Adrenocorticosteroids
&
Adrenocortical Antagonists

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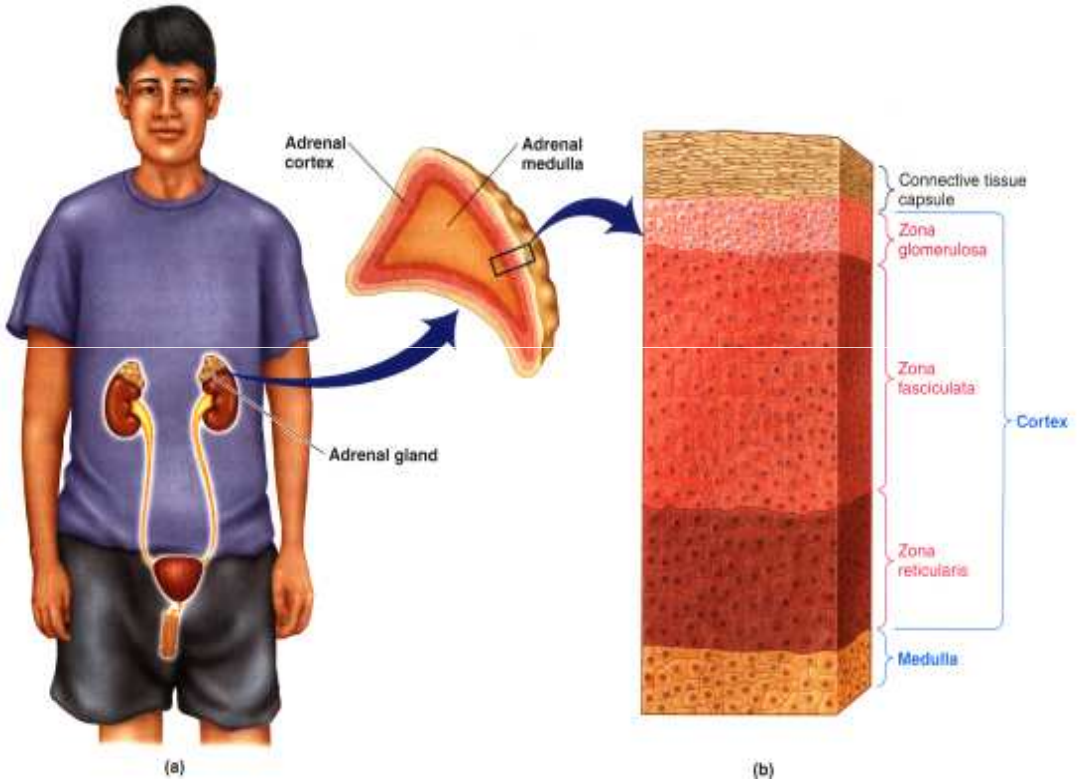
Adrenal Histology



Adrenocorticosteroids

- The adrenal cortex releases a large number of steroids into the circulation.
- Some have minimal biologic activity and function primarily as precursors, and there are some for which no function has been established.
- The hormonal steroids may be classified as those having important effects on intermediary metabolism (glucocorticoids), those having principally salt-retaining activity (mineralocorticoids), and those having androgenic or estrogenic activity.
- In humans, the major glucocorticoid is cortisol and the most important mineralocorticoid is aldosterone.
- Quantitatively, dehydroepiandrosterone (DHEA) is the major adrenal androgen. However, DHEA and two other adrenal androgens, androstenediol and androstenedione, are weak androgens or estrogens, mostly by peripheral conversion to testosterone and dehydrotestosterone or estradiol and estrone.
- Adrenal androgens constitute the major endogenous precursors of estrogen in women after menopause and in younger patients in whom ovarian function is deficient or absent.

Hormones of adrenal gland

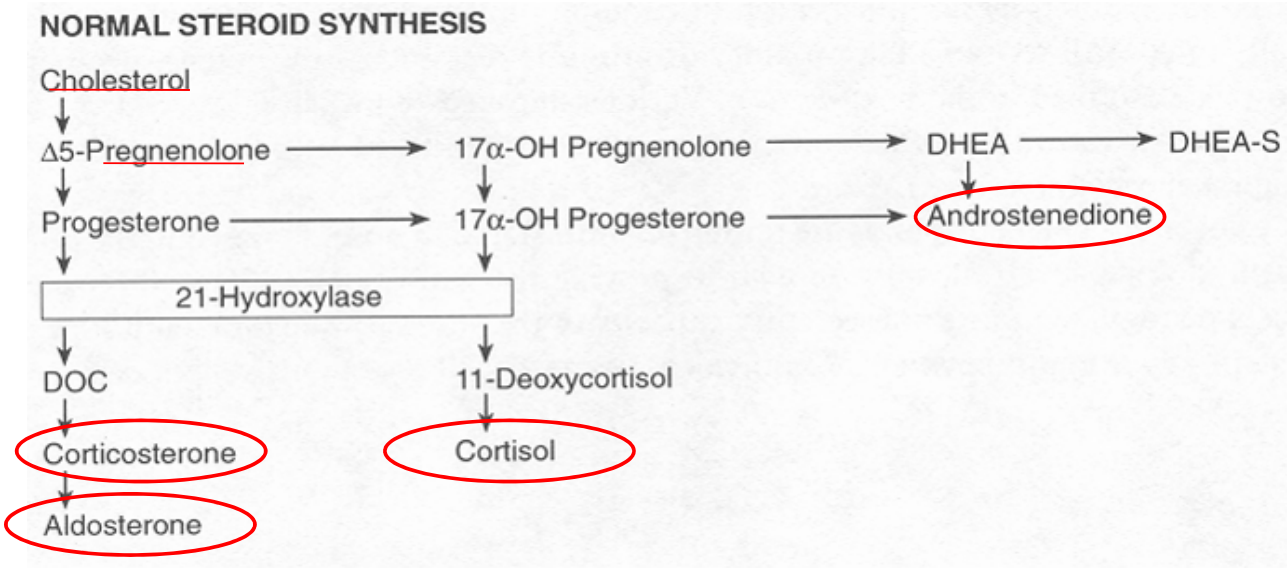
- Adrenal gland produces two types of hormones:
  - Adrenocorticosteroides (produced by adrenal cortex)
  - Catecholamines (produced by adrenal medulla)

