

Disorders of the endocrine system 2

Parathyroid glands

Adrenal glands

Gonads

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Content

- **Disorders of parathyroid function**
(hypoparathyroidism and hyperparathyroidism)
- **Disorders of adrenal cortex function**(decreased and increased secretion of aldosterone, cortisol and androgens)
- **Disorders of adrenal marrow function**
(pheochromocytoma)
- **Disorders of gonadal function** (decreased and increased testicular and ovarian function)

Parathyroid glands

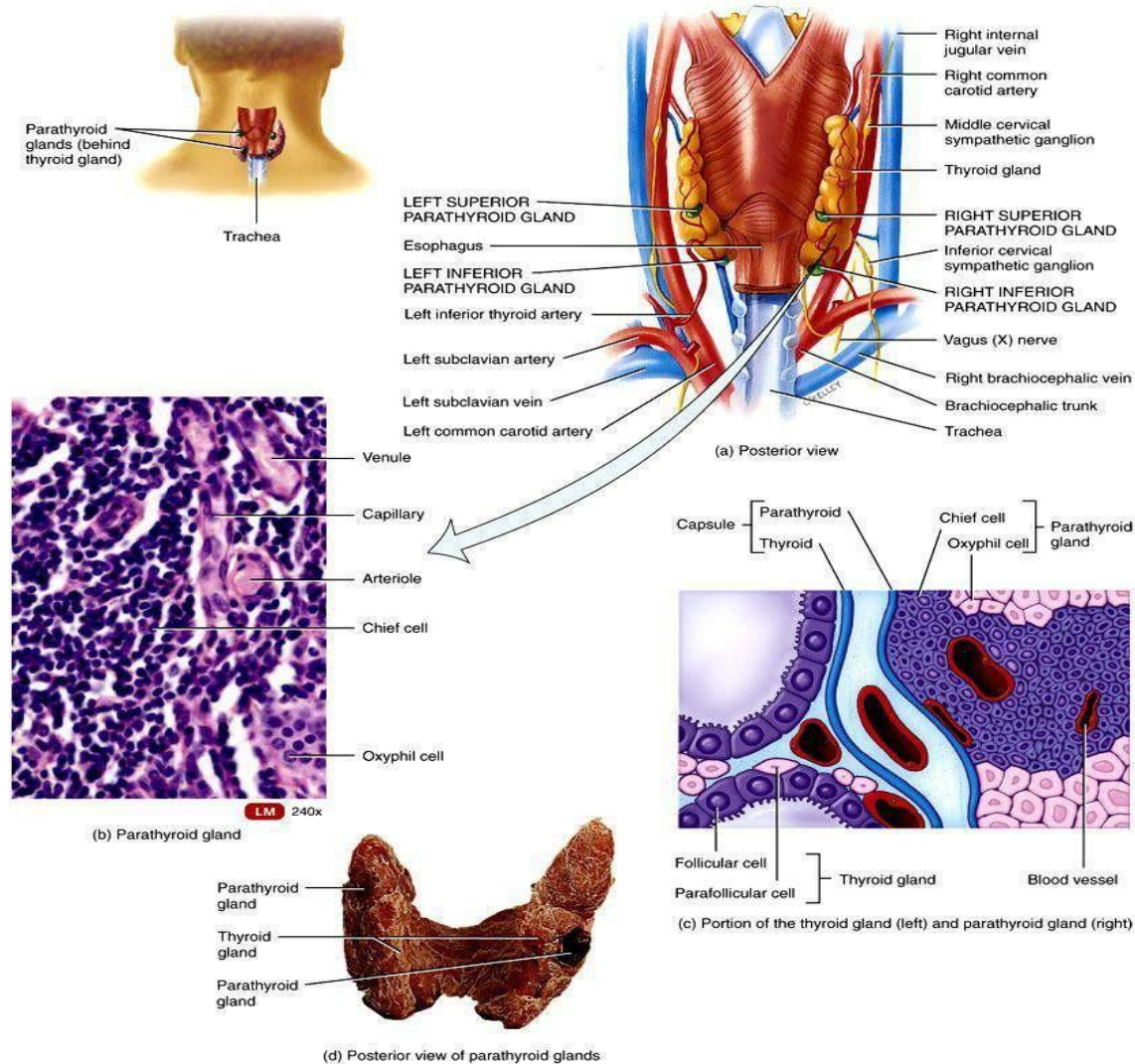
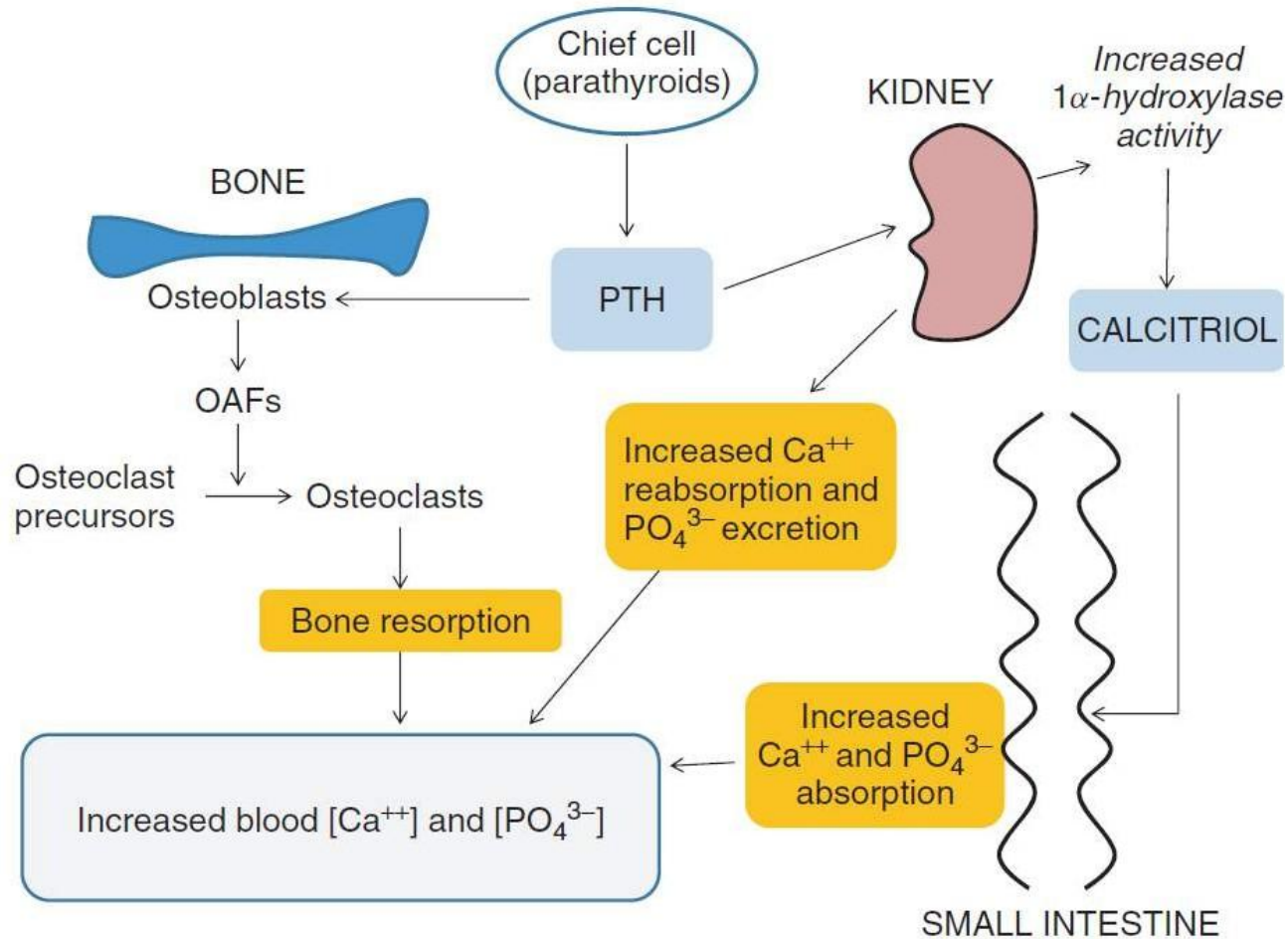


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Parathyroid glands

- Most often two pairs, located along the lobes of the thyroid gland
- **Parathyroid hormones(PTH)**
 - The main regulator of the metabolism of calcium, phosphorus and magnesium ions in the blood
 - Increases the number and activity of osteoclasts
 - Increases bone resorption
- The level of Ca^{+2} in the blood directly regulates the secretion of calcitonin and PTH

Parathyroid glands



Disorders of parathyroid function

- **Hypoparathyroidism**

- Primary hypoparathyroidism
- Pseudo-hypoparathyroidism (resistance of peripheral tissues)
- Secondary hypoparathyroidism (result of hypercalcemia)

- **Hyperparathyroidism**

- Primary hyperparathyroidism: disorder at the level of the parathyroid glands, such as adenoma, cancer, hyperplasia of the parathyroid glands (hyperproduction of PTH)
- Secondary hyperparathyroidism: chronic hypocalcemia (compensatory response - increase in PTH production)
- Tertiary hyperparathyroidism
- Pseudohyperparathyroidism: **ectopic production of PTH (in tumors of the lung (microcell), kidney, liver, pancreas)**

Primary hypoparathyroidism

ETIOLOGY:

- surgical removal of the parathyroid glands,
 - radiation,
 - autoimmune processes,
 - infiltrative diseases
-
- It occurs as a result of disorders of the parathyroid glands with reduced production of PTH

Primary hypoparathyroidism

PATHOPHYSIOLOGY:

- Considering the function (disorder of Ca^{+2} metabolism)
 - **Biochemical changes:**
 - Hypocalcemia (symptoms are related to hypocalcemia)
 - Hyperphosphatemia
 - **Neuromuscular disorders:**
 - Increased neuromuscular excitability (from paresthesias to muscles spasms, bronchospasm or laryngospasm, and in severe cases generalized tonic-clonic spasms)
 - prolonged QT interval

Secondary hypoparathyroidism

- It happens **as a result of hypercalcemia**:
 - Vitamin D hypervitaminosis
 - Sarcoidosis (increased $\alpha 1$ hydroxylase activity)
 - Malignant bone tumors
 - Thyrotoxicosis
- The **concentration of Ca^{+2} is high, and PTH concentration is low** (negative feedback loop)

Primary vs secondary hypoparathyroidism

- **Primary as a result of damage to the glands themselves, while secondary occurs as a result of hypercalcemia**

Primary hyperparathyroidism

ETIOLOGY:

- adenoma (81%),
- cancer (4%),
- hyperplasia of the parathyroid glands

PATHOPHYSIOLOGY:

- **Biochemical changes:**
 - hypercalcemia, hypophosphatemia, hypercalciuria
- **Clinical symptoms are the result of:**
 - Hypercalcemia (reduced NMR)
 - Hypercalciuria (with the possibility of forming kidney stones)

Primary hyperparathyroidism

- Hypercalcemia leads to:
 - Disorders of nerve cell depolarization
 - Contractions of the smooth muscles of the blood vessels of the brain with vasoconstriction, the development of ischemia and hypertensive encephalopathy (accompanied by disturbances of consciousness up to coma)
 - Heart rhythm disorders (ventricular extrasystoles, even up to fibrillation), rarely spastic contractions of the myocardium
 - Hypertension due to spasm of smooth muscles in the walls of arteries and arterioles, reduction of flow through the kidney (with stimulation of the renin-angiotensin system)
 - Decreased ability of the kidneys to concentrate urine, with the occurrence of polyuria and dehydration
 - Calcifications of soft tissues (if concentration of Ca^{+2} is over 4mmol/L)

Primary hyperparathyroidism

- Clinical symptoms:
- **Neuromuscular disorders:**
 - muscle weakness, anorexia, vomiting, shortened QT interval (ECG)
- **Mental disorders:**
 - emotional instability, depression, psychoses
- **Renal disorders:**
 - reduced ability to concentrate (polyuria, nocturia)

Secondary hyperparathyroidism

- It occurs due to disorders that reduce the concentration of ionized/free calcium in the plasma:
 - Malnutrition with insufficient intake of vitamin D and calcium
 - Impaired lipid absorption (lower absorption with steatorrhea)
 - Disorders of vitamin D metabolism in kidney diseases
 - Disorders of vitamin D metabolism during therapy with some anticonvulsant drugs
 - In chronic renal failure

Tertiary hyperparathyroidism

- It happens as a result of **long-term** secondary hyperparathyroidism
- Due to long-term stimulation of the parathyroid glands with low concentrations of calcium, the secretion of parathyroid hormone becomes autonomous (independent of the concentration of calcium in the blood).

Content

- Disorders of parathyroid function
(hypoparathyroidism and hyperparathyroidism)
- **Disorders of adrenal cortex function** (decreased and increased secretion of aldosterone, cortisol and androgens)
- Disorders of adrenal marrow function
(pheochromocytoma)
- Disorders of gonadal function (decreased and increased testicular and ovarian function)

Adrenal glands

Two different regions (**structurally and functionally**)

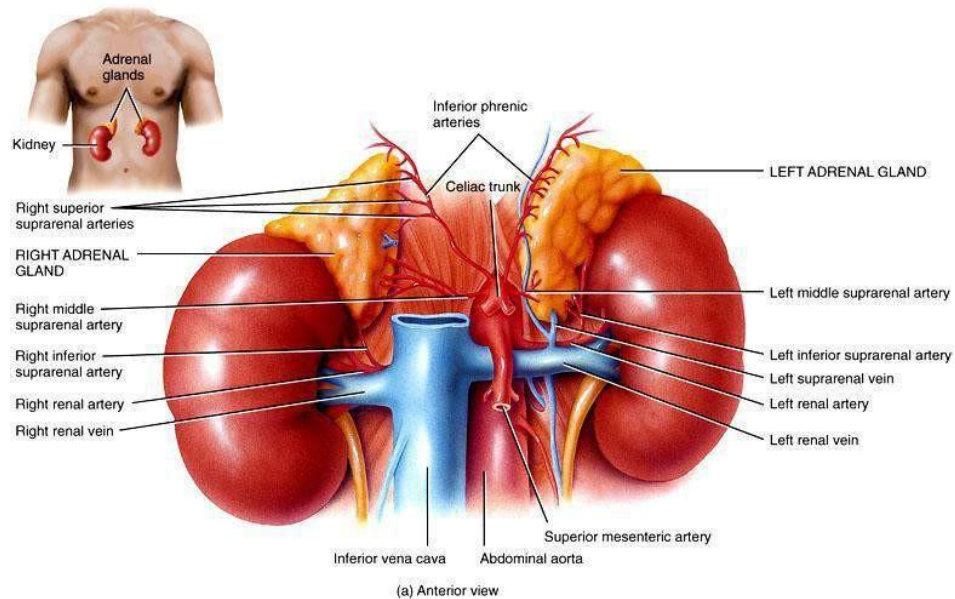
- **Adrenal cortex**

- **Mineralocorticoids** maintain mineral homeostasis
- **Glucocorticoids** maintain glucose homeostasis
- **Androgen** have a significant masculinizing effect
 - Dehydroepiandrosterone (DHEA) is only significant in the female sex

