

Министерство здравоохранения республики Беларусь
Учреждение образования
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии
Обсуждено на заседании кафедры
Протокол №7 от 30.08.2017

МЕТОДИЧЕСКАЯ РАЗРАБОТКА

Для проведения занятия со студентами
3 курса ФПСЗС, обучающихся на английском языке
по патологической физиологии

Тема: Патофизиология эндокринной системы.

Theme: Pathophysiology of endocrine system

Время 3 ак. часа

Actuality of the theme. The diseases in the basis of which is the disturbance of the endocrine glands functions are widely spread in all the world. On data the WHO, on a planet is not less then 200 millions people suffer by diffuse toxicgoiter. The diseases of parathyreoid glands meet not so often. Because of large number and deleted accommodation of the glands of disease and the casual damages seldom lead them to destruction of such amount of parathyreoid tissues to cause it insufficiency.

Learning goals of the lesson: to study etiology and pathogenesis of endocrine system disorders

Educational goals of the lesson: formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

Objectives of the lesson:

1. To know basic mechanisms of impaired functional activity of endocrine glands.
2. To be able to explain violations of central regulation of functioning endocrine glands, role of te "feedback" mechanism in pathogenesis of endocrine disorders.
3. To know main types, etiology and pathogenesis of endocrine disorders.
4. To know general principles of diagnosis and therapy of endocrine disorders.

To repeat the following questions from related disciplines to ensure absolute mastery of the material:

1. Structure of endocrine gland (histology, cytology, embryology disciplines).
2. Functional interrelation between hypothalamus, pituitary and peripheral gland (normal physiology discipline).

Control questions of the lesson:

1. Violation of feedbacks and mechanisms of self-regulation in neuroendocrine system.
2. Main types of endocrine disorders: classification principles, general characteristics, general mechanisms.
3. Pathology of hypothalamic-pituitary system.
4. Typical forms of adrenal gland pathology, their manifestations.
5. Thyroid gland disorders.
6. Violations of parathyroid glands.
7. Dysfunction of sex glands.
8. General characteristics of detection methods and principles of therapy of endocrine disorders.

Calculation of study time

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

Additional materials:

Endocrine system is a set of anatomically and histologically differentiated structures producing hormones.

Hormones are synthesized in:

- endocrine glands (hypothalamus, pituitary, thyroid gland, parathyroid glands, sex glands)
- set of cells or single cells (neurosecreting cells of hypothalamus, pancreas islet cells (insulin), GIT (APUD system), interstitial cells of kidneys, endocrine cells of lungs, epithelial cells of thymus)

Chemical nature of hormones:

- Amino acid derivatives
- Peptide hormones
- Lipid derivatives

1. Amino acid derivatives

Derivatives of tyrosine

- Catecholamines (epinephrine, dopamine)
- Thyroid hormones (dipeptides)

Tryptophan derivative

- Melatonin

2. Peptide hormones

Glycoproteins from anterior pituitary

- thyroid-stimulating hormone (TSH)
- luteinizing hormone (LH)
- follicle-stimulating hormone (FSH)

Peptides and small proteins

- Digestive tract hormones
- Pituitary hormones
- Pancreatic hormones

3. Lipid derivatives

Steroid hormones (derived from cholesterol):

- with the intact steroid ring (adrenal and gonadal steroids)
- with the steroid ring cleaved (metabolites of vit D)

- *Eicosanoids (derived from arachidonic acid)*

Basic mechanisms of the endocrine glands dysfunction :

1. violation of central mechanisms of gland regulation
2. pathological processes in gland
3. peripheral (outside glandular) mechanisms of violations of hormone activity

VIOLATION OF CENTRAL MECHANISMS OF REGULATION

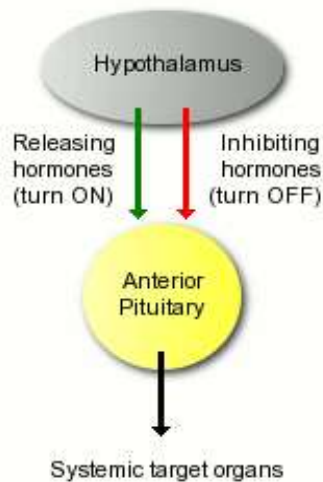
Causes:

- infectious
- inflammation
- vascular lesions
- injury
- tumor

Regulation the endocrine glands:

- transpituitary way of regulation of the endocrine glands
- parapituitary way of regulation of the endocrine glands
- ✓ secondary with disturbances in the limbic system (hippocampus, amygdala, olfactory brain) and overlying levels of CNS
- ✓ unspecific humoral regulation (by ions, metabolites)