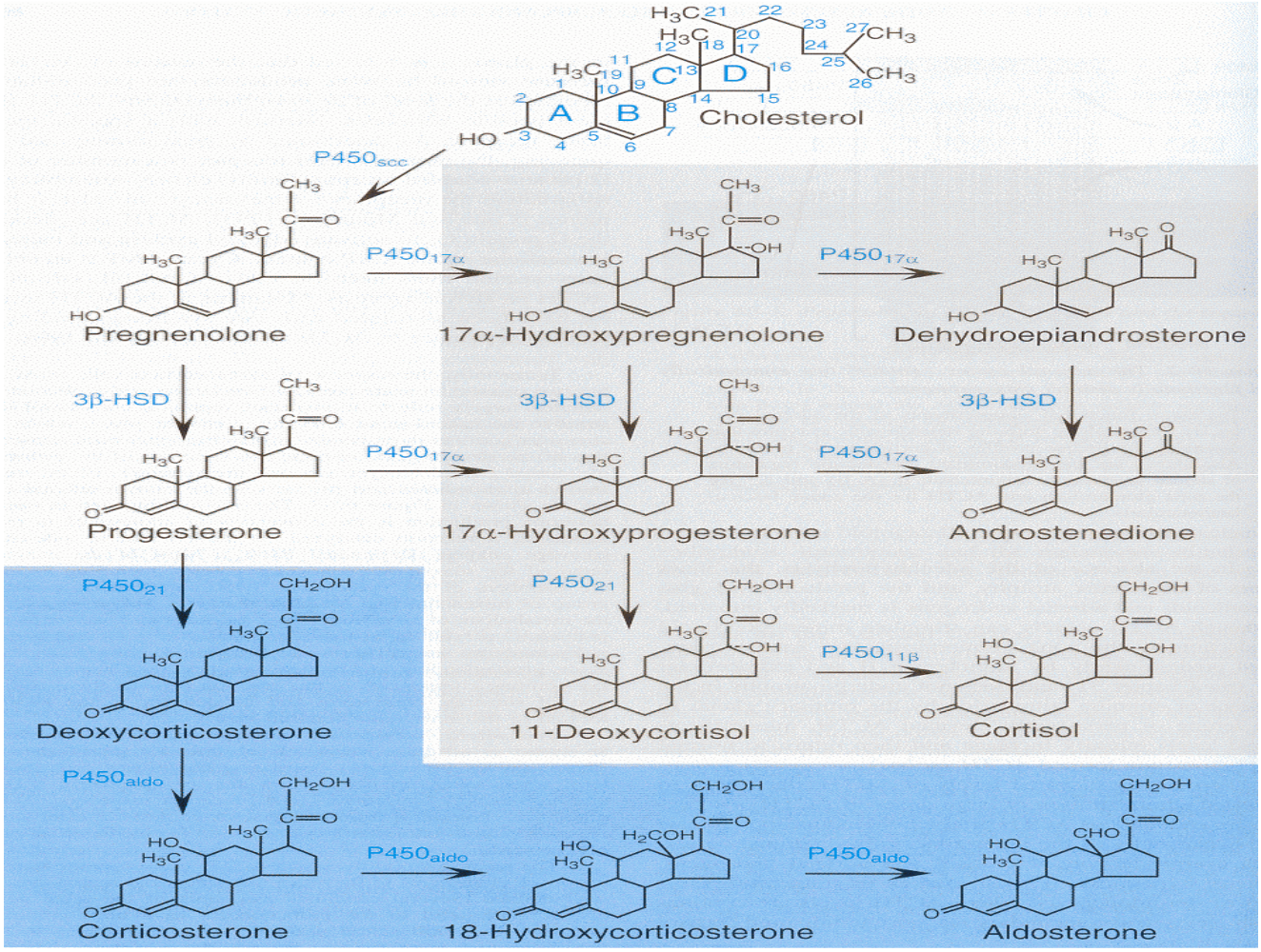
TABLE 18–5 The Adrenal Hormones

Region/Zone	Hormone(s)	Primary Targets	Hormonal Effects	Regulatory Control
CORTEX				
Zona glomerulosa	Mineralocorticoids (primarily aldosterone)	Kidneys	Increase renal reabsorption of Na^+ and water (especially in the presence of ADH) and accelerate urinary loss of K^+	Stimulated by antiotensin II, elevated plasma K^+, or a fall in plasma Na^+; inhibited by (ANP and BNP)
Zona fasciculata	Glucocorticoids (cortisol (hydrocortisone), corticosterone)	Most cells	Release amino acids from skeletal muscles and lipids from adipose tissues; promote liver formation of glucose and glycogen; promote peripheral utilization of lipids; anti-inflammatory effects	Stimulated by ACTH from anterior lobe of pituitary gland
Zona reticularis	Androgens		Not important in adult men.	Stimulated by ACTH
