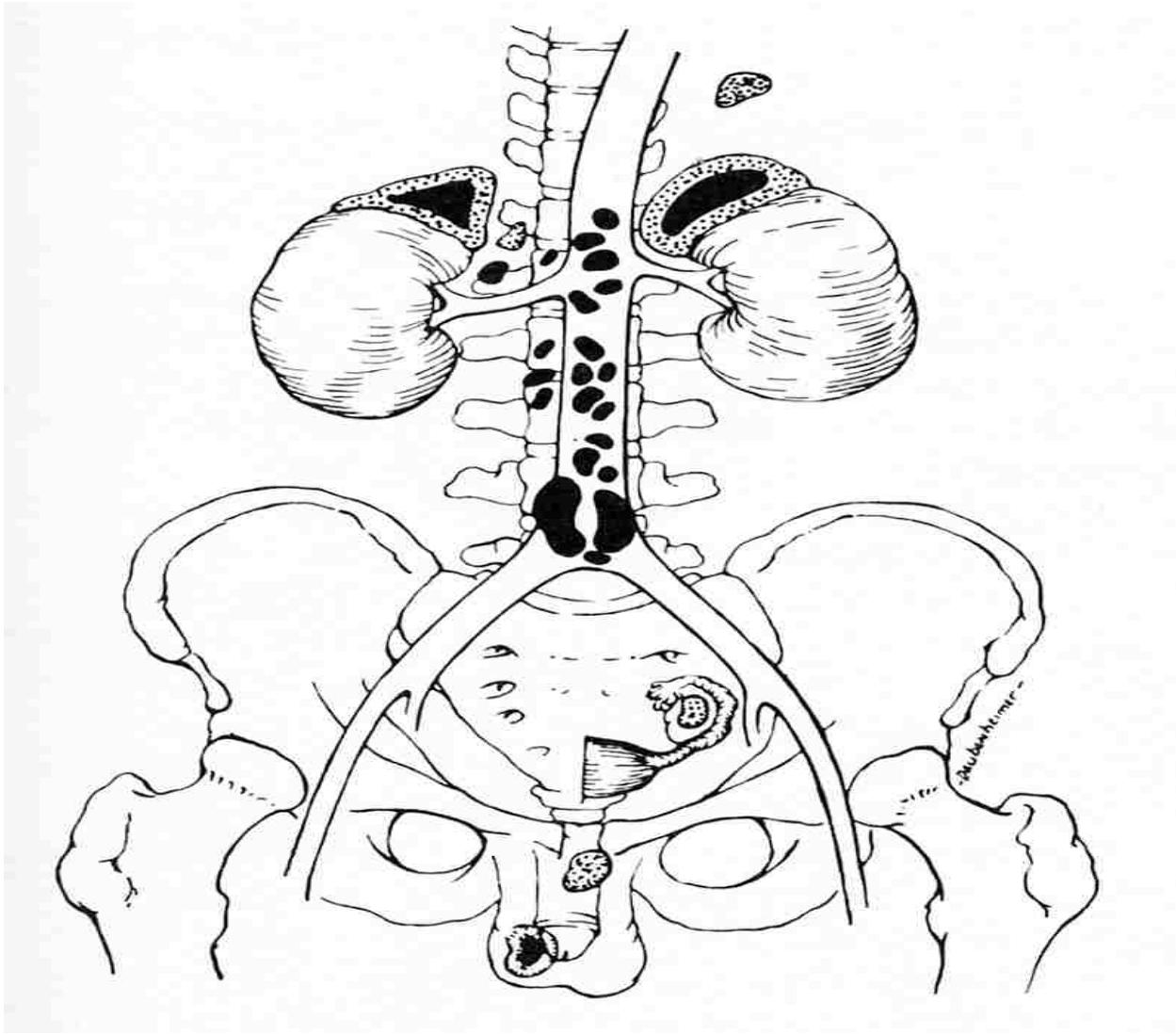
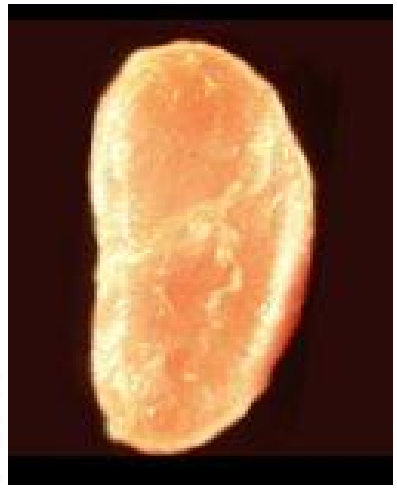
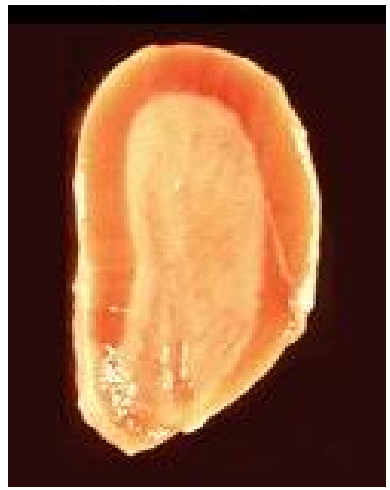
Adrenal Glands

