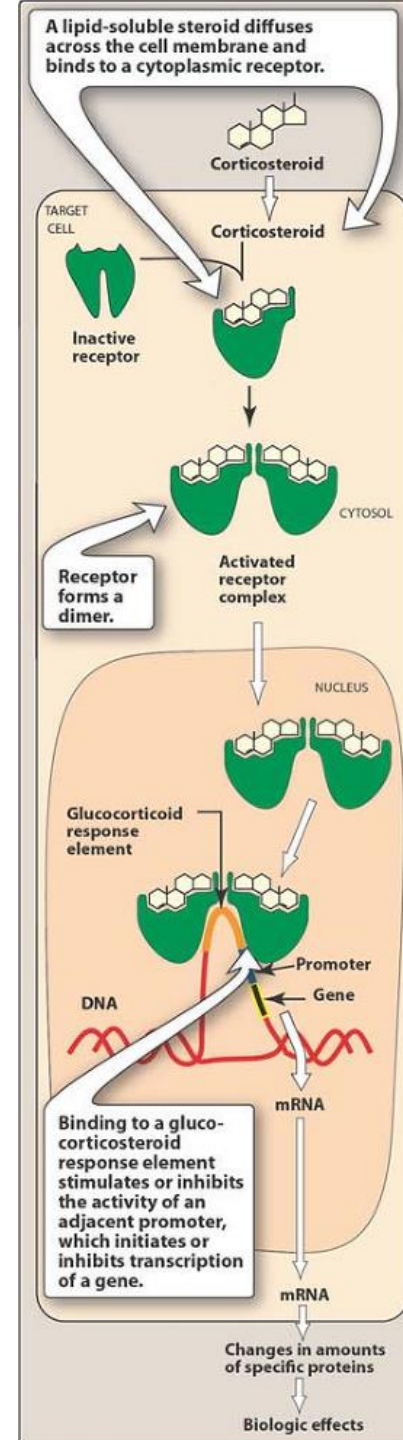
- Secretion by the two inner zones and, to some extent, the outer zone is controlled by pituitary ACTH.
- Glucocorticoids serve as feedback inhibitors of ACTH and CRH secretion.
- **Hormones of the adrenal cortex are used in:**
 1. Replacement therapy
 2. In the treatment and management of asthma as well as other inflammatory diseases, such as rheumatoid arthritis
 3. In the treatment of severe allergic reactions
 4. In the treatment of some cancers



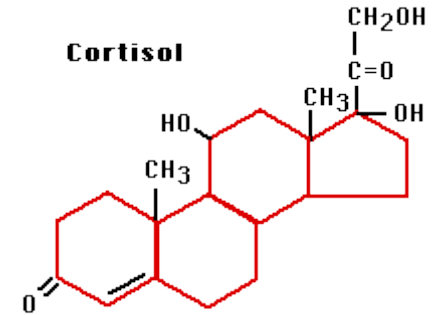
Glucocorticoids

The adrenocorticoids bind to specific intracellular cytoplasmic receptors in target tissues.

The **glucocorticoid receptor** is widely distributed throughout the body, whereas the **mineralocorticoid receptor** is confined mainly to excretory organs, such as the kidney, colon, and salivary and sweat glands >>>> glucocorticoid has wider spectrum of activity than mineralocorticoid.



Glucocorticoids

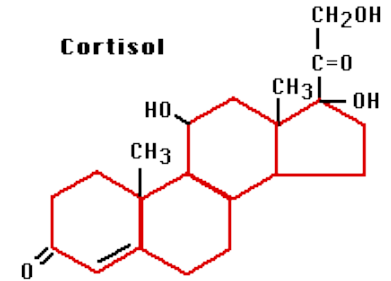


- Cortisol is the principal glucocorticoid.
- Glucocorticoid production is diurnal, with a peak early in the morning followed by a decline and then a secondary, smaller peak in the late afternoon.
- Factors such as **stress** influence secretion.