MEDULLA	Epinephrine, norepinephrine	Most cells	Increases cardiac activity, blood pressure, glycogen breakdown, blood glucose levels; releases lipids by adipose tissue	Stimulated during sympathetic activation by sympathetic preganglionic fibers

Biosynthesis

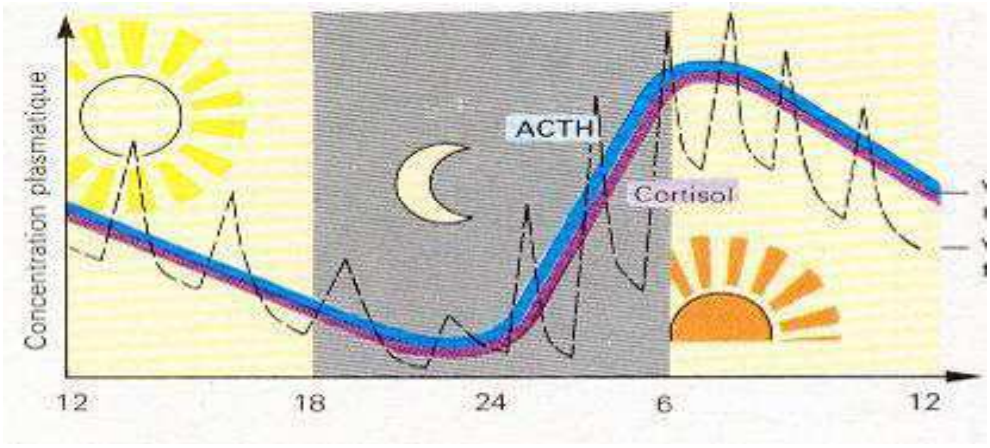
- Cholesterol forms pregnenolone
- Pregnenolone is the common precursor for the synthesis of all steroid hormones.





Cortisol

➢Cortisol basic secretion : circadien and ultradien rythmes



➢Secretion 20 mg/day

➢plasmatic concentration = 4 µg/dl mid night

20µg/dl à 8h morning

Cortisol

➢ Cortisol (also called hydrocortisone, compound F) exerts a wide range of physiologic effects, including regulation of intermediary metabolism, cardiovascular function, growth, and immunity.

➢ Its synthesis and secretion are tightly regulated by the CNS, which is very sensitive to negative feedback by the circulating cortisol and exogenous (synthetic) glucocorticoids.

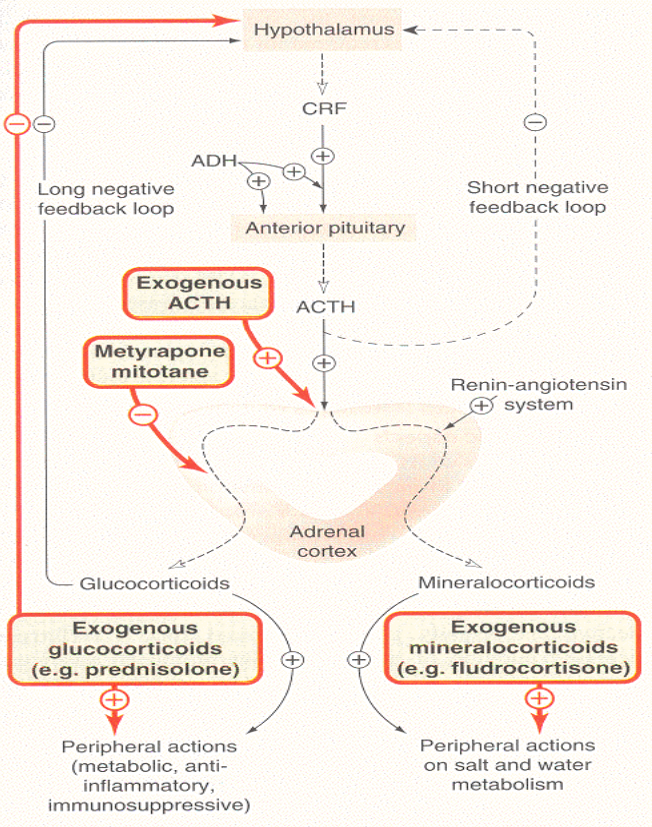
➢ Cortisol is synthesized from cholesterol.