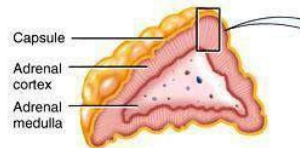
- **Adrenal medulla**

- It represents a **modified sympathetic ganglion** autonomic nervous system
- **It enhances the sympathetic response**
- **Hormones:** epinephrine (adrenaline) and norepinephrine (noradrenaline)

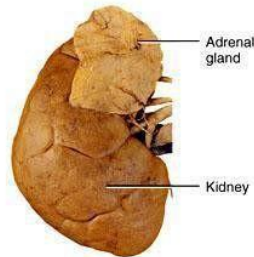
Adrenal glands



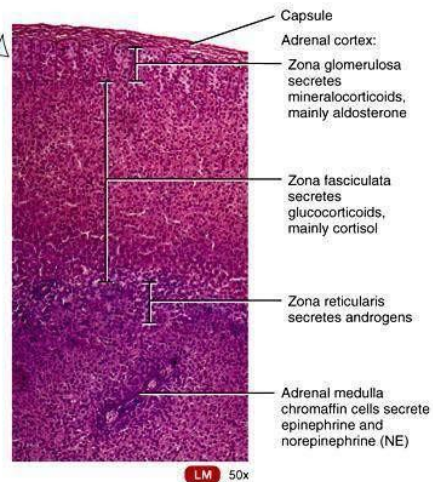
(a) Anterior view



(b) Section through left adrenal gland



(c) Anterior view of adrenal gland and kidney



(d) Subdivisions of the adrenal gland

Adrenal hormones

- Mineralocorticoids
 - Regulation function:
 - Homeostasis of ions
 - Sodium conservation
 - Potassium secretion
 - Blood pressure
 - Volume of circulating volume (blood)
 - Excretion of H^+

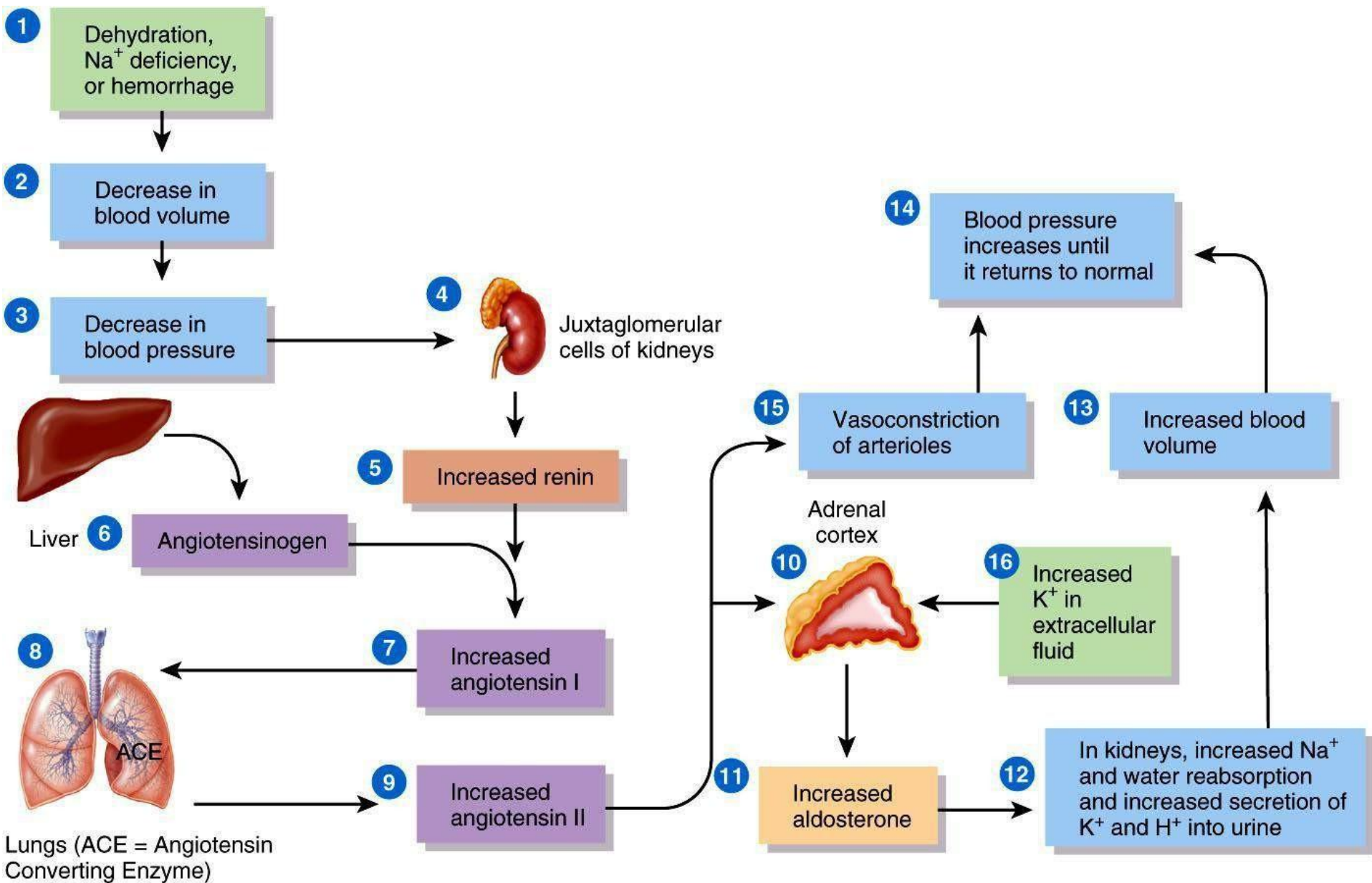
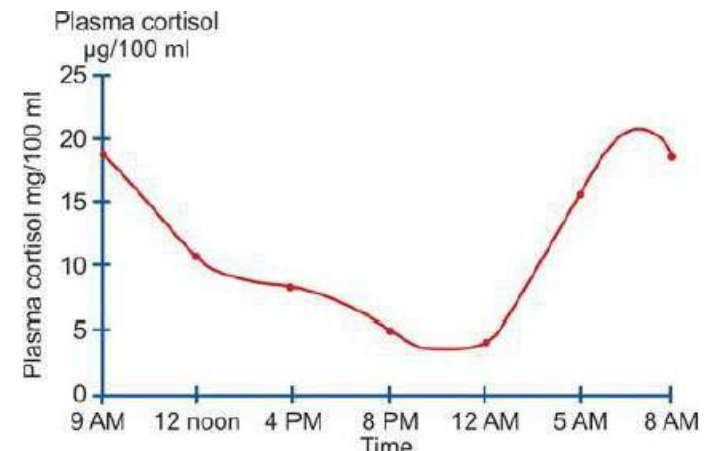


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Adrenal hormones

- Glucocorticoids
- Cortisol (hydrocortisone), corticosterone and cortisone
- Secretion under the control of ACTH (pituitary)
- Cortisol effect:
 - The glucose synthesis through the process of gluconeogenesis
 - Lipolysis
 - Degradation of proteins
 - Resistance to stress
 - Anti-inflammatory effects

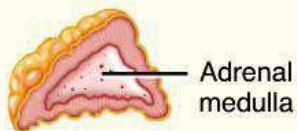
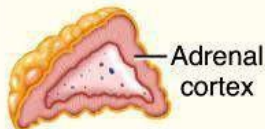


Adrenal hormones

- Androgen
- Dehydroepiandrosterone (DHEA)
- Little effect on adult men because the testicles (and testosterone) play a dominant role
- Women
 - increases libido
 - it is converted to estrogens
 - after menopause androgen conversion is the only source of estrogen (previously before menopause and ovaries)
- Androgens stimulate axillary and pubic hairiness during puberty
- Secretion is dominantly controlled by ACTH

TABLE 18.8**Summary of Adrenal Gland Hormones**

HORMONES AND SOURCE	CONTROL OF SECRETION	PRINCIPAL ACTIONS
ADRENAL CORTEX HORMONES		
Mineralocorticoids (mainly aldosterone) from zona glomerulosa cells	Increased blood K^+ level and angiotensin II stimulate secretion.	Increase blood levels of Na^+ and water and decrease blood level of K^+ .
Glucocorticoids (mainly cortisol) from zona fasciculata cells	ACTH stimulates release; corticotropin-releasing hormone (CRH) promotes ACTH secretion in response to stress and low blood levels of glucocorticoids.	Increase protein breakdown (except in liver), stimulate gluconeogenesis and lipolysis, provide resistance to stress, dampen inflammation, and depress immune responses.
Androgens (mainly dehydroepiandrosterone or DHEA) from zona reticularis cells	ACTH stimulates secretion.	Assist in early growth of axillary and pubic hair in both sexes; in females, contribute to libido and are source of estrogens after menopause.
ADRENAL MEDULLA HORMONES		
Epinephrine and norepinephrine from chromaffin cells	Sympathetic preganglionic neurons release acetylcholine, which stimulates secretion.	Produce effects that enhance those of the sympathetic division of the autonomic nervous system (ANS) during stress.



Adrenal gland function disorders

- Adrenal **cortex** functional disorders:
 - Reduced function (hypofunction)
 - Increased function (hyperfunction)
- Adrenal **medulla** functional disorders:
 - Reduced function (hypofunction)
 - Increased function (hyperfunction)

Adrenal cortex function disorders

- **Hypofunction:**
 - **Primary level:** deficiency of cortisol and aldosterone
 - **Secondary Level:** only cortisol deficiency
(Important Difference)
- **Hyperfunction:**
 - **Cortisol:** hypercorticism (Cushing's syndrome)
 - **Aldosterone:** hyperaldosteronism (Conn's sy)
 - **Androgen:** adrenal virilism

Hypofunction of the adrenal glands cortex

Hypocorticism

- **Lack of adrenal cortex hormone secretion**
- **Division:**
- according to the **level of the lesion**
 - Primary - defect at the level of the adrenal cortex
 - Secondary - defect at the pituitary/hypothalamus level (inadequate secretion of ACTH)
- **By duration**
 - Acute
 - Chronic
- **Division according to the presence of diseases of other endocrine glands**
 - Isolated
 - As part of pluriglandular autoimmune insufficiency

Primary hypocorticism

Etiology of primary adrenal insufficiency:

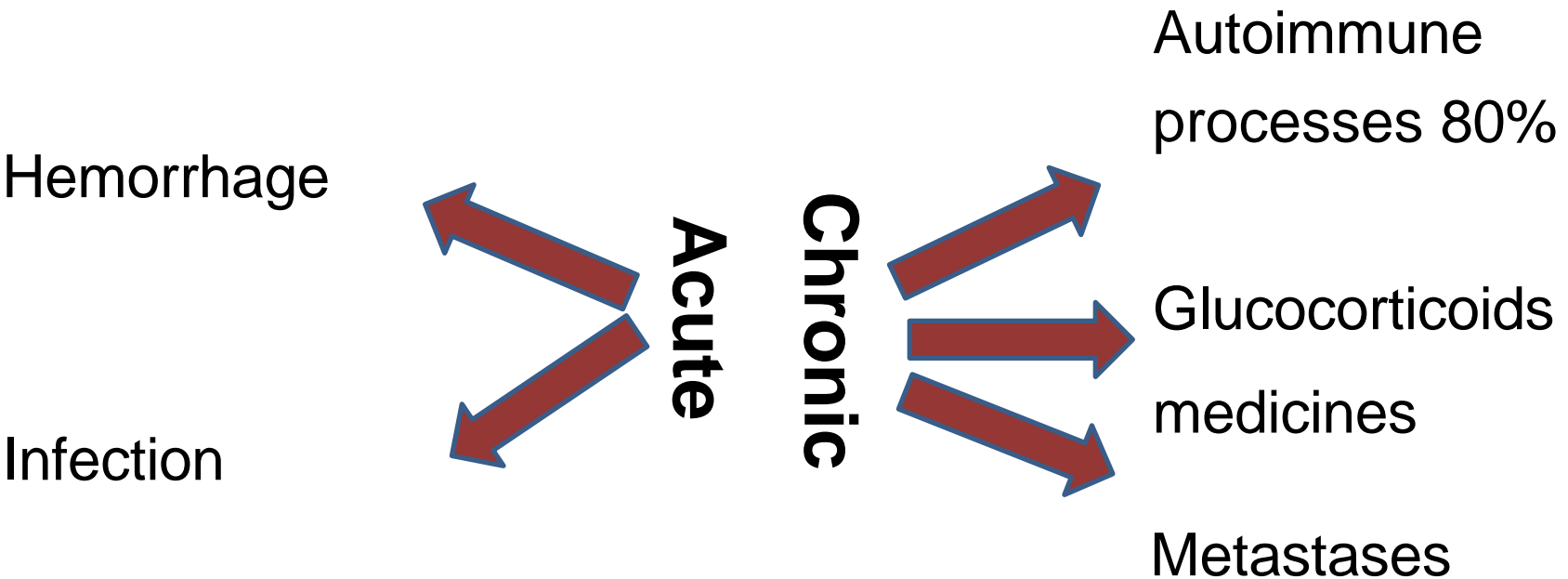
- **Anatomical destruction of the adrenal gland** (acute or chronic)
 - Idiopathic (autoimmune)
 - Surgical intervention
 - Infections (TB, fungi, viruses – AIDS)
 - Hemorrhage
 - Metastases
- **Metabolic inefficiency in hormone production**
 - Congenital adrenal hyperplasia
 - Enzyme inhibitors (Ketoconazole)
 - Cytostatics
- **ACTH-blocking antibodies**
- **ACTH receptor gene mutations**
- **Congenital adrenal hypoplasia**

Secondary hypocorticism

Etiology of secondary adrenal insufficiency:

- Hypopituitarism caused by **hypothalamic-pituitary disorders**(lesions, non-secreting tumors)
- Suppression of the hypothalamic-pituitary-adrenal axis
 - **Exogenous** administration of glucocorticoids (for therapeutic purposes when used for more than 21 days)
 - **Endogenous** (relative - after removal of adrenal tumors in hypercorticism - "dormant adrenal syndrome")