TRANSPITUITARY REGULATION

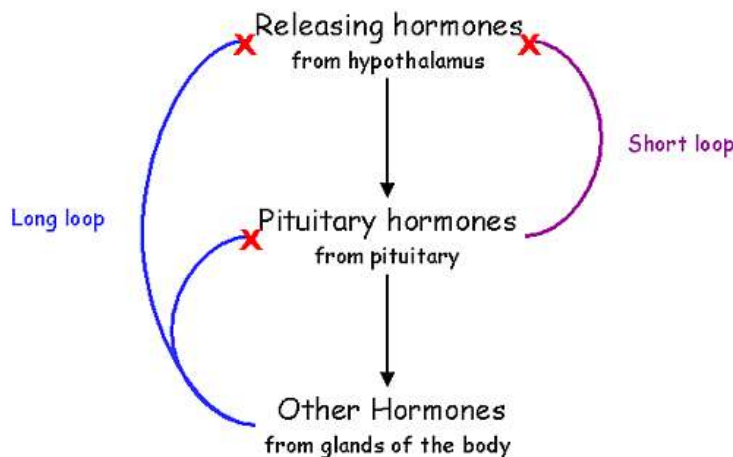


Transpituitary regulation is basic for thyroid, adrenal cortex and sex glands

Transpituitary regulation:

1. synthesis of peptides by neurosecretory cells of mediobasal part of hypothalamus → moving by axons → reach adenohypophysis → **stimulate** (liberins or releasing-factors: thyroliberin, gonadoliberin, etc.) or **inhibit** (statins: thyrostatin, somatostatin etc.) formation of tropic hormones
2. formation of appropriate tropic hormone
3. Tropic hormones act on appropriate targets and stimulate derivation of hormones in appropriate glands (STH stimulates formation of somatomedines in tissues polypeptide hormones)

Feedback loops in the endocrine system



Feedback mechanism of regulation

type — regulated parameter the concentration of hormone in blood (cortisol, thyroid hormones secretion)
type — regulated parameter the content of a controlled substance (blood glucose or Ca^{2+})

Endocrine feedback loops

- Long loop
- Short loop
- Negative
- Positive

Classification of endocrine dysfunction with transpituitary regulation

According to origin:

- Primary (hypothalamic)
- Secondary (pituitary)
- Thirdly (peripheral)

PARAPITUITARY REGULATION

- It is mainly neuro-conductor, basic for adrenal medulla, islets of Langerhans and parathyroid glands

Influence of CNS on function of endocrine glands:

- secretory
- vascular
- trophic
- CNS
- Stress → sympathetic NS activation → adrenal medulla secretes catecholamines (norepinephrine & epinephrine)

Unspecific humoral regulation

Examples: Low blood Ca^{2+} → parathyroid gland → secrete parathyroid hormone (PTH) → higher blood Ca^{2+} → reduced secretion of PTH

High blood sugar → pancreas to secrete insulin → lowering of blood sugar

PATHOLOGICAL PROCESSES IN GLAND

Classification

According to a level of hormone production:

- Hypofunctional (decrease in formation of hormones by this gland)
- Hyperfunctional (increase in formation of hormones by this gland)

According to the volume of injury:

- Partial (violated formation of any from one of several secretory gland hormones e.g., adrenal)
- Subtotal
- Total (violated formation of all hormones secreted by the gland)

- monoglandular process – disorders in one gland
- pluriglandular process – disorders in several glands

- Disorders of hormones biosynthesis
- Disorders of hormones secretion

Reasons of protein-peptide hormones synthesis disorders are:

1. disorders of transcription
2. disorders of translation
3. deficiency of essential aminoacids
4. deficiency of ATP
5. disorders of posttranslatory modification and activation

Table Major action and source of selected hormones

Source	Hormone	Major Action
Hypothalamus	Releasing and inhibiting hormones Corticotropin-releasing hormone (CRH) Thyrotropin-releasing hormone (TRH) Growth hormone-releasing hormone (GHRH) Gonadotropin-releasing hormone (GnRH)	Controls the release of pituitary hormones
Anterior pituitary	Growth hormone (GH)	Stimulates growth of bone and muscle, promotes protein synthesis and fat metabolism, decreases carbohydrate metabolism
	Adrenocorticotrophic hormone (ACTH)	Stimulates synthesis and secretion of adrenal cortical hormones
	Thyroid-stimulating hormone (TSH)	Stimulates synthesis and secretion of thyroid hormone
	Follicle-stimulating hormone (FSH)	Female: stimulates growth of ovarian follicle, ovulation Male: stimulates sperm production
	Luteinizing hormone (LH)	Female: stimulates development of corpus luteum, release of oocyte, production of estrogen and progesterone Male: stimulates secretion of testosterone, development of interstitial tissue of testes
Posterior pituitary	Antidiuretic hormone (ADH) Oxytocin	Increases water reabsorption by kidney Stimulates contraction of pregnant uterus, milk ejection from breasts after childbirth