➢ In the normal adult, in the absence of stress, 10–20 mg of cortisol is secreted daily.

➢ The rate of secretion follows a circadian rhythm governed by pulses of ACTH that peak in the early morning hours and after meals.

Control of Glucocorticoid Secretion
(The hypothalamic/pituitary/adrenal (HPA) axis)

In health, when there is not stress, cortisol suppresses secretion of CRH and ACTH by a negative feedback mechanism



Pharmacokinetics

➢ In plasma, **cortisol is bound** to circulating proteins. Corticosteroid-binding globulin (**CBG**), which synthesized by the liver, binds 90% of the circulating hormone under normal circumstances. The remainder is free (about 5–10%) or loosely bound to albumin (about 5%) and is available to exert its effect on target cells.

➢ **Synthetic corticosteroids** such as dexamethasone are largely **bound to albumin** rather than CBG.

➢ The **half-life of cortisol** in the circulation is normally about **60–90 minutes**; half-life may be increased when hydrocortisone is administered in large amounts or when stress, hypothyroidism, or liver disease is present.

➢ **Only 1% of cortisol is excreted unchanged** in the urine as free cortisol.

➢ **Many cortisol metabolites are conjugated with glucuronic acid** or sulfate in the liver; they then reenter the circulation and are excreted in the urine.

Mechanism of Action

- Most of the known effects of the glucocorticoids are mediated by widely distributed glucocorticoids receptors. These proteins are members of the superfamily of **nuclear receptors**. All these receptors interact with the promoters and regulate the transcription of target genes.
- Free hormone from the plasma and interstitial fluid enters the cell and binds to the receptor, inducing conformational changes. The ligand-bound receptor complex then is actively transported into the nucleus, where it interacts with DNA and nuclear proteins.
- The **ligand-bound receptor also forms complexes with and influences the function of other transcription factors**, such as NF-κB, which contribute to the regulation of transcription of their responsive genes.
- These transcription factors have broad actions on the regulation of growth factors, proinflammatory cytokines, etc, and mediate the anti-growth, anti-inflammatory, and immunosuppressive effects of glucocorticoids.
- The effects of glucocorticoids are mainly due to proteins synthesized from mRNA transcribed by their target genes.
- **Some of the effects of glucocorticoids can be attributed to their binding to aldosterone receptors** (AR). Indeed, ARs bind aldosterone and cortisol with similar affinity.

Metabolic Effects

- The glucocorticoids have important **dose-related effects on carbohydrate, protein, and fat metabolism**.

- The net results of these actions are most apparent in the fasting state, when the supply of glucose from **gluconeogenesis**, the **release of amino acids from muscle catabolism**, the **inhibition of peripheral glucose uptake**, and the **stimulation of lipolysis** all contribute to maintenance of an adequate glucose supply to the brain.

- Glucocorticoids increase serum glucose levels and thus **stimulate insulin release** and inhibit the uptake of glucose by muscle cells.

Catabolic and Antianabolic Effects

➢ Although glucocorticoids stimulate protein and RNA synthesis in the liver, they have catabolic and **antianabolic effects in lymphoid and connective tissue, muscle, fat, and skin**.

➢ **Supraphysiologic amounts of glucocorticoids** lead to **decreased muscle mass** and weakness and thinning of the skin.

➢ Catabolic and antianabolic **effects on bone** are the cause of **osteoporosis** in Cushing's syndrome and impose a major limitation in the long-term therapeutic use of glucocorticoids.

➢ In **children, glucocorticoids reduce growth**. This effect may be partially prevented by administration of growth hormone in high doses.

Anti-Inflammatory and Immunosuppressive Effects

➢ Glucocorticoids dramatically **reduce the manifestations of inflammation**.

➢ This is due to their profound **effects on the function of peripheral leukocytes** and to their **suppressive effects on the inflammatory cytokines** and chemokines and on other mediators of inflammation.

➢ Glucocorticoids also **inhibit the functions of tissue macrophages** and other antigen-presenting cells.

➢ Glucocorticoids influence the inflammatory response by **reducing the prostaglandin, leukotriene**, and platelet-activating factor synthesis that results from activation of **phospholipase A2**.

➢ **Complement** activation is unaltered, but its effects are **inhibited**.
➢ **Antibody production can be reduced** by large doses of steroids, though it is unaffected by moderate dosages.

➢ Glucocorticoids **decrease capillary permeability** by reducing the amount of histamine released by basophils and mast cells.

Other Effects

➢ On the nervous system: Adrenal insufficiency is associated with depression. Increased amounts of glucocorticoids often produce behavioral disturbances.

➢ Glucocorticoids given chronically suppress the pituitary release of ACTH, GH, TSH, and LH.

➢ Large doses of glucocorticoids induce the development of peptic ulcer.

➢ They also promote fat redistribution in the body, with increase of facial, and supraclavicular fat.

➢ They increase the number of platelets and red blood cells.

➢ In the absence of physiologic amounts of cortisol, renal function is impaired, vasopressin secretion is augmented.

➢ Glucocorticoids have important effects on the development of the fetal lungs. Indeed, the structural and functional changes in the lungs near term are stimulated by glucocorticoids.