Etiology of the primary acquired hypocorticism

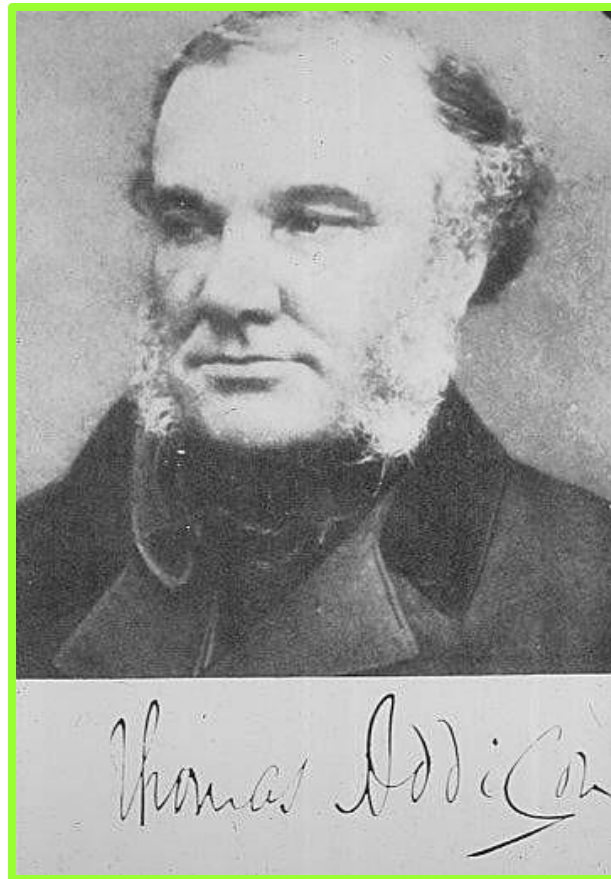


Addison's disease

(primary chronic hypocorticism)

- For the first time Dr Thomas Addison in the middle of the 19th century
- Incidence 0.4-1 per 100,000 people
- The most common cause:
 - autoimmune destruction of adrenal glands
 - earlier: TBC
- Can be found at all age groups
- Equally represented between the sexes
- Adrenal insufficiency occurs when it breaks down 90% of the adrenal cortex

MD Thomas Addison



Addison's disease: pathophysiological disorders

- **Low values (primary) of aldosterone and cortisol**
 - Decreased concentration of Na^{+1} and increased K^{+1} concentration in the blood, with metabolic acidosis
 - Hypovolemia, dehydration, prerenal form of azotemia (increased urea concentration)
 - Hypoglycemia occurs
 - Weakness, fatigue, muscle weakness, muscle pain, nausea, vomiting, anorexia, weight loss
 - Often positive anti-adrenal antibodies
- **Compensatory increased values of renin and ACTH**
 - Hyperpigmentation of the skin and mucous membranes

Addison's disease: pathophysiological disorders

- In the **early stages of the disease** hormone secretion:
 - sufficient in basal conditions,
 - insufficient in case of increased demands under stress (reduced functional reserve) (during infection, injury, surgical procedures)
- **In the later stages with the development of the disease:**
secretion of hormones is insufficient even at basal conditions
 - the most severe consequences due to lack mineralocorticoids: Na^{+1} deficiency and hypovolemia, which can lead to hypovolemic shock, with hyperkalemia and metabolic acidosis)

Addison's disease: pathophysiological disorders

- **Decreased secretion of cortisol:**
 - **general weakness** and emotional lability
 - reduced gluconeogenesis and increased sensitivity on insulin: **morning hypoglycemia**
 - loss of appetite and body weight
- **Increased secretion of peptides arising from pro-opio-melanocortin** (only in primary form of disease):
 - **Hyperpigmentation of the skin and mucous membranes of the mouth can be found**

Addison's disease: pathophysiological disorders



Primary and secondary hypocorticism: main differences

- **Primary:**

- Creation disorder mineralocorticoids and glucocorticoids
- Increased secretion of ACTH (compensation)
- With increased secretion of peptides arising from pro-opio-melanocortin (MSH), **hyperpigmentation of** skin and mucous membranes in the oral cavity

- **Secondary:**

- Disturbance of secretion mainly glucocorticoids, without mineralocorticoid secretion disorders
- No increase in ACTH and MSH (without **hyperpigmentation**)

Acute adrenal crisis (Addison's crisis)

- **Sudden manifested hypocorticism**
- In persons with reduced function of adrenal glands, even with relatively little physical or mental stress
- **Complaints:**
 - Sudden, penetrating pain in the lower back, stomach and legs
 - Vomiting, diarrhea and dehydration
 - Arterial hypotension and hypovolemic shock
 - Hypoglycemia
 - Disturbance of consciousness
- **Fatal outcome**, if not diagnosed and treated

Secondary hypocorticism

- **Causes**
 - isolated pituitary hormone deficiency **ACTH**
 - isolated hypothalamic hormone deficiency **CRF**
 - **lesions of the hypothalamus and pituitary gland** (tumors, infection, granulomas)
 - **Postpartum** (Sy Sheehan)
 - **exogenous application of glucocorticoids**
- **Aldosterone level** is almost normal (RAA system)
- **Manifestations:**
 - dominate the disorder due to lack of cortisol,
 - no hyperpigmentation
 - there are no consequences of aldosterone deficit or renin spike

Congenital adrenal hyperplasia (CAH)

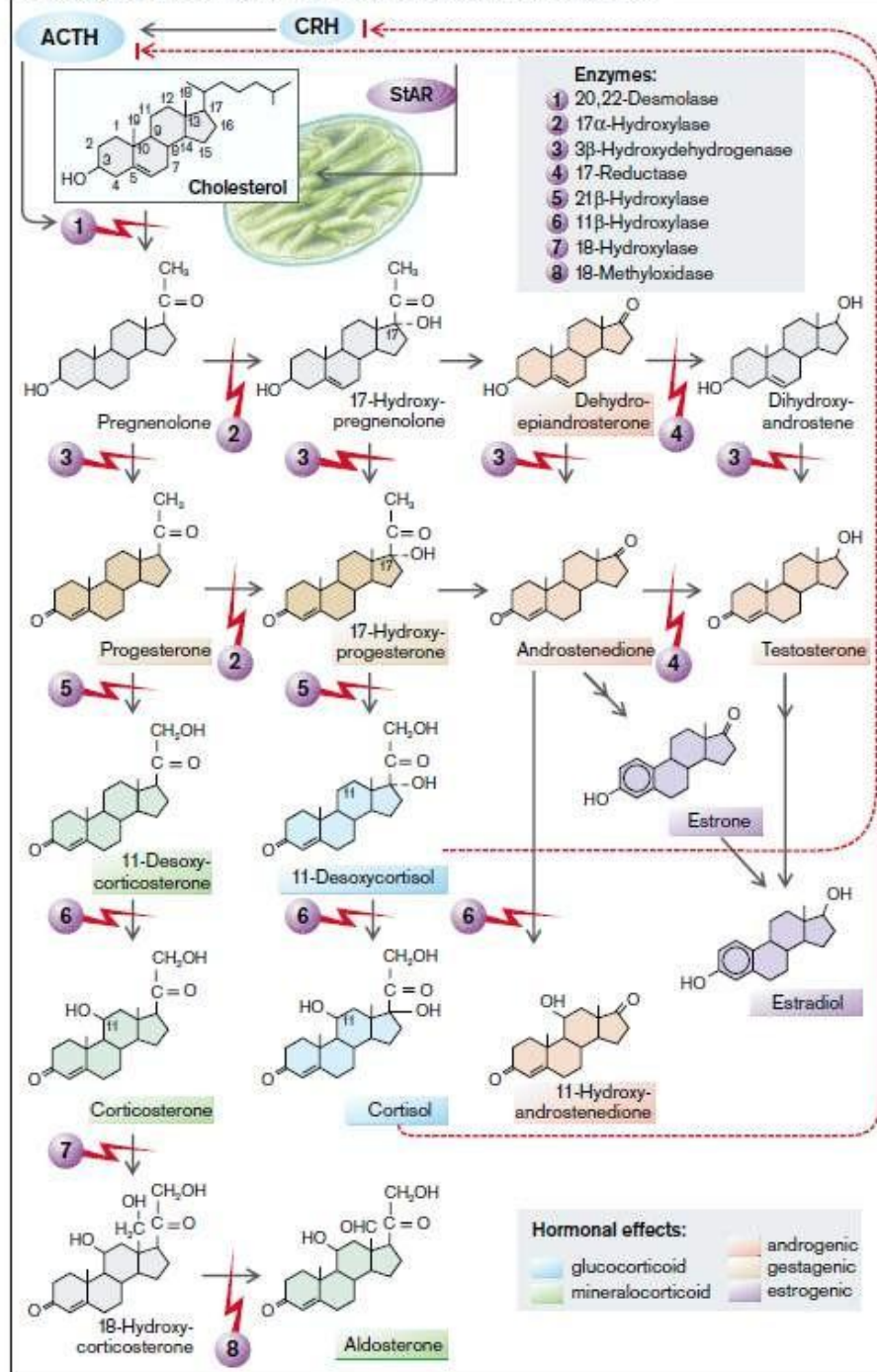
- Condition accompanied by reduced concentration and/or activity of one of **enzyme needed for the synthesis of steroid hormones** in the adrenal cortex
- **Hereditary autosomal recessive diseases**

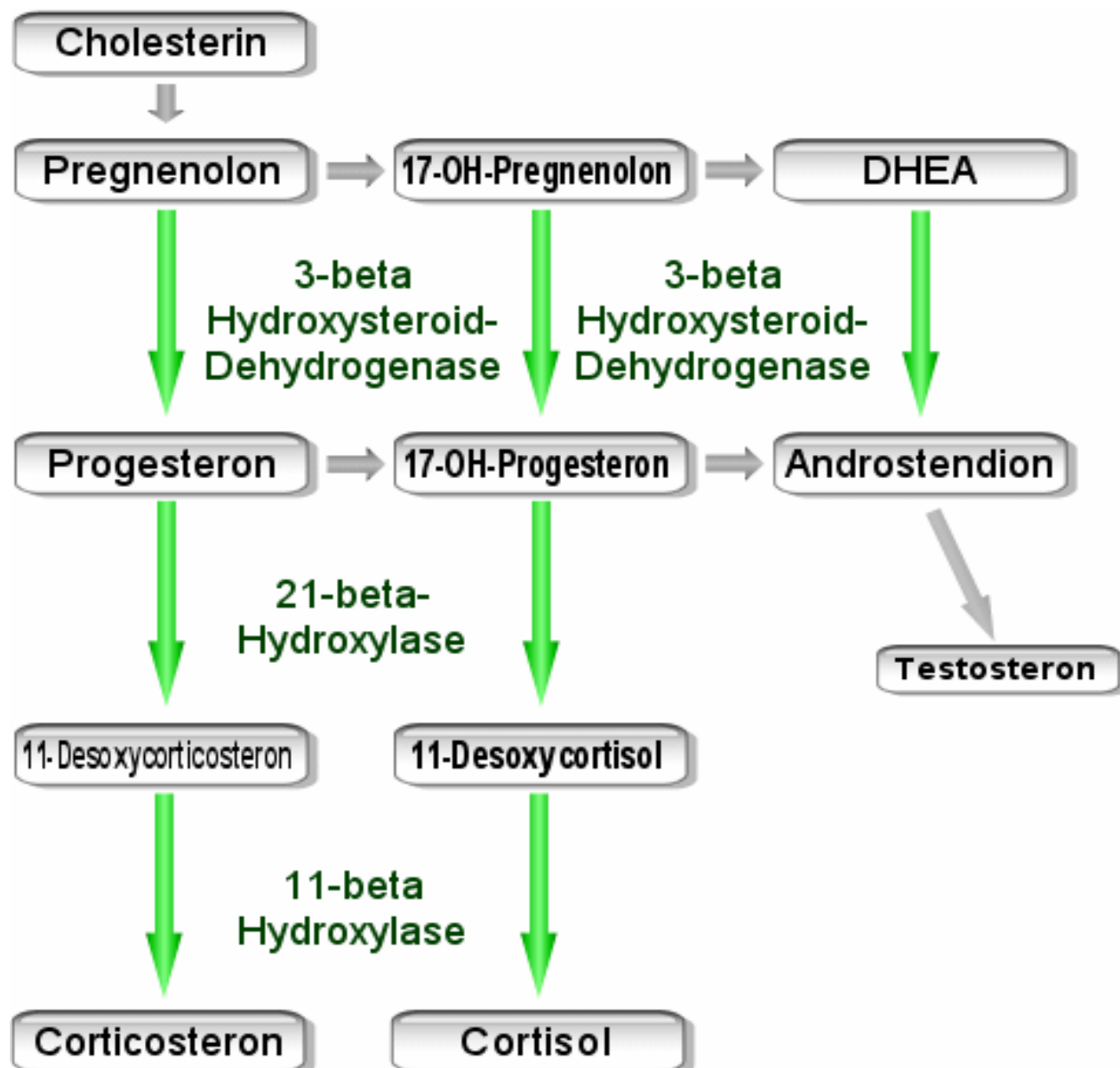
Congenital adrenal hyperplasia (CAH)

Pathogenesis:

- Concentration is reduced **cortisol** in plasma (due to the deficiency of the enzyme necessary for its synthesis)
- Concentration is increased **ACTH** (negative feedback)
- **Hyperplasia** adrenal cortex
- **Increased synthesis of steroids** that is synthesize **before the enzyme block**
- Clinical presentation **depends from the type of disorders** (missing enzyme)

A. Enzyme Defects in Formation of Adrenocortical Hormones





Congenital adrenal hyperplasia (CAH)

