

# Corticosteroids

The steroidal nature of adrenocortical hormones was established in 1937, when Reichstein synthesized desoxycorticosterone.

In humans, hydrocortisone (cortisol) is the main carbohydrate-regulating steroid, and aldosterone is the main electrolyte-regulating steroid

The mammalian adrenal cortex is divided into three concentric zones: the zona glomerulosa, zona fasciculata, and zona reticularis.

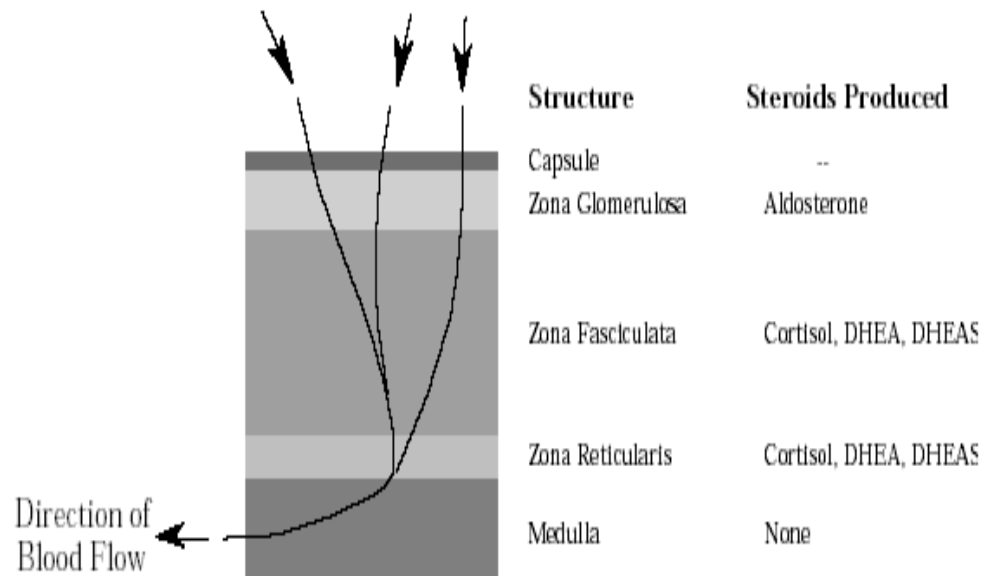
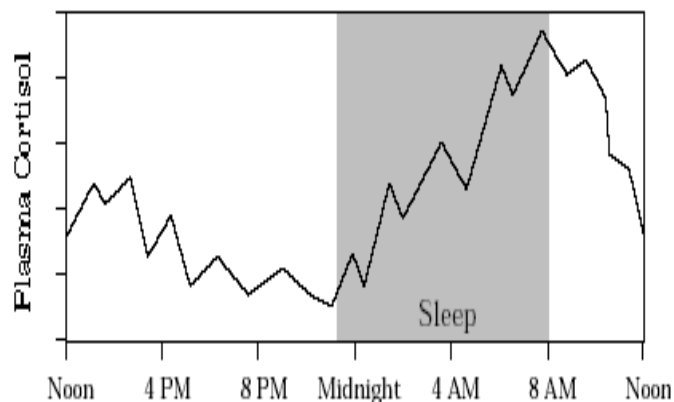
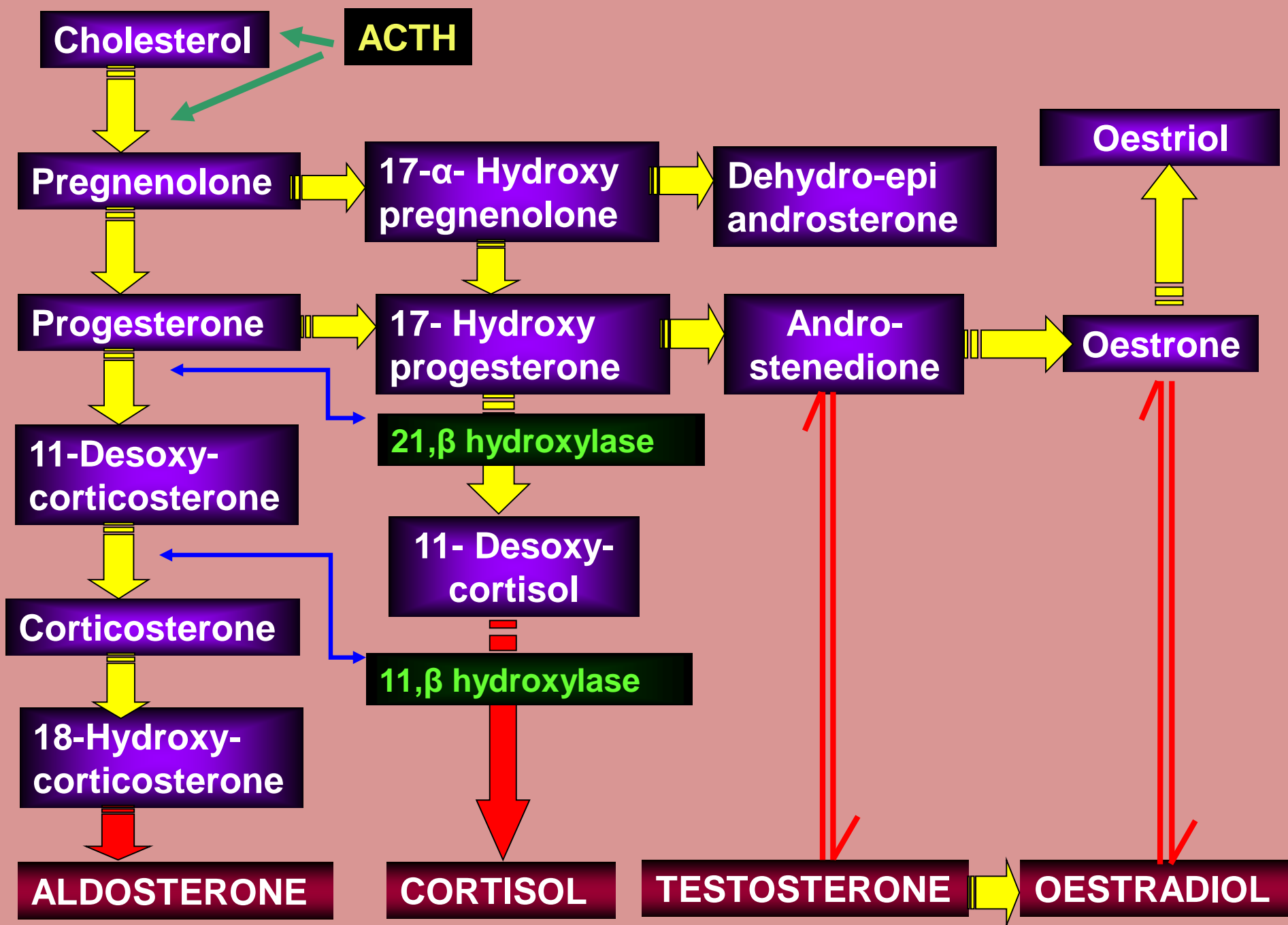
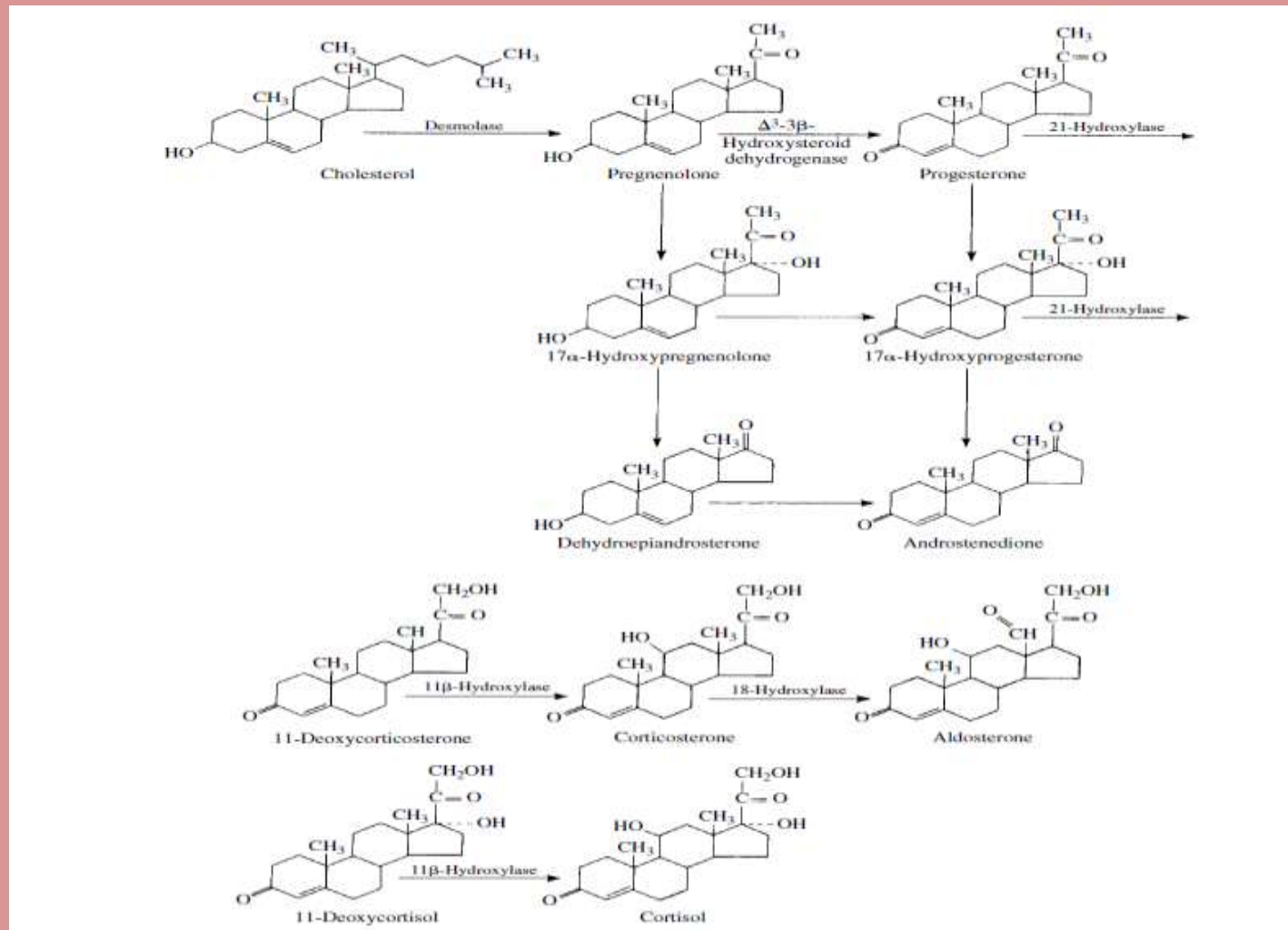