Synthetic Corticosteroids

Pharmacokinetics

➢ The synthetic corticosteroids are in most cases rapidly and completely absorbed when given by mouth.

➢ The compounds are excreted in the free form.

➢ In some cases, the agent given is a prodrug - eg, prednisone is rapidly converted to the active product prednisolone in the body.

Pharmacodynamics

➢ The actions of the synthetic steroids are similar to those of cortisol.

➢ They bind to the specific intracellular receptor proteins and produce the same effects but have different ratios of glucocorticoid to mineralocorticoid potency.

How Administered

- Topical – skin rashes - hydrocortisone
- Eye drops / ear drops: cortisone ear drops or Prednisolone Ophthalmic suspension
- Nasal – Nasonex
- Tablet or liquid form – prednisone, Decadron
- IV – methyl prednisone or Solu-medrol
- Inhaled - asthmatic

Clinical Pearl

- Whenever possible the physician / nurse practitioner will prescribe a topical, nasal spray, eye drops or inhaled dosage before going to an oral route or intravenous route.

- Oral and intravenous routes are usually higher dosages and more likely to have side effects.

Classification of Corticosteroids
ORAL CORTICOSTEROIDS

• **Glucocorticoid Effect (dose equivalent)**		**Mineralocorticoid effect**	**Duration of effect** (in hours)
• **SHORT ACTING**			
• Cortisone	25mg	++++	8-12 hours
• Hydrocortisone	20mg	++++	8-12 hours
• **INTERMEDIATE-ACTING**			
• Prednisolone	5mg	++	18-36 hours
• Triamcinolone	4mg	-	18-36 hours
• Methylprednisolone	4mg	-	18-36 hours
• Fludrocortisone	-	++++	24-36 hours
• **LONG-ACTING**			
• Dexamethasone	750 micrograms	-	36-54 hours
• Betamethasone	750 micrograms	-	36-54 hours

INHALED CORTICOSTEROIDS

	dose equivalent for adverse effects	Time in circulation*
• Beclometasone	1000 micrograms -	19.5 hours
• Budesonide	1000 micrograms -	6.9 hours
• Fluticasone propionate	500 micrograms -	43.2 hours

*calculated as 3 times the terminal half life.

➢ Glucocorticoids have become important agents for use in the treatment of many inflammatory, allergic, hematologic, and other disorders.

➢ **Symptom control:** asthma, allergic rhinitis, rheumatoid arthritis and related connective tissue disorders, temporal arteritis, inflammatory bowel disease, inflammatory skin conditions, chronic pain, anaphylactic shock

➢ **Prevention**: transplant rejection, respiratory distress in the newborn, cerebral oedema

➢ **Treatment**: certain tumours, hyperkalaemia, some blood disorders

➢ **Replacement therapy** in Addison's disease (under-activity of the adrenal cortex).

Diagnosis and Treatment of Disturbed Adrenal Function

- **Chronic Adrenocortical Insufficiency (Addison's Disease)**
- **Acute Adrenocortical Insufficiency**
- **Congenital Adrenal Hyperplasia**
- **Cushing's Syndrome**
- **Aldosteronism**
- **Corticosteroids and Nonadrenal Disorders**
- **Use of Glucocorticoids for Diagnostic Purposes**

Chronic Adrenocortical Insufficiency (Addison's Disease)

- Is characterized by weakness, fatigue, weight loss, hyperpigmentation, hypotension and inability to maintain the blood glucose level during fasting.

- In primary adrenal insufficiency, about 20–30 mg of hydrocortisone must be given daily, with increased amounts during periods of stress.

- Although hydrocortisone has some mineralocorticoid activity, this must be supplemented by an appropriate amount of a salt-retaining hormone such as fludrocortisone.

- Long-acting synthetic glucocorticoids should not be administered to these patients.

Acute Adrenocortical Insufficiency

➢ When acute adrenocortical insufficiency is suspected, treatment must be instituted immediately.

➢ Therapy consists of correction of fluid and electrolyte abnormalities and treatment of precipitating factors in addition to large amounts of parenteral hydrocortisone.

Congenital Adrenal Hyperplasia

➢This group of disorders is characterized by specific defects in the synthesis of cortisol. The most common defect is a decrease in or lack of P450c21 (21 -hydroxylase) activity.

➢This would lead to a reduction in cortisol synthesis and produce a compensatory increase in ACTH release. The gland becomes hyperplastic and produces abnormally large amounts of precursors such as 17-hydroxyprogesterone that can be diverted to the androgen pathway.

➢ In pregnancies at high risk for congenital adrenal hyperplasia, fetuses can be protected from genital abnormalities by administration of dexamethasone to the mother.

➢ However, the most reliable method of detecting this disorder is the increased response of plasma 17- hydroxyprogesterone to ACTH stimulation.

