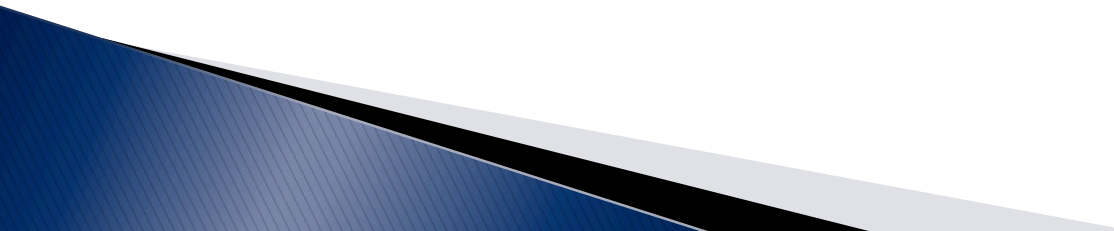
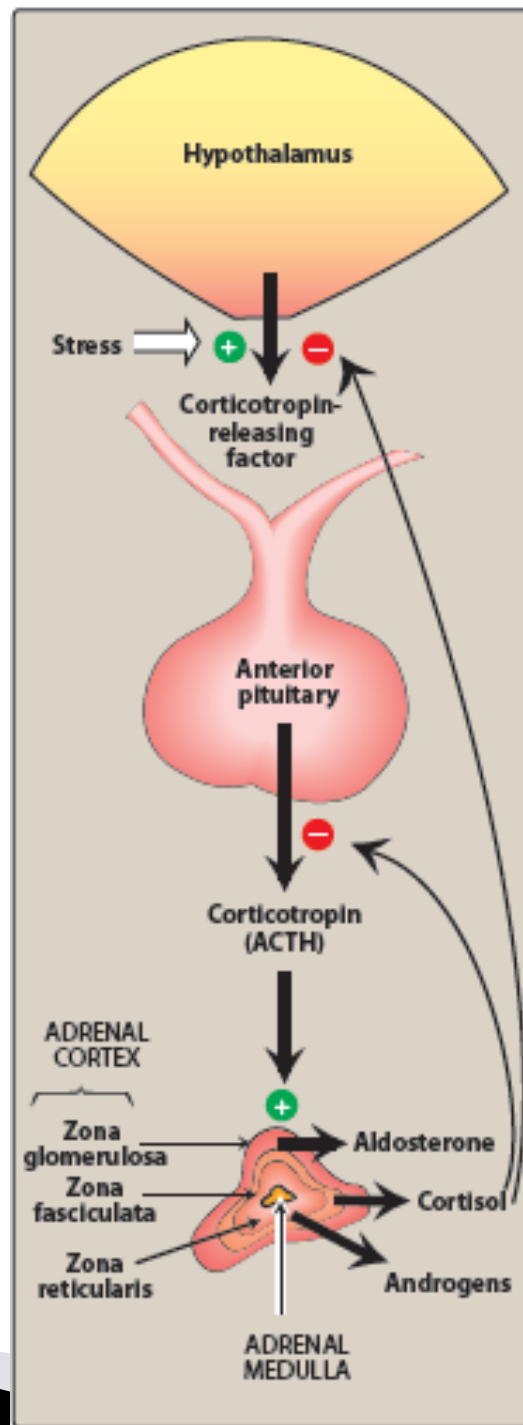


Adrenal Hormones

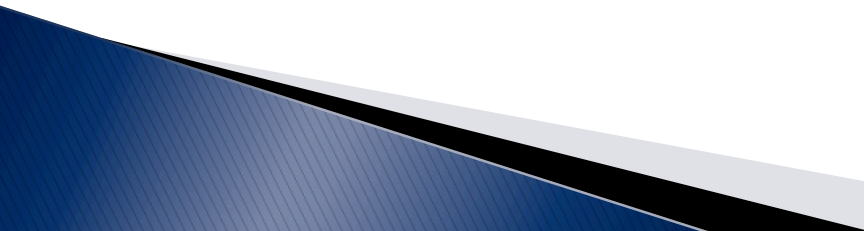


- ▶ The adrenal gland consists of the cortex and the medulla
 - ▶ The adrenal medulla secretes epinephrine
 - ▶ The adrenal cortex synthesizes and secretes two major classes of steroid hormones, the adrenocorticosteroids (glucocorticoids and mineralocorticoids) and the adrenal androgens
- 