Source	Hormone	Major Action
Adrenal cortex	Mineralocorticosteroids, mainly aldosterone Glucocorticoids, mainly Cortisol	Increases sodium absorption, potassium loss by kidney Affects metabolism of all nutrients; regulates blood glucose levels, affects growth, has anti-inflammatory action, and decreases effects of stress
	Adrenal androgens, mainly dehydroepiandrosterone (DHEA) and androstenedione	Have minimal intrinsic androgenic activity; they are converted to testosterone and dihydrotestosterone in the periphery
Adrenal medulla	Epinephrine Norepinephrine	Serve as neurotransmitters for the sympathetic nervous system
Thyroid (follicular cells)	Thyroid hormones: triiodothyronine (T ₃), thyroxine (T ₄)	Increase the metabolic rate; increase protein and bone turnover- increase responsiveness to catecholamines; necessary for fetal and infant growth and development
Thyroid C cells	Calcitonin	Lowers blood calcium and phosphate levels
Parathyroid glands	Parathyroid hormone	Regulates serum calcium
Pancreatic islet cells	Insulin	Lowers blood glucose by facilitating glucose transport across cell membranes of muscle, liver, and adipose tissue
	Glucagon	Increases blood glucose concentration by stimulation of glycogenolysis and glyconeogenesis
	Somatostatin	Delays intestinal absorption of glucose
Kidney	1,25-Dihydroxyvitamin D	Stimulates calcium absorption from the intestine
Ovaries	Estrogen	Affects development of female sex organs and secondary sex characteristics
	Progesterone	Influences menstrual cycle; stimulates growth of uterine wall; maintains pregnancy
Testes	Androgens, mainly testosterone	Affect development of male sex organs and secondary sex characteristics; aid in sperm production

PERIPHERAL (OUTSIDE GLANDULAR) MECHANISMS OF VIOLATIONS OF HORMONE ACTIVITY

Peripheral mechanisms of violations of hormone activity

- hormones transport
- metabolic inactivation of hormones
- interaction of hormones with peripheral target-cells.

Types of hormones reception:

- Membrane type (peptide hormones and catecholamines)
- Intracellular type (steroid and thyroid hormones)

The influence of hormones on cells

- influences on permeability of biological membranes
- stimulation or oppression of enzymes activity
- influences on the genetic apparatus of a cell

The mechanism of steroids transport to the genetic locus:

1. Binding the hormone with receptor protein in the cytoplasm
2. Modification of complex hormone +receptor
3. Penetration of complex to the nucleus and selectively connecting with a specific part of chromatin

HYPOTHALAMUS

Effect of Vasopressin (ADH)

- **Vasoconstriction**
- **Concentrates urine**
- gluconeogenesis
- platelet aggregation
- release of VIII and vWb factor

The clinically relevant posterior pituitary syndromes involve ADH and include **diabetes insipidus** and **secretion of inappropriately high levels of ADH**.

Diabetes insipidus. ADH deficiency causes diabetes insipidus, a condition characterized by excessive urination (polyuria) due to an inability of the kidney to resorb water properly from the urine. It can result from a variety of processes, including head trauma, tumors, and inflammatory disorders of the hypothalamus and pituitary as well as surgical procedures involving these organs. The condition can also arise spontaneously, in the absence of an underlying disorder. Diabetes insipidus from ADH deficiency is designated as *central* to differentiate it from *nephrogenic* diabetes insipidus, which is a result of renal tubular unresponsiveness to circulating ADH. The clinical manifestations of the two diseases are similar and include the excretion of large volumes of dilute urine with an inappropriately low specific gravity. Serum sodium and osmolality are increased as a result of excessive renal loss of free water, resulting in thirst and polydipsia. Patients who can drink water can generally compensate for urinary losses; patients who are obtunded, bedridden, or otherwise limited in their ability to obtain water may develop life-threatening dehydration

Syndrome of inappropriate ADH (SIADH) secretion. ADH excess causes resorption of excessive amounts of free water, resulting in *hyponatremia*. The most frequent causes of SIADH include the secretion of ectopic ADH by malignant neoplasms (particularly small-cell carcinomas of the lung), drugs that increase ADH secretion, and a variety of central nervous system disorders, including infections and trauma.^[6] The clinical manifestations of SIADH are dominated by hyponatremia, cerebral edema, and resultant neurologic dysfunction. Although total body water is increased, blood volume remains normal, and peripheral edema does not develop

PITUITARY GLAND

The pituitary gland is composed of two morphologically and functionally distinct components: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). The anterior pituitary constitutes about 80% of the gland. The production of most pituitary hormones is controlled predominantly by positive-acting releasing factors from the hypothalamus, which are carried to the anterior pituitary by a portal vascular system. Prolactin is the major exception; its primary hypothalamic control is inhibitory, through the action of dopamine. Pituitary growth hormone also differs in that it receives both stimulatory and inhibitory influences via the hypothalamus. In routine histologic sections of the anterior pituitary, a colorful array of cells is present that contain eosinophilic cytoplasm (acidophil), basophilic cytoplasm (basophil), or poorly staining cytoplasm (chromophobe) cells:

1. **Somatotrophs**, producing growth hormone (GH): These acidophilic cells constitute half of all the hormone-producing cells in the anterior pituitary.
2. **Lactotrophs** (mammothrophs), producing prolactin: These acidophilic cells secrete prolactin, which is essential for lactation.
3. **Corticotrophs**: These basophilic cells produce adrenocorticotrophic hormone (ACTH), pro-opiomelanocortin (POMC), melanocyte-stimulating hormone (MSH), endorphins, and lipotropin.
4. **Thyrotrophs**: These pale basophilic cells produce thyroid-stimulating hormone (TSH).
5. **Gonadotrophs**: These basophilic cells produce both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH stimulates the formation of graafian follicles in the ovary, and LH induces ovulation and the formation of corpora lutea in the ovary. The same two hormones also regulate spermatogenesis and testosterone production in males.