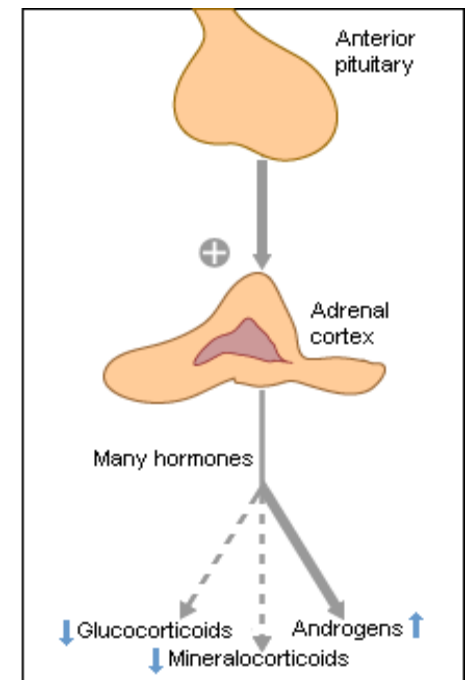
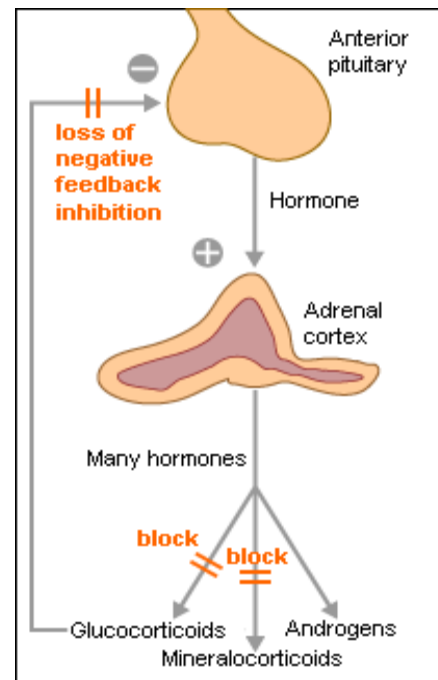
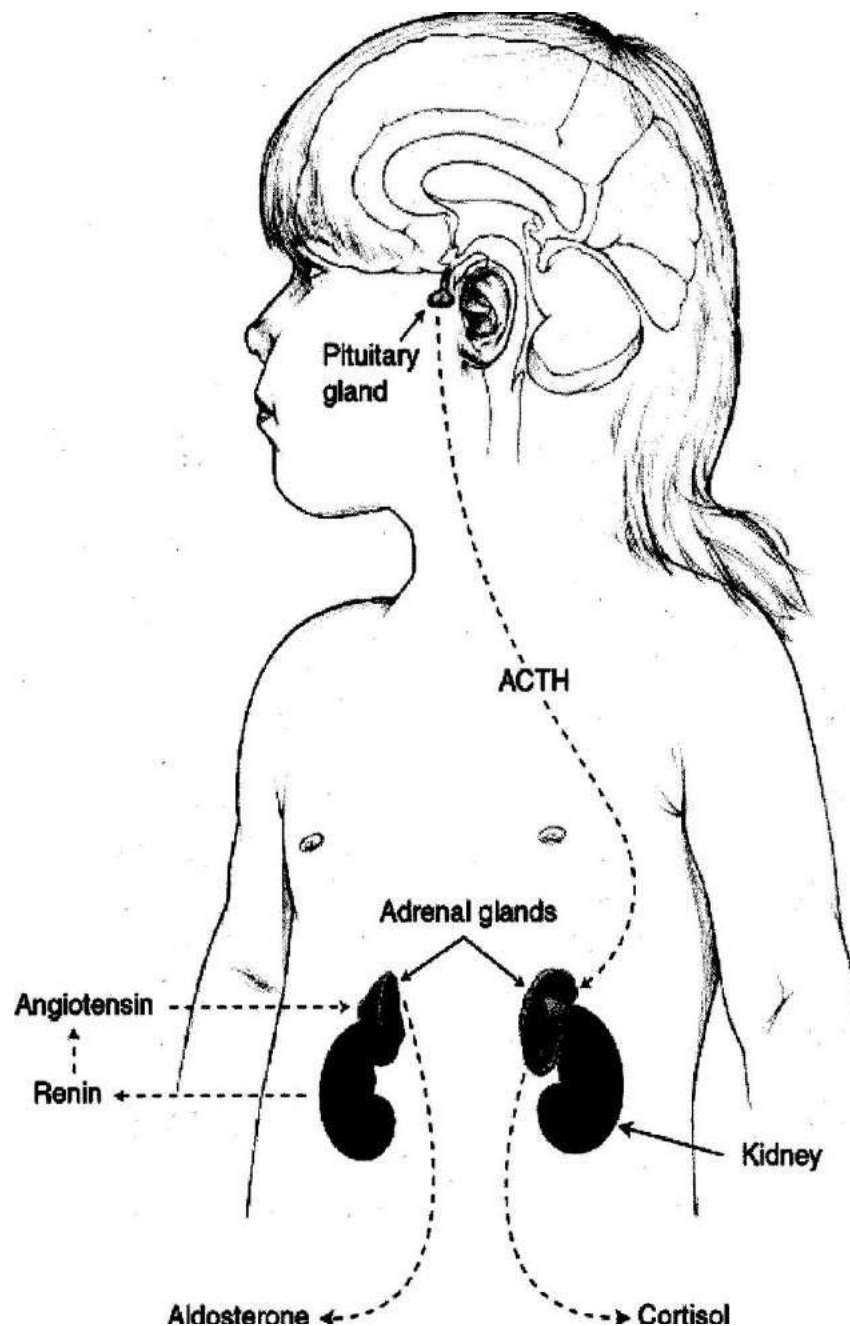
Forms of the disease:

- **Deficiency of 21-hydroxylase**
- **Deficiency of 11-beta hydroxylase**
- **Deficiency of 17-alpha hydroxylase**
- **Deficiency of 3-beta hydroxysteroid dehydrogenase**
- Aldosterone synthase deficiency

Congenital adrenal hyperplasia (CAH)

Deficiency of 21-hydroxylase

- The most common form (90%)
- Enzyme 21-hydroxylase is crucial for the synthesis **glyco and mineralocorticosteroids**
 - With a **complete block in the secretion**, the synthesis of both cortisol and aldosterone is reduced
 - With a **incomplete block in the secretion**, the synthesis of cortisol is reduced
- Because of **reduced cortisol concentrations**:
 - negative feedback is activated,
 - ACTH concentration increases,
 - adrenal hyperplasia occurs
 - the synthesis of adrenal androgens and others metabolite (17-OH progesterone) increased



**Enzyme deficiency
21-hydroxylase
blocks production
glucocorticoids and
mineralocortico-**

and that

**Cortisol is low and
adenohypophysis is not
inhibited**

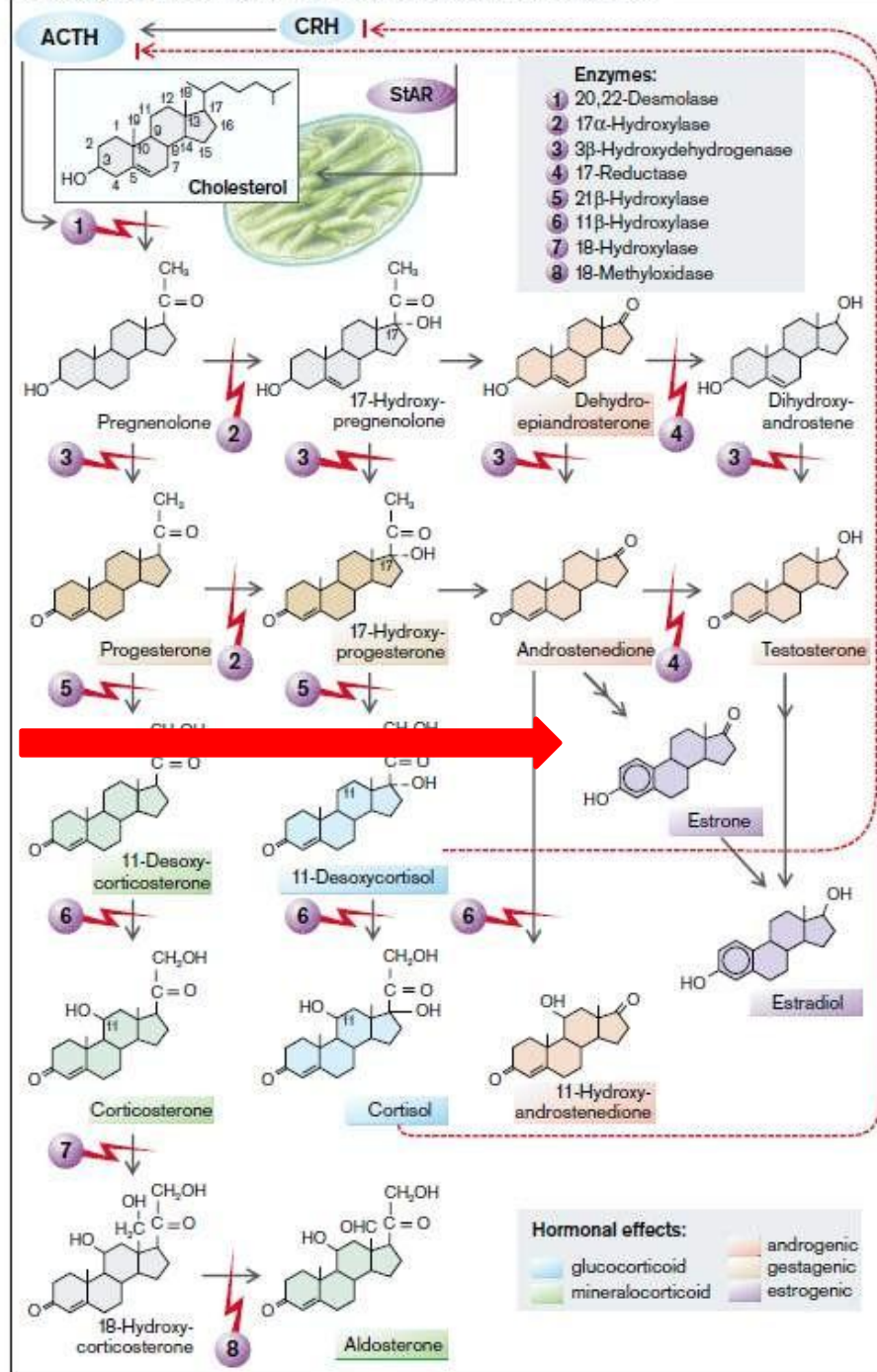
That's why the adenohypophysis
produces a larger one
amount of ACTH to
stimulated the bark
adrenal gland. The bark
can only yes
produces androgens,
which are located in
high
concentration. The bark
adrenal gland
hypertrophy.

Congenital adrenal hyperplasia (CAH)

Consequences of 21-hydroxylase deficiency:

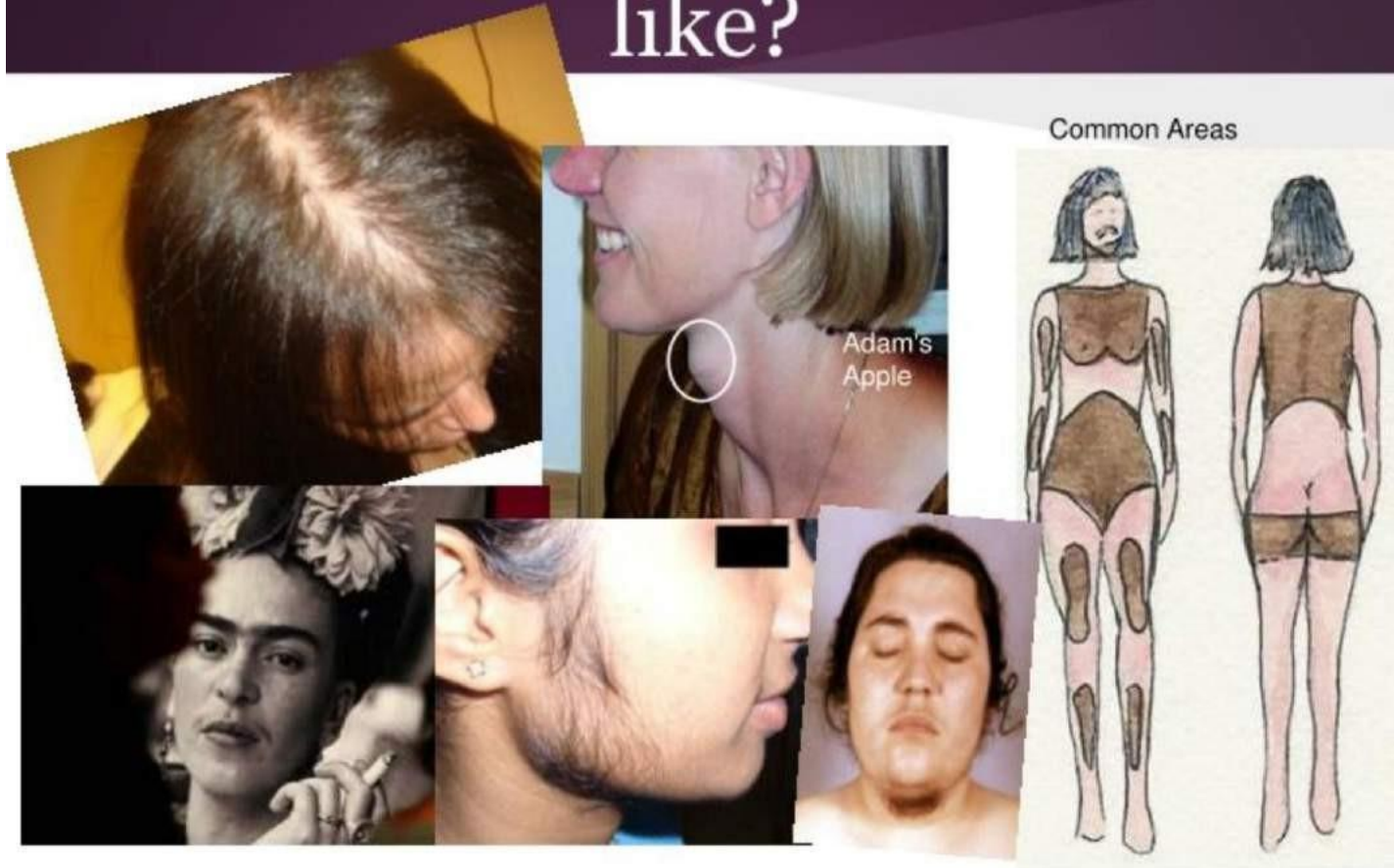
- **Females:** intrauterine virilization of external genital organs of fetus (**pseudohermaphroditism**)
- **Male:** false/pseudo precocious puberty in boys
- **Both sexes:** adrenal crisis with salt loss, accelerated growth of long bones with premature closure of the epiphyses (eventual lower growth)

A. Enzyme Defects in Formation of Adrenocortical Hormones



Adrenal virilism

What does Virilism look like?