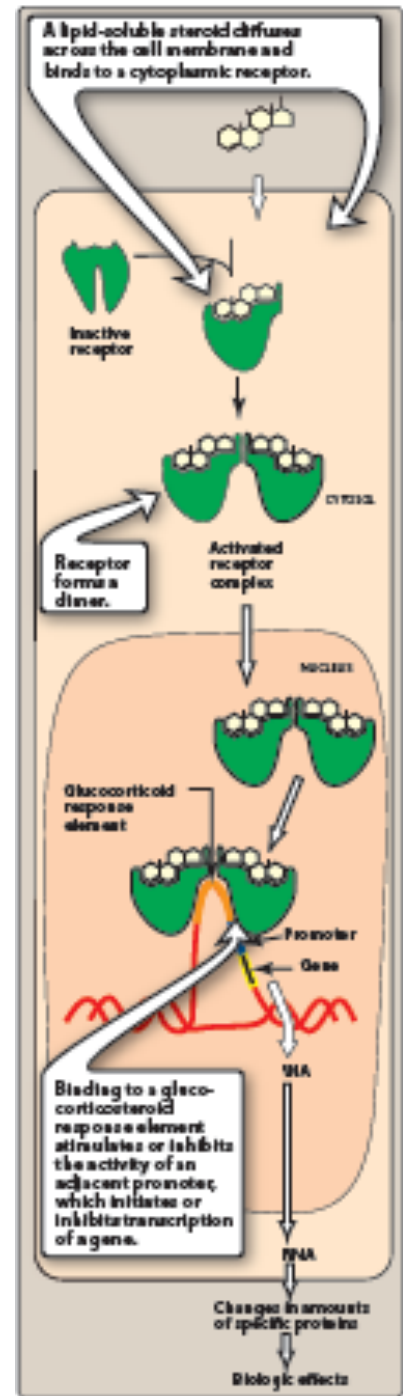
- ▶ The adrenal cortex is divided into three zones that synthesize various steroids from cholesterol and then secrete them
- ▶ The outer zona glomerulosa produces mineralocorticoids which are responsible for regulating salt and water metabolism (**aldosterone**)
- ▶ The middle zona fasciculata synthesizes glucocorticoids which are involved with normal metabolism and resistance to stress (**cortisol**)
- ▶ The inner zona reticularis secretes adrenal androgens (dehydroepiandrosterone).
- ▶ Secretion is controlled by pituitary **ACTH** which is released in response to the hypothalamic **CRH**
- ▶ Glucocorticoids serve as feedback inhibitors of ACTH and CRH secretion



Adrenocorticosteroids

- ▶ The adrenocorticoids bind to specific intracellular cytoplasmic receptors in target tissues
 - ▶ The glucocorticoid receptor is widely distributed throughout the body
 - ▶ The mineralocorticoid receptor is found mainly in excretory organs, such as the kidney, colon, and salivary and sweat glands
 - ▶ Both mineralocorticoid and glucocorticoid receptors are found in the brain
- 

- ▶ After dimerizing, the receptor-hormone recruits certain co-activator (or co-repressor) proteins
 - The complex translocates into the nucleus where it attaches to gene promoter elements, acting as a transcription factor to turn genes on (when complexed with co-activators) or off (when complexed with co-repressors), depending on the tissue
- ▶ This mechanism requires time to produce an effect



- ▶ Other glucocorticoid effects, such as their interaction with catecholamines to mediate relaxation of bronchial musculature or lipolysis, have effects that are immediate

Glucocorticoids

- ▶ Cortisol is the principal human glucocorticoid
 - Its 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 and levels of the circulating steroid influence secretion
 - The effects of cortisol are many and diverse

Glucocorticoids

▶ All glucocorticoids:

1. Promote normal intermediary metabolism
2. Increase resistance to stress
3. Alter blood cell levels in plasma
4. Have anti-inflammatory action
5. Affect other components of the endocrine system
6. Can have effects on other systems

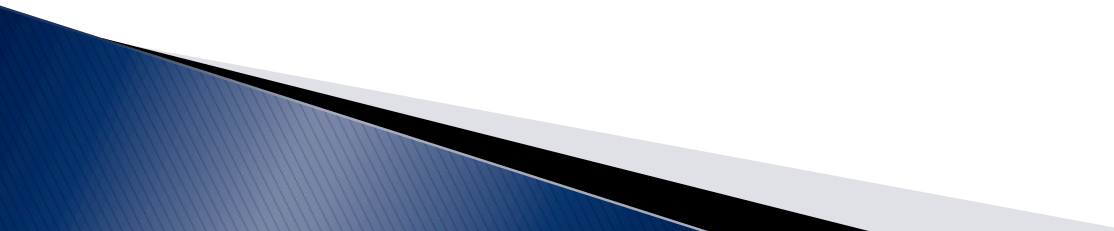
Glucocorticoids

Promote metabolism

- ▶ Glucocorticoids favor gluconeogenesis through increasing amino acid uptake by the liver and kidney and elevating activities of gluconeogenic enzymes
- ▶ Stimulate protein catabolism (except in the liver) and lipolysis providing building blocks and energy that are needed for glucose synthesis
- ▶ Glucocorticoid insufficiency may result in hypoglycemia (e.g. during stressful periods or fasting)

Glucocorticoids

Increase resistance to stress

- ▶ By raising plasma glucose levels, glucocorticoids provide the body with the energy it requires to combat stress caused, for example, by trauma, fright, infection, bleeding, or debilitating disease
 - ▶ Glucocorticoids can cause a modest rise in blood pressure, by enhancing the vasoconstrictor action of adrenergic stimuli on small vessels
- 

Glucocorticoids

Alter blood cell levels in plasma:

- ▶ Glucocorticoids cause a decrease in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue
 - The decrease in circulating lymphocytes and macrophages compromises the body's ability to fight infections
 - This property is important in the treatment of leukemia
- ▶ Glucocorticoids increase the blood levels of hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes

Glucocorticoids

Have anti-inflammatory action

- ▶ Dramatically reduce the inflammatory response and suppress immunity
- ▶ The exact mechanism is complex and incompletely understood
 - The lowering and inhibition of peripheral lymphocytes and macrophages plays a role
 - The indirect inhibition of phospholipase A2 which blocks the release of arachidonic acid
 - Cyclooxygenase-2 synthesis in inflammatory cells is reduced, lowering the availability of prostaglandins
 - Interference with mast cell degranulation results in decreased histamine and capillary permeability


Glucocorticoids

Affect other components of the endocrine system

- ▶ Feedback inhibition of corticotropin production by elevated glucocorticoids causes inhibition of further synthesis of both glucocorticoid and thyroid-stimulating hormones

Glucocorticoids

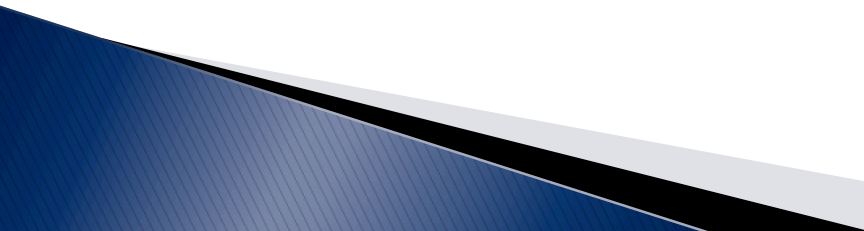
Can have effects on other systems

- ▶ Adequate cortisol levels are essential for normal glomerular filtration
 - ▶ High doses of glucocorticoids stimulate gastric acid and pepsin production and may exacerbate ulcers
 - ▶ Effects on the central nervous system that influence mental status
 - ▶ Chronic glucocorticoid therapy can cause severe bone loss and myopathy
- 