Hypopituitarism

Hypopituitarism, which is characterized by a decreased secretion of pituitary hormones, is a condition that affects many of the other endocrine systems. Typically, 70% to 90% of the anterior pituitary must be

destroyed before hypopituitarism becomes clinically evident.¹ The cause may be congenital or result from a variety of acquired abnormalities:

- Tumors and mass lesions—pituitary adenomas, cysts, metastatic cancer, and other lesions
- Pituitary surgery or radiation
- Infiltrative lesions and infections—hemochromatosis, lymphocytic hypophysitis
- Pituitary infarction—infarction of the pituitary gland after substantial blood loss during childbirth (Sheehan's syndrome)
- Pituitary apoplexy—sudden hemorrhage into the pituitary gland
- Genetic diseases—rare congenital defects of one or more pituitary hormones
- Empty sella syndrome—an enlarged sella turcica that is not entirely filled with pituitary tissue
- Hypothalamic disorders—tumors and mass lesions (e.g., craniopharyngiomas and metastatic malignancies), hypothalamic radiation, infiltrative lesions (e.g., sarcoidosis), trauma, infections

The manifestations of hypopituitarism usually occur gradually, but it can present as an acute and life-threatening condition. Patients usually report being chronically unfit, with weakness, fatigue, loss of appetite, impairment of sexual function, and cold intolerance. However, ACTH deficiency (secondary adrenal failure) is the most serious endocrine deficiency, leading to weakness, nausea, anorexia, fever, and postural hypotension.

Hypopituitarism is associated with increased morbidity and mortality. Anterior pituitary hormone loss tends to follow a typical sequence, especially with progressive loss of pituitary reserve caused by tumors or previous pituitary radiation therapy (which may take 10 to 20 years to produce hypopituitarism). Usually GH secretion is lost first, then LH and FSH, followed by TSH deficiency. ACTH is usually the last to become deficient. Treatment of hypopituitarism includes treating any identified underlying cause. Hormone deficiencies are treated with replacement of the target gland hormone. Cortisol replacement is started when ACTH deficiency is present; thyroid replacement when TSH deficiency is detected; and sex hormone replacement when LH and FSH are deficient. GH replacement is being used increasingly to treat GH deficiency.

Clinical Findings in Hypopituitarism

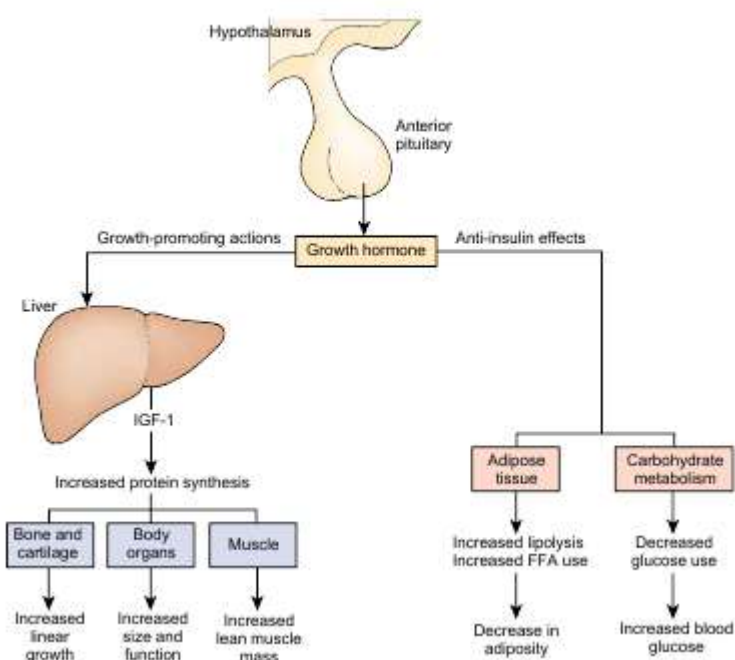
Trophic Hormone Deficiency	Discussion
Gonadotropins (FSH, LH)	Children have delayed puberty. Adult females have secondary amenorrhea. Males have impotence. GnRH stimulation test: <i>No</i> significant increase of FSH/LH in hypopituitarism, eventual increase of FSH/LH in hypothalamic disease
Growth hormone (GH)	Decreased GH decreases synthesis and release of IGF-1. Children have growth delay: delayed fusion of epiphyses; bone growth does <i>not</i> match the age of the child. Adults have hypoglycemia: decreased gluconeogenesis. Arginine and sleep stimulation tests: <i>no</i> increase in GH or IGF-1; normally, GH and IGF-1 are released at 5 AM
Thyroid-stimulating hormone (TSH)	Secondary hypothyroidism: decreased serum T ₄ and TSH. Cold intolerance, constipation, weakness. <i>No</i> increase in TSH after TRF stimulation
Adrenocorticotrophic hormone (ACTH)	Secondary hypocortisolism: decreased ACTH and cortisol. Hypoglycemia: decreased gluconeogenesis. Hyponatremia: mild SIADH (loss of inhibitory effect of cortisol on ADH). Metyrapone test: stimulation test of pituitary ACTH reserve; metyrapone inhibits adrenal 11-hydroxylase, which causes a decrease in cortisol and a corresponding increase in plasma ACTH (pituitary) and 11-deoxycortisol (adrenal), which is proximal to the enzyme block; in hypopituitarism, neither ACTH or 11-deoxycortisol are increased. Short ACTH stimulation test: <i>no</i> increase in serum cortisol over decreased baseline levels. Prolonged ACTH stimulation test: eventual increase in cortisol over the decreased baseline value once the adrenal gland is restimulated

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin growth factor; LH, luteinizing hormone; SIADH, syndrome of inappropriate antidiuretic hormone; T₄, thyroxine; TRF, thyrotropin-releasing factor.

GROWTH HORMONE

Growth hormone, also called somatotropin, is a 191–amino acid polypeptide hormone synthesized and secreted by special cells in the anterior pituitary called somatotropes. For many years, it was thought that GH was produced primarily during periods of growth. However, this has proved to be incorrect because the rate of GH production in adults is almost as great as in children. GH is necessary for growth and contributes to the regulation of metabolic functions. All aspects of cartilage growth are stimulated by GH; one of the most striking effects of GH is on linear bone growth, resulting from its action on the epiphyseal growth plates of long bones. The width of bone increases because of enhanced periosteal growth; visceral and endocrine organs, skeletal and cardiac muscle, skin, and connective tissue all undergo increased growth in response to GH. In many instances, the increased growth of visceral and endocrine organs is accompanied by enhanced functional capacity. For example, increased growth of cardiac muscle is accompanied by an increase in cardiac output. In addition to its effects on growth, GH facilitates the rate of protein synthesis by all of the cells of the body; it enhances fatty acid mobilization and increases the use of fatty acids for fuel; and it maintains or increases blood glucose levels by decreasing the use of glucose for fuel. GH has an initial effect of increasing insulin levels. However, the predominant effect of prolonged GH excess is to increase glucose levels despite an insulin increase. This is because GH induces a resistance to insulin in the peripheral tissues, inhibiting the uptake of glucose by muscle and adipose tissues. Many of the effects of GH depend on a family of peptides called insulin-like growth factors (IGF), also called somatomedins, which are produced mainly by the liver. GH cannot directly produce bone growth; instead, it acts indirectly by causing the liver to produce IGF. These peptides act on cartilage and bone to promote their growth. At least four IGFs have been identified; of these, IGF-1 (somatomedin C) appears to be the more important in terms of growth, and it is the one that usually is measured in laboratory tests. The IGFs have been sequenced and have structures that are similar to that of proinsulin. This undoubtedly explains the insulin-like activity of the IGFs and the weak action of insulin on growth. IGF levels are themselves influenced by a family of at least six binding factors called IGF-binding proteins (IGFBPs).

GH is carried unbound in the plasma and has a half-life of approximately 20 to 50 minutes. The secretion of GH is regulated by two hypothalamic hormones: GH-releasing hormone (GHRH), which increases GH release, and somatostatin, which inhibits GH release. A third hormone, the recently identified ghrelin, also may be important. These hypothalamic influences (i.e., GHRH and somatostatin) are tightly regulated by neural, metabolic, and hormonal factors. The secretion of GH fluctuates over a 24-hour period, with peak levels occurring 1 to 4 hours after onset of sleep (i.e., during sleep stages 3 and 4). The nocturnal sleep bursts, which account for 70% of daily GH secretion, are greater in children than in adults. GH secretion is stimulated by hypoglycemia, fasting, starvation, increased blood levels of amino acids (particularly arginine), and stress conditions such as trauma, excitement, emotional stress, and heavy exercise. GH is inhibited by increased glucose levels, free fatty acid release, cortisol, and obesity. Impairment of secretion, leading to growth retardation, is not uncommon in children with severe emotional deprivation.



Pituitary dwarfism (nanism)

- Reduction of content STH, GTH
- Growth (less than 130 cm) Predomination of dimensions of torso over limbs
- Wrinkled face, old appearance
- Often combined with deficit GTH → immaturity of sexual glands and secondary genital signs → Sterility
- Infantilism in behavior, reduction of memory, mental efficiency without mental disturbances

Gigantism

- If the hypersecretion begins before closure of the growth centers in long bones occurs excessive height
- Increase growth in 10 years to 190 cm and in 18 years of age to 250 cm
- Growth of internal organs → development of cardio-vascular deficiency

Acromegaly

- hypersecretion of STH begins after the growth centers have closed → the bones grow in bulk and width
- increase of the mass of soft tissues and internal organs
- Coarsening of facial features
- Prominent jaw and frontal sinus Broadening of hands and feet
- Hyperhidrosis
- Macroglossia

ADRENAL GLANDS

There are 2 parts: cortex and medulla.

Cortex:

- glucocorticoids (cortisol)
- mineralocorticoids (aldosterone)
- sexual ones (androgens, estrogens)

Medullar:

- noradrenaline
- adrenaline

ADRENAL CORTEX

The adrenal glands are paired endocrine organs consisting of both cortex and medulla, which differ in their development, structure, and function. Beneath the capsule of the adrenal is the narrow layer of zona glomerulosa. An equally narrow zona reticularis abuts the medulla. Intervening is the broad zona fasciculata, which makes up about 75% of the total cortex. The adrenal cortex synthesizes three different types of steroids: (1) glucocorticoids (principally cortisol), which are synthesized primarily in the zona fasciculata and to a lesser degree in the zona reticularis; (2) mineralocorticoids, the most important being aldosterone, which is generated in the zona glomerulosa; and (3) sex steroids (estrogens and androgens), which are produced largely in the zona reticularis. The adrenal medulla is composed of chromaffin cells, which synthesize and secrete catecholamines, mainly epinephrine. Catecholamines have many effects that allow rapid adaptations to changes in the environment.

Diseases of the adrenal cortex can be conveniently divided into those associated with hyperfunction and those associated with hypofunction.

Adrenocortical hyperfunction (hyperadrenalism)

Just as there are three basic types of corticosteroids elaborated by the adrenal cortex, so there are three distinctive hyperadrenal syndromes:

- Cushing syndrome, characterized by an excess of cortisol;
- hyperaldosteronism;
- adrenogenital or virilizing syndromes caused by an excess of androgens. The clinical features of these syndromes overlap somewhat because of the overlapping functions of some of the adrenal steroids.

Hypercortisolism (Cushing Syndrome)

This disorder is caused by any condition that produces elevated glucocorticoid levels. Cushing syndrome can be broadly divided into exogenous and endogenous causes. The vast majority of cases of Cushing syndrome are the result of the administration of exogenous glucocorticoids ("iatrogenic" Cushing syndrome). The endogenous causes can, in turn, be divided into those that are ACTH dependent and those that are ACTH independent

Cortisol effect

Target tissue	Effect	Mechanisms
Muscle	Catabolic	Inhibition of Gl uptake and metabolism. ↓ protein synthesis. ↑ AA and lactate release.
Fat	Lipolytic	Stimulation of lipolysis. ↑ free fat acids and glycerol release.
Liver	Synthetic	↑ GNG. ↑ glycogen synthesis. ↑ glucose-6-phosphatase activity. ↑ Gl in blood (hyperglycemia).
Immune system	Suppression	↓ Lc, Mc, Eph, Bph. Inhibition of IL2 production by T-Lc. ↓ antibody and PG production.
	Antiinflammatory	↓ Nph, Mc, Lc migration to sites of injury.
Target tissue	Effect	Mechanisms
Cardiovascular	↑ cardiac output. ↑ peripheral vascular tone	Permissive effect of catecholamines, contraction of the peripheral vessels.
Renal	↑ glomerular filtration rate. Involved in water and electrolyte balance Regulating balance.	Na ⁺ and water retention
Other	Resistance to stress. Insulin antagonism.	↑ GL in blood

Cushing's disease = hypercorticism = ↑ ACTH (anterior pituitary)

Cushing's syndrome = hypercorticism = ↑ GC

Clinical Features of Cushing Syndrome

- Obesity or weight gain
- Facial plethora, Rounded face
- Decreased libido, Menstrual irregularity
- Thin skin, Hirsutism, Easy bruising
- Decrease in linear growth in children
- Hypertension
- Depression/emotional liability
- Glucose intolerance
- Weakness
- Osteopenia or fracture, Nephrolithiasis

Developing slowly over time, Cushing syndrome can be quite subtle in its early manifestations. Early stages of the disorder may present with hypertension and weight gain. With time the more characteristic central pattern of adipose tissue deposition becomes apparent in the form of truncal obesity, moon facies, and accumulation of fat in the posterior neck and back (buffalo hump). Hypercortisolism causes selective atrophy of fast-twitch myofibers, resulting in decreased muscle mass and proximal limb weakness. Glucocorticoids induce gluconeogenesis and inhibit the uptake of glucose by cells, with resultant hyperglycemia, glucosuria and polydipsia (secondary diabetes). The catabolic effects cause loss of

collagen and resorption of bones. Consequently the skin is thin, fragile, and easily bruised; wound healing is poor; and cutaneous striae are particularly common in the abdominal area. Bone resorption results in the development of osteoporosis, with consequent backache and increased susceptibility to fractures. Persons with Cushing syndrome are at increased risk for a variety of infections, because glucocorticoids suppress the immune response. Additional manifestations include several mental disturbances, including mood swings, depression, and frank psychosis, as well as hirsutism and menstrual abnormalities.

Hyperaldosteronism

Primary - **Conn's syndrome**

Secondary - decreased renal perfusion, edema (heart, liver, kidney), pregnancy

- Na⁺ retention → hypertension
- K⁺ excretion → weakness, paralysis
- Cl⁻ excretion → alkalosis → tetania

In secondary hyperaldosteronism, in contrast, aldosterone release occurs in response to activation of the renin-angiotensin system. It is characterized by increased levels of plasma renin and is encountered in conditions such as the following:

- Decreased renal perfusion (arteriolar nephrosclerosis, renal artery stenosis)
- Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome)
- Pregnancy (due to estrogen-induced increases in plasma renin substrate)

Clinical Course.

The clinical sine qua non of hyperaldosteronism is hypertension. With an estimated prevalence rate of 5% to 10% among nonselected hypertensive patients, primary hyperaldosteronism may be the most common cause of secondary hypertension (i.e., hypertension secondary to an identifiable cause). The prevalence of hyperaldosteronism increases with the severity of hypertension, reaching nearly 20% in patients who are classified as having treatment-resistant hypertension. Through its effects on the renal mineralocorticoid receptor, aldosterone promotes sodium reabsorption, which secondarily increases the reabsorption of water, expanding the extracellular fluid volume and elevating cardiac output. In addition, aldosterone contributes to endothelial dysfunction by decreasing glucose-6-phosphate dehydrogenase levels, which, in turn, reduces endothelial nitric oxide synthesis and causes oxidative stress. The long-term effects of hyperaldosteronism-induced hypertension are cardiovascular compromise (e.g., left ventricular hypertrophy and reduced diastolic volumes) and an increase in the prevalence of adverse events such as stroke and myocardial infarction. Hypokalemia was considered a mandatory feature of primary hyperaldosteronism, but increasing numbers of normokalemic patients are now diagnosed. Hypokalemia results from renal potassium wasting and, when present, can cause a variety of neuromuscular manifestations, including weakness, paresthesias, visual disturbances, and occasionally frank tetany. The diagnosis of primary hyperaldosteronism is confirmed by elevated ratios of plasma aldosterone concentration to plasma renin activity; if this screening test is positive, a confirmatory aldosterone suppression test must be performed, since many unrelated causes can alter the plasma aldosterone and renin ratios.

Adrenogenital syndrome

Disorders of sexual differentiation, such as virilization or feminization, can be caused by primary gonadal disorders and several primary adrenal disorders. The adrenal cortex secretes two compounds—dehydroepiandrosterone and androstenedione—that can be converted to testosterone in peripheral tissues. Unlike gonadal androgens, ACTH regulates adrenal androgen formation; thus, excess secretion can occur either as a “pure” syndrome or as a component of Cushing disease. The adrenal causes of androgen excess include adrenocortical neoplasms and a group of disorders that have been designated congenital adrenal hyperplasia (CAH). CAH represents a group of autosomal-recessive, inherited metabolic errors, each characterized by a deficiency or total lack of a particular enzyme involved in the biosynthesis of cortical steroids, particularly cortisol. Steroidogenesis is then channeled into other pathways, leading to increased production of androgens, which accounts for virilization. Simultaneously, the deficiency of cortisol results in increased secretion of ACTH, resulting in adrenal hyperplasia. Certain enzyme defects may also impair aldosterone secretion, adding salt wasting to the virilizing syndrome. Other enzyme deficiencies may be incompatible with life or, in rare instances, may involve only the aldosterone

pathway without involving cortisol synthesis. Thus, there is a spectrum of these syndromes; the following remarks focus on the most common.

Types:

- Isosexual
- Heterosexual
 - ✓ Born with pseudohermaphroditism
 - ✓ Adult:
 - Virilization (female)
 - Feminization (male)

Three distinctive syndromes have been described:

- salt-wasting (classic) adrenogenitalism,
- simple virilizing adrenogenitalism,
- nonclassic adrenogenitalism, a mild disease that may be entirely asymptomatic or associated only with symptoms of androgen excess during childhood or puberty.

The salt-wasting syndrome results from an inability to convert progesterone into deoxycorticosterone because of a total lack of the hydroxylase. Thus, there is virtually no synthesis of mineralocorticoids, and concomitantly, there is a block in the conversion of hydroxyprogesterone into deoxycortisol resulting in deficient cortisol synthesis. This pattern usually comes to light soon after birth, because in utero the electrolytes and fluids can be maintained by the maternal kidneys. There is salt wasting, hyponatremia, and hyperkalemia, which induce acidosis, hypotension, cardiovascular collapse, and possibly death. The concomitant block in cortisol synthesis and excess production of androgens, however, lead to virilization, which is easily recognized in the female at birth or in utero but is difficult to recognize in the male. Males with this disorder are generally unrecognized at birth but come to clinical attention 5 to 15 days later because of some salt-losing crisis.

Simple virilizing adrenogenital syndrome without salt wasting (presenting as genital ambiguity) occurs in approximately a third of patients with 21-hydroxylase deficiency. These patients generate sufficient mineralocorticoid for salt reabsorption and prevent a salt-wasting “crisis.” However, the lowered glucocorticoid level fails to cause feedback inhibition of ACTH secretion. Thus, the level of testosterone is increased, with resultant progressive virilization.

Nonclassic or late-onset adrenal virilism is significantly more common than the classic patterns already described. There is only a partial deficiency in 21-hydroxylase function, which accounts for the later onset. Individuals with this syndrome may be virtually asymptomatic or have mild manifestations, such as hirsutism, acne, and menstrual irregularities. Nonclassic CAH cannot be diagnosed on routine newborn screening, and the diagnosis is usually rendered by demonstration of biosynthetic defects in steroidogenesis.

Virilization

- hirsutism
- acne
- irregular menstruation
- Signs of masculinization:
 - deepening of the voice
 - increased muscle mass
 - a receding hairline at the temples
 - clitoral enlargement
 - increased libido

Adrenocortical insufficiency

Primary Acute Adrenocortical Insufficiency

Acute adrenal cortical insufficiency occurs in a variety of clinical settings.

- As a crisis in individuals with chronic adrenocortical insufficiency precipitated by any form of stress that requires an immediate increase in steroid output from glands incapable of responding
- In patients maintained on exogenous corticosteroids, in whom rapid withdrawal of steroids or failure to increase steroid doses in response to an acute stress may precipitate an adrenal crisis, as a result of the inability of the atrophic adrenals to produce glucocorticoid hormones

- As a result of massive adrenal hemorrhage, which damages the adrenal cortex sufficiently to cause acute adrenocortical insufficiency—as occurs in newborns following prolonged and difficult delivery with considerable trauma and hypoxia. Newborns are particularly vulnerable because they are often deficient in prothrombin for at least several days after birth. It also occurs in some patients maintained on anticoagulant therapy, in postsurgical patients who develop disseminated intravascular coagulation and consequent hemorrhagic infarction of the adrenals, and as a complication of bacteremic infection; in this last setting, it is called Waterhouse-Friderichsen syndrome

Waterhouse-Friderichsen Syndrome

This uncommon but catastrophic syndrome is characterized by the following:

- Overwhelming bacterial infection, classically *Neisseria meningitidis* septicemia but occasionally caused by other highly virulent organisms, such as *Pseudomonas* species, pneumococci, *Haemophilus influenzae*, or even staphylococci
- Rapidly progressive hypotension leading to shock
- Disseminated intravascular coagulation associated with widespread purpura, particularly of the skin
- Rapidly developing adrenocortical insufficiency associated with massive bilateral adrenal hemorrhage

Primary Chronic Adrenocortical Insufficiency (Addison Disease)

- ↓ appetite, loss of weight
- hypoglycemia
- dysfunction of GIT (nausea, vomiting, diarrhea, abdominal pain)
- arterial hypotension
- muscular weakness
- eosinophilia
- tachycardia
- hypovolemia
- hyperpigmentation of skin (in exposed to solar radiation places) – bronze skin
- dysphoria, irritability, short temper, depression
- tetany due to an excess of phosphates
- paresthesia, and sensory loss of limbs, sometimes to the point of paralysis due to an excess of potassium
- women: menstruation irregular or disappear
- men: develop impotence

ADRENAL MEDULLA

The adrenal medulla is developmentally, functionally, and structurally distinct from the adrenal cortex. It is composed of specialized neural crest (neuroendocrine) cells, termed chromaffin cells, and their supporting (sustentacular) cells. The adrenal medulla is the major source of catecholamines (epinephrine, norepinephrine) in the body. Neuroendocrine cells similar to chromaffin cells are widely dispersed in an extra-adrenal system of clusters and nodules that, together with the adrenal medulla, make up the paraganglion system. These extra-adrenal paraganglia are closely associated with the autonomic nervous system and can be divided into three groups based on their anatomic distribution: (1) branchiomic, (2) intravagal, and (3) aorticosympathetic. The most important diseases of the adrenal medulla are neoplasms, which include neoplasms of chromaffin cells (pheochromocytomas) and neuronal neoplasms (neuroblastic tumors).

Pheochromocytoma

Pheochromocytomas are neoplasms composed of chromaffin cells, which synthesize and release catecholamines and in some instances peptide hormones. It is important to recognize these tumors because they are a rare cause of surgically correctable hypertension.

The dominant clinical manifestation of pheochromocytoma is hypertension, observed in 90% of patients. Approximately two thirds of patients with hypertension demonstrate paroxysmal episodes, which are described as an abrupt, precipitous elevation in blood pressure, associated with tachycardia, palpitations, headache, sweating, tremor, and a sense of apprehension. These episodes may also be associated with pain in the abdomen or chest, nausea, and vomiting. Isolated paroxysmal episodes of

hypertension occur in fewer than half of patients; more commonly, patients demonstrate chronic, sustained elevation in blood pressure punctuated by the aforementioned paroxysms. The paroxysms may be precipitated by emotional stress, exercise, changes in