OBJECTIVES:

At the end of this block of lectures, the student should be able to:

1. Describe the anatomical relationship between the adrenal cortex and adrenal medulla, as well as the functional zonation within the adrenal cortex.
2. Identify the systems controlling adrenocortical function as well as the major biological actions of the principal hormones secreted by the adrenal cortex.
3. Describe the functional elements, as well as the control mechanisms, involved in the hypothalamo-pituitary-adrenocortical system.
4. Describe the types, patterns, and mechanisms involved in ACTH and cortisol release.
5. Describe the elements and mechanisms involved in the control of aldosterone secretion from the zona glomerulosa of the adrenal cortex.
6. Describe the pathways involved in the synthesis of the major steroid hormones from the adrenal cortex, namely cortisol, aldosterone, and DHEA.
7. Explain the role of proteolytic cleavage in the production of ACTH in the anterior pituitary gland, as well as the relationship between ACTH and its precursor molecule and related peptides.
8. Describe the principal biological actions of corticosteroids and other secretions of the adrenal cortex.
9. Describe the mechanisms of corticosteroid action.
10. Explain the etiologies and symptomologies of the following disorders of adrenocortical function

   a. primary and secondary hypercortisolism
   b. primary and secondary hypocortisolism
   c. the various forms of congenital adrenal hyperplasia.
   d. primary and secondary hyperaldosteronism.

Suggested Reading: Costanzo 3rd Edition, pp. 408-420

1. **OVERVIEW OF ADRENAL GLAND** (Figure 1.)
The adrenal gland is roughly triangulated in shape and sits on top of each kidney (hence, the name "adrenal").

A. Embryogenesis and morphology of adrenal gland

1. The adrenal gland is comprised of 2 separate endocrine organs coming from different embryonic origins and secreting chemically different hormones.
2. The adrenal cortex or outer portion is derived from mesoderm and is comprised of three zones of lipid laden epitheloid cells interspersed with sinusoids.
   
   a. Zona glomerulosa is the outer zone where epitheloid cells are arranged as "glomeruli" or "whorls" comprising 15% of the adrenal cortex.
   
   b. Zona fasciculata is the middle zone where epitheloid cells are arranged as straight columns of single cells or "fascicles" comprising 80% of adrenal cortex.
   
   c. Zona reticularis is the innermost zone exhibiting a haphazard or "reticular" arrangement of epitheloid cells comprising 5% of cortex.
3. The *adrenal medulla* is the inner portion derived from *ectoderm* in which the hormone secreting cells are *modified postganglionic sympathetic* neurons (or chromaffin cells, based on their staining characteristics).

B. Hormones and control systems of adrenal gland

1. The adrenal cortex produces *steroid* hormones, derived from cholesterol. Steroid hormones are classified into several types based upon their function. These types are:
   
   a. *Corticosteroids* which are further classified as:
      
      i. *Glucocorticoids*, which elevate blood glucose among other effects, the most well-known example is *cortisol* (also referred to as *hydrocortisone*).
      
      ii. *Mineralocorticoids* which function to conserve sodium, the most well-known example being *aldosterone*.
   
   b. Sex hormones, which are further classified as:
      
      i. *Progestins, estrogens, and androgens*.

2. The adrenal medulla produces catecholamines, hormones derived from the amino acid, tyrosine:

   a. The major catecholamine secreted by the adrenal medulla is *epinephrine* and, to a lesser extent, *norepinephrine*.

3. Control systems of the adrenal gland

   a. The adrenal cortex contains 2 distinct control systems that are regionally localized:
      
      i. *Pituitary-adrenocortical system* where the anterior pituitary (via ACTH) controls *cortisol* secretion. The system is called into play when the organism is confronted with stress (z. fasciculata and reticularis).
      
      ii. *Renin-angiotensin-adrenocortical system* controls *aldosterone* secretion and is involved in electrolyte and fluid balance (z. glomerulosa).

   b. The adrenal medulla is a component of the sympathetic nervous system also involved in the stress response.
II. PITUITARY - Adrenocortical System: Control of cortisol secretion (Figure 2.)

A. Elements of the system and their functions

1. Central nervous system (brain) involves:
   a. Extrahypothalamic structures, such as the reticular formation, thalamo-neocortical structures, and limbic system.
   b. The hypothalamus, which is a nodal way-station receiving input from the above extrahypothalamic structures.
      i. Neurosecretory neurons in the hypothalamus produces corticotrophin releasing hormone (CRH).
      ii. CRH:
          • is a polypeptide of 41 amino acids.
          • is transported from the median eminence of the hypothalamus to anterior pituitary via the hypothalamo-hypophyseal portal system.
          • stimulates release of ACTH from the anterior pituitary.

2. Anterior pituitary which contains basophilic cells (react to basic stain) that produce the peptide hormone, ACTH (adrenocorticotropic hormone)
3. **Adrenal cortex** (specifically the zonae fasciculata and reticularis) where ACTH exerts the following effects:

   a. promotes adrenocortical growth;
   b. stimulates steroid production and secretion (primarily cortisol, as well as adrenal androgens);
   c. maintenance of adrenocortical sensitivity to ACTH stimulation.

4. **Corticosteroid binding proteins in plasma**:

   a. Under basal (nonstress) conditions 90-95% of circulating cortisol is bound to plasma proteins in a noncovalent fashion.
   b. The 2 prominent plasma binding proteins are:
      
      i. **Albumin**
         
         - exhibits low affinity (weak), high capacity binding for cortisol;
         - binds about 15% circulating cortisol;
         - and is relatively insignificant, physiologically.
      
      ii. **CBG** (corticosteroid binding globulin, also referred to as transcortin)
         
         - exhibits high affinity (strong), limited capacity (or saturable) binding of cortisol;
         - binds 75-80% circulating cortisol;
         - physiologically significant form of cortisol binding.

   c. Functions of corticosteroid plasma proteins
      
      i. Increases the solubility of steroid in plasma.
      ii. Controls the distribution of (or parcels) steroids to tissues.

5. **Liver and other target tissues**

   a. Biological responses to corticosteroids
   b. Metabolic inactivation and clearance of corticosteroids
      
      i. Increases polarity of corticosteroids due to chemical modification and conjugation with glucuronide and sulfate and clearance of these conjugates by the kidney.
ii. Determines biological half-life of corticosteroids (between 60-90 minutes).

B. Regulation of cortisol secretion (servomechanisms) (Fig. 2)

1. Negative feedback effect of cortisol on ACTH secretion
   a. An inverse relationship exists between plasma cortisol and ACTH.
      i. ACTH hypersecretion occurs after direct lowering of cortisol (e.g., bilateral adrenalectomy, inhibition of steroidogenesis, primary hypocortisolism).
      ii. ACTH hyposecretion (and, often times, adrenal atrophy) occurs after exogenous glucocorticoid treatment or primary hypercortisolism (autonomous adrenal tumor).
   b. Glucocorticoid feedback occurs both in brain (hypothalamic and extrahypothalamic structures) and anterior pituitary (which is the primary site of glucocorticoid feedback).
   c. Alterations of CBG levels could influence level of function of the pituitary-adrenocortical system via glucocorticoid feedback.
      i. Reason: unbound cortisol is the feedback signal, based on the following evidence:
         • Elevated CBG stimulates pituitary-adrenal function;
         • Decreased CBG is inhibitory.
      ii. CBG production by the liver is stimulated by estrogen, thyroxine and progesterone and inhibited by testosterone and liver dysfunction.
   d. Altered hepatic clearance of cortisol could also alter pituitary-adrenal function by the negative feedback mechanism.
      i. Reason: plasma cortisol level is the result of a balance between cortisol secretion and clearance.
         • Increased clearance (i.e., shortened half-life) would stimulate the pituitary-adrenocortical system.
• Decreased clearance (prolonged half-life) would inhibit the pituitary-adrenocortical system.

ii. Clearance is stimulated by thyroxine, food intake, and hypertension and is inhibited by androgen, restricted food intake, liver disease.

e. Glucocorticoid feedback is a "crude" controller of pituitary adrenocortical function:

i. It determines the upper and lower levels of the system.

ii. It does not appear to determine the patterns of pituitary-adrenal secretion which occur under basal and stress conditions.

2. Types and patterns of ACTH and cortisol release.

![Figure 3. Circadian pattern of cortisol in plasma](image_url)

Figure 3. Circadian pattern of cortisol in plasma

a. Under basal (non-stress) conditions one sees a circadian or diurnal pattern (Figure 3).

i. A recurring pattern in plasma ACTH and cortisol occurring approximately every 24 hours (hence, “circadian”).

ii. Changes in cortisol are a consequence of ACTH and, therefore, the latter precedes the former by a short interval (15-30 minutes) (not shown in Figure 3).

iii. In an individual with a normal activity pattern (active during day and asleep at night):
• Average hormone (ACTH and cortisol) levels are highest at about 8:00 a.m. (upon waking from sleep).
• Average hormone levels decline during the day (period of greatest activity) and are lowest levels at about 1:00 a.m.
• Average hormone levels increase during sleep reaching peak levels at about 8:00 a.m.

iv. In reality, hormone secretion occurs as episodic bursts of hormone release.

• During the rising phase of the circadian pattern, the frequency of "bursting" activity is greater than during the declining phase.
• Circadian patterns can be absent in adrenocortical hypersecretion disorders (e.g., Cushing's syndrome).
• In evaluating patients, the circadian and episodic nature of basal secretion of the pituitary-adrenocortical axis should be considered, thus requiring multiple measurements of serum hormone levels, and/or collection of urinary steroids at different blocks of time during the day.

v. Plasma cortisol concentrations during non-stress conditions stays within 5 µg/100 ml to 20 µg/100 ml (.25 to 1.00 µM) and most hormone is bound by plasma protein.

vi. Circadian pattern is determined by the activity pattern of the individual.

• Individuals with night-time occupations have circadian rhythms that are the "mirror-images" of individuals with day-time occupations.

vii. Circadian patterns are not regulated by negative feedback.

b. Stress-induced ACTH and subsequent cortisol release result from the release of CRH from the hypothalamus (Figure 4).

i. Acute (short-lived) stress
• ACTH release appears as a "spike" reaching peak levels at 2.5 to 5 minutes.
  
  o Cortisol levels peak between 15 to 30 minutes after the stress and return to basal levels by 60 minutes.
  o Stress-induced plasma cortisol levels may reach 70 µg/100 ml - 100 µg/100 ml (3 to 5 µM).
  o Most of this cortisol is *not* bound to plasma protein and hence accessible to the cells.

ii. Prolonged stress (several hours)

• ACTH and cortisol are maintained, but not indefinitely.

![Figure 4. Serum ACTH and cortisol after acute or prolonged stress](image-url)
III. RENIN - ANGIOTENSIN SYSTEM: Regulation of Aldosterone Secretion (Figure 5):

- The general function of aldosterone is to conserve Na\(^+\) and, hence, maintain fluid volume.
- Stimuli for aldosterone secretion are decreased blood volume (major stimulus), electrolyte alterations (increased plasma K\(^+\)); very high doses of ACTH, and stimulation of sympathetic innervation of kidney.

A. Renin-Angiotensin System

1. Dynamics of renin-angiotensin system.
   a. Decreased blood volume produces decreased renal arterial pressure.
   b. Decreased renal arterial pressure is sensed by stretch receptors of juxtaglomerular (JG) cells.
      i. This results in increased renin secretion from JG cells.

Figure 5. Renin-angiotensin-aldosterone system
c. The *macula densa* monitors Na\(^+\) and Cl\(^-\) filtration in the distal tubules.
   
i. Decreased delivery of these electrolytes to distal tubules also evokes increased renin secretion from JG cells.

d. Renin then converts angiotensinogen (a protein produced by the liver) to angiotensin I, a decapeptide.
e. Angiotensin I then loses 2 amino acids at its C-terminal end under the influence of angiotensin converting enzyme (*ACE*) to form angiotensin II (octapeptide).
f. Angiotensin II stimulates aldosterone release from the zona glomerulosa.
g. Stimulation of Na\(^+\) retention by aldosterone retains body fluid and restores renal arterial pressure, thus shutting off of the original stimulus for the system, hypovolemia.
h. Angiotensin II is inactivated in plasma by proteolysis (angiotensinases).
i. The following *alternate* renin-angiotensin pathway also exists:
   
i. Angiotensin I is converted to a nonapeptide, (Des Asp\(^1\)) Angiotensin I, by an aminopeptidase in plasma and tissues.
   
ii. (Des Asp\(^1\)) Angiotensin I is converted to the heptapeptide, (Des Asp\(^1\)) Angiotensin II (or Angiotensin III), by ACE.
   
iii. Angiotensin III appears to be as potent as Angiotensin II in stimulating aldosterone release but possess only about 50% of its pressor activity.

j. Renin and aldosterone exhibit circadian patterns like cortisol but not as pronounced.
   
i. Circadian patterns occur independent of posture.
   
ii. Aldosterone circulates bound primarily to albumin and is metabolized in a fashion similar to cortisol.
   
iii. The half life of aldosterone is approximately 30 minutes.
   
iv. Standing tends to elevate serum renin and aldosterone levels. Why?

IV. **BIOSYNTHESIS** (Figure 6) and degradation of steroid hormones.
A. General overview and pertinent concepts

1. Steroid hormones are derived from cholesterol and contain the following characteristics (Fig 6):
   a. a steroid nucleus, which is comprised of 17 carbons;
   b. the steroid nucleus is roughly planar containing 3 hexane rings (A,B,C) and one pentane ring (D);
   c. rings may contain double bonds (represented as Δ), hydroxyl and keto groups;
   d. certain constituents (side chains and hydroxyl) may be above or below the plane of the nucleus:
      i. below the plane is designated as α (dashed line)
      ii. above the plane is designated as β (solid line);

2. Adrenal cortex produces representatives of all of the different families of naturally occurring steroids, such as:
   a. 21 carbon steroids - steroid nucleus (17 carbons), methyls 18 and 19, and a 2 carbon sidechain (carbons 20 and 21)
      i. progestins (e.g., progesterone)
      ii. corticosteroids (e.g., cortisol, aldosterone):
   b. 19 carbon steroids - steroid nucleus, methyls 18 and 19
      i. androgens (DHEA, testosterone)
   c. 18 carbons steroids - steroid nucleus, methyl 18
      i. estrogens (estradiol-17β)
Figure 6. Adrenal Cortex Steroidogenesis
B. Steroidogenic pathways

1. Cholesterol side chain cleavage (also referred to as the desmolase reaction):
   a. Cholesterol (27 carbons) \(\rightarrow\) \(\Delta^5\) pregnenolone (21 carbons) and isocaproic acid (6 carbons);
   b. Cholesterol side chain cleavage is the site of ACTH action.

2. Steroidogenesis in the zona glomerulosa - aldosterone production
   a. Daily production of aldosterone occurs independent of ACTH stimulation.
   b. Regulated by angiotensin II and III (downstream).
   c. Pathway from \(\Delta^5\) pregnenolone to aldosterone.
      i. 3 \(\beta\)-ol dehydrogenase:isomerase (3\(\beta\)-hydroxysteroid dehydrogenase:isomerase):
         - \(\Delta^5\) pregnenolone \(\rightarrow\) progesterone.
         - progesterone is a \(\Delta^4\), 3 ketosteroid.
         - \(\Delta^4\), 3 ketosteroid is a common feature of many steroid hormones).
      ii. 21-hydroxylase (unique to adrenal cortex):
         - progesterone \(\rightarrow\) 11-deoxycorticosterone (DOC).
         - DOC is a potent mineralocorticoid.
      iii. 11\(\beta\)-hydroxylase (unique to adrenal cortex):
         - DOC \(\rightarrow\) corticosterone (Cpd. B) (a major secretory product of the adrenal cortex).
         - corticosterone exhibits both glucocorticoid and mineralocorticoid activities.
         - corticosterone production is about 3 mg/day.
      iv. 18-hydroxylase (unique to adrenal cortex):
         - corticosterone \(\rightarrow\) 18-hydroxycorticosterone.
         - 18-hydroxylase present in z. glomerulosa not z. fasciculata and reticularis.
         - site of action of Angiotensin II and III.
v. 18-hydroxysteroid dehydrogenase (unique to adrenal cortex):

- 18-hydroxycorticosterone $\rightarrow$ aldosterone.
- aldosterone is the most potent naturally occurring mineralocorticoid.
- aldosterone circulates primarily as a hemiacetal formed between the 18-aldehyde and 11-hydroxy groups (Fig. 7).
- aldosterone production is about 0.15 mg/day.

![Aldosterone](image1.png)

![Aldosterone hemiacetal](image2.png)

Figure 7. Aldosterone and aldosterone hemiacetal

3. Steroidogenesis in zonae fasciculata and reticularis - cortisol production

a. Cortisol production regulated by ACTH (cholesterol side chain cleavage).

b. Referred to as the “17α-hydroxylase pathway”.

c. Production of cortisol (in z. fasciculata and reticularis) follows essentially the same sequence of enzyme reactions as does the production of corticosterone (in z. glomerulosa), except for the fact that cortisol is 17α-hydroxylated and corticosterone is not.

d. Pathway from $\Delta^5$ pregnenolone $\rightarrow$ cortisol.

   i. 17α-hydroxylase (unique to z. fasciculata/reticularis *not* z. glomerulosa):
• $\Delta^5$ pregnenolone $\rightarrow 17\alpha$ hydroxypregnenolone.
  • progesterone $\rightarrow 17\alpha$-hydroxyprogesterone.

ii. 3-ß-ol dehydrogenase: isomerase (3ß-hydroxysteroid dehydrogenase: isomerase):
  • $\Delta^5$ pregnenolone $\rightarrow$ progesterone.
  • $17\alpha$-hydroxypregnenolone $\rightarrow 17\alpha$-hydroxyprogesterone.

iii. 21-hydroxylase (unique to adrenal cortex):
  • $17\alpha$-hydroxyprogesterone $\rightarrow$ 11-deoxycortisol.

iv. 11ß-hydroxylase (unique to adrenal cortex):
  • 11-deoxycortisol $\rightarrow$ cortisol (Cpd. F, hydrocortisone).
  • cortisol production is about 20-30 mg/day.
  • cortisol exhibits both glucocorticoid and mineralocorticoid activities.
  • cortisol is the principal glucocorticoid secreted by the adrenal cortex.

4. Steroidogenesis in zonae fasciculata and reticularis: adrenal androgen and estrogen production (Figure 6).

  a. This pathway is also a component of $17\alpha$-hydroxylase pathway.
  b. Pathway from $\Delta^5$ pregnenolone and progesterone (through androgens) to estradiol.

  i. $17\alpha$-hydroxylase:
    • as above, generating $17\alpha$-hydroxyprenenolone, and $17\alpha$-hydroxyprogesterone.

  ii. C-17, 20 lyase:
    • $17\alpha$-hydroxypregnenolone $\rightarrow$ DHEA (dehydroepiandrosterone) and $17\alpha$-hydroxyprogesterone $\rightarrow$ androstenedione.
    • reaction involves elimination of 20,21 side chain to form a C19 steroid.
    • DHEA is a weak androgen.
• DHEA is a major source of androgen in the female.
• DHEA is secreted as a sulfate (20-30 mg/day).

iii. 3β-ol dehydrogenase:isomerase:
• DHEA --> androstenedione.
• androstenedione is a weak androgen (immediate precursor of testosterone).
• androstenedione is a $\Delta^4,3$-ketosteroid as well as a 17-ketosteroid.

iv. 17β-hydroxysteroid dehydrogenase:
• androstenedione --> testosterone.
• testosterone is the major male sex hormone.

v. Aromatase (formation of aromatic A-ring):
• testosterone -----> 19 nortestosterone.
• 19-nortestosterone -----> estradiol 17β.

Note: 17β-hydroxysteroid dehydrogenase and aromatase are also major enzymes in the gonads (testes and ovary).

C. Functional Zonation of the Adrenal Cortex - things to know.

1. Zona glomerulosa:
   a. is the only source of aldosterone, does not produce cortisol or sex steroids.
   b. contains 18-hydroxylase.
   c. does not contain of 17α-hydroxylase.
   d. is the target for angiotensin II and III (18-hydroxylation)
   e. is relatively insensitive to ACTH.

2. Zonae fasciculata and reticularis:
   a. is the source of cortisol and sex steroids, and does not produce aldosterone.
   b. contains 17α-hydroxylase and C17,20 lyase (both required for adrenal androgen production).
   c. does not contain 18-hydroxylase.
   d. is dependent upon ACTH.
D. Degradation of Corticosteroid Hormones

1. Involves modification of corticosteroids by liver.
2. Major reaction is A-ring reduction: conversion of Δ4,3-ketone to a tetrahydroderivative of the compound.
3. Other modifications of corticosteroids that occur in liver are:
   a. 11-hydroxy configuration is oxidized to 11-keto (a reversible reaction) by the enzyme 11β-hydroxysteroid dehydrogenase (cortisol converted to cortisone).
   b. Reduction of C-20 ketone configuration to C-20 hydroxyl configuration.
   c. Cleavage of C17-C20 bond (leading to formation of 17-ketosteroid).
   d. Conjugation of steroid at position 3 to form glucuronides and sulfates which increases aqueous solubility of the compound.
4. Excretion in urine of above metabolic products which tend be more water soluble.

V. ACTH and related peptide hormones

A. ACTH and related peptide hormones (α and β-Melanophore stimulating hormones [MSH], β-Lipoptrophic hormone [LPH], and β-Endorphin) are derived by proteolytic cleavage (post-translational modification) from the peptide precursor, pro-opiomelanocortin (POMC).

1. POMC is detected in anterior lobe, intermediate lobe and brain.
2. Secreted hormones of this family are produced by proteolytic cleavage at basic amino acid residues (such as, Arg-Lys, Arg-Arg, Lys-Arg, Lys-Lys).
3. Processing of POMC varies, depending on cellular site.
   a. The anterior lobe generates primarily ACTH and β-endorphin.
   b. The intermediate lobe generates primarily α-MSH.
   c. The brain generates primarily ACTH, β-endorphin, and α-MSH.
4. Functions or effects of products of POMC (other than ACTH)
   a. MSH's: darken skin by dispersion of melanosomes (pigmenting granules).
      i. MSH shares homology with ACTH (which has inherent MSH activity). This homology may
explain hyperpigmentation in humans under certain conditions.

ii. Glucocorticoids also inhibit MSH release.

b. $\beta$-LPH (lipotropic hormone or lipotropin)
   
i. $\beta$-LPH is lipolytic in action.

c. $\beta$-Endorphin
   
i. Exhibit endogenous opiate activity and may play a role in mood states and analgesia.
   
ii. $\beta$-Endorphin release is stimulated by CRH and is inhibited by glucocorticoids, as is ACTH.

VI. EFFECTS OF ADRENOCORTICAL SECRETIONS

A. Glucocorticoids: cortisol, corticosterone

1. Intermediary metabolism.

   a. Protein breakdown via a catabolic and/or antianabolic action in non hepatic tissues leading to the release of amino acids.

   b. Carbohydrate metabolism

      i. Stimulation of gluconeogenesis indirectly (via amino acids and lipids) and directly (via gluconeogenic enzymes) leading to elevation in blood glucose.

   c. Lipid metabolism:

      i. Glucocorticoids exhibit a permissive effect on growth hormone induced lipolysis which promotes a centripetal fat redistribution (accumulation of fat in the trunk and head and loss of fat in the extremities).

2. Feedback inhibition on ACTH secretion - as discussed previously.

3. Cardiovascular effects:

   a. Glucocorticoids enhance vascular reactivity to catecholamines (a permissive effect).
i. This effect is produced by retardation of catecholamine inactivation by the enzyme COMT (catechol-o-methyl transferase).

b. Glucocorticoids also evoke a positive inotropic effect on the myocardium.
c. Glucocorticoids also have inherent mineralcorticoid (Na retaining) activity which tends to elevate blood pressure.

4. Nervous system effects:
   a. When corticosteroids are absent (as in adrenocortical insufficiency) the following may occur:
      i. slower EEG alpha-waves.
      ii. increased sensitivity (decreased threshold) to olfactory and gustatory stimuli.
   b. Cortisol also can alter behavior as follows:
      i. producing euphoria, psychotic episodes and depression.

5. Gastrointestinal effects:
   a. Glucocorticoids increase gastric acid and pepsin secretion.
      i. Thus, glucocorticoid therapy is contraindicated in individuals prone to ulcers.
   b. Glucocorticoids promote intestinal lipid absorption.

6. Skeletal muscle effects:
   a. Skeletal muscles readily fatigue in adrenocortical insufficiency.
      i. This effect may be related to intermediary metabolism.
   b. Glucocorticoids promote muscle wasting via the protein antianabolic effect.

7. Effects on water metabolism (involve 2 opposing actions):
a. Increased glomerular filtration rate (GFR) which promotes excretion of water load is a result of their vasoactive and metabolic effects (which tend to increase solute concentration).

b. Mineralcorticoid effect which promotes fluid retention.

8. Hematologic effects:
   a. Decreased eosinophils, basophils and lymphocytes.
      i. Glucocorticoids have been used in the treatment of lymphoid-derived cancers.
   b. Decreases size of lymph nodes and thymus.
      i. Proliferation of some, but not all lymphocytes inhibited.
      ii. Programmed cell death ("apoptosis") of some, but not all lymphocytes.
   c. Increased neutrophils, platelets and RBC's.

   a. In adrenocortical insufficiency, individuals are unable to survive even the mildest stresses.
      i. Individuals collapse and may die, a situation called "adrenal crisis"
      ii. Adrenal crisis appears to result from vascular collapse due to absence of vasoactive corticosteroids.
      iii. A rapid outpouring of stress-induced cortisol is required for survival.

10. Effects on bone metabolism:
    a. Pharmacologic or pathologically high levels of cortisol promote bone dissolution (osteoporosis).
    b. Bone dissolution is due to breakdown of the protein matrix and glucocorticoid actions on calcium metabolism (antagonism of Vitamin D effect on intestine and increased renal Ca^{++} excretion).

11. Anti-inflammatory effect:
a. The anti-inflammatory effect of glucocorticoids is a pharmacologic action and of significant therapeutic value.

b. The characteristics of this effect are:

i. decreased vascular permeability
ii. decreased migration of cells
iii. decreased swelling of tissues
iv. increasing capillary resistance to infiltration.

c. The mechanism of glucocorticoid anti-inflammatory action involve:

i. stabilization of lysosomal membranes which inhibits autolysis of cells in response to injury, and
ii. inhibition kinin production.

12. Immunosuppressive (anti-allergic) actions of glucocorticoids:

a. This effect is related to lympholytic action of glucocorticoids and involves inhibition of antibody production and inhibition of histamine release after antibody-antigen interactions.

b. Glucocorticoids are administered to patients receiving organ transplants to reduce host rejection.

c. Glucocorticoids impair the bacteriocidal and phagocytic potency of white blood cells.

i. Hence, they decrease the body's ability to ward off infection and make the individual more vulnerable to infection, even though discomfort may be reduced.

B. Mineralocorticoids: aldosterone, DOC, corticosterone

1. Mineralocorticoids promote Na\(^+\) reabsorption in exchange for K\(^+\) and H\(^+\) in the distal tubules and collecting ducts of the kidney (as well as the sweat glands, salivary glands and intestinal mucosa).

2. Aldosterone excess produces hypokalemic alkalosis.

3. Concomitant with Na\(^+\) retention are exchanges in intracellular and extracellular fluid volumes.

4. Spironolactone is an aldosterone antagonist useful in the treatment of hyperaldosteronism (and also useful as a diuretic).

C. Adrenal androgens: DHEA and derivatives.

1. Two thirds of the urinary 17-ketosteroids are adrenal in origin
2. Adrenal androgens provide a major anabolic component of the female (can have virilizing effects and promote protein synthesis).

3. Etiocholanolone, a 17-ketosteroid, is an A-ring reduced metabolic product of adrenal androgen which is pyrogenic (fever producing), presumably because it antagonizes the stabilizing action of cortisol on lysosomal membranes.

D. Adrenal estrogens.

1. Excess adrenal estrogens can have feminizing effects.

VII. MOLECULAR MECHANISMS OF CORTICOSTEROID ACTION

A. Corticosteroids enter cells passively and bind to cytosolic or nuclear intracellular receptors (i.e., specific, saturable, and high affinity)

1. Corticosteroid binding activates the receptor by causing its dissociation from heat shock protein

B. Activated corticosteroid-receptor complex interacts with the genome at the appropriate glucocorticoid response element (GRE).

C. Transcription rate of specific genes are altered affecting mRNA production, and subsequently translation (protein synthesis).

D. Aldosterone action in kidney epithelial cell involves:

1. Increased passive diffusion of Na\(^{+}\) across luminal membrane into cell.
2. Activation of the Na\(^{+}\)-K\(^{+}\) ATPase on serosal membrane which pumps Na\(^{+}\) into extracellular fluid.
3. Increased luminal negativity relative to cell resulting from Na internalization promotes tubular secretion of K\(^{+}\) and H\(^{+}\).

E. Glucocorticoid vs. mineralocorticoid receptors

1. Mineralocorticoids exert their effect through **Type I** receptors

   a. Type I receptors have an affinity for both cortisol and aldosterone. The preference (or specificity) for mineralocorticoids is enzymatically mediated.

      i. Mineralocorticoid targets have \(11\beta\)-hydroxysteroid dehydrogenase, an enzyme that converts cortisol to
cortisone (cortisone has a low affinity for Type I receptors)

ii. Because of its structure, aldosterone is not transformed by 11\(\beta\)-hydroxysteroid dehydrogenase.

b. A component of licorice (glycyrrhizic acid, glycyrrhetinic acid, glycyrrhizinic acid - all the same) inhibits 11\(\beta\)-hydroxysteroid dehydrogenase.

i. Therefore, high dietary licorice (e.g., chewing tobacco) can produce apparent mineralocorticoid excess because cortisol is not converted to cortisone under these circumstances.

2. Type II receptors mediate glucocorticoid effects

VIII. PHARMACOLOGY OF ADRENOCORTICAL STEROIDS (This is traditionally MII material and is for reference only - You will not be held responsible for this material on the exam)

A. Synthetic steroids

1. Chemical modification of the cortisol molecule tends to amplify glucocorticoid activity and diminish mineralocorticoid activity, among these are:

   a. introduction of a double bond (\(\Delta\)) in A-ring;
   b. introduction of \(\alpha\)-fluorine at position 9;
   c. introduction of \(\alpha\)-hydroxy or \(\alpha\)-methyl at position 16;

2. These modifications produce synthetic corticosteroids such as prednisolone, prednisone, triamcinolone, and dexamethasone

3. Altered activity is partially due to differences in receptor affinity, prolonged biological half-lives, reduced plasma binding

B. Relative glucocorticoid and mineralocorticoid potencies of naturally occurring and synthetic corticosteroids are listed in the following table:
## RELATIVE ACTIVITIES (in vivo)

<table>
<thead>
<tr>
<th>STEROID</th>
<th>GLUCOCORTICOID</th>
<th>MINERALOCORTICOID</th>
</tr>
</thead>
<tbody>
<tr>
<td>cortisol (Cpd. F)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>cortisone (Cpd.E)*</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>corticosterone (Cpd.B)</td>
<td>0.3</td>
<td>2.0</td>
</tr>
<tr>
<td>deoxycorticosterone (DOC)</td>
<td>0.0</td>
<td>15.0</td>
</tr>
<tr>
<td>aldosterone</td>
<td>0.3</td>
<td>300-500</td>
</tr>
<tr>
<td>$\Delta^1$ cortisol (prednisolone)</td>
<td>5.0</td>
<td>0.3</td>
</tr>
<tr>
<td>$\Delta^1$-cortisone (prednisone)</td>
<td>4.0</td>
<td>0.2</td>
</tr>
<tr>
<td>16α-hydroxy, 9α-fluoroprednisolone (triamcinolone)</td>
<td>6.0</td>
<td>0.0</td>
</tr>
<tr>
<td>16α-methyl, 9α-fluoroprednisolone (dexamethasone)</td>
<td>30</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Cortisone does not readily bind to the glucocorticoid receptors. However it is transformed to cortisol by the hepatic enzyme, 11β-hydroxysteroid dehydrogenase.*
IX. DISORDERS OF ADRENOCORTICAL FUNCTION

A. Hypercortisolism (Cushing's syndrome) (Fig. 8)

1. Cushing’s syndrome is characterized by elevated levels of cortisol and the absence of diurnal variation in plasma cortisol.
2. Cushing syndrome results from several etiologies, as follows:
   a. Primary hypercortisolism
      i. Here cortisol is secreted autonomously from an adrenal tumor (accounts for 10-15% of the cases of Cushing's syndrome).
      ii. ACTH levels are low due to negative feedback effect of excess cortisol.
   b. Secondary hypercortisolism
      i. Here hypercortisolism is due ACTH hypersecretion from the anterior pituitary (also referred to Cushing's "Disease" and comprising about 75% of all cases of Cushing’s Syndrome)
      ii. ACTH hypersecretion can be due to
          • corticotrophs in anterior pituitary (most common cause); or
          • a lesion in hypothalamus causing elevation of CRH which would then evoke ACTH hypersecretion.
      iii. Cushing's disease also implies dysfunction of glucocorticoid feedback mechanism. Why?
      iv. ACTH hypersecretion can also result from ectopic ACTH secretion from a nonpituitary source.
      v. Bilateral adrenal hyperplasia results from excess ACTH stimulation.
   c. Iatrogenic Cushing's syndrome (physician-induced)
      • Results from exogenous ACTH or corticosteroids.
   d. Why would a "dexamethasone suppression test" aid in the differential diagnosis of various etiologies of hypercortisolism?
3. Clinical characteristics of Cushing’s syndrome

a. Symptoms resulting from protein catabolic effects of cortisol:

   i. Muscle wasting.
   ii. Poor wound healing.
   iii. Thin skin (easy bruisability).
   iv. Decreased head hair growth.
   v. Centripetal fat redistribution (only if patient is well-nourished).

   - formation of stretch lines in abdomen (with centripetal fat redistribution).
   - "moon face".
   - “buffalo hump” on the back.

   vi. Hyperglycemia (abnormal glucose tolerance or mild diabetes) due to cortisol effects on intermediary metabolism.

   vii. Hypertension (B.P., 180/110) due to vasoactive glucocorticoid effects and mineralocorticoid effects of cortisol.

   viii. Facial hirsutism and acne due to the hypersecretion of adrenal androgens and/or the conversion of cortisol to 17-ketosteroids peripherally.

   ix. Virilization in females.
x. Osteoporosis and skeletal deformities due to the promotion of bone dissolution by cortisol.

xi. Psychological changes such as psychotic episodes and depression which may result from high cortisol levels.

xii. Gastrointestinal difficulties such as peptic ulcers.

xiii. Poor resistance to infection due to the anti-inflammatory and anti-allergic actions of excess cortisol.

B. Hypocortisolism (also referred to as adrenal insufficiency) (Fig. 9)

1. Characterized by low levels of cortisol, that results from several causes:

   a. **Primary hypocortisolism**

      i. May result from massive lesions in both adrenals (Addison's disease), or from
      ii. Deficiencies in steroidogenic enzymes.

         • such enzyme deficiencies called collectively "Congenital Adrenal Hyperplasia",
         • depending on the site of the enzyme block these disorders produce a particular array of symptoms to be discussed below.

   b. **Secondary hypocortisolism**

      i. may result from the following:

         • panhypopituitarism, or
         • an isolated ACTH deficiency or,
         • physician-induced (iatrogenic) after termination of long-term corticosteroid therapy.

      ii. secondary hypocortisolism involves atrophy of the zonae fasciculata and reticularis.
2. Clinical characteristics of hypocortisolism:

   a. Hypoglycemic episodes.

   b. Hyperpigmentation.

      i. in primary hypocortisolism (only where the pituitary is functional).

      ii. most likely due to elevated levels of ACTH (ACTH contains homologies to MSH).

   c. Hypotension (and associated dizziness, syncope, small heart size)

      i. occurs in Addison's disease where the zona glomerulosa is non-functional (not in secondary hypocortisolism).

   d. Muscle weakness and fatigue.

   e. Psychological changes such as irritability and lack of concentration.

   f. Gastrointestinal difficulties - fatty stools (steatorrhea),

      i. due to impaired lipid absorption

   g. Lymphoid hypertrophy.

   h. Adrenal crisis.
C. Congenital Adrenal Hyperplasia (CAH) - another form of hypocortisolism (Fig. 10)

1. Results from a relative or absolute deficiency in a steroidogenic enzyme within the adrenal cortex.
   a. Produces an impairment or elimination of cortisol secretion.
   b. Glucocorticoid feedback relationship is thus disrupted causing ACTH hypersecretion which produces:
      i. bilateral adrenal hyperplasia.
      ii. hypersecretion of steroids other than cortisol which produce unique symptoms in addition to those listed above associated with simpler forms of hypocortisolism.

2. CAH may be manifest in utero or becomes apparent in adolescence but rarely emerges in adult life.

![Figure 10. Congenital Adrenal Hyperplasia (General Characteristics).](image)

3. Specific enzyme deficiencies and associated specific symptoms (Fig. 11)
   a. C-20 hydroxylase (cholesterol desmolase) deficiency - congenital adrenal "lipoid" hyperplasia (Fig 11. A)
      i. impaired conversion of cholesterol to pregnenolone
ii. leads to general steroid deficiency
iii. very rare condition - about 30-40 cases
iv. occurs in utero
v. not compatible with survival

b. 3ß-hydroxysteroid dehydrogenase (3ß-ol dehydrogenase) deficiency (Fig. 11. B)
   i. leads to impaired formation of progesterone and 17α-hydroxy progesterone
   ii. excess ACTH and steroidogenic block results in increased adrenocortical DHEA production
   iii. excess androgen has virilizing effects - referred to as the "adrenogenital syndrome."
   iv. inability to form mineralocorticoids leads to sodium loss and associated side effects (e.g., hypotension)

c. 21-hydroxylase deficiency (Fig. 11. C)
   i. most common form of adrenogenital syndrome (incidence 1 in 14,000)
   ii. conversion of progestin to DOC and deoxycortisol is impaired
   iii. excess ACTH and block results in increased adrenocortical androgen secretion (virilization)
   iv. mineralocorticoid deficiency results in sodium loss and associated symptoms

d. 11ß-hydroxylase deficiency (Fig 11. D)
   i. a rarer form of adrenogenital syndrome
   ii. conversion of DOC to corticosterone and deoxycortisol to cortisol are impaired
   iii. excess ACTH and block results in increased adrenocortical androgen secretion (virilization)
   iv. accumulation of DOC, a potent mineralocorticoid (hypertension along with hypokalemic alkalosis)
   v. aldosterone output would be low, because of DOC-induced expansion of fluid volume inhibiting renin-angiotensin system.

e. 17α-hydroxylase (and 17,20 lyase) deficiency (Fig 11. E)
   i. congenital adrenal hyperplasia without adrenogenital effects
ii. cortisol production is reduced because of the absence of 17α-hydroxylation.
   - androgen production also impaired as a result of this deficiency.

iii. pathway leading to DOC and corticosterone production is favored, both of which possess significant mineralocorticoid activity (hence, hypertension and hypokalemic alkalosis)

iv. low aldosterone levels also occur due to expansion of plasma volume and suppression of renin-angiotensin system

v. this defect also occurs in the gonad leading to a female phenotype at birth and male pseudohermaphroditism

vi. rare - about 50 cases reported
Figure 11. B
Figure 11. C
11-beta hydroxylase block
(virilization, hypertension, hypokalemic alkalosis, low aldosterone).

Figure 11. D
Figure 11. Specific steroidogenic enzyme blocks leading to congenital adrenal hyperplasia.

D. Hyperaldosteronism

1. Elevated plasma levels of aldosterone

   a. Primary hyperaldosteronism (Conn's syndrome)
i. due to an adrenocortical adenoma  
ii. exhibits decreased levels of renin (why?)

b. Secondary hyperaldosteronism - stimulation of aldosterone release from a source outside of the adrenal cortex

i. produced by activation of the renin-angiotensin system due to a variety of conditions, such as:
   
   • decreased plasma volume  
   • impaired renal blood flow and/or perfusion pressure (e.g., as a result of renal vasoconstriction).

ii. produced by primary rise in renin secretion resulting from juxtaglomerular apparatus hyperplasia (Bartter’s syndrome).

2. Symptoms of hyperaldosteronism, predictable on the basis of actions of aldosterone:

   a. Hypertension;  
   b. Hypokalemic alkalosis—due to the loss of K\(^+\) and H\(^+\) in exchange for Na\(^+\) and accompanying weakness;  
   c. Polyuria resulting from nephropathy and secondary polydipsia.

X. STUDY QUESTIONS - All type A

1. Which pair of enzymes best represents the pathway for adrenal DHEA production from delta 5-pregnenolone?

   A. cholesterol desmolase, C-17,20-lyase  
   B. 3-beta-ol dehydrogenase:isomerase, 17-alpha hydroxylase  
   C. 17-alpha hydroxylase, C-17,20-lyase  
   D. 17-alpha hydroxylase, 3-beta-ol dehydrogenase:isomerase  
   E. 21-hydroxylase, 11-beta-hydroxylase

2. Which of the following hormones or treatments could produce adrenal enlargement, hyperglycemia, and thymic involution in hypophysectomized subjects?

   A. CRH  
   B. ACTH  
   C. chronic stress  
   D. cortisol
3. Which of the following treatments would be least effective in elevating serum cortisol levels in a subject with a deficiency in CRH?

A. mild stress  
B. CRH  
C. ACTH  
D. cortisol  
E. cortisone

4. Which of the following would be a consequence of a deficiency in angiotensin converting enzyme (ACE)?

A. involution of the zona fasciculata  
B. hypertension  
C. renin deficiency  
D. angiotensin II deficiency  
E. aldosterone excess

5. All of the following would be a consequence of ACTH deficiency except:

A. adrenal involution  
B. lymphoid hypertrophy  
C. muscle wasting  
D. tendency toward hypoglycemia  
E. adrenal crisis

6. A deficiency in which of the following adrenocortical steroidogenic enzymes leads to virilization and hypertension?

A. cholesterol desmolase  
B. 17-alpha hydroxylase  
C. 3 beta hydroxysteroid dehydrogenase  
D. 21-hydroxylase  
E. 11-beta hydroxylase

7. A deficiency in which of the following adrenocortical steroidogenic enzymes leads to hypertension without virilization?

A. cholesterol desmolase  
B. 17-alpha hydroxylase  
C. 3 beta hydroxysteroid dehydrogenase  
D. 21-hydroxylase
E. 11-beta hydroxylase

8. A drug that selectively blocks adrenal 11 beta-hydroxylase would most likely produce all of the following except:

A. elevated ACTH
B. enlarged adrenals
C. virilization
D. elevated aldosterone
E. hypokalemic alkalosis

9. Chronic treatment with which of the following drugs would most likely produce adrenocortical atrophy, low cortisol levels, and little or no change in blood pressure?

A. cortisol
B. ACTH
C. dexamethasone
D. a 17-alpha hydroxylase inhibitor
E. deoxycorticosterone