The effects of cortisol are:

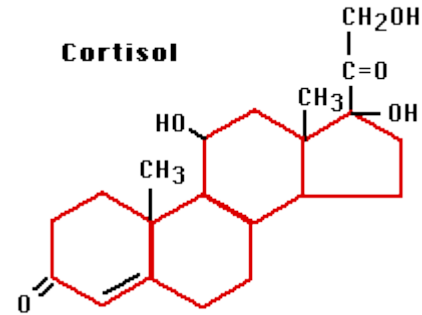
1. Glucocorticoids favor gluconeogenesis and stimulate protein catabolism (except in the liver) and lipolysis >>>> providing the building block for glucose synthesis >>>> Hyperglycemia

Glucocorticoids



2. **Increase resistance to stress: (HOW?!)** By raising plasma glucose levels >>> provide the body with the energy it requires to combat stress.
3. Glucocorticoids can cause a **modest rise in BP**, apparently by enhancing the vasoconstrictor action of adrenergic stimuli on small vessels.
4. **Alter blood cell levels in plasma: (HOW?!)**
 - ii. Glucocorticoids cause a decrease in eosinophils, basophils, monocytes
 - iii. Lymphocytes by redistributing them from the circulation to lymphoid tissue
 - iv. Increase the blood levels of hemoglobin, erythrocytes, platelets, and neutrophils.

Glucocorticoids



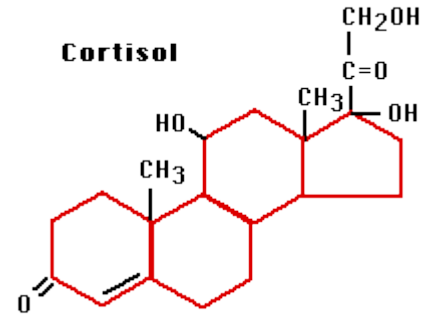
6. Have anti-inflammatory action:

- vi. Reduce the inflammatory response
- vii. Suppress immunity

The mechanism may be due to:

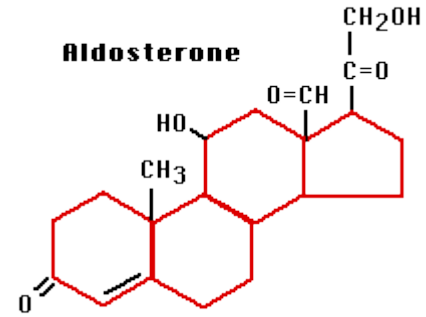
- A. The lowering and inhibition of peripheral lymphocytes and macrophages
- B. Indirect inhibition of phospholipase A₂, reduced COX-2 synthesis in inflammatory cells.
- C. Decreased histamine release.