Figure 1. Cartoon of Adrenal Morphology.

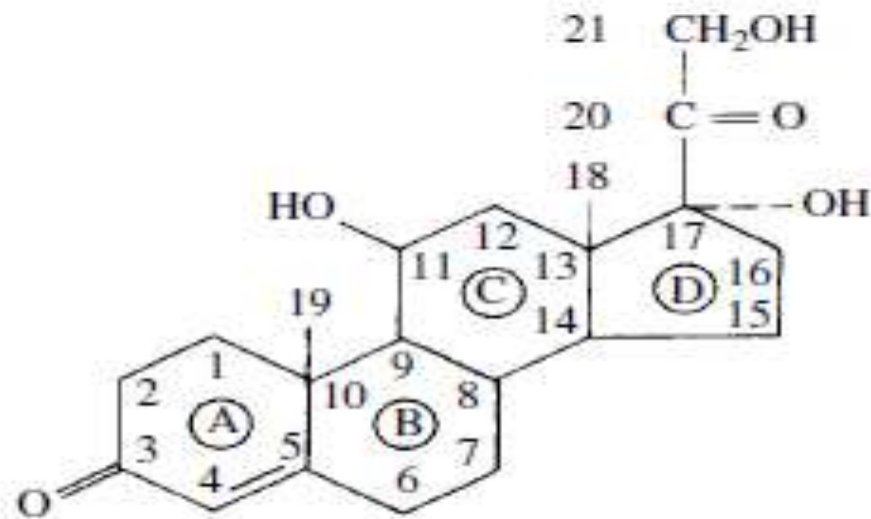


- The adrenal gland synthesizes steroids from cholesterol
- Cholesterol is transported into the mitochondria of steroidogenic tissue, where side chain cleavage is carried out