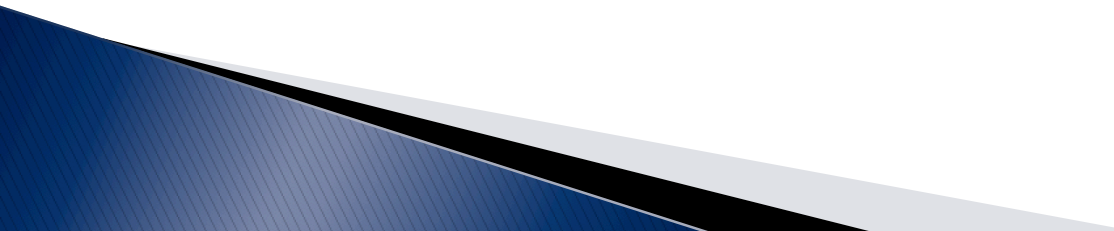
Mineralocorticoids

- ▶ Mineralocorticoids help to control the body's water volume and concentration of electrolytes, especially Na^+ and K^+
- ▶ Aldosterone acts on kidney tubules and collecting ducts, causing a reabsorption of sodium, bicarbonate, and water
- ▶ Aldosterone decreases reabsorption of potassium, which, with H^+ is lost in the urine
- ▶ Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands
- ▶ Elevated aldosterone levels may cause alkalosis and hypokalemia
- ▶ Retention of sodium and water leads to an increase in blood volume and blood pressure.
- ▶ Hyperaldosteronism is treated with **spironolactone**

Corticosteroids

- ▶ Betamethasone (Betnovate[®], Valecort[®], Diprosan[®])
 - ▶ Cortisone
 - ▶ Dexamethasone (Dexacort Forte[®], Decort[®])
 - ▶ Fludrocortisone (Florinef[®])
 - ▶ Hydrocortisone
 - ▶ Methylprednisolone (Medrol[®])
 - ▶ Prednisolone (Prednitab[®], Prednicort[®])
 - ▶ Prednisone
 - ▶ Triamcinolone (Oracort[®], Kenalog[®])
- 


Corticosteroids: Inhaled and nasal sprays

- ▶ Beclomethasone
 - ▶ Budesonide
 - ▶ Fluticasone
 - ▶ Flunisolide
 - ▶ Ciclesonide
 - ▶ Mometasone
 - ▶ Triamcinolone
- 

Therapeutic uses of the adrenal corticosteroids

- ▶ Several semisynthetic derivatives of the glucocorticoids have been developed that vary in their anti-inflammatory potency, in the degree to which they cause sodium retention, and their duration of action

Therapeutic uses of the adrenal corticosteroids

1. Replacement therapy for primary adrenocortical insufficiency (Addison disease)
 2. Replacement therapy for secondary or tertiary adrenocortical insufficiency
 3. Diagnosis of Cushing syndrome
 4. Replacement therapy for congenital adrenal hyperplasia
 5. Relief of inflammatory symptoms
 6. Treatment of allergies
 7. Acceleration of lung maturation
- 

Addison's Disease

- ▶ Primary adrenocortical insufficiency
- ▶ Symptoms
 - Hypoglycemia, fatigue, hypotension
 - Increased skin pigmentation
 - GI disturbances: anorexia, vomiting, diarrhea
 - Low plasma cortisol, accompanied by high plasma ACTH levels

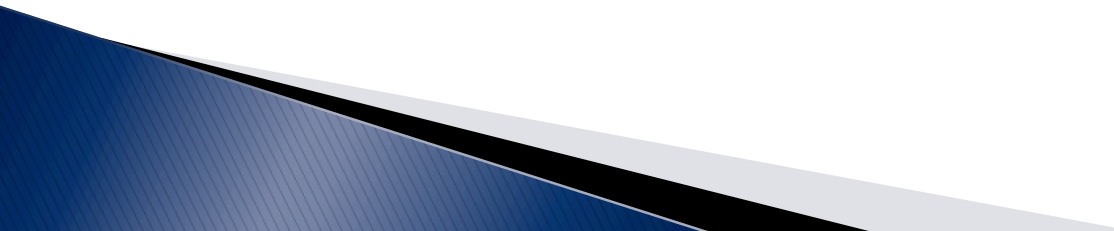
Therapeutic uses of the adrenal corticosteroids