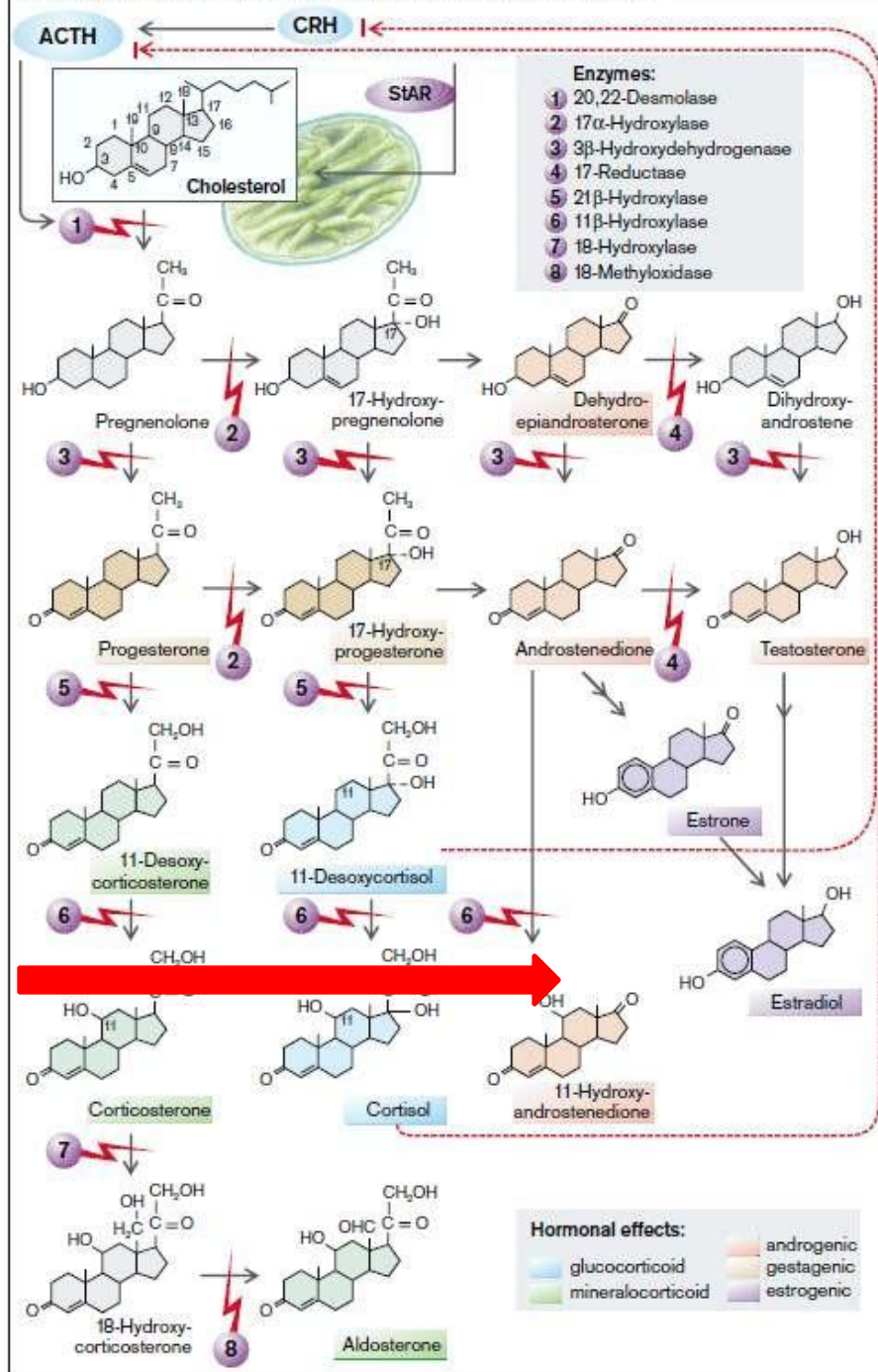


Congenital adrenal hyperplasia (SAN)

11-hydroxylase enzyme deficiency

- 11 hydroxylation is **the last step** in the cortisol synthesis
- **Consequences of the 11-hydroxylase deficiency:**
 - cortisol synthesis is reduced,
 - ACTH grows,
 - 11-deoxy-steroids are increasing
- Clinical manifestations:
 - hypertension
 - masculinization

A. Enzyme Defects in Formation of Adrenocortical Hormones



Hyperfunction of the adrenal glands cortex

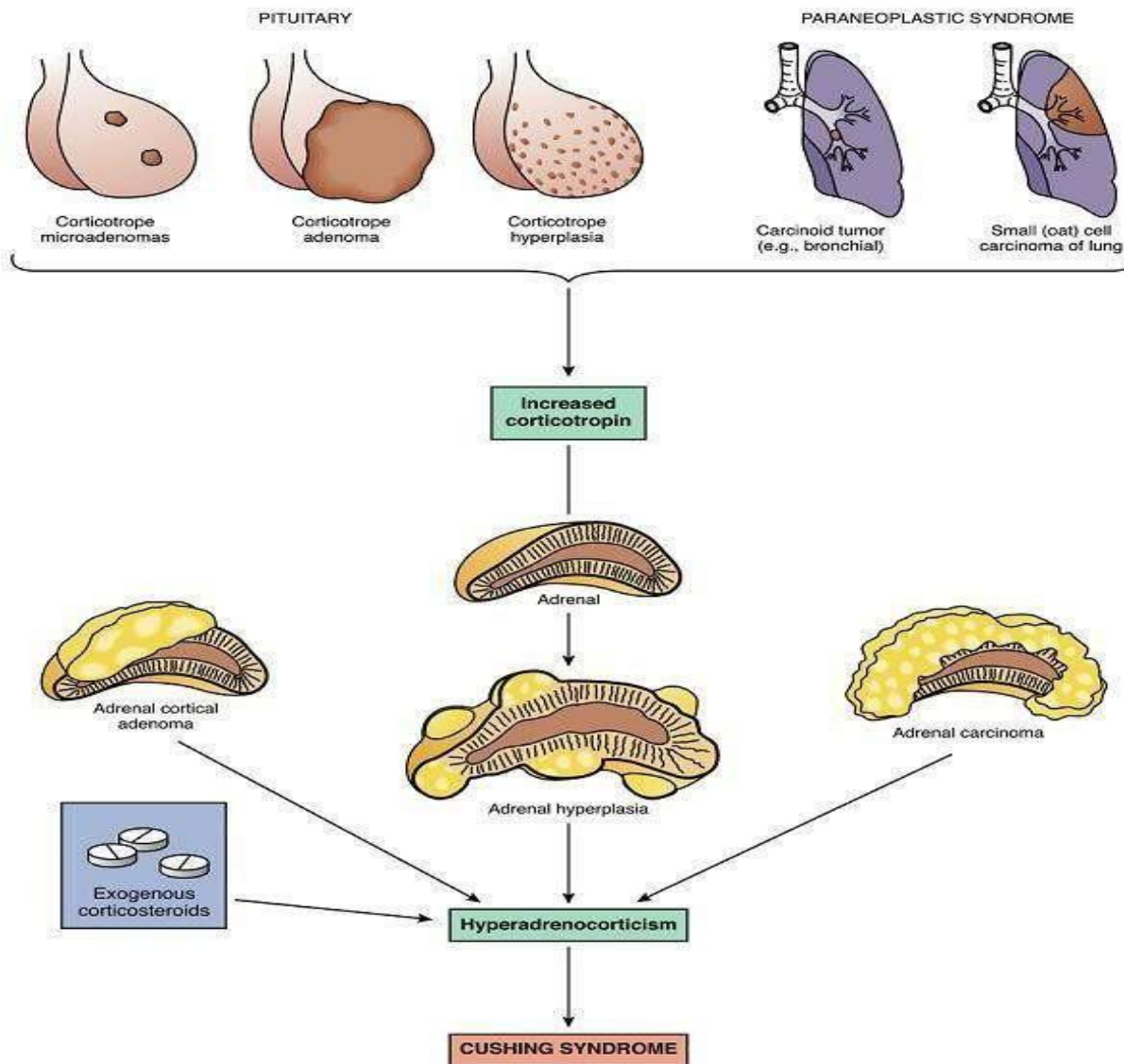
Cortical hyperfunction of the adrenal glands

- **Increased production of cortisol:**
hypercorticism (Cushing Sy \neq Cushing Mb)
- **Increased production of aldosterone:**
aldosteronism (Conn's sy)
- **Increased androgen production:**
adrenal virilism (adrenogenital sy)

Cortical hyperfunction of the adrenal glands

Cushing's syndrome: etiology

- **ACTH-dependent hypercorticism** (Cushing's disease - Cushing Mb)
 - Production ACTH from **pituitary gland**
 - **Ectopic production of ACTH or CRF (Carcinoma of the bronchus and pancreas, carcionoid)**
- **ACTH independent hypercorticism (primary)**
 - Macronodular hyperplasia
 - Micronodular hyperplasia
 - Adrenal adenomas and carcinomas
 - Iatrogenically therapeutic



Cushing's syndrome

Pathogenesis of Cushing's syndrome:

- **Catabolism of connective tissue**

(fatigue, muscle weakness, stretch marks, petechiae, hematomas, osteoporosis)

- **Metabolic disorders**

(hyperglycemia, dyslipidemia, metabolic alkalosis, hypokalemia)

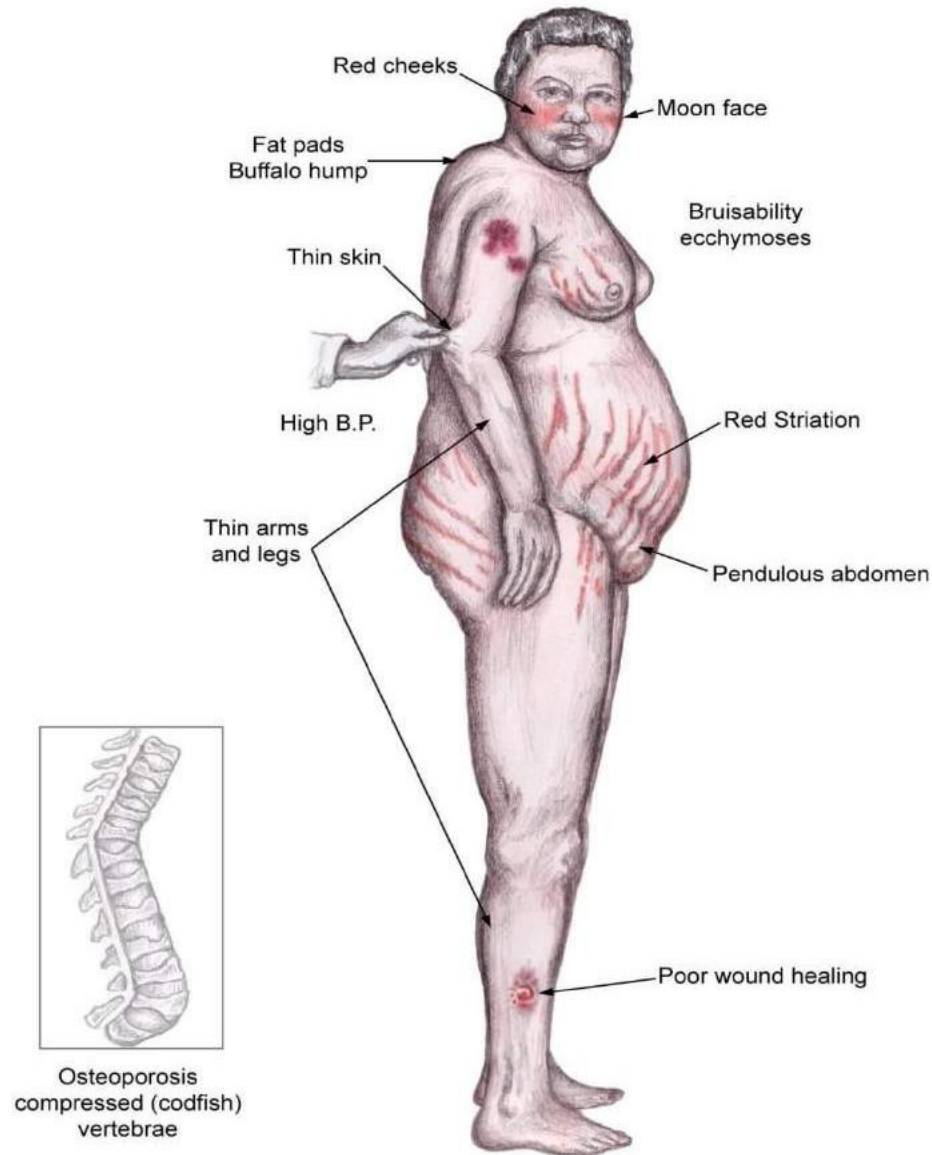
- **Fat tissue redistribution**

(centripetal obesity, facies lunata, buffalo torso)

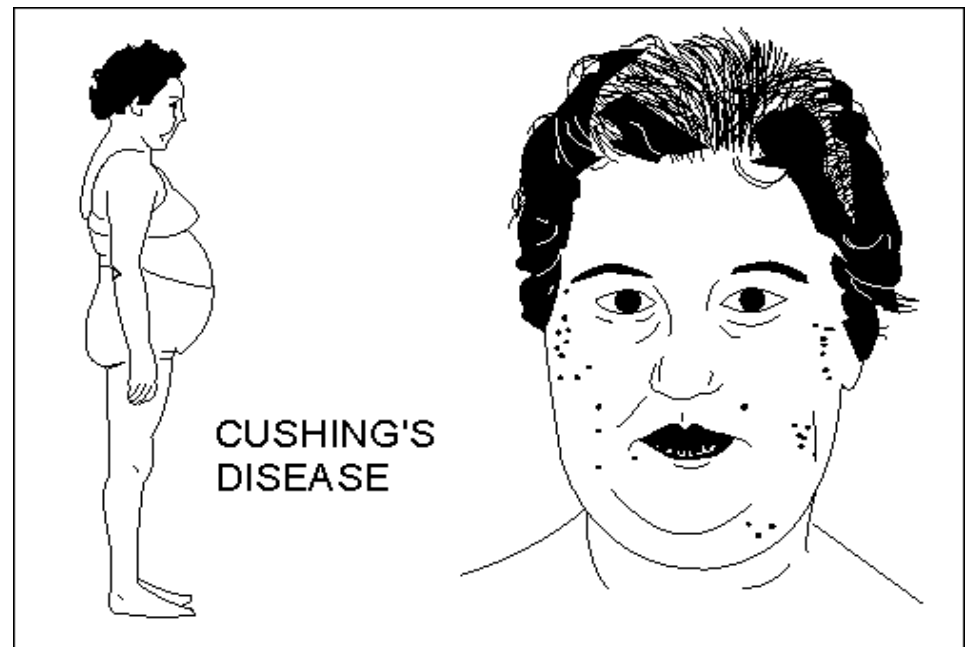
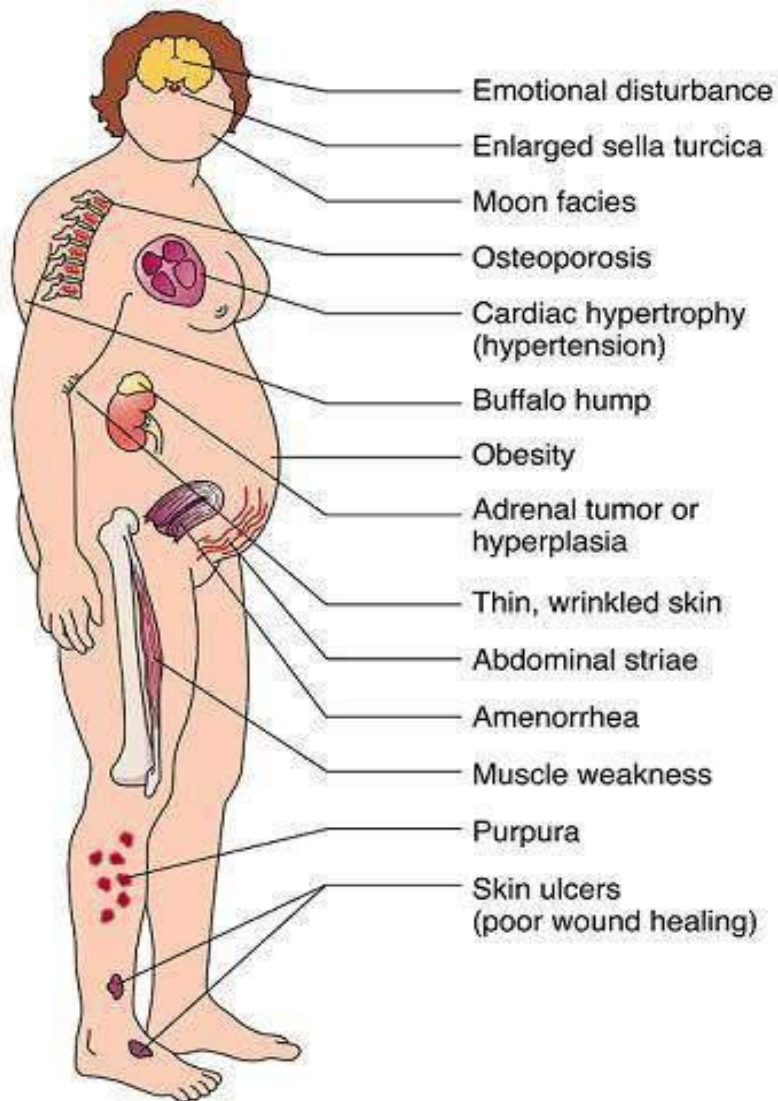
- **Other:**