Glucocorticoids



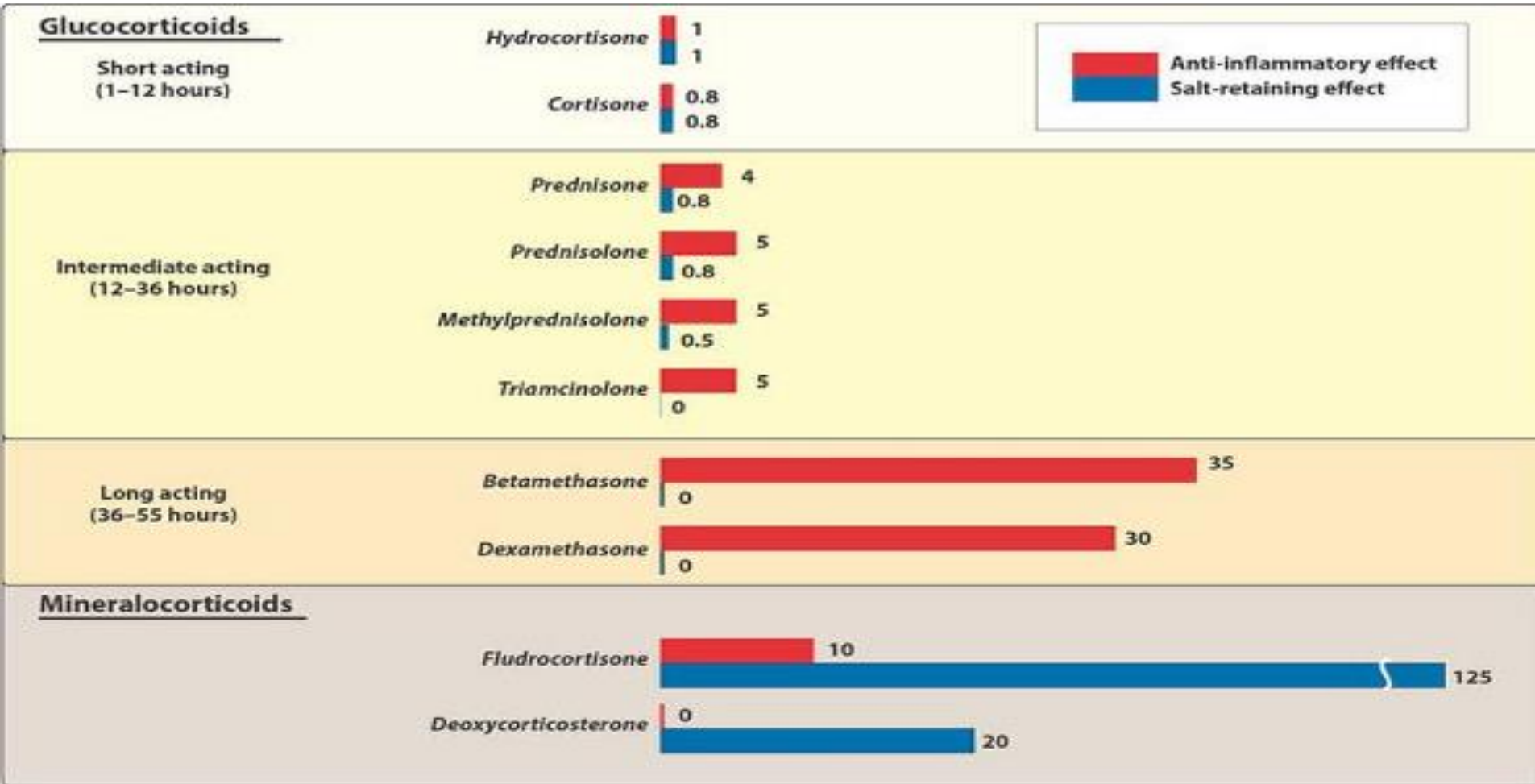
7. **Affect other components of the endocrine system:**
 - vii. Feedback inhibition of ACTH and TSH production by glucocorticoids.
 - viii. In contrast, GH production is increased (**important**).
8. Adequate cortisol is essential for normal renal GF
9. High doses of glucocorticoids stimulate gastric acid and pepsin production and may exacerbate ulcers.
10. On CNS, they influence mental status.
11. Chronic glucocorticoid therapy can cause severe bone loss.
Myopathy and weakness.

Mineralocorticoids



- Mineralocorticoids help to control the body's **water volume** and **concentration of electrolytes**, especially sodium and potassium.
- Aldosterone acts on kidney tubules and collecting ducts, causing a reabsorption of sodium, bicarbonate, and water.
- Conversely, aldosterone decreases reabsorption of potassium, which, with H⁺, is then lost in the urine.
- Elevated aldosterone levels may cause alkalosis and hypokalemia.
- Retention of sodium and water leads to an increase in blood volume and blood pressure.

Classification of corticosteroids



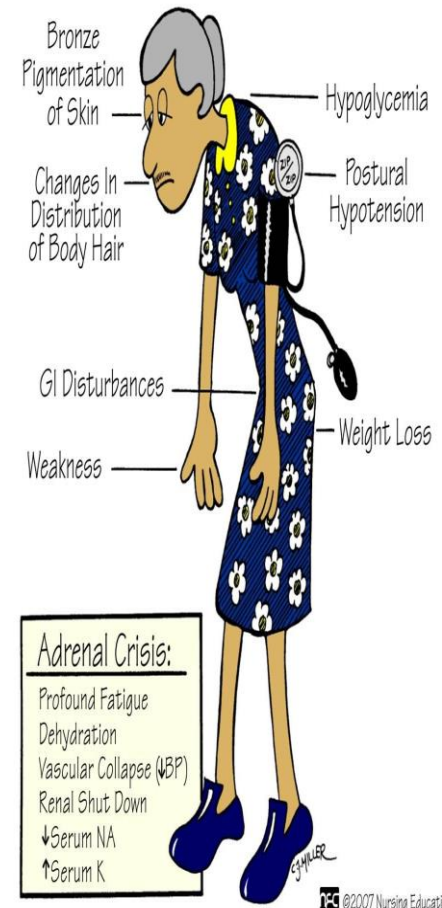
Several **semisynthetic** derivatives of the glucocorticoids have been developed that vary in:

1. Their anti-inflammatory potency
2. Degree to which they cause sodium retention
3. Duration of action

Therapeutic uses of the adrenal corticosteroids

1. Replacement therapy for primary adrenocortical insufficiency (Addison's disease):
 - Hydrocortisone (cortisol), is given to correct the deficiency.
 - The dosage of hydrocortisone is divided so that two-thirds of the normal daily dose is given in the morning and one-third is given in the afternoon. (why?!!)
 - Administration of **fludrocortisone**, a potent synthetic mineralocorticoid with some glucocorticoid activity, may also be necessary to raise the mineralocorticoid activity to normal levels.

ADDISON'S DISEASE



Therapeutic uses of the adrenal corticosteroids

- 2. Replacement therapy for secondary or tertiary adrenocortical insufficiency:** The adrenal cortex responds to corticotropin (ACTH) administration by synthesizing and releasing the adrenal corticosteroids. Hydrocortisone is also used for these deficiencies.

- 3. Diagnosis of Cushing's syndrome:** Dexamethasone suppression test is used to diagnose the cause of an individual's case of Cushing's syndrome.

Therapeutic uses of the adrenal corticosteroids

- 4. Replacement therapy for congenital adrenal hyperplasia:**
Treatment requires administration corticosteroids to normalize hormone levels by suppressing release of CRH and ACTH>>>>
This decreases production of adrenal androgens.
- 5. Relief of inflammatory symptoms:** Glucocorticoids reduce rheumatoid and osteoarthritic inflammations, as well as inflammatory conditions of the skin.

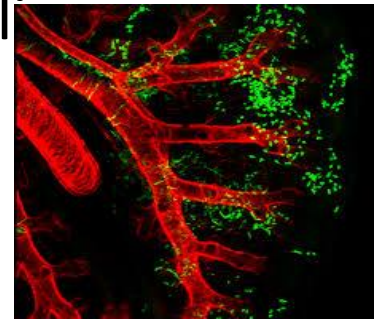


Therapeutic uses of the adrenal corticosteroids

- 6. Treatment of allergies:** Glucocorticoids are beneficial in the treatment of asthma, allergic rhinitis, and allergic reactions. Beclomethasone, triamcinolone, and others are applied through inhalation.



- 7. Acceleration of lung maturation:** Respiratory distress syndrome is a problem in premature infants. Cortisol enhances lung maturation. A dose of beclomethasone is administered intramuscularly to the before del



Pharmacokinetics

- The only glucocorticoid that has **no** effect on the fetus in pregnancy is prednisone.
- Prednisone is a prodrug that is not converted to the active compound, **prednisolone**, in the fetal liver.

Dosage:

- When large doses of the hormone are required over an extended period of time (more than 2 weeks) >>>>>
suppression of the hypothalamic-pituitary-adrenal (HPA) axis occurs. (important!)

-

Pharmacokinetics

- To prevent this adverse effect, a regimen of **alternate-day administration** of the adrenocortical steroid may be useful. This schedule allows the HPA axis to recover/function on the days the hormone is not taken.
- Withdrawal from corticosteroids can be a serious problem (**WHY?!**), because if the patient has experienced HPA suppression.
- Abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal >>>> **So, the dose must be tapered gradually.**

Adverse effects

- The common side effects of long-term corticosteroid therapy are:

- 1. Osteoporosis** is due to

- A. The ability of glucocorticoids to suppress intestinal Ca^{2+} absorption
- B. Inhibit bone formation
- C. Decrease sex hormone synthesis

Alternate-day dosing does not prevent osteoporosis. Patients are advised to take calcium and vitamin D supplements.