Cushing's Syndrome

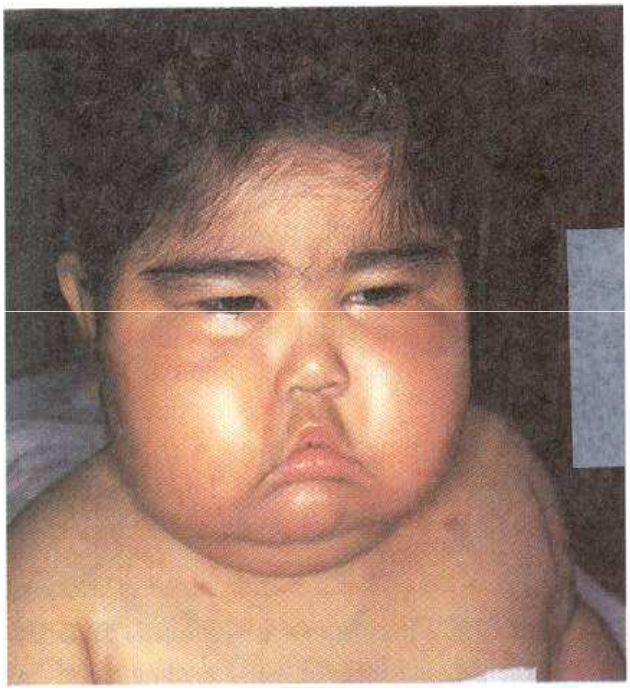
- Is usually the result of **bilateral adrenal hyperplasia secondary to an ACTH secreting pituitary adenoma** but occasionally is due to tumors or ectopic production of ACTH by other tumors.

- The **manifestations** are those associated with the chronic presence of **excessive glucocorticoids.**
  - a **rounded face** and **trunk obesity** are striking in appearance.
  - The **manifestations of protein loss** include **muscle wasting, thinning,**
  - and **poor wound healing,**
  - and **osteoporosis.**
  - **mental disorders,**
  - **hypertension,**
  - and **diabetes.**

- Is treated by **surgical removal of the tumor** producing ACTH or cortisol, **irradiation** of the pituitary tumor, or **resection** of one or both adrenals.

Moon Face

High-dose corticosteroid therapy produces a characteristic "moon face" appearance.



Aldosteronism

- Primary aldosteronism usually results from the excessive production of aldosterone by an adrenal adenoma. However, it may also result from abnormal secretion by hyperplastic glands or from a malignant tumor.

- The clinical findings of hypertension, weakness, and tetany are related to the continued renal loss of potassium, which leads to hypokalemia, alkalosis, and elevation of serum sodium concentrations.

- these patients have low (suppressed) levels of plasma renin activity and angiotensin II.

- It may be detected by an increased ratio of plasma aldosterone to renin.

- Patients are generally improved when treated with spironolactone.

Corticosteroids and Nonadrenal Disorders

- The synthetic analogs of cortisol are useful in the treatment of a diverse group of diseases unrelated to any known disturbance of adrenal function.

- The usefulness of corticosteroids in these disorders is a function of their ability to suppress inflammatory and immune responses.

- In general, attempts should be made to bring the disease process under control using medium- to intermediate-acting glucocorticoids such as prednisone and prednisolone.

- Therapy should not be decreased or stopped abruptly.

- The presence of diabetes, peptic ulcer, osteoporosis, and psychologic disturbances should be taken into consideration, and cardiovascular function should be assessed.

Use of Glucocorticoids for Diagnostic Purposes

- It is sometimes necessary to suppress the production of ACTH in order to identify the source of a particular hormone or to establish whether its production is influenced by the secretion of ACTH.

- In these circumstances, it is advantageous to employ a very potent substance such as dexamethasone.

- The **dexamethasone suppression test** is used for the diagnosis of Cushing's syndrome.

Toxicity

- The major undesirable effects of the glucocorticoids are the result of their hormonal actions, which lead to Cushing's syndrome.

- When the glucocorticoids are used for short periods (less than 2 weeks), it is unusual to see serious adverse effects even with moderately large doses.

- However, insomnia, behavioral changes, and acute peptic ulcers are occasionally observed even after only a few days of treatment.

Side Effects

- Moon face, buffalo hump, obese trunk (love handles), acne, weight gain
- CNS: nervousness, insomnia, depression, aggravation of pre-existing mental disorders
- Musculoskeletal: long term use can cause osteoporosis, muscle weakness and atrophy
- GI: peptic ulcer, increased appetite
- Cardiovascular: fluid retention
- Ocular: increased intraocular pressure, glaucoma, cataracts

➢ In general, patients treated with corticosteroids should be on high protein and potassium-enriched diets.

Adrenal Suppression

➢ When corticosteroids are administered for more than 2 weeks, adrenal suppression may occur.

➢ If treatment extends over weeks to months, the patient should be given appropriate supplementary therapy.

➢ It may take 2–12 months for the hypothalamic-pituitary-adrenal axis to function acceptably, and cortisol levels may not return to normal for another 6–9 months.

➢ The glucocorticoid-induced suppression is not a pituitary problem, and treatment with ACTH does not reduce the time required for the return of normal function.

Contraindications & Cautions

Special Precautions

➢ Patients receiving these drugs must be **monitored carefully** for the development of **hyperglycemia, glycosuria, sodium retention** with edema or **hypertension, hypokalemia, peptic ulcer, osteoporosis**, and **hidden infections**.