- HTA, emotional changes, androgenization of women, tendency to infections

Clinical manifestations



Clinical manifestations



Hyperaldosteronism

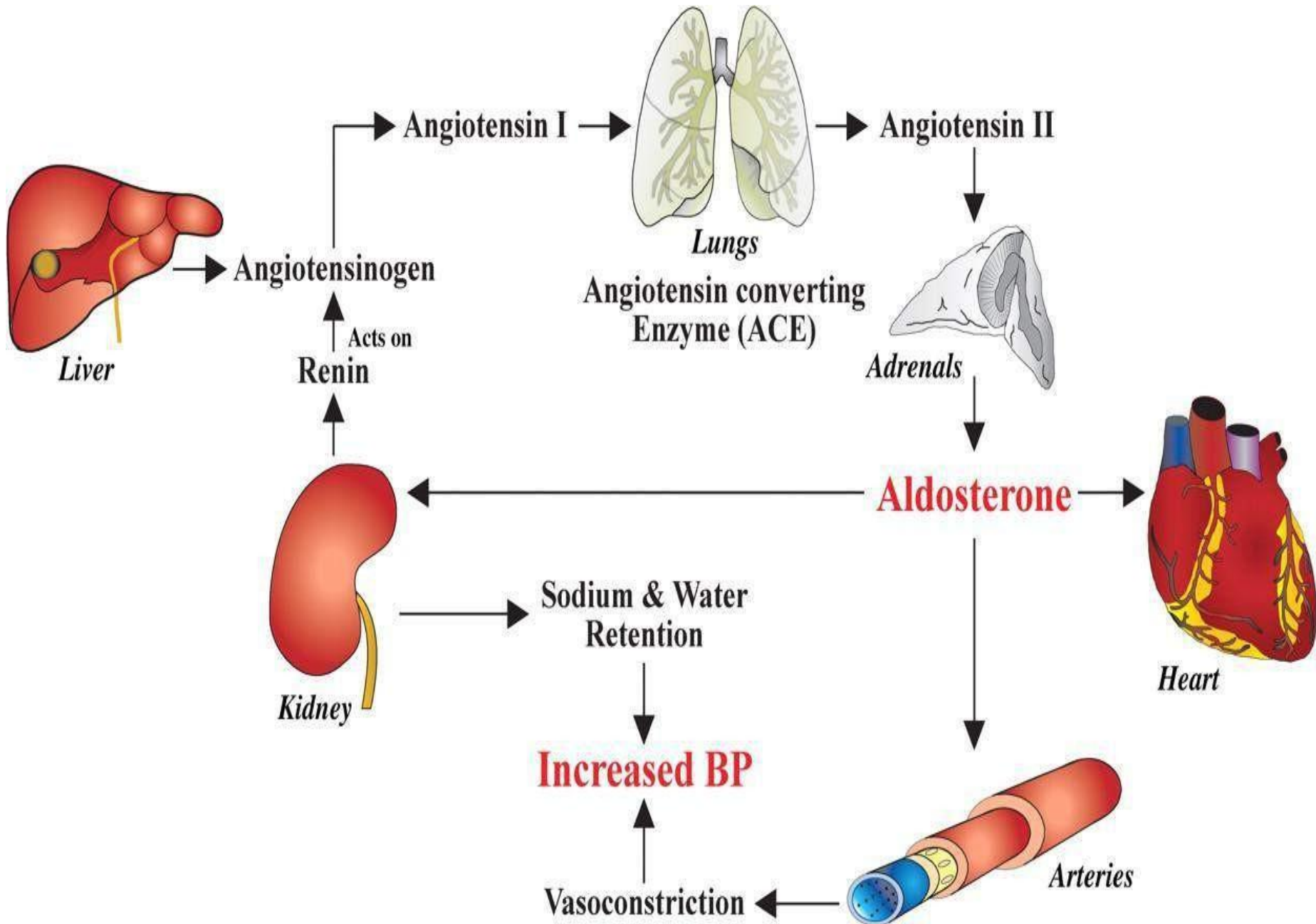
- **Hyperproduction of mineralocorticoids (aldosterone)**
- Etiology:
 - Primary
 - Secondary
- Pathophysiology
 - **Primary:** mineralocorticoid hyperproduction because disorders in the adrenal cortex (renin activity is compensatory reduced)
 - **Secondary:** hyperproduction of mineralocorticoids due to increased renin activity (hypovolemia, Tu of the juxtaglomerular apparatus)

Primary hyperaldosteronism (Conn's syndrome)

- **Hyperproduction of mineralocorticoids**
- **Etiology:**
 - Unilateral and bilateral adenoma - M. Conn (65-70%)
 - Bilateral hyperplasia (30%)
 - Adenocarcinoma (<1%)
 - Idiopathic
- **Pathophysiology**
 - Diastolic arterial hypertension without edema
 - Hypokalemia (sometimes hyponatremia)
 - Metabolic alkalosis

Symptoms and signs of primary hyperaldosteronism

- **Hypersecretion of aldosterone**- consequences:
 - Hyponatremia
 - Hyperchloremia
 - Hypervolemia
 - Hypokalemic alkalosis that manifests itself:
 - episodes of muscle weakness
 - paresthesias
 - transient paralysis
 - tetany
 - Diastolic arterial hypertension with headache
 - Hypokalemic nephropathy with polyuria and polydipsia



The content

- Parathyroid function disorders gland (hypoparathyroidism and hyperparathyroidism)
- Adrenal cortex function disorders (decreased and increased secretion of aldosterone, cortisol and androgens)
- **Adrenal medulla function disorders (phaeochromocytoma)**
- Disorders of gonadal function (reduced i increased testicular function, decreased and increased ovarian function)

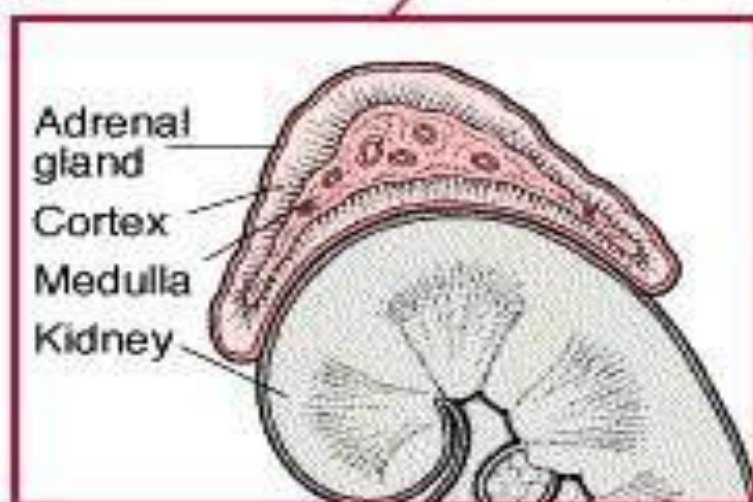
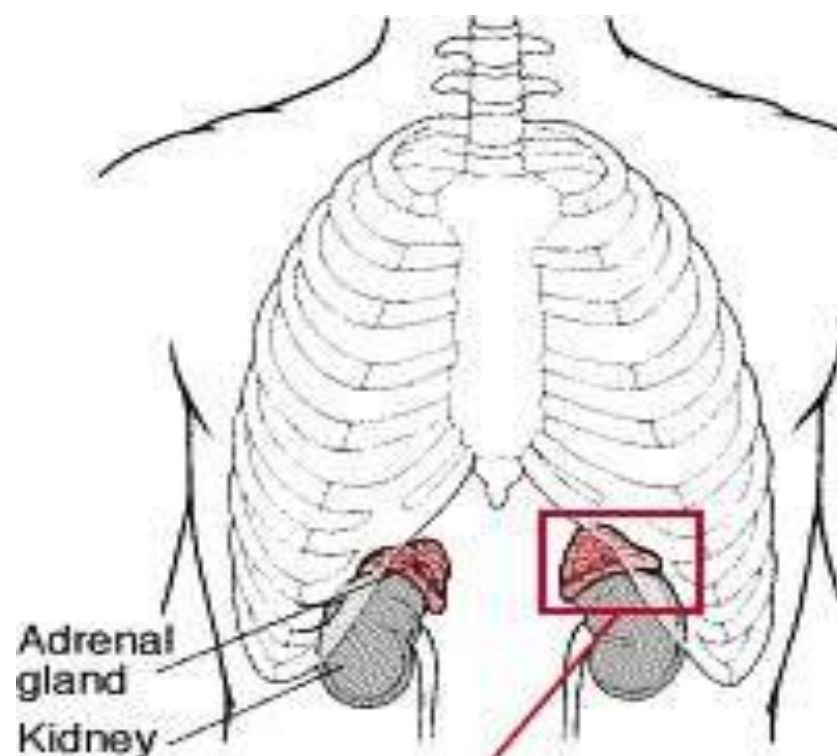
Adrenal medulla function disorders

- **Hyperfunction of the adrenal medulla**
 - pheochromocytoma
- **Hypofunction of the adrenal medulla**
 - without significant clinical significance

Adrenal medulla function

disorders: pheochromocytoma

- **Pheochromocytoma** is a tumor of neuro-ectodermal origin of secreting cells **catecholamines** (sympathetic-adrenal system)
- The tumor may be located **in the adrenal medulla** or in other parts of **sympathetic nervous system** (extraadrenal pheochromocytoma - paraganglioma)



Adrenal medulla function disorders: pheochromocytoma

Epidemiology:

- The incidence is 0.8 per 100,000 patients/year
- **0.1 to 1% of patients with arterial hypertension** has pheochromocytoma
- Half of the pheochromocytomas are detected at autopsy was not diagnosed for life (due to the specificity (episode) of hormone secretion)

Adrenal medulla function disorders: pheochromocytoma

Etiology

- Sporadic shape
- Hereditary shape (5%)
 - MEN 2A
 - MEN 2B
 - M. Von Hippel-Lindau
 - M. Von Recklinghausen

Adrenal medulla function

disorders: pheochromocytoma

Pathophysiology:

- Secretion of **excessive amounts of catecholamines**
- **Continuously** or **in episodes**
- **All catecholamines** or **some certain species**
 - **Noradrenaline** - hypertension
 - **Adrenaline** - metabolic abnormalities
(glucose intolerance: 10% have DM)
 - **Dopamine**

Pathoanatomy of pheochromocytoma

("10% rule")

- **Localization**

1. **Adrenal medulla (90%)**
2. **Extramedullary (10%)**

- **Unilateral (90%) or bilateral (10%)**

- **Unifocal (90%) or multilocular (10%)**

- **Adult (90%) or juvenile (10%)**

- **Benign (90%) or malignant (10%)**

Adrenal medulla function

disorders: pheochromocytoma

Arterial hypertension (90-100%)

- **Characteristics:**

- permanent ("fixed") approx 50%
- episodic (paroxysmal) approx 30%

- **Paroxysmal attacks:**

- Several times a day to once every several years
- The start: spontaneous or with some provocation (stomach kick, bending over)
- Different clinical picture during the attack (often hyperglycemia and leukocytosis)
- After attacks exhaustion and fatigue

- **Orthostatic hypotension** (due to constantly elevated catecholamine blunted postural reflexes, reduction of extracellular fluid volume, secretion of adrenomodulin)

Pancreas

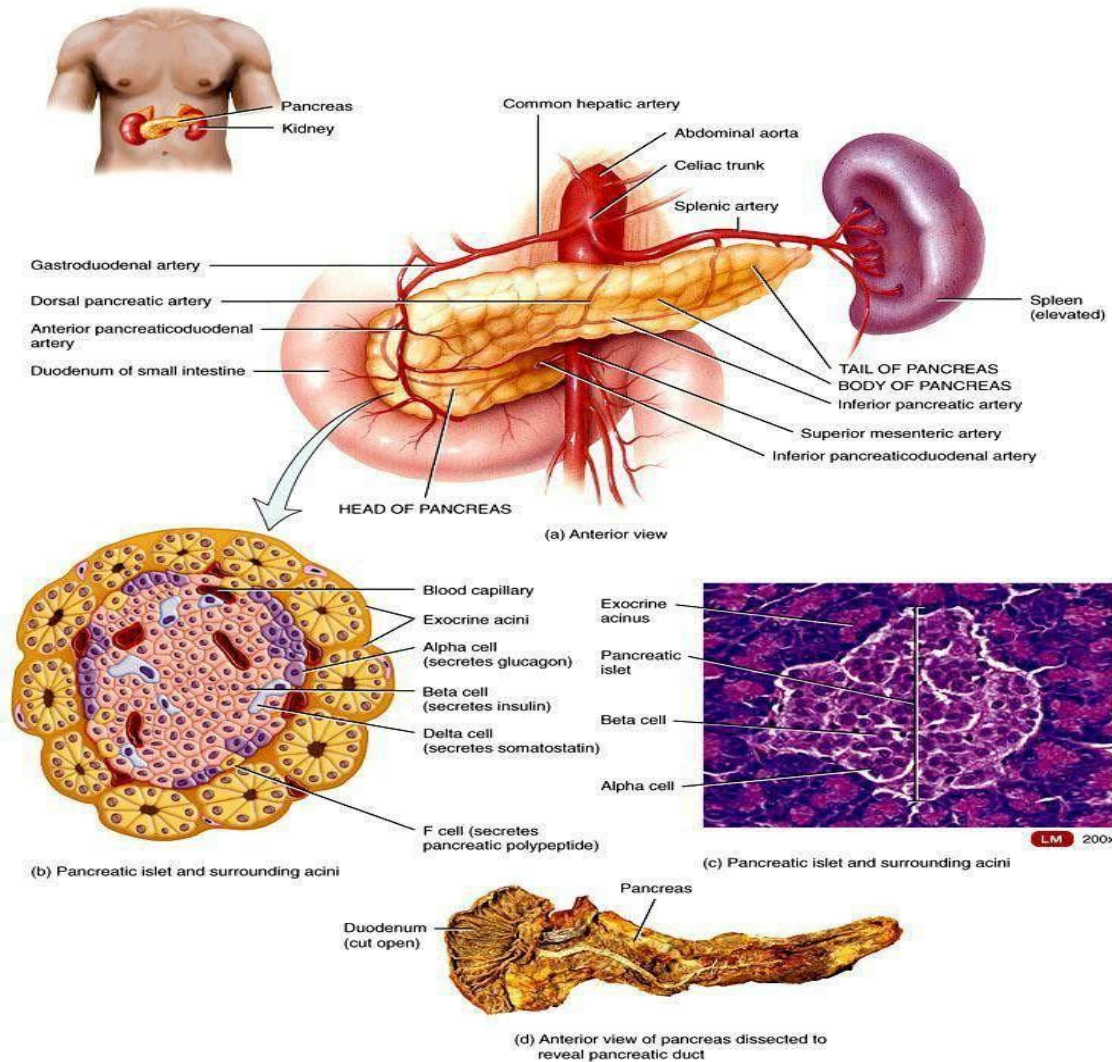


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Pancreas

- It has both exocrine and endocrine function
- Produce digestive enzymes
- Pancreatic islets (Islets of Langerhans)
 - Alpha or α cells secrete glucagon - increase glycemia
 - Beta or β cells secrete insulin - reduce glycemia
 - Delta or δ cells secrete somatostatin - inhibit secretion of both insulin and glucagon
 - F cells secrete pancreatic polypeptide – inhibits somatostatin, contraction of the gallbladder and secretion of pancreatic digestive enzymes