- 2. Cushing-like syndrome**

- 3. Increased frequency of cataracts**

- 4. Hyperglycemia may develop and lead to diabetes mellitus**

- 5. Hypokalemia**

- 6. Decreased growth in children**

- 7. Increased appetite**

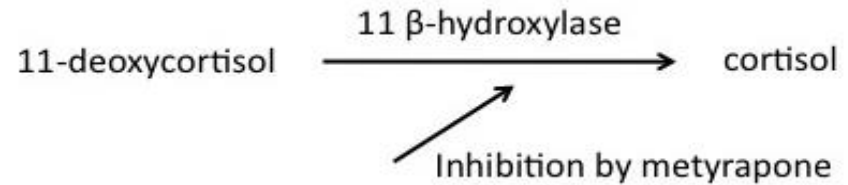
- 8. Increased risk of infection**

- 9. Peripheral edema**

- 10. Coadministration of medications that induce or inhibit the hepatic mixed-function oxidases may require adjustment of the glucocorticoid dose (WHY?!) because they are metabolized by liver P450s**

Inhibitors of adrenocorticoid biosynthesis

Metyrapone



- Is used for tests of adrenal function
- Can be used for the treatment of pregnant women with Cushing's syndrome.
- It interferes with corticosteroid synthesis by blocking the final step (11-hydroxylation) in glucocorticoid synthesis, leading to an increase in **11-deoxycortisol** as well as **adrenal androgens** and the potent **mineralocorticoid 11-deoxycorticosterone**. (why?! This inhibition stimulates ACTH secretion)