Replacement therapy for primary adrenocortical insufficiency (Addison disease)

- ▶ Diagnosed by the lack of patient response to corticotropin administration
- ▶ **Hydrocortisone** which is identical to natural cortisol, is given to correct the deficiency
 - Leaving condition untreated results in death
- ▶ 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
- ▶ Administration of **fludrocortisone**, a potent synthetic mineralocorticoid with some glucocorticoid activity, raise the mineralocorticoid activity to normal levels

Therapeutic uses of the adrenal corticosteroids

Replacement therapy for secondary or tertiary adrenocortical insufficiency

- ▶ Caused by a defect either in CRH production by the hypothalamus or in corticotropin production by the pituitary
 - ▶ The synthesis of mineralocorticoids in the adrenal cortex is less impaired than that of glucocorticoids
 - ▶ Hydrocortisone is used for treatment
- 

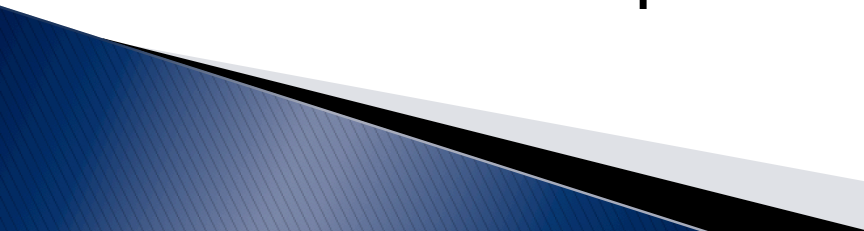
Therapeutic uses of the adrenal corticosteroids

Diagnosis of Cushing syndrome

- ▶ Caused by a hypersecretion of glucocorticoids that results either from excessive release of corticotropin by the anterior pituitary or an adrenal tumor
- ▶ The **dexamethasone** suppression test is used to diagnose and differentiate the cause of Cushing syndrome
- ▶ Dexamethasone suppresses cortisol release in individuals with pituitary-dependent Cushing syndrome, but it does not suppress glucocorticoid release from adrenal tumors
- ▶ Chronic treatment with high doses of glucocorticoid is a frequent cause of iatrogenic Cushing syndrome

Therapeutic uses of the adrenal corticosteroids

Replacement therapy for congenital adrenal hyperplasia

- ▶ A group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones
 - ▶ This condition may lead to virilization in females due to overproduction of adrenal androgens
 - ▶ Treatment requires administration of sufficient corticosteroids to normalize the patient's hormone levels by suppressing release of CRH and ACTH
 - ▶ This decreases production of adrenal androgens
- 

Therapeutic uses of the adrenal corticosteroids

Relief of inflammatory symptoms

- ▶ Glucocorticoids dramatically reduce inflammation (for example, rheumatoid and osteo–arthritic inflammation as well as inflammatory conditions of the skin), including redness, swelling, heat, and tenderness that are present at the inflammatory site
- ▶ Cause redistribution of leukocytes to other body compartments, thereby lowering their blood concentration and
- ▶ Decrease in the concentration of lymphocytes (T and B cells), basophils, eosinophils, and monocytes
- ▶ Inhibit the ability of leukocytes and macrophages to respond to mitogens and antigens
- ▶ Decrease production of prostaglandins and leukotrienes
- ▶ Stabilize mast cell and basophil membranes (Inhibiting histamine release) and diminishing the activation of the kinin system

Therapeutic uses of the adrenal corticosteroids

Treatment of allergies

- ▶ Glucocorticoids are beneficial in the treatment of the symptoms of bronchial asthma; allergic rhinitis; and drug, serum, and transfusion allergic reactions
- ▶ These drugs are **not** curative
- ▶ **Triamcinolone** and others are applied topically to the respiratory tract through inhalation from a metered-dose dispenser
 - This minimizes systemic effects and allows the patient to significantly reduce or eliminate the use of oral steroids