The content

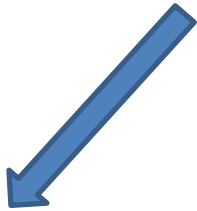
- Parathyroid function disorders gland (hypoparathyroidism and hyperparathyroidism)
- Adrenal cortex function disorders (decreased and increased secretion of aldosterone, cortisol and androgens)
- Adrenal medulla function disorders (phaeochromocytoma)
- **Disorders of gonadal function (reduced i increased testicular function, decreased and increased ovarian function)**

Ovaries and testicles

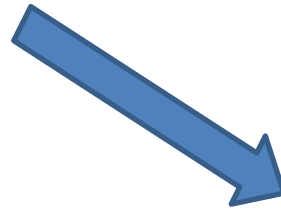
- **Gonads – produce sex cells and hormones**
- **Ovaries** as organs produce **2 estrogens** (estrone and estradiol) and **progesterone**
 - Along with pituitary hormones FSH and LH regulate the menstrual cycle, maintain pregnancy, prepare mammary glands for lactation, maintain secondary sexual characteristics in women
 - **Inhibin** inhibits FSH
 - **Relaxin** is created during pregnancy
- **Testicles** they create **testosterone** - regulates the process spermatogenesis and the creation and maintenance of male secondary sexual characteristics
 - **Inhibin** inhibits FSH

Hormonal control of the testes

- In PUBERTY increases secretion of gonadotropin releasing hormone (GnRH) in the hypothalamus
- In one moment of maturity **GnRH at the level of the adenohypophysis stimulates an increase in the secretion of LH and FSH**



LH stimulates the Leydig cells to **secrete testosterone**



FSH acts indirectly on **process of spermatogenesis**

Androgens in men

- They have an important function in development up to and after puberty

1. Prenatal development and later

1. They stimulate the male pattern of the reproductive system and testicular descent
2. They stimulate the development of external genitalia

2. Development of male sexual characteristics

1. During puberty, they are responsible for the development of male organs and development male secondary sexual characteristics

3. Development of sexual function

1. Androgens contribute to male behavior, spermatogenesis and libido

4. Stimulation of anabolism

1. They stimulate protein synthesis - greater muscle and bone mass in men

Female reproductive cycle

- **Much more complex** compared to men – changes **on several organs at the same time**
 - **The function of this system in women must be harmonized and coordinated (hormonally determined)**
1. **Ovarian cycle** - **series of events in ovaries** which occur during and after oocyte maturation
 2. **Uterine (menstrual) cycle**- simultaneous **series of changes in the endometrium of the uterus** which prepares it for **acceptance** fertilized eggs
 3. **Harmonized ovarian and uterine cycle**

Hormonal regulation of the female reproductive cycle

- **Gonadotropin-releasing hormone (GnRH)**
 - It is secreted in the hypothalamus and controls the ovarian and menstrual cycle
 - Stimulates release of FSH and LH from the adenohypophysis
- **FSH**
 - Initiates growth **follicles**
 - Stimulates ovarian follicles to secrete **estrogens**
- **LH**
 - Stimulates the future **development of ovarian follicles**
 - Stimulates ovarian follicles to **secrete estrogens**
 - Stimulates the thecal cells of the developing follicle to produce **androgenic to make them converted into estrogens**
 - Triggers **ovulation**
 - Enables creation of **corpus luteum** – which produces estrogens, but and **progesterone, relaxin and inhibin**

Hormonal regulation of the female reproductive cycle

- Estrogens (dominant in the first half of MC)

secreted by ovarian follicles

- Enable the development and maintenance of female reproductive organs and secondary sexual characteristics
- Increase protein anabolism, including building stronger bones
- They reduce the level of cholesterol
- They inhibit release GnRH, LH and FSH (can also potentiate)

- Progesterone (dominant in the second half of MC)

- They are secreted **mostly in corpus luteum** (second phase of the cycle)
- Together with estrogens, it works on **preparation and maintenance endometrium for implantation and mammary glands for milk production**
- Inhibits secretion of GnRH and LH

Hormonal regulation of the female reproductive cycle

- Relaxin (in the second part of MC)

- Produced by corpus luteum
- It relaxes the uterus (inhibits contractions of the myometrium for better implantation in the uterus)
- At the end of pregnancy, increases flexibility of pubic symphysis and dilatation of the cervix of the uterus

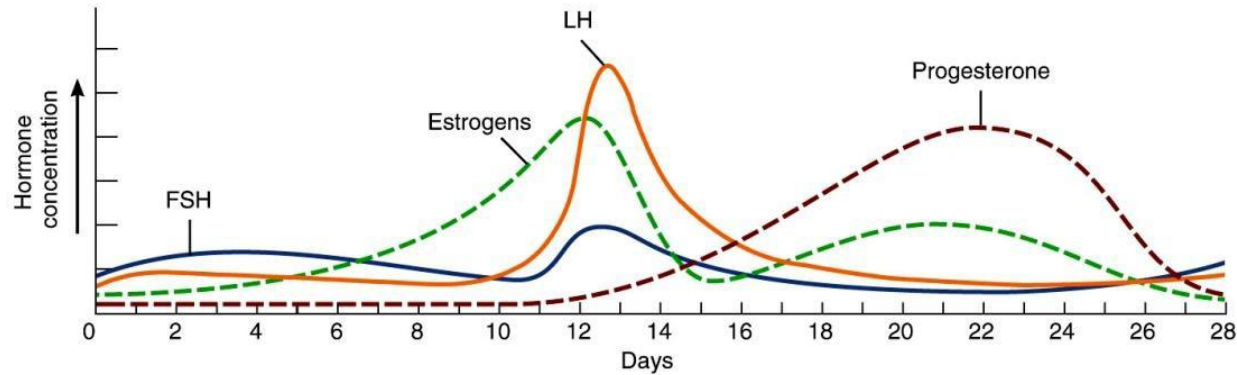
- Inhibin (in the first and second part of MC)

- It is secreted by the granulosa cells of other growing follicles and corpus luteum
- It inhibits secretion of FSH and LH

Hormonal regulation of the female reproductive cycle

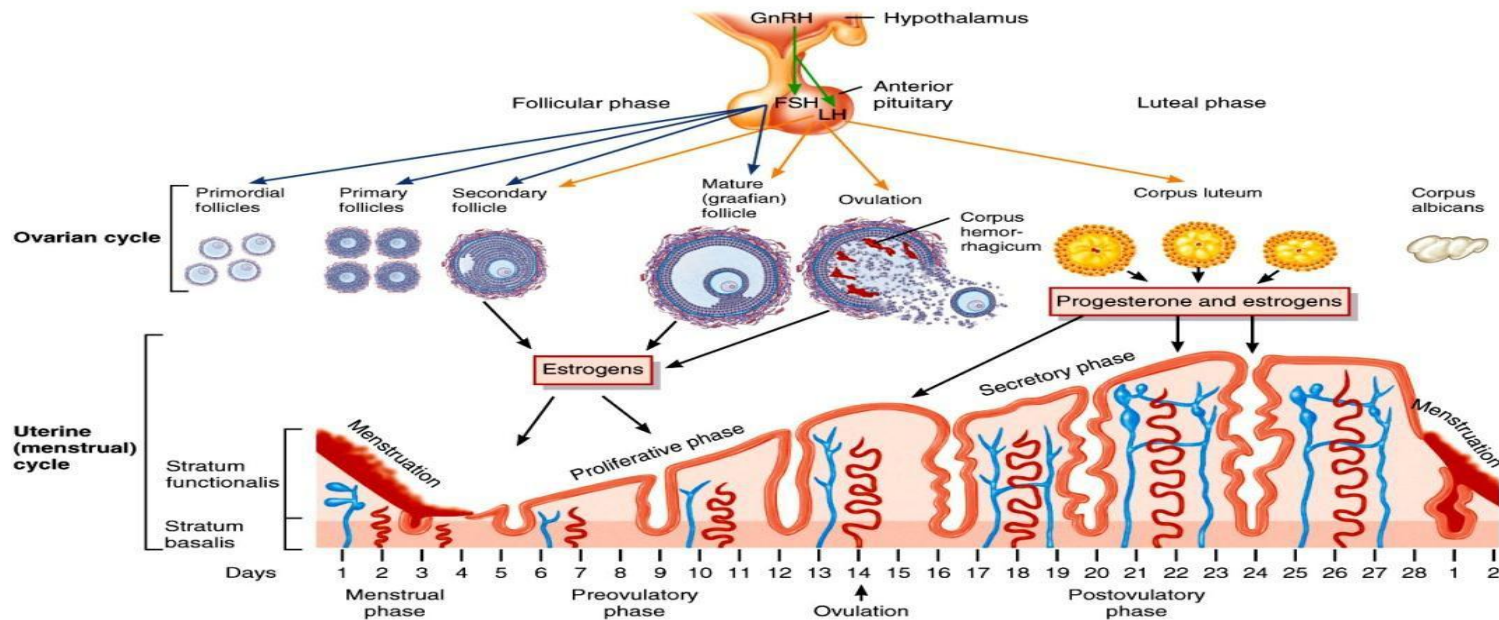
- **Female reproductive cycle:**
 - Typical duration 24-35 days
 - Average duration 28 days
- **The four stages of the reproductive cycle:**
 - Menstrual phase
 - Preovulatory phase
 - Ovulation
 - Postovulatory phase

Hormonal regulation of the female reproductive cycle



(b) Changes in concentration of anterior pituitary and ovarian hormones

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(a) Hormonal regulation of changes in the ovary and uterus

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Menstrual phase

–The first day of menstrual bleeding - the first day of a new cycle

- Events in the ovary:

- Under the influence of FSH, several primordial follicles develop into primary follicles and then into secondary follicles
 - It takes several months
 - Follicles that begin to develop in one cycle can only mature in the following few cycles

- Events in the uterus:

- Menstrual bleeding occurs due to a decrease in estrogen and progesterone levels that stimulate release of **prostaglandin** which lead to **constriction of the spiral arterioles of the uterus**
- Endometrial cells remain **without oxygen** and they begin to decay
- Only the basal layer remains - **stratum basalis**

Preovulatory phase

- The most variable length (7 days and longer)
- Lasts from 6 to 13 days if MC lasting 28 days
- Events in the ovaries
 - Some secondary follicles begin to secrete estrogens and inhibin
 - A dominant follicle is formed – one follicle outgrows all others
 - Estrogens and inhibin secreted from the dominant follicle they have an inhibitory effect on FSH, causing the growth of other follicles to stop

Preovulatory phase

- Normally, one dominant follicle becomes mature, (De Graaf's) follicle

– Events in the uterus

- Estrogens stimulate the recovery of the endometrium from basal layer
- Cells of stratum basale begins to divide to create a new functional layer - stratum functionalis
- The thickness of the endometrium doubles
- In the uterine cycle, **the preovulatory phase is also called the proliferative phase** because the endometrium has proliferated and is ready to accept a fertilized egg

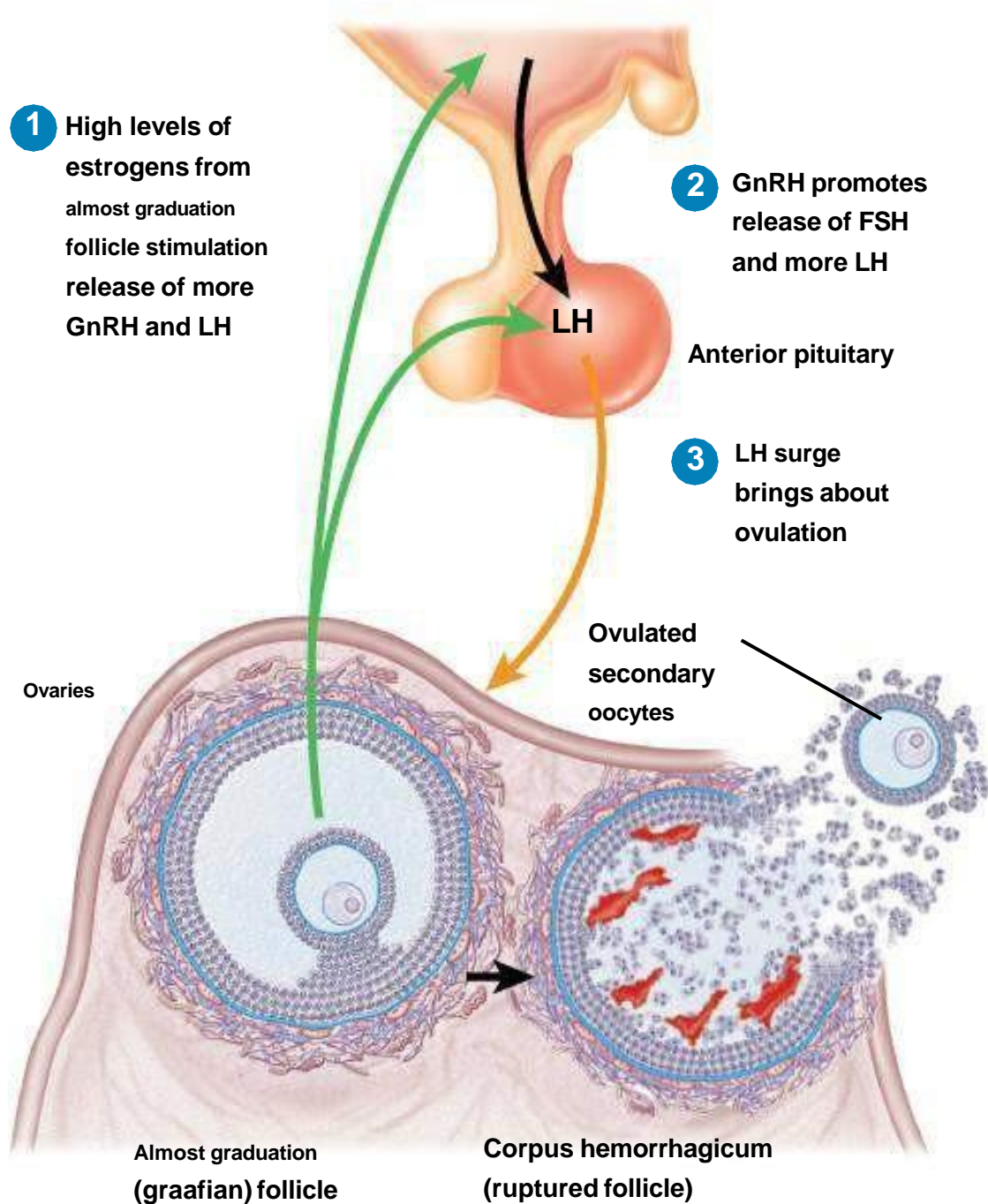
Ovulation

- High levels of estrogen that were secreted during preovulatory phase inhibiting to other hormones, now trigger a positive feedback loop and increase LH and GnRH secretion.
- Rupturing of mature (De Graaf's) follicle and release of secondary oocytes
- **In 14th day (if cycle lasting 28 days)** - more precisely this rupturing occurs 14 days before the end of the cycle (for cycles lasting longer or shorter than 28 days)