# Synthetic Corticosteroids

The ultimate aim in altering the steroid molecule is to decrease sodium-retaining activity and to increase anti-inflammatory glucocorticoid activity

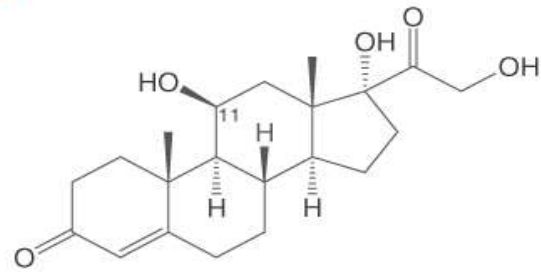


**FIGURE 60.4**

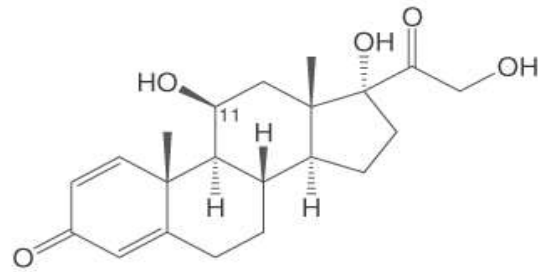
Basic corticosteroid nucleus.

# Glucocorticoid Analogues

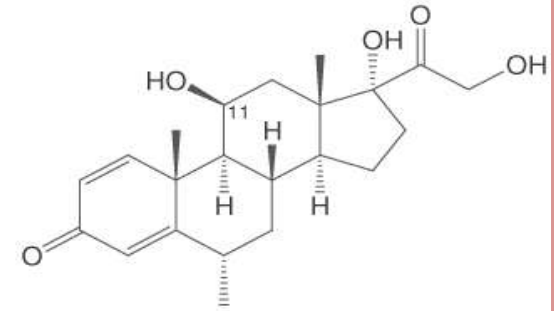
A



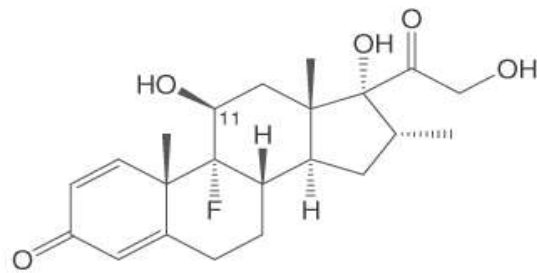
Cortisol



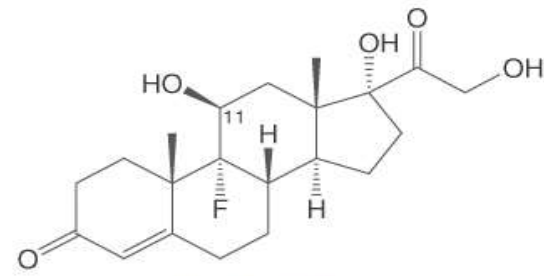
Prednisolone



Methylprednisolone

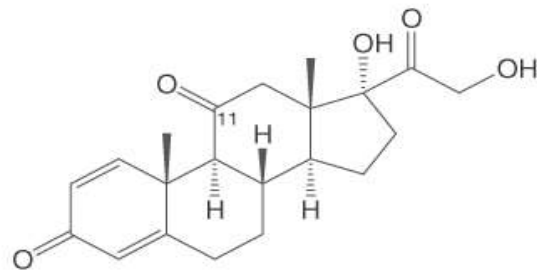


Dexamethasone

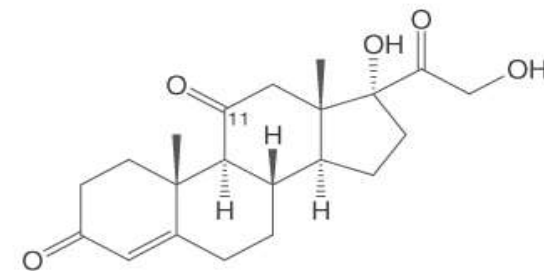


Fludrocortisone

B



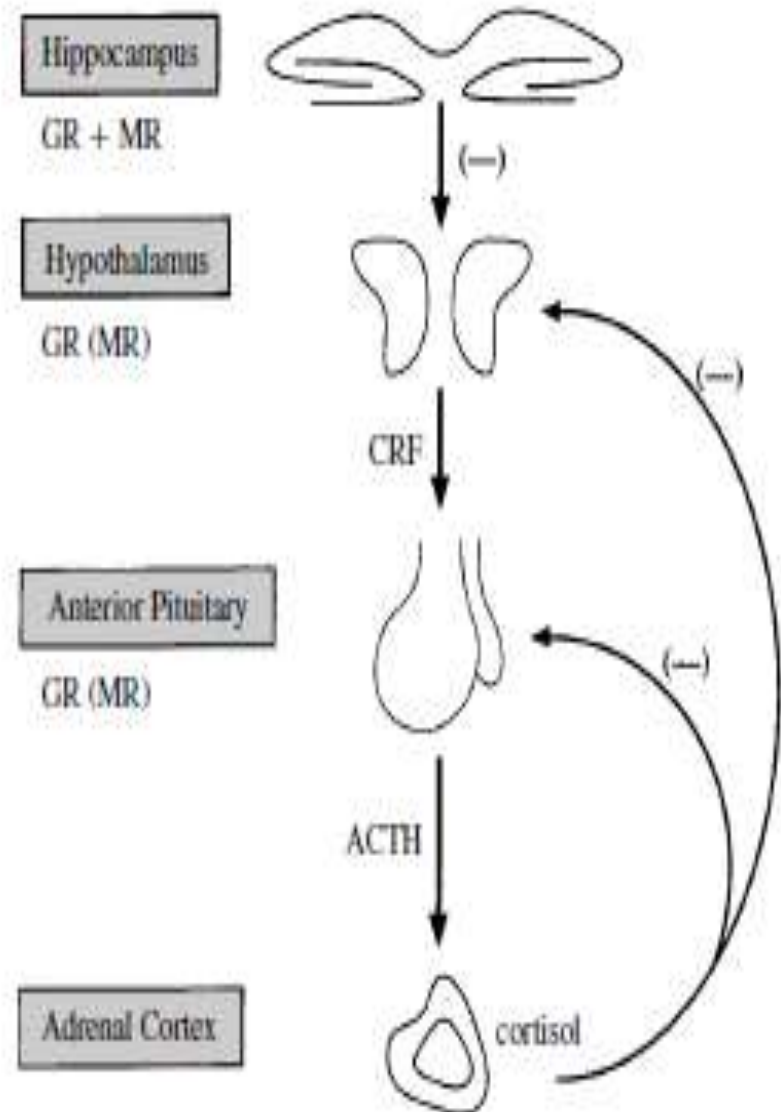
Prednisone



Cortisone

## Negative feedback mechanism

- The role of the hypothalamic–pituitary axis in the regulation of adrenocortical hormone synthesis and release.
- The major physiological stimulus for the synthesis and release of glucocorticoids is corticotropin (ACTH) secreted from the anterior pituitary gland.



# Pharmacological Actions

- The pharmacological actions of steroids are generally an extension of their physiological effects
- Glucocorticoids (*e.g.*, prednisolone) used to suppress inflammation, allergy and immune responses.
- Anti-inflammatory therapy is used in many illnesses (*e.g.*, RA, UC, BA, eye and skin inflammations).
- tissue transplantation and lymphopoiesis (leukemias and lymphomas).
- Striking improvements can be obtained, but **severe adverse effects** are ensue.



# Pharmacological Actions

- For most clinical purposes, synthetic glucocorticoids are used because they have a higher affinity for the receptor, are less activated and have little or no salt-retaining properties.
- **Hydrocortisone** used for: orally for replacement therapy, i.v. for shock and asthma, topically for eczema (ointment) and enemas (ulcerative colitis).
- **Prednisolone** the most widely used drug given orally in inflammation and allergic diseases.

# Pharmacological Actions

- **Betamethasone** and **dexamethasone**: very potent, w/o salt-retaining properties; thus, very useful for high-dose therapies (*e.g.*, cerebral edemas).
- **Beclometasone, dipropionate, budesonide**: pass membranes poorly; more active when applied topically (severe eczema for local anti-inflammatory effects) than orally; used in asthma, (aerosol).
- **Triamcinolone**: used for severe asthma and for local joint inflammation (intra-articular inj.).