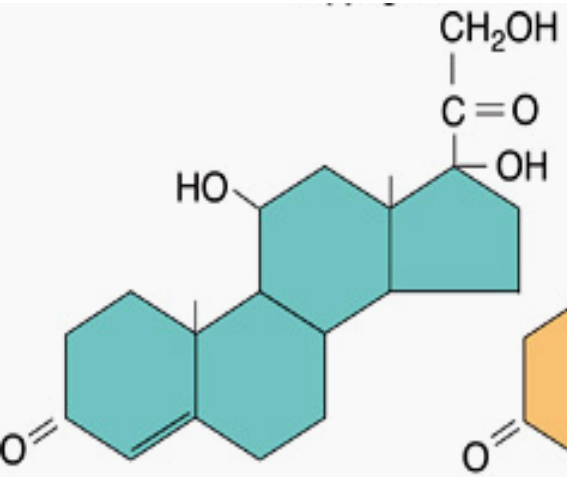
Dr. Isabel Hwang
Department of Physiology
Faculty of Medicine
University of Hong Kong
May 2007

Adrenal glands (Supra-renal glands)

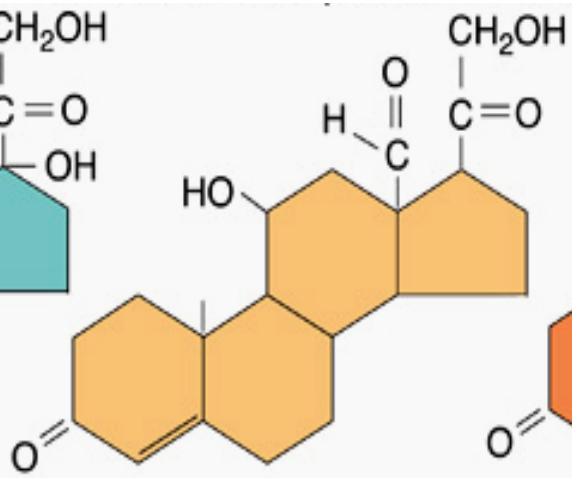




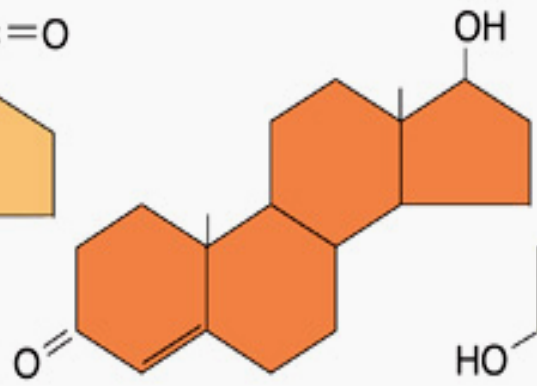




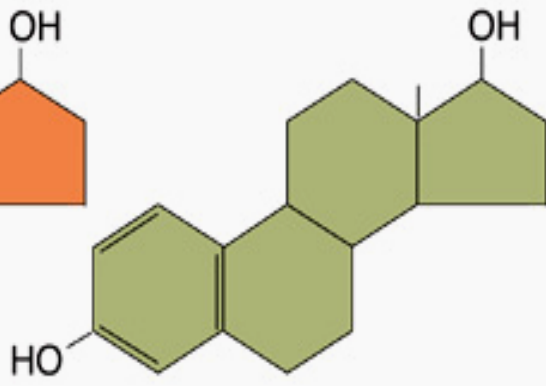
Cortisol