1 High levels of estrogens from almost graduation follicle stimulation release of more GnRH and LH

2 GnRH promotes release of FSH and more LH

3 LH surge brings about ovulation



Postovulatory phase

- It has the most constant duration
- Lasts 14 days in a 28-day cycle (days 15-28)
- Events in one of the ovaries
 - After ovulation, mature follicle collapses and creates corpus luteum under the influence of LH
 - Secretes progesterone, estrogen, relaxin and inhibin
 - In the ovarian cycle, this is the luteal phase

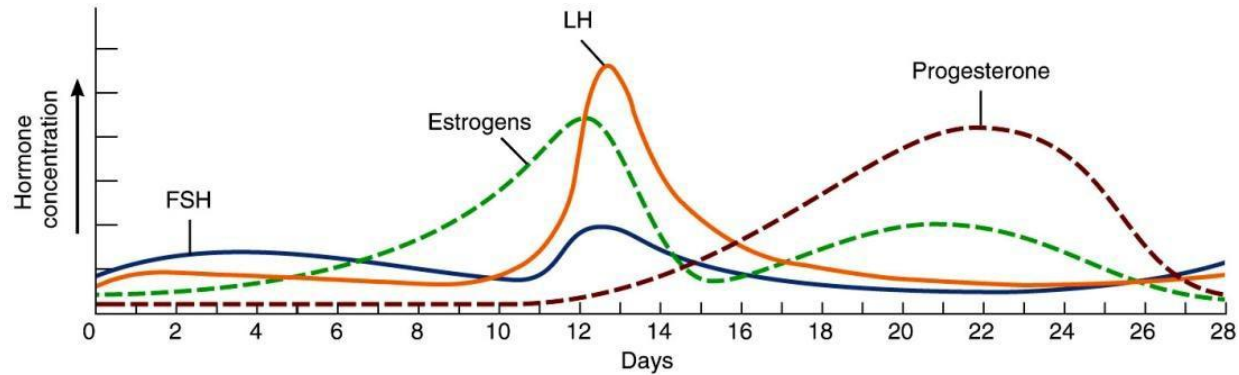
Corpus luteum

- If **oocyte fertilization does not occur**, corpus luteum lasts about 2 weeks
 - **Degenerates in corpus albicans** and levels of **progesterone, estrogen and inhibin decrease**
 - due to the loss of negative feedback **increasing release GnRH, FSH and LH now starts**
 - **increasing release of this hormones** leads to **initiation of new follicle growth** and the beginning of new MC
- If **the oocyte is fertilized**, corpus luteum lasts longer than 2 weeks
 - **Because human chorionic gonadotropin (hCG)** (which is produced by the chorion of the embryo day 8 after fertilization) **stimulates maintenance and operation of the corpus luteum**

Events in the uterus

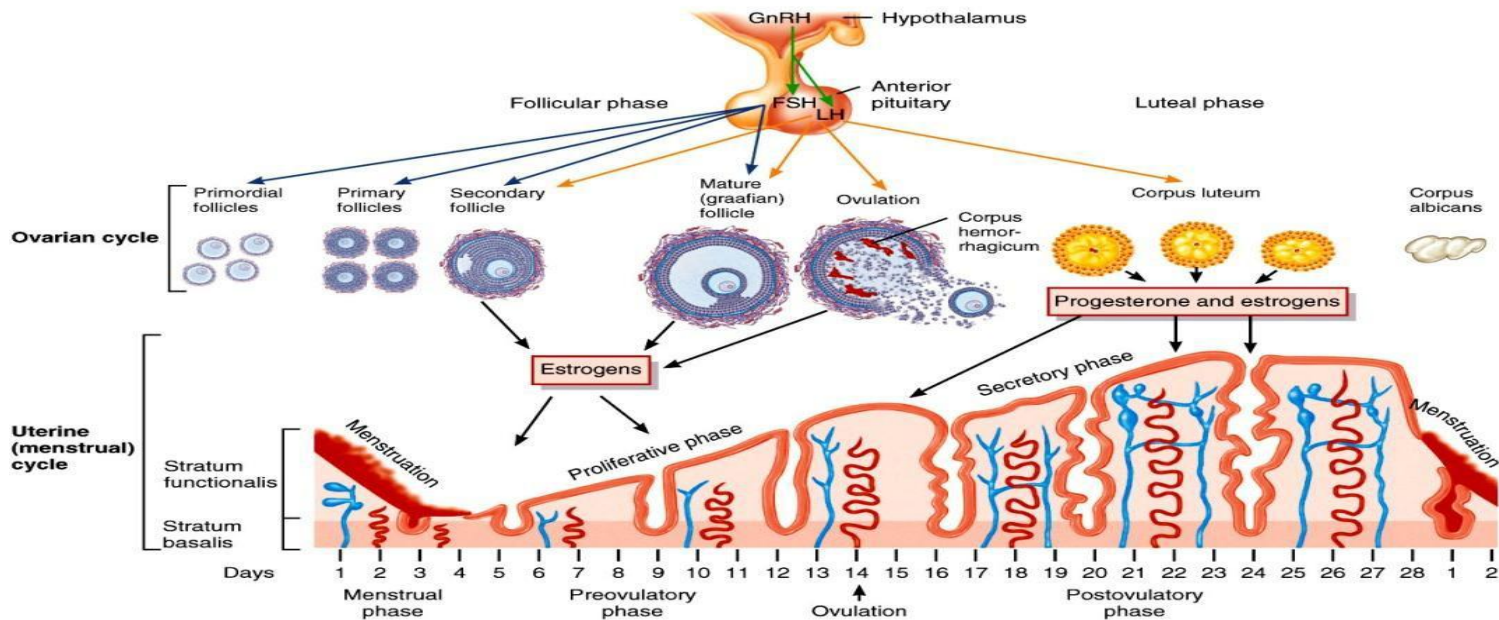
- **Progesterone and estrogen produced by the corpus luteum lead to the growth of the endometrium**
- Due to the secretory activity of the endometrial glands, this phase of the uterine cycle is called **secretory phase**
- **Changes occur until 7 days after ovulation when the fertilized oocyte should be found in the uterine cavity**
- If fertilization does not occur, the progesterone and estrogen levels decrease due to the degeneration of the corpus luteum
- **Drop in estrogen and progesterone concentration brings to deterioration of the endometrium and menstruation bleeding**

Female reproductive cycle



(b) Changes in concentration of anterior pituitary and ovarian hormones

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(a) Hormonal regulation of changes in the ovary and uterus

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Hormonal interactions in the ovarian and uterine cycle

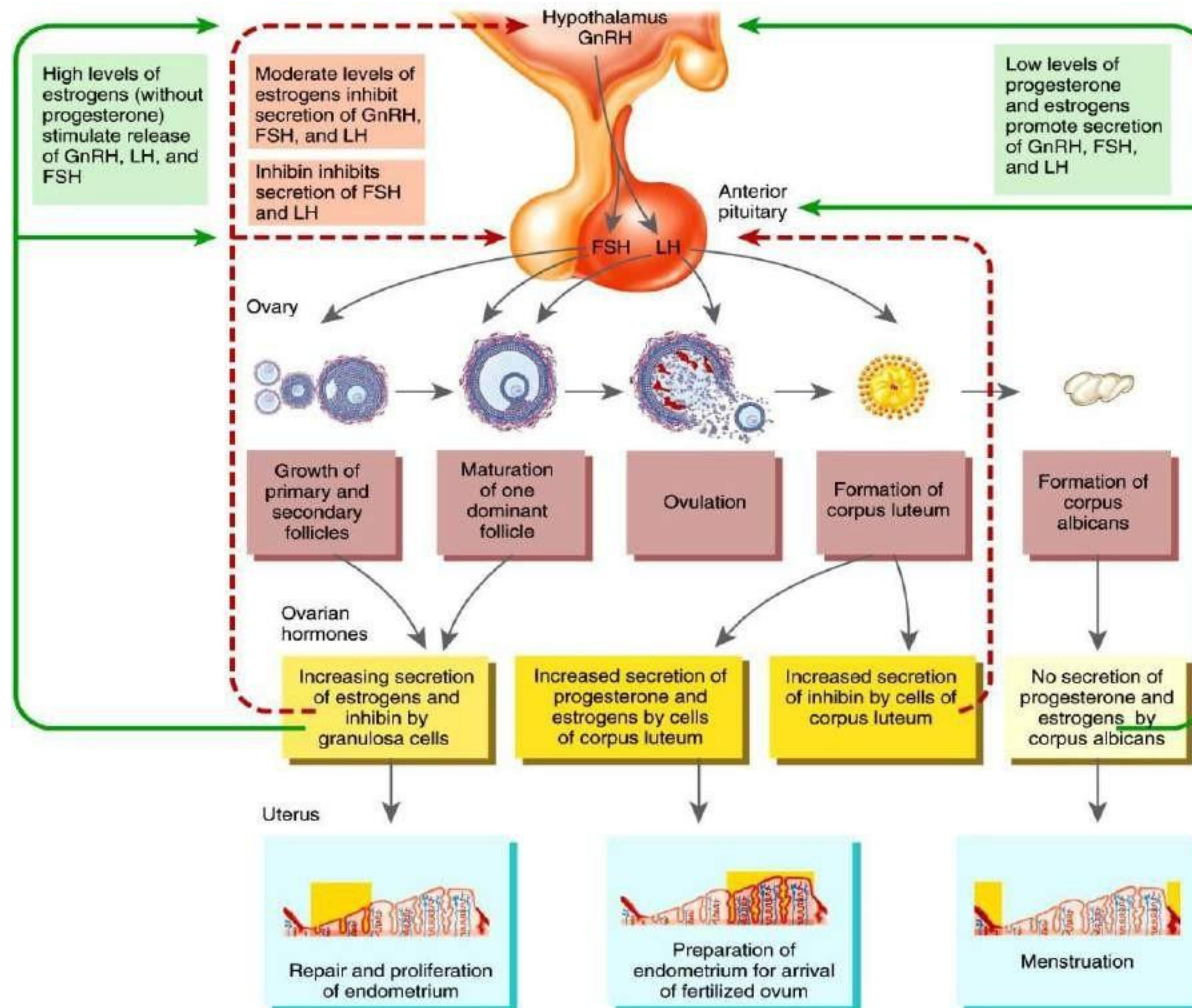


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Disorders of gonadal function

- **Testicular function disorders:**
 - Testicular hypofunction
 - Testicular hyperfunction
- **Disorders of ovarian function:**
 - Ovarian hypofunction
 - Ovarian hyperfunction

Disorders of gonadal function: testicular hypofunction

Etiology:

- **Primary hypogonadism (hypergonadotropic)**
testicular disorder:
 - Congenital disorders in the development of testicles due to genetic disorders (Klinefelter syndrome, 47XXY) and cryptorchism
 - Acquired disorders: infections, radiation
- **Secondary and tertiary hypogonadism (hypogonadotropic):** disorder at the level of the pituitary gland and hypothalamus

Disorders of gonadal function: testicular hypofunction

Pathogenesis:

• before puberty:

- Complete absence of changes characteristic for puberty
 - undeveloped external genitalia,
 - secondary sexual characteristics **do not develop**
- Development of eunuchoid body proportions:
 - there is no closure of the epiphyses of the long bones at puberty, which allows for further growth (long extremities in relation to the body)

• after puberty:

- loss of secondary sexual characteristics

Disorders of gonadal function: testicular hyperfunction

In children:

- Level disturbances **hypothalamus and pituitary gland** (true premature puberty)
 - the testicles are enlarged
 - testosterone is secreted
 - secondary characteristics develop prematurely
 - spermatogenesis is established
- **False precocious puberty**
 - testosterone concentration is high due to **testicles or adrenal glands tumors** with testicular atrophy and no spermatogenesis

Disorders of gonadal function: ovarian hypofunction

- **Primary ovarian hypofunction**
(hypergonadotropic hypogonadism)
 - **Etiology:**
 - gonadal dysgenesis (Turner - 45 X0, gonadal dysgenesis and morphological anomalies)
 - autoimmune damage ovaries
 - **Pathogenesis:**
 - Before puberty there are no changes characteristic for puberty (secondary sexual characteristics, menarche)
 - After puberty: secondary amenorrhea or occurrence uterine bleeding -premature menopause
- **Secondary and tertiary ovarian hypofunction**
(hypogonadotropic hypogonadism)

Disorders of gonadal function: ovarian hyperfunction

- **Primary: ovaries disorder level**
(estrogen-secreting tumor)
 - Before puberty causes **false precocious puberty**
(gonadotropin concentration low, no ovulation)
- **Secondary and tertiary (disorders of pituitary and hypothalamic levels)**
 - Before puberty causes real precocious puberty

The content

- Disorders of the function of the parathyroid glands (hypoparathyroidism and hyperparathyroidism)
- Disorders of the function of the adrenal cortex (reduced and increased secretion of aldosterone, cortisol and androgens)
- Disorders of adrenal medulla function (phaeochromocytoma)
- Disorders of gonadal function (reduced and increased testicular and ovarian function)