# ACTIONS OF THE CORTICOSTEROIDS

## Carbohydrate, Protein, and Fat Metabolism

- The glucocorticoids increase blood glucose and liver glycogen levels by stimulating gluconeogenesis.
- The source of this augmented carbohydrate production is protein
- the protein catabolic actions of the glucocorticoids result in a negative nitrogen balance.
- The inhibition of protein synthesis by glucocorticoids brings about a transfer of amino acids from muscle and bone to liver, where amino acids are converted to glucose.

## *Electrolyte and Water Metabolism*

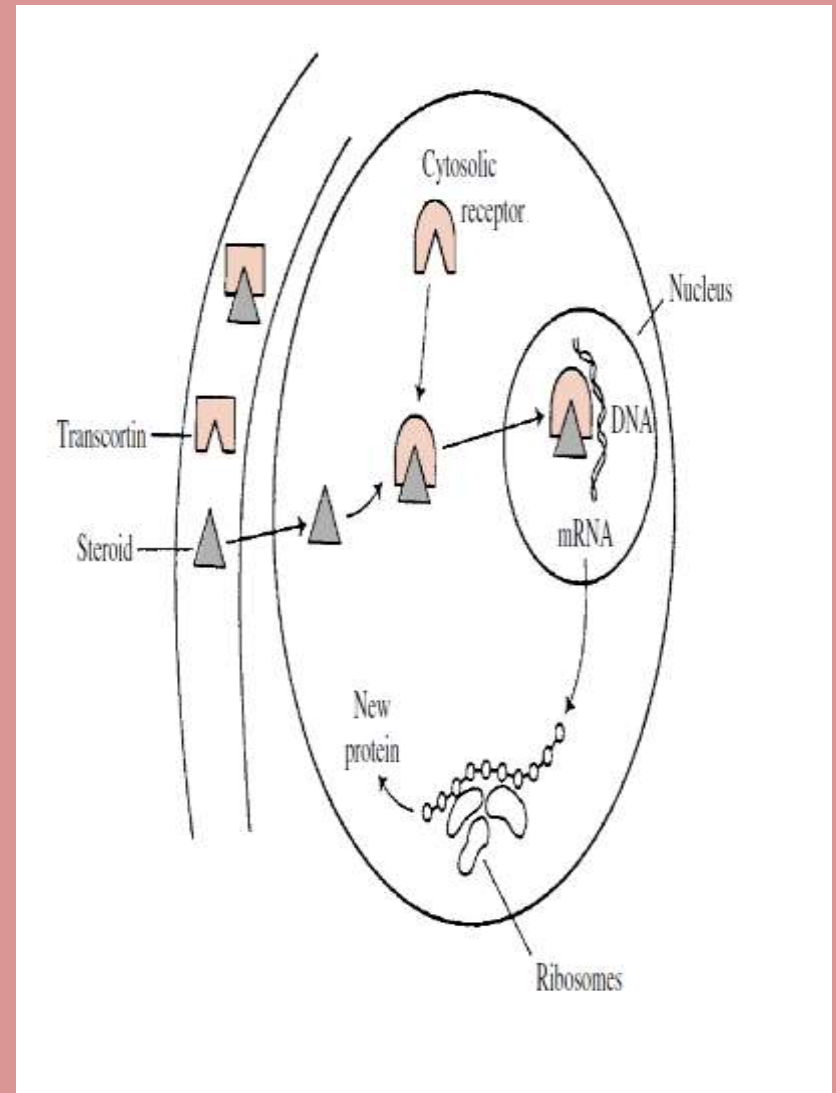
- Another major function of the adrenal cortex is the regulation of water and electrolyte metabolism.
- The steroid-binding specificity of mineralocorticoid and glucocorticoid receptors overlaps in the distal cortical cells and collecting tubules, so that glucocorticoids may mediate mineralocorticoid-like effects

Mineralocorticoid can increase the rate of sodium reabsorption and potassium excretion severalfold. This will occur physiologically in response to sodium or volume depletion or both. The primary site of this effect is the distal tubule

## Cardiovascular Function

- Glucocorticoids directly stimulate cardiac output and potentiate the responses of vascular smooth muscle to the pressor effects of catecholamines and other vasoconstrictor agents.
- The presence of steroid receptors on vascular smooth muscle suggests a direct effect on vasomotor activity.
- *Thus, corticosteroids appear to play an important role in the regulation of blood pressure by modulating vascular smooth muscle tone*