Therapeutic uses of the adrenal corticosteroids

Acceleration of lung maturation

- ▶ Respiratory distress syndrome is a problem in premature infants
- ▶ Fetal cortisol is a regulator of lung maturation
- ▶ **Betamethasone** or **dexamethasone** is administered IM to the mother 48 hours prior to birth, followed by a second dose 24 hours before delivery

Corticosteroids

- ▶ Synthetic glucocorticoid preparations can be administered orally and are readily absorbed from the GIT
- ▶ Selected compounds can also be administered IV, IM, intra-articularly, topically, or as an aerosol for either oral inhalation or intranasal delivery
- ▶ Greater than 90% of the absorbed glucocorticoids is bound to plasma proteins (corticosteroid-binding globulin or albumin)
- ▶ Corticosteroids are metabolized by the liver and the products are excreted by the kidney
 - Coadministration of medications that induce or inhibit the hepatic mixed-function oxidases may require adjustment of the glucocorticoid dose

Corticosteroids

- ▶ Factors considered in determining dosage:
 - Glucocorticoid versus mineralocorticoid activity
 - Duration of action
 - Type of preparation
 - Time of day when the steroid is administered
- ▶ 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
 - To prevent this adverse effect, a regimen of alternate–day administration of the adrenocortical steroid may be useful
 - This allows the HPA axis to recover/function on the days the hormone is not taken

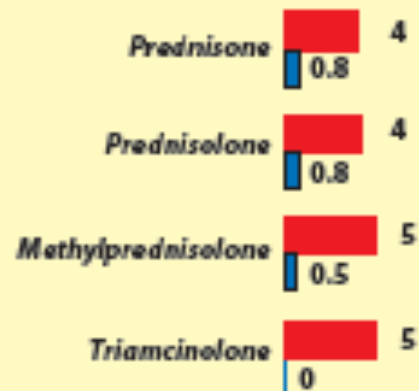
Glucocorticoids

Short acting
(1-12 hours)



Anti-inflammatory effect
Salt-retaining effect

Intermediate acting
(12-36 hours)



Long acting
(36-55 hours)



Mineralocorticoids



IM

Triamcinolone

IV, IM

Betamethasone
Dexamethasone
Hydrocortisone
Methylprednisolone
Prednisolone

Inhaled and nasal sprays

Beclomethasone
Budesonide
Ciclesonide
Flunisolide
Fluticasone
Mometasone
Triamcinolone



Oral

Cortisone
Dexamethasone
Methylprednisolone
Prednisone



Topical



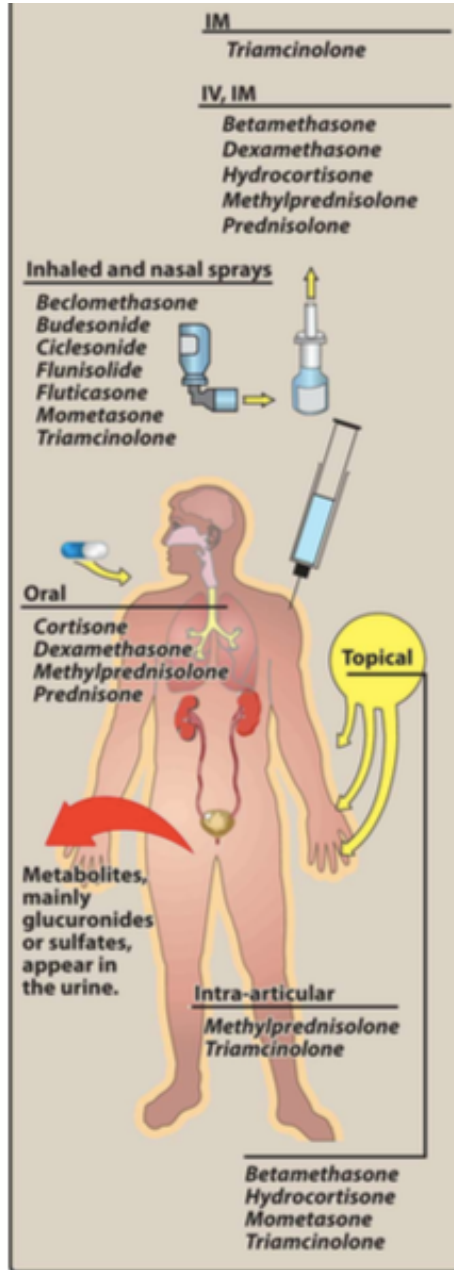
Metabolites,
mainly
glucuronides
or sulfates,
appear in
the urine.