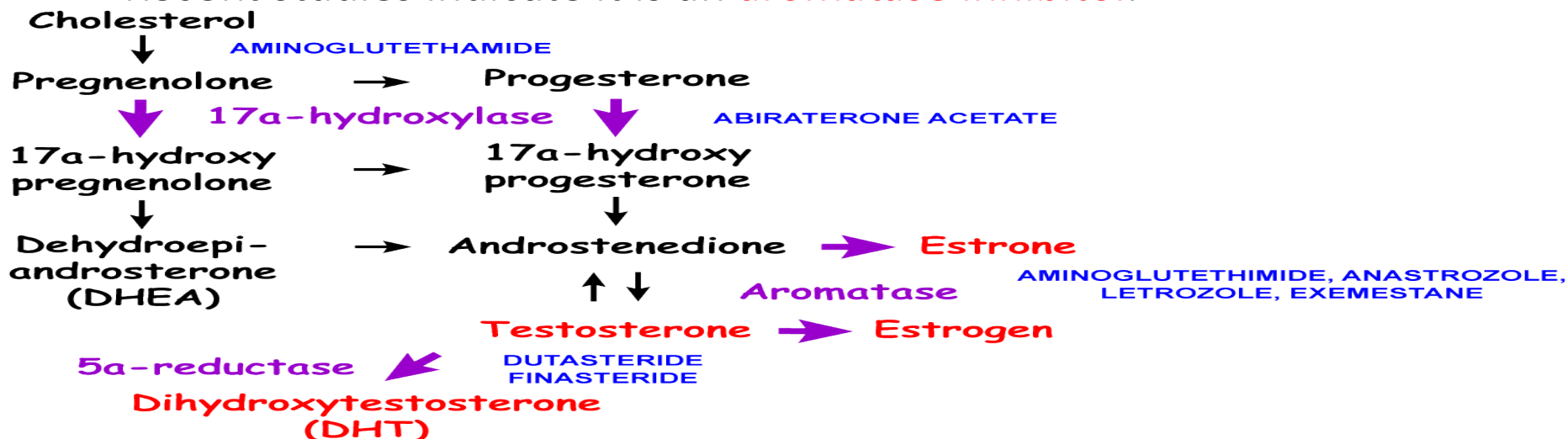
The adverse effects

1. Salt and water retention (**WHY?!**)
2. Hirsutism (**WHY?!**)
3. Transient dizziness
4. Gastrointestinal disturbances

Inhibitors of adrenocorticotoid biosynthesis

Aminogluteth**imide**

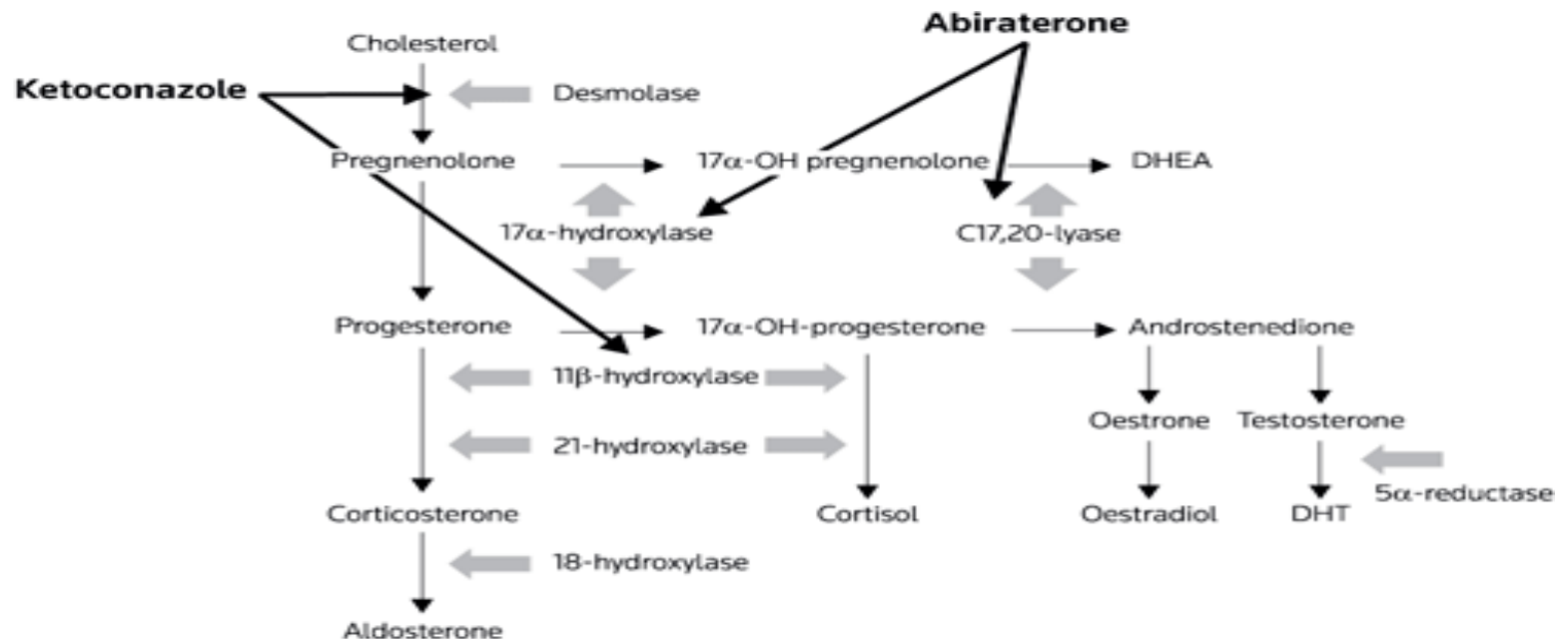
- This drug acts by inhibiting the conversion of cholesterol to pregnenolone.
- As a result, the synthesis of **all** hormonally active steroids is reduced.
- Aminoglutethimide has been used therapeutically in the treatment of:
 1. Breast cancer to reduce or eliminate androgen and estrogen production.
 2. Useful in the treatment of malignancies of the adrenal cortex to reduce the secretion of steroids.
- Recent studies indicate it is an **aromatase inhibitor**.



Inhibitors of adrenocorticoid biosynthesis

Ketoconazole

- Is an antifungal agent
- Strongly inhibits **all** gonadal and adrenal steroid hormone synthesis.
- It is used in the treatment of patients with Cushing's syndrome.



Inhibitors of adrenocorticoid biosynthesis

Mifepristone

- At high doses, mifepristone is a potent **glucocorticoid antagonist** as well as an **antiprogesterin**.
- Its use is presently limited to the treatment of inoperable patients with ectopic ACTH syndrome.
(cancer with increased POMC)

Inhibitors of adrenocorticoid biosynthesis

Spironolactone

- It competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney.
- It can also antagonize aldosterone and testosterone synthesis.
- It is effective against hyperaldosteronism.
- It is also useful in the treatment of hirsutism in women (WHY?!) probably due to interference at the androgen receptor of the hair follicle.
- Adverse effects include :
- Hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

Inhibitors of adrenocorticoid biosynthesis

Eplerenone

- Eplerenone specifically acts as an **aldosterone antagonist**.
- This specificity avoids the side effect of gynecomastia associated with spironolactone.
- It is an antihypertensive.