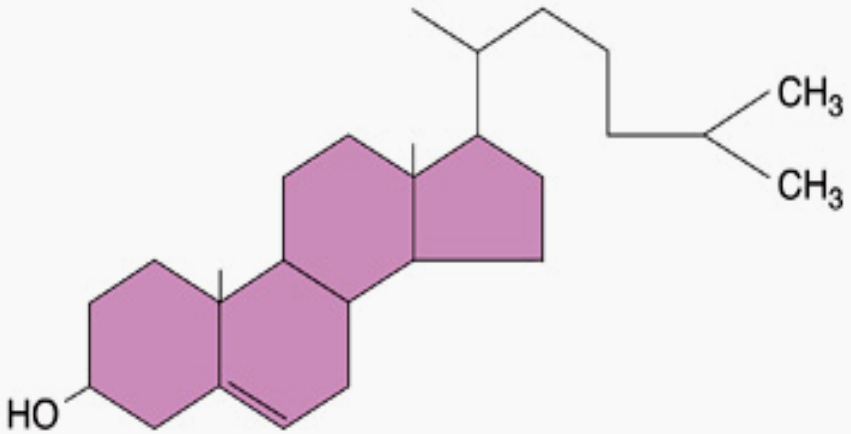
Aldosterone



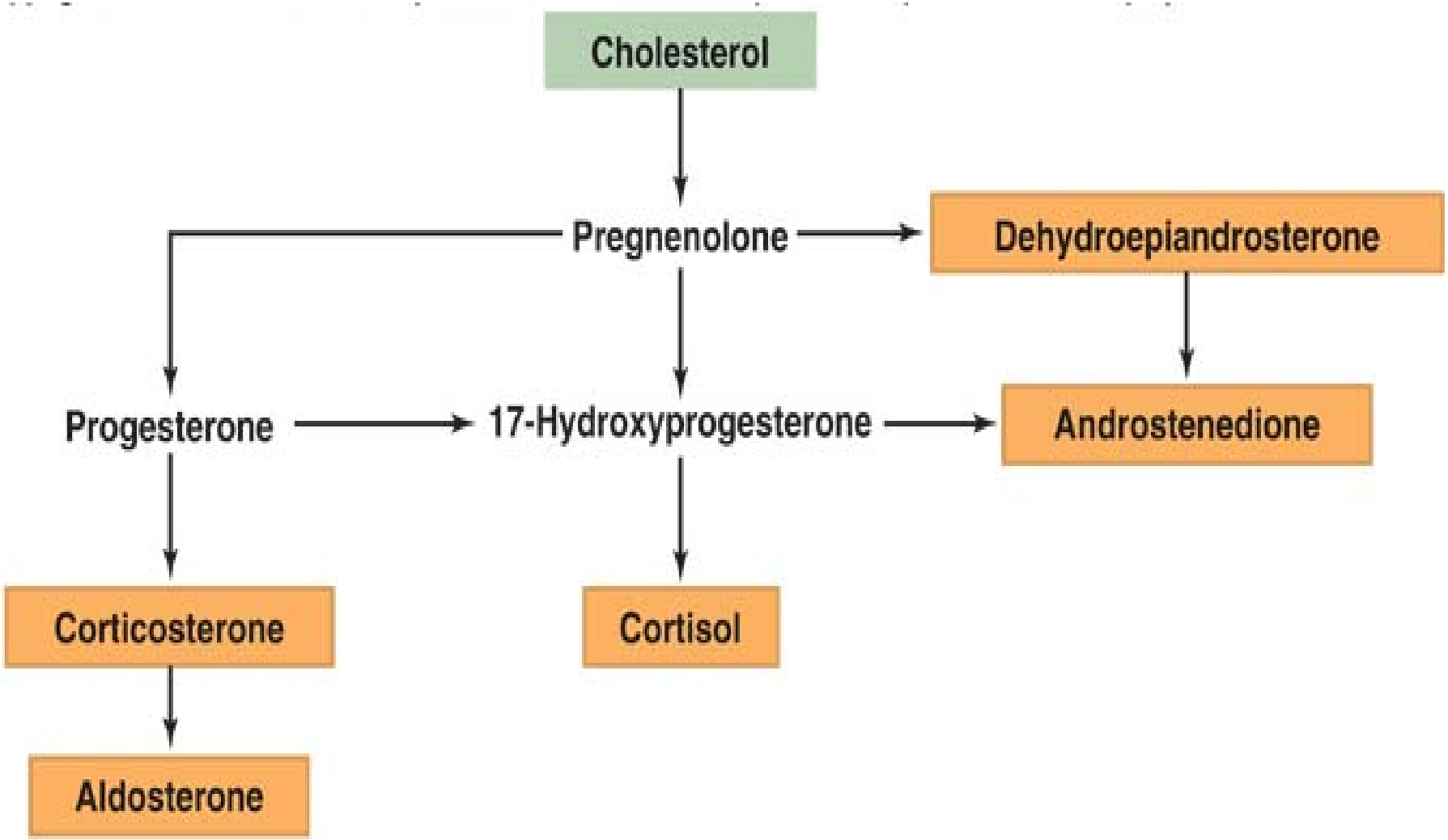
Testosterone



Estradiol



Cholesterol


Cholesterol
Pregnenolone
Dehydroepiandrosterone
Progesterone
17-Hydroxyprogesterone
Androstenedione
Corticosterone
Cortisol
Aldosterone

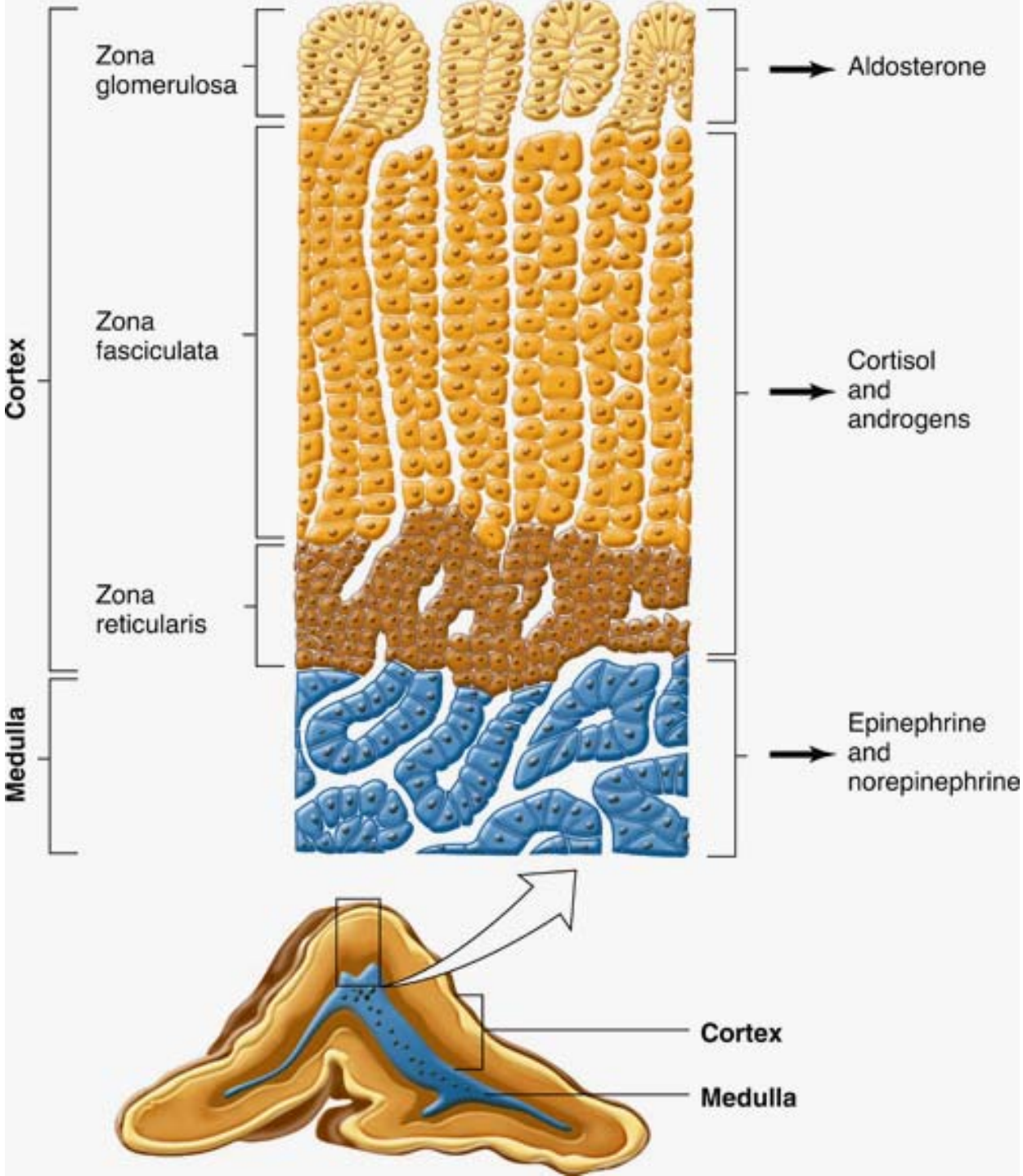
Adrenal cortex.