➢ The **dosage should be kept as low as possible**, and intermittent administration (eg, alternate-day) should be employed.

Contraindications

➢These agents must be used with **great caution in patients with** peptic ulcer, heart disease or hypertension with heart failure, certain infectious illnesses such as varicella and tuberculosis, psychoses, diabetes, osteoporosis, or glaucoma.

Interactions (Not a complete list)

- The effects of some drugs and appliances are antagonised: anti-epileptics, anti-diabetics, anti-hypertensives, growth hormone, intra-uterine contraceptive devices.
- The dose of corticosteroids is effectively reduced by:
  - co-administration with antacids, within 2 hours
  - carbamazepine, phenytoin, rifampicin, theophylline
- The dose of corticosteroids is effectively increased by:
  - erythromycin, ketoconazole, itraconazole, ciclosporin, some anti-virals

Antagonists of Adrenocortical Agents

Synthesis Inhibitors & Glucocorticoid Antagonists

Metyrapone

- Metyrapone is a relatively selective inhibitor of steroid synthesis.

- Inhibits 11- hydroxylation, interfering with cortisol and corticosterone synthesis.

- In the presence of a normal pituitary gland, there is a compensatory increase in 11-deoxycortisol secretion.

- This agent has not been widely used for the treatment of Cushing's syndrome. It may be useful in the management of severe manifestations of cortisol excess in conjunction with radiation or surgical treatment.

- It is the only adrenal-inhibiting medication that can be administered to pregnant women with Cushing's syndrome.

- The major adverse effects observed are salt and water retention and hirsutism resulting from androgen synthesis.

- The drug has been withdrawn from the market in the USA.

Aminoglutethimide

- Aminoglutethimide blocks the conversion of cholesterol to pregnenolone and causes a reduction in the synthesis of all hormonally active steroids.

- Aminoglutethimide can be used in conjunction with metyrapone or ketoconazole to reduce steroid secretion in patients with Cushing's syndrome.

- It has been shown to enhance the metabolism of dexamethasone.

Ketoconazole

- Ketoconazole, an antifungal imidazole derivative, is a potent and rather nonselective inhibitor of adrenal and gonadal steroid synthesis.

- Its inhibitory effects on steroid biosynthesis are seen only at higher doses than that needed to treat fungal infections.

- This compound inhibits P450c17, and P450c11 enzymes required for steroid hormone synthesis.

- Ketoconazole has been used for the treatment of patients with Cushing's syndrome due to several causes.

Mifepristone

- This compound is a glucocorticoid receptor antagonist.

- High doses of mifepristone exert antiglucocorticoid activity by blocking the glucocorticoid receptors.

- To date, the application of mifepristone can only be recommended for inoperable patients with ectopic ACTH secretion or adrenal carcinoma who have failed to respond to other therapeutic manipulations.

Mitotane

- Mitotane has adrenolytic properties.

- About one-third of patients with adrenal carcinoma show a reduction in tumor mass.

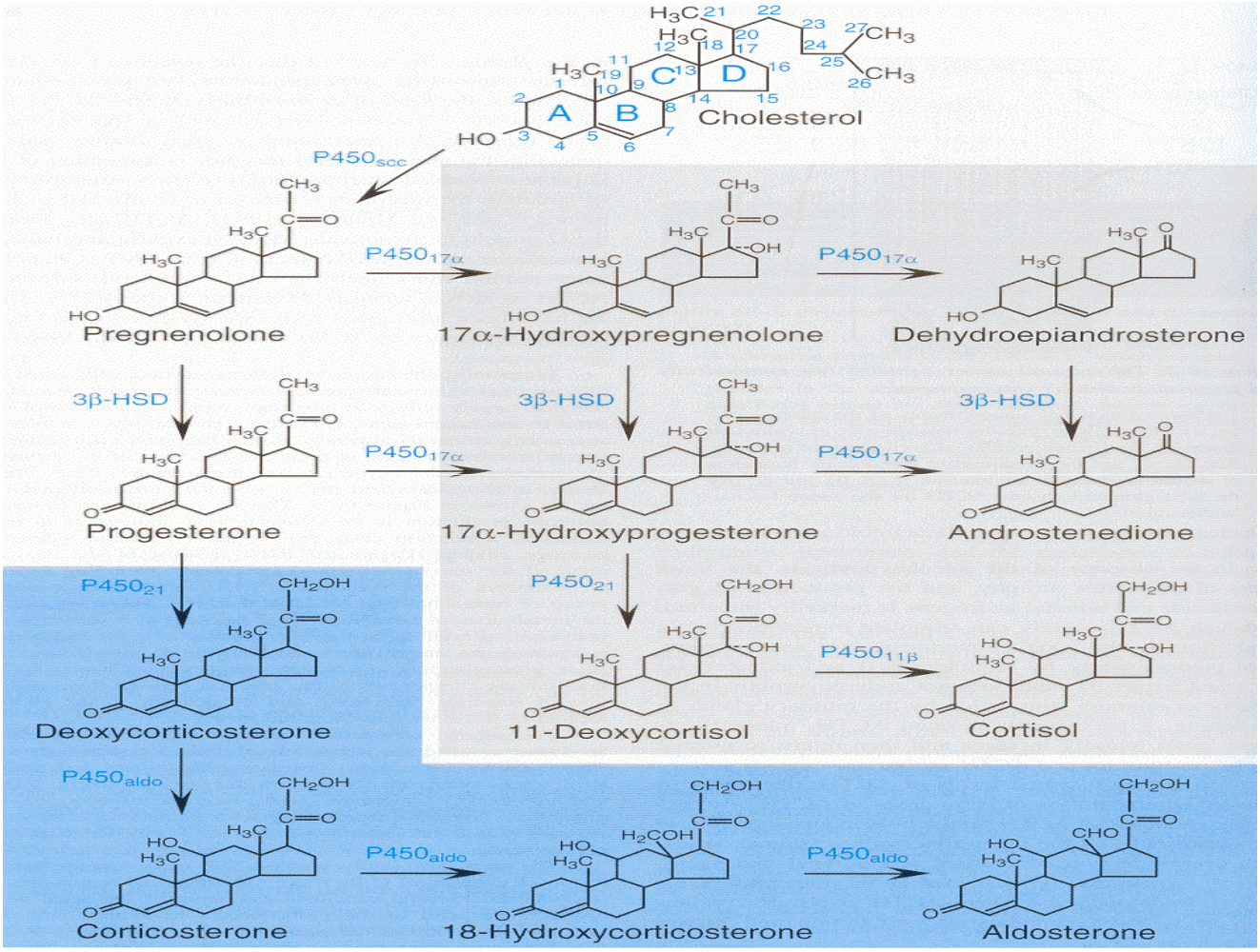
- In 80% of patients, the toxic effects are sufficiently severe to require dose reduction.

- The drug has been withdrawn from the market in the USA.

Trilostane

➢Trilostane is a 17 hydroxysteroid dehydrogenase inhibitor that interferes with the synthesis of adrenal and gonadal hormones and is comparable to aminoglutethimide.

➢Its side effects are predominantly gastrointestinal.



Mineralocorticoids
(Aldosterone, Deoxycorticosterone, Fludrocortisone)

- The most important mineralocorticoid in humans is aldosterone.

- However, small amounts of deoxycorticosterone (DOC) are also formed and released.

- Fludrocortisone, a synthetic corticosteroid, is the most commonly prescribed salt-retaining hormone.

Aldosterone

- The rate of aldosterone secretion is subject to several influences.

- ACTH produces a moderate stimulation of its release, but this effect is not sustained for more than a few days in the normal individual.

- Although aldosterone is no less than one third as effective as cortisol in suppressing ACTH, the quantities of aldosterone produced by the adrenal cortex and its plasma concentrations are insufficient to participate in any significant feedback control of ACTH secretion.

- In the absence of ACTH, aldosterone secretion falls to about half the normal rate, indicating that other factors, eg, angiotensin, are able to maintain and perhaps regulate its secretion.

Physiologic & Pharmacologic Effects

- Aldosterone and other steroids with mineralocorticoid properties promote the reabsorption of sodium from the distal convoluted and cortical collecting renal tubules, loosely coupled to the excretion of potassium and hydrogen ion.

- Excessive levels of aldosterone produced by tumors or overdosage with synthetic mineralocorticoids lead to hypernatremia, hypokalemia, metabolic alkalosis, increased plasma volume, and hypertension.

- Mineralocorticoids act by binding to the mineralocorticoid receptor in the cytoplasm of target cells, especially principal cells of the distal convoluted and collecting tubules of the kidney.

Deoxycorticosterone (DOC)

- DOC, serves as a precursor of aldosterone. Its half-life when injected into the human circulation is about 70 minutes.

- The control of its secretion differs from that of aldosterone in that the secretion of DOC is primarily under the control of ACTH.

Fludrocortisone

- Is a potent steroid with both glucocorticoid and mineralocorticoid activity, is the most widely used mineralocorticoid.

- Used in the treatment of adrenocortical insufficiency associated with mineralocorticoid deficiency.

Mineralocorticoid Antagonists

➢ In addition to agents that interfere with aldosterone synthesis, there are steroids that compete with aldosterone for binding sites and decrease its effect peripherally.

Spironolactone

➢ Its onset of action is slow, and the effects last for 2–3 days after the drug is discontinued.

➢ It is used in the treatment of primary aldosteronism.

➢ This agent is also useful in preparing these patients for surgery.

➢ Spironolactone is also an androgen antagonist and as such is used in treatment of hirsutism in women.

➢ Spironolactone can be used also as a diuretic. The drug has benefits in heart failure greater than those predicted from its diuretic effects alone.

➢ Adverse effects of spironolactone include hyperkalemia, cardiac arrhythmia, menstrual abnormalities, sedation, headache, gastrointestinal disturbances, and skin rashes.

Eplerenone,

- a new aldosterone antagonist, has been approved for the treatment of hypertension.
- This aldosterone receptor antagonist is somewhat more selective than spironolactone and has no reported effects on androgen receptors.
- The most common toxicity is hyperkalemia but this is usually mild.

Drospirenone,

- a progestin in a new oral contraceptive, also antagonizes the effects of aldosterone.