Intra-articular

Methylprednisolone
Triamcinolone

Betamethasone
Hydrocortisone
Mometasone
Triamcinolone



Corticosteroids Adverse effects

- ❖ The risk for adverse effects depended both on dose and duration of therapy
- ❖ The common side effects of long-term corticosteroid therapy:
 - ▶ Osteoporosis is the most common adverse effect due to the ability of glucocorticoids to suppress intestinal Ca^{2+} absorption, inhibit bone formation, and decrease sex hormone synthesis
 - Alternate-day dosing does not prevent osteoporosis
 - Patients are advised to take calcium and vitamin D supplements
 - Drugs that are effective in treating osteoporosis may also be beneficial.

Corticosteroids Adverse effects

- ▶ Cushing-like syndrome (redistribution of body fat, puffy face, increased body hair growth, acne, insomnia, and increased appetite) is observed when excess corticosteroids are present
- ▶ Increased appetite is not necessarily an adverse effect (it is one of the reasons for the use of prednisone in cancer chemotherapy)

Corticosteroids Adverse effects

- ▶ Increased frequency of cataracts occurs with long-term corticosteroid therapy
- ▶ Hyperglycemia may develop and lead to diabetes mellitus
 - Diabetic patients should monitor their blood glucose and adjust their medications accordingly
- ▶ Hypokalemia caused by corticosteroid therapy can be counteracted by potassium supplementation
- ▶ Long-term, low-dose glucocorticoid therapy can lead to numerous serious adverse effects

Corticosteroids Adverse effects

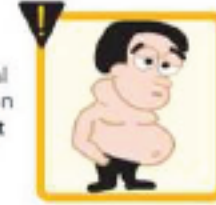
Decreased growth in children



Glaucoma



Centripetal distribution of body fat



Negative calcium balance



Impaired wound healing



Hirsutism



Osteoporosis

Increased risk of infection



Peptic ulcer



Increased appetite

Emotional disturbances



Hypokalemia



Hypertension



Peripheral edema

Corticosteroids withdrawal

- ▶ Withdrawal from these drugs can be a serious problem
 - If the patient has experienced HPA suppression, abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal
 - There is also a possibility of psychological dependence on the drug
 - Withdrawal might also cause an exacerbation of the disease,
 - The dose must be tapered according to the individual (Possibly through trial and error)
 - The patient must be monitored carefully

Inhibitors of adrenocorticoid biosynthesis or function

- ▶ Spironolactone (Aldactone[®], Spironol[®], Spirone[®])
- ▶ Eplerenone (Inspra[®])
- ▶ Ketoconazole (Nizoral[®])

Inhibitors of adrenocorticoid biosynthesis or function

Ketoconazole

- ▶ An antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis
- ▶ It is used in the treatment of patients with Cushing syndrome

Inhibitors of adrenocorticoid biosynthesis or function

Spironolactone:

- ▶ An antihypertensive drug
- ▶ Competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney
- ▶ It can also antagonize aldosterone and testosterone synthesis
- ▶ Effective against hyperaldosteronism
- ▶ Useful in the treatment of hirsutism in women, due to interference at the androgen receptor of the hair follicle
- ▶ Adverse effects:
 - Hyperkalemia
 - Gynecomastia
 - Menstrual irregularities
 - Skin rashes

Inhibitors of adrenocorticoid biosynthesis or function

Eplerenone:

- ▶ Eplerenone specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist
 - ▶ This specificity avoids the side effect of gynecomastia that is associated with the use of spironolactone
 - ▶ It is approved as an antihypertensive
- 