I. Introduction.

- **The adrenal consists of the cortex and the medulla.**

- **The cortex is made up of 3 zones: zona glomerulosa, zona fasciculata and zona reticularis**

- **Adrenocorticosteroids are bound to corticosteroid-binding globulins (to slow elimination from plasma)**


Zona glomerulosa
Zona fasciculata
Zona reticularis
Cortex
Medulla
Aldosterone
Cortisol and androgens
Epinephrine and norepinephrine
Cortex
Medulla

The adrenal cortex has 3 distinct layers

1. The zona glomerulosa

- Accounts for approx. 15% of the adrenal cortex
- Secretes significant amounts of aldosterone because it contains the enzyme aldosterone synthase
- Secretion regulated mainly by AngII and K

2. The zona fasciculata

- Accounts for about 75% of the adrenal cortex
- Secretes glucocorticoid cortisol and corticosterone
- Also a small amounts of adrenal androgens and estrogens
- Secretion regulated by ACTH

3. The zona reticularis

- The innermost layer of the cortex
- Secretes adrenal androgens (e.g. dehydroepiandrosterone DHEA, small amounts of estrogen and glucocorticoids
- Secretion regulated by ACTH

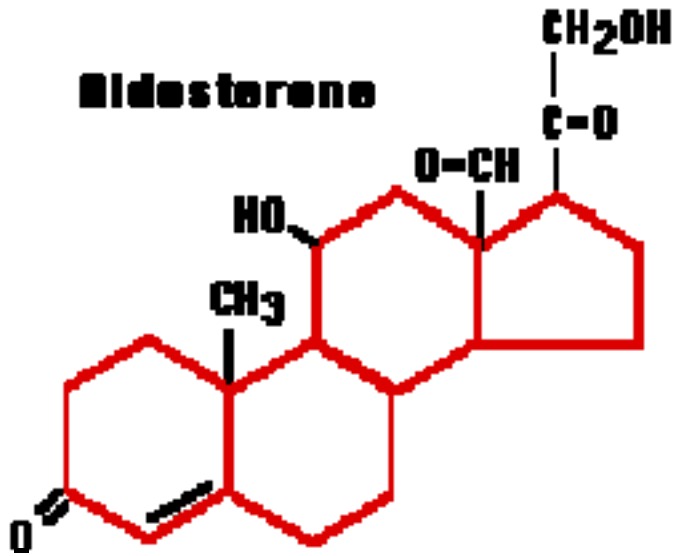
The Adrenal Cortex

The cells of the adrenal cortex secrete a variety of steroid hormones (>30). These fall into three classes:

- **Glucocorticoids (e.g., cortisol)**
- **Mineralocorticoids (e.g., aldosterone)**
- **Androgens (e.g., testosterone)**

Mineralocorticoids

- The mineralocorticoids get their name from their effect on mineral metabolism.
- The most important of them is the steroid aldosterone.
- Accounts for about 90% of all mineralocorticoid activity
- About 60% are bound to plasma proteins
- Half life is about 20 min



Other minearalcorticoids

- Desoxycorticosterone (1/30 activity compared to aldosterone, small amounts secreted)
- Corticosterone (little mineralocorticoid activity)
- 9α-fluorocortisol (synthetic, slightly more potent than aldosterone

II. Functions of aldosterone.

1. Renal reabsorption of sodium in the principal cells of the collecting tubules and also in the distal tubules and collecting ducts (excretion of potassium and hydrogen ions) and water.