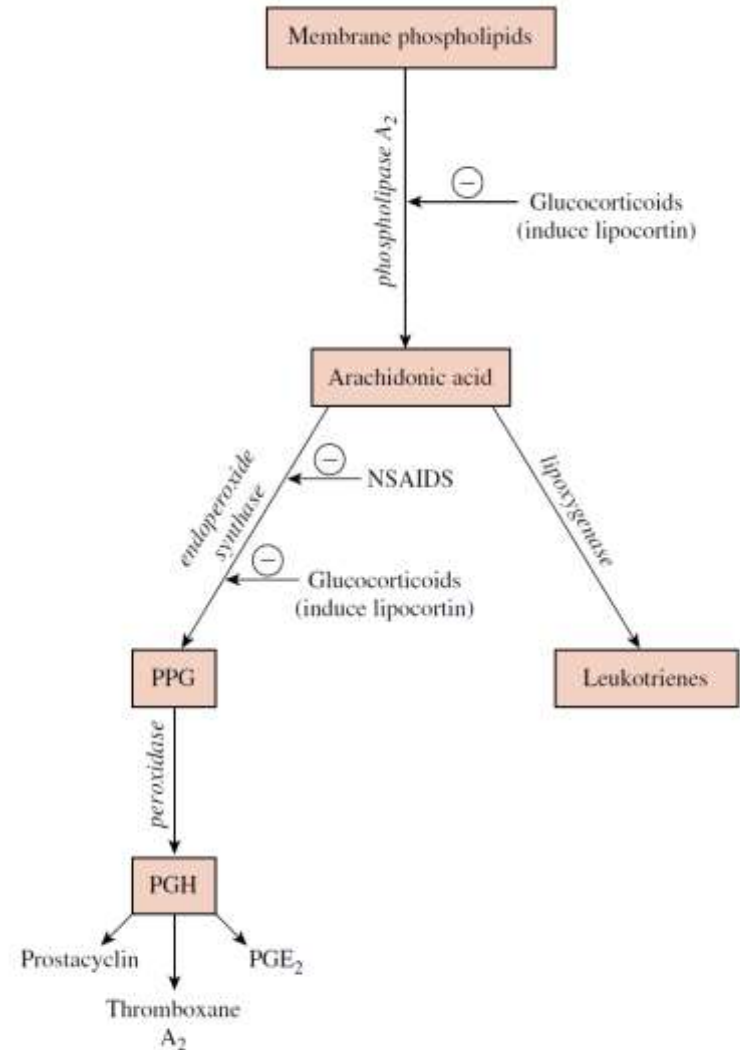
- Steroids transported by transcortin enter the target cell by diffusion and then form a complex with its cytosolic receptor protein.
- Glucocorticoids bind to cytoplasmic glucocorticoid receptors containing two subunits of the heat shock protein that belong to the 90-kDa family.
- The heat shock protein dissociates, allowing rapid nuclear translocation of the receptor–steroid complex.
- Within the nucleus, the glucocorticoid receptor induces gene transcription by binding to specific sequences on DNA called glucocorticoid response elements in the promoter– enhancer regions of responsive genes



- Metabolites of arachidonic acid, including prostaglandins (PG), thromboxanes, and leukotrienes, are considered strong candidates as mediators of the inflammatory process.

- Steroids may exert a primary effect at the inflammatory site by inducing the synthesis of a group of proteins called lipocortins. These proteins suppress the activation of phospholipase A<sub>2</sub>, thereby decreasing the release of arachidonic acid and the production of proinflammatory effect

- Another possible glucocorticoid-sensitive step is the PG endoperoxide H synthase (or cyclooxygenase) (COX) mediated conversion of arachidonate to PG endoperoxides