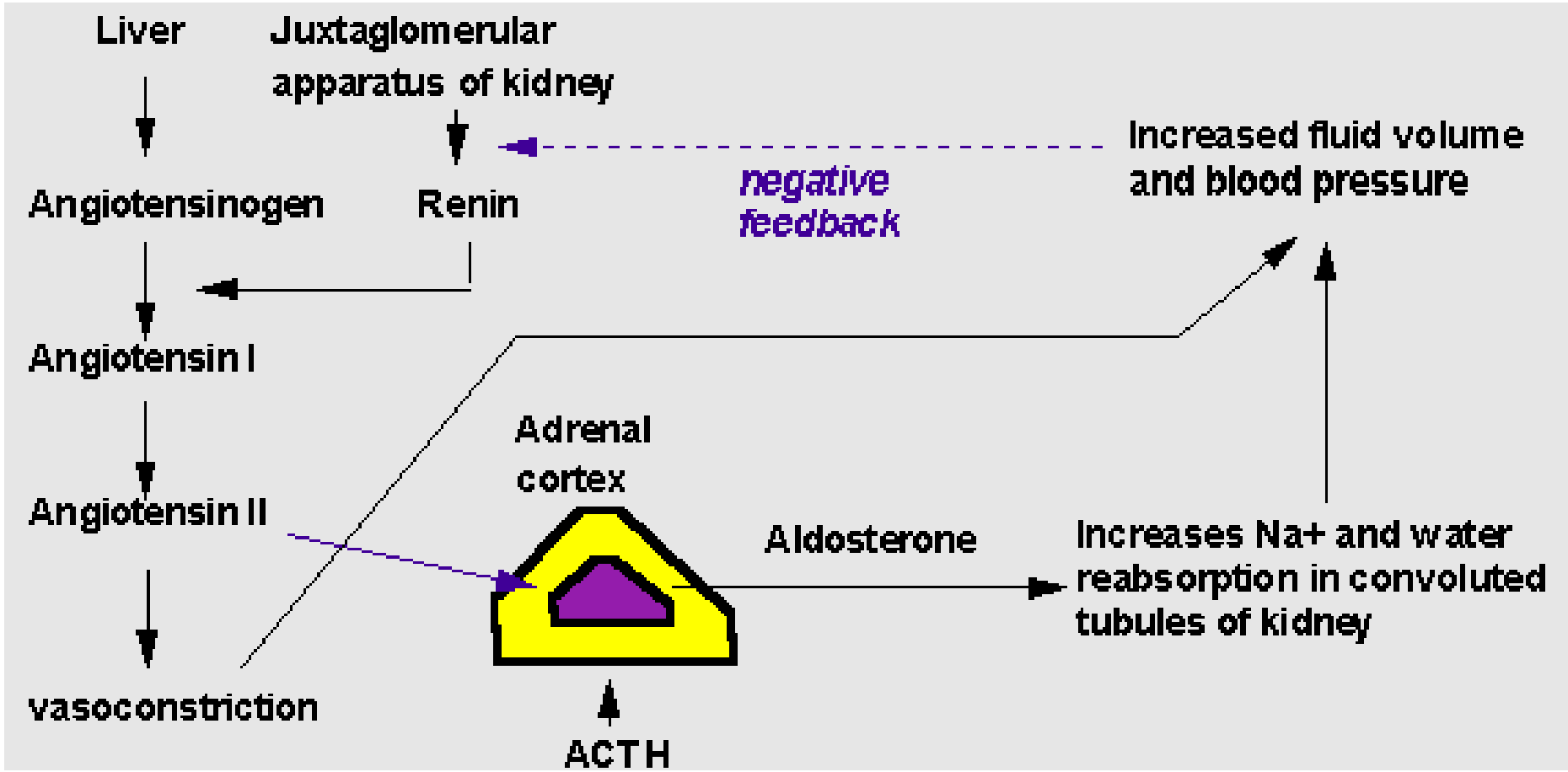
2. Control of blood volume.

(Excess → hypokalemia, alkalosis, hypertension)
(Deficient → hyperkalemia, acidosis, hypotension)

IV. Regulation of aldosterone secretion.

(In order of importance)

1. **Increased K**
2. **Increased activity of Renin-angiotensin system.**
3. **Increased sodium – through renin.**
4. **ACTH**


Liver
Juxtaglomerular apparatus of kidney
Angiotensinogen
Renin
negative feedback
Increased fluid volume and blood pressure
Angiotensin I
Angiotensin II
Adrenal cortex
Aldosterone
Increases Na+ and water reabsorption in convoluted tubules of kidney
vasoconstriction
ACTH

Glucocorticoid

- Cortisol (very potent, 95% of all glucocorticoid activity)
- Corticosterone (~4% of total glucocorticoid activity, less potent than cortisol)
- Cortisone (synthetic, as potent as cortisol)
- Dexamethasone (synthetic, 30 times as potent as cortisol)

III. Functions of cortisol.

1. Carbohydrate metabolism.

- ↑ gluconeogenesis (from amino acids)
- ↑ glycogenolytic effects of glucagon & adrenaline
- Decrease glucose uptake & utlilization

(Excessive → hyperglycaemia, insulin resistance*)
(Deficient → hypoglycaemia)

- High amounts of glucocorticoids seems to reduce the sensitivity of many tissues, notably the skeletal muscles and adipose tissue, to insulin
- High levels of FA may impair the actions of insulin on tissues
- Therefore, adrenal diabetes results (injection of insulin only alleviates but cannot remove the effect because of tissue resistance to insulin)

2. Protein metabolism.

Increase protein breakdown (e.g. from muscle) for gluconeogenesis

(Excessive → muscle wasting, weakening of blood vessel wall)

3. Fat metabolism.

Increase lipolysis and fatty acid mobilisation (from adipose tissue)

- Fat breakdown helps to shift the ultilisation of glucose for energy to ultilisation of fatty acid in times of stress or starvation

- Also, the increased use of fatty acid as metabolic energy is an important pathway for more long term conservation of body glucose and glycogen

4. **Maintenance of blood pressure.**

Permissive – through inhibition of enzyme that destroys norepinephrine at sympathetic nerve endings.