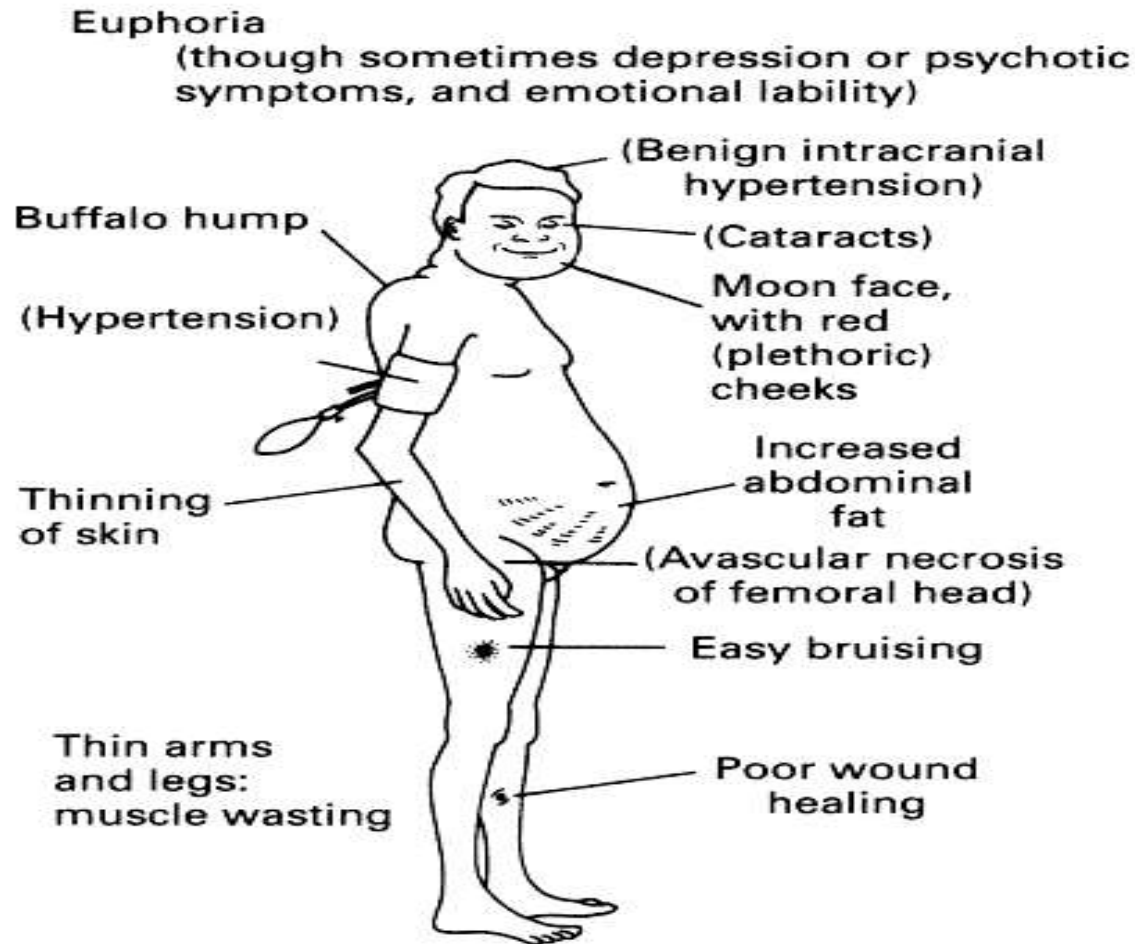


**FIGURE 60.6**

Possible site or sites of action of glucocorticoids on prostanoid production.



# Steroids adverse effects



Also:

*Osteoporosis*

Tendency to hyperglycaemia

Negative nitrogen balance

Increased appetite

*Increased susceptibility to infection*

Obesity

# THERAPEUTIC USES OF STEROID HORMONES

## *Replacement Therapy*

- Adrenal insufficiency may result from hypofunction of the adrenal cortex (primary adrenal insufficiency, Addison's disease) or from a malfunctioning of the hypothalamic–pituitary system (secondary adrenal insufficiency).
- In treating primary adrenal insufficiency, one should administer sufficient cortisol to diminish hyperpigmentation and abolish postural hypotension; which are the cardinal signs of Addison's disease.

## *Inflammatory States*

- glucocorticoids possess a wide range of effects on virtually every phase and component of the inflammatory and immune responses,
  - they have assumed a major role in the treatment of a wide spectrum of diseases with an inflammatory or immune-mediated component.
- 
- Rheumatoid arthritis is the original condition for which antiinflammatory steroids were used,
  - Intraarticular glucocorticoid injections have proven to be efficacious, particularly in children.
- However,
- the detrimental effects of glucocorticoids on growth are significant for children with active arthritis.
  - steroids offer symptomatic relief from this disorder by abolishing the swelling, redness, pain, and effusions,  
they do not cure
  - Progressive deterioration of joint structures and the disease process may be exacerbated after steroid therapy is terminated