(Excessive → hypertension)
(Deficient → hypotension)

5. Anti-inflammatory

- depress the immune response (stabilizing lysosomes), especially cell- mediated immune responses.

For this reason, glucocorticoids are widely used in therapy:

- to reduce the inflammatory destruction of rheumatoid arthritis and other autoimmune diseases

- to prevent the rejection of transplanted organs

- to control asthma

Cortisol is also important in resisting stress

- Stress stimulates ACTH increase in ant. pituitary gland and therefore cortisol secretion
- Types of stress include the following

- Trauma
- Infection
- Coldness and heat
- Surgical operation

Regulation of cortisol secretion.

1. **Hypothalamico-pituitary- adrenal axis**

CRH → ACTH → cortsiol.

2. **Negative feed-back**

long -loop – by free cortisol

short-loop – by ACTH on CRH secretion.

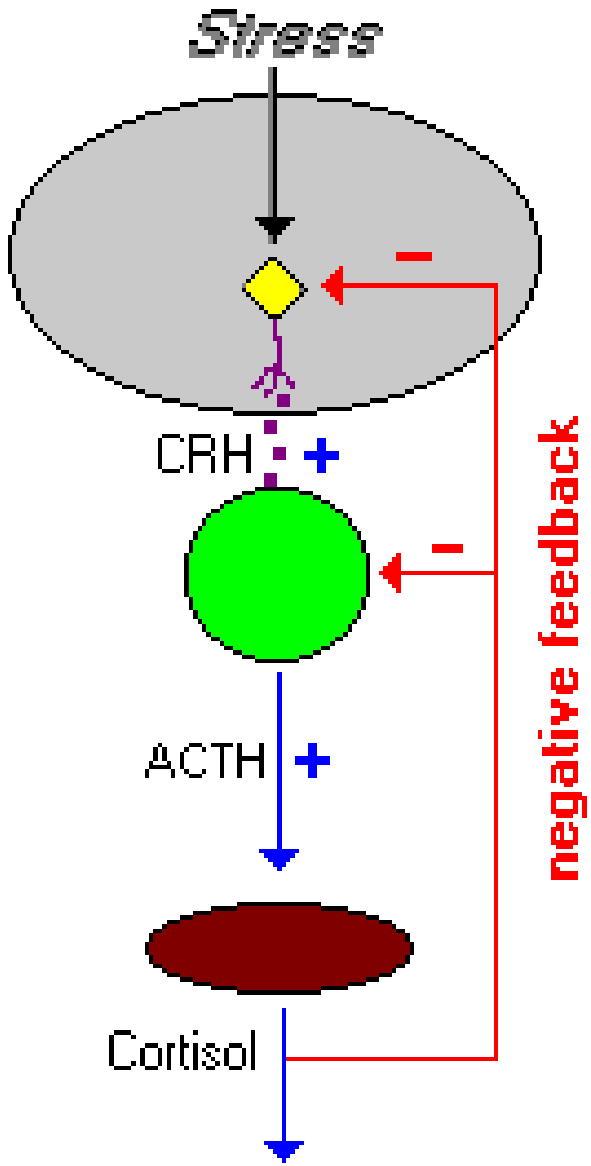
3. ***Stress*** **(Stress overrides negative feed-back i.e. cortisol secretion is stimulated even though cortisol level is high, but magnitude is diminished)**

4. **Diurnal rhythm.**

high in the morning

low in late afternoon and night

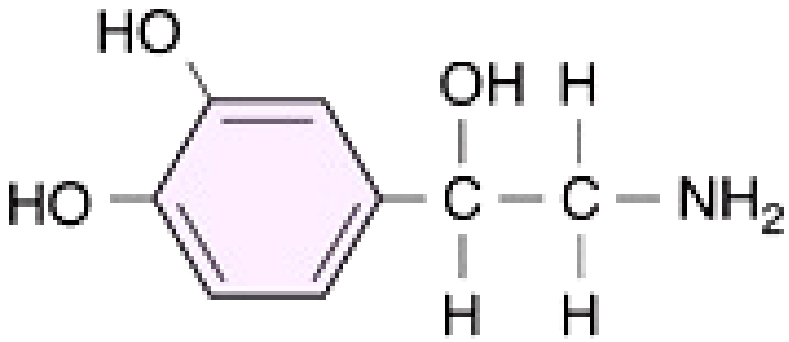
Virtually any type of physical or mental stress results in elevation of cortisol concentrations in blood due to enhanced secretion of CRH in the hypothalamus



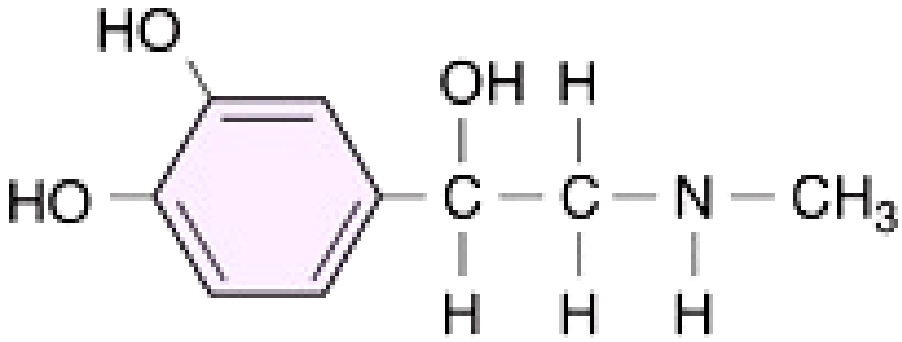
Adrenal medulla

Release of epinephrine (80%)/ norepinephrine (20%) (adrenaline/Noradrenaline)

- **is triggered by sympathetic stimulation in response to physical or mental stress.**
- **Has same effects on the different organs as caused by the sympathetic stimulation**
- **act directly on blood vessels, usually causing vasoconstriction (by alpha receptor stimulation), but sometimes epinephrine can cause vasodilation if it binds to beta adrenergic receptor**



Norepinephrine



Epinephrine

Adrenergic Receptors and Mechanism of Action

- **The physiologic effects of epinephrine and norepinephrine are initiated by their binding to adrenergic receptors on the surface of target cells.**

Receptor	Effectively Binds	Effect of Ligand Binding
Alpha$_1$	Adrenaline, Noradrenaline	Increased free calcium
Alpha$_2$	Adrenaline, Noradrenaline	Decreased cyclic AMP
Beta$_1$	Adrenaline, Noradrenaline	Increased cyclic AMP
Beta$_2$	Adrenaline	Increased cyclic AMP

- **Complex physiologic responses result from adrenal medullary stimulation because there are multiple receptor types which are differentially expressed in different tissues and cells**
- **Receptors – adrenaline (equally on alpha & beta)**
  - noradrenaline (mainly on alpha, beta receptor Beta$_1$ only)

Epinephrine (EP) vs Norepinephrine (NEP)

1. EP has greater effect on stimulating bete receptors, therefore has greater effect on cardiac stimulation
2. EP causes weaker constriction of blood vessels in muscles than NEP
3. NEP causes greater increase in TPR and arterial pressure
4. EP increases the CO more than NEP
5. EP has 5-10 times more effective in increasing metabolic effect as NEP

Common stimuli for secretion

- **Exercise,**
- **Hypoglycemia,**
- **Hemorrhage and**
- **Emotional stress**

TABLE 11–4 *Actions of the Sympathetic Nervous System, Including Epinephrine Secreted by the Adrenal Medulla, During Stress*

1. Increased hepatic and muscle glycogenolysis (provides a quick source of glucose)
2. Increased breakdown of adipose tissue triglyceride (provides a supply of glycerol for gluconeogenesis and of fatty acids for oxidation)
3. Decreased fatigue of skeletal muscle
4. Increased cardiac function (e.g., increased heart rate)
5. Diverting blood from viscera to skeletal muscles by means of vasoconstriction in the former beds and vasodilation in the latter
6. Increased lung ventilation by stimulating brain breathing centers and dilating airways

Disorders of the adrenal

Cushing's syndrome (Hypercortisolism)

1. Causes

- Adenoma of ant. Pituitary gland
  ↑↑ ACTH→ adrenal hyperplasia → cortisol overproduction
- Abnormal function of hypothalamus causes overproduction of CRH → ↑↑ ACTH
- Ectopic secretion of ACTH from tumor elsewhere in the body, e.g. pancreas
- Adenoma of the adrenal cortex

2. Clinical features – “moon face”

plethora (reddish face & neck)

trunk obesity

purple abdominal striae (loss of collagen in subcutaneous tissue and increases tearing)

excessive bruising

poor wound healing

hypertension (mineral effects of cortisol)

hyperglycaemia

osteoporosis (loss of protein in bone)

muscular weakness

mental abnormalities

hirsutism (due to adrenal androgens)

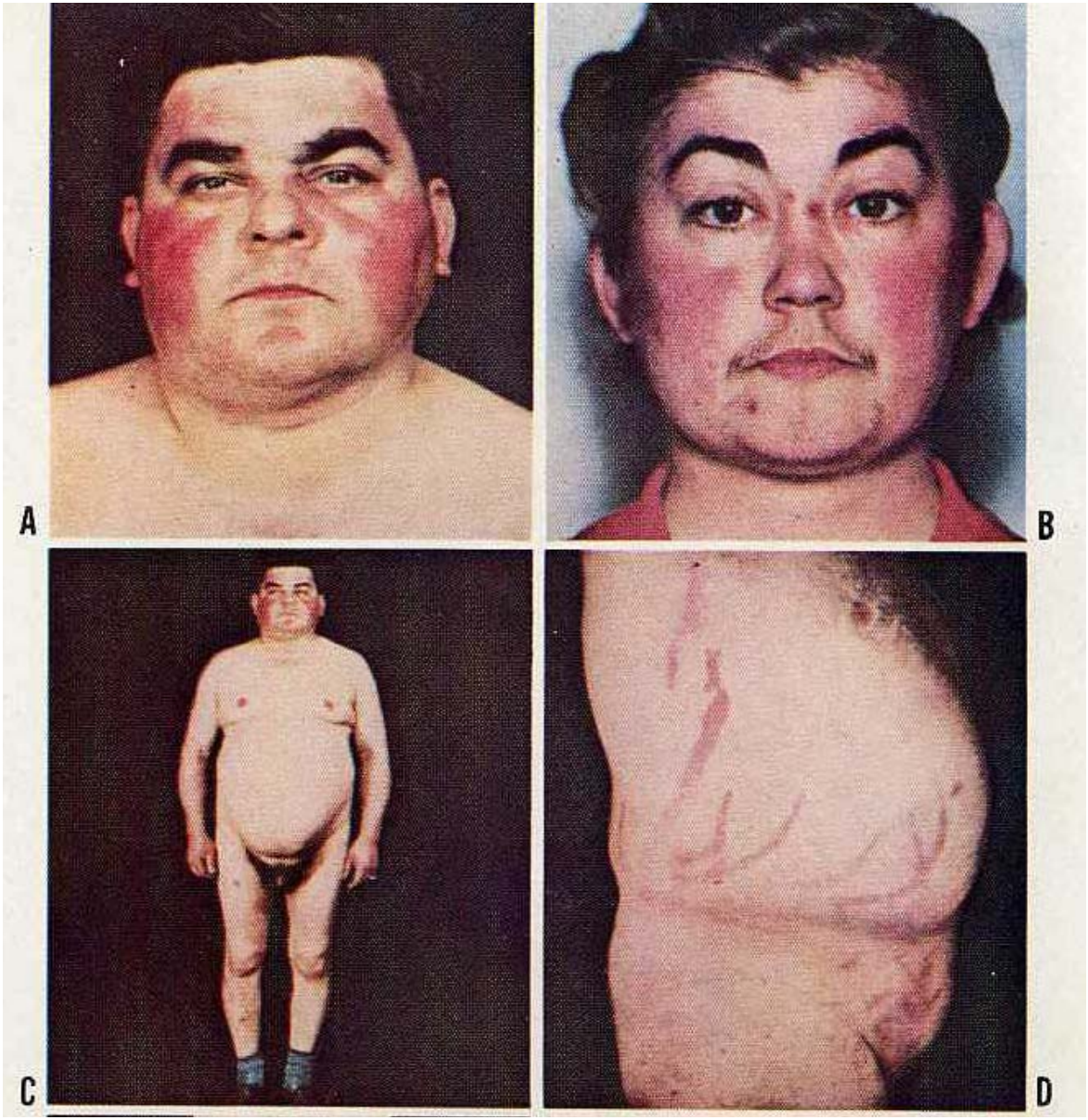
skin pigmentation (due to ↑ ACTH).

Hypersecretion of adrenal steroids results in a medical condition called Cushing's syndrome, which includes hypertension (abnormally high blood pressure) and, seen here, "moon face," with upper-body obesity.

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.

Cushing's Syndrome

A. Round, red face; short
thick neck.
B. Typical moon face with *hirsutism
C. Red moon face
Truncal obesity with prominent abdomen and relatively thin extremities
D. Purplish-red striae and protuberant abdomen



* Abnormal hairiness, especially an adult male pattern of hair distribution in women.

3. **Diagnoses – loss of circadian (24 hour) rhythm in plasma cortisol**

Dexamethasone (a synthetic glucocorticoid) suppression test (ACTH-dependent or ACTH-independent)

In patients with overproduction of ACTH due to pituitary adenoma or hypothalamic-pituitary dysfunction, large doses of dexamethasone cannot suppress ACTH secretion

In patients with primary adrenal hypersecretion of cortisol (ACTH-independent), ACTH level is usually low or undetectable

Measurement of plasma ACTH

4. Treatment - surgery (adrenal tumours)

- Radiotherapy or surgery (pituitary tumour)

- drugs to block cortisol synthesis (e.g. mitotane)

- or bilateral adrenalectomy (ectopic ACTH syndrome)

B. Primary hypoadrenalism (Addison's disease)

- rare, underproduction of cortisol and aldosterone

1. Causes – destruction of adrenal cortex by autoimmune disease; cancer or tuberculous destruction

2. Clinical features – excessive urinary loss of Na and Cl ions

diuresis (dehydration,cardiac output)
hypoglycaemia (CORT)
muscle weakness (CORT)
skin pigmentation (due to ACTH)
hypotension (CORT, ALD)
inability to withstand stress (CORT)

Treatment for Addison’s disease-

- Replacement therapy (daily administration of mineralcorticoid and glucocorticoid)

C. Primary aldosteronism (Conn's syndrome). (Hyper-aldosterone secretion)

1. Causes – adrenal adenoma or idiopathic* adrenal hyperplasia.

2. Clinical features – hypertension and hypokalaemia
   K depletion and Na retention
   alkalosis (under-acidity of the body)
   muscle weakness (due to hypokalemia and on action potential transmission by nerve fibres)
   polyuria (excess urination)
   polydipsia (excess thirst)
   reduced renin level (strong –ve feedback by Ald, excess fluid volume and arterial pressure)

*Iodiopathic-self-originated, with unknown cause

Hyperplasia (↑cell no) vs. Hypertrophy (↑ size of a tissue)

Diagnoses – blood pressure, serum K and aldosterone
plasma renin activity

Treatment – surgical removal of tumour, or *spironolactone (to block aldosterone action).

*** Aldosterone antagonist and diuretic, used to treat low renin hypertension and Conn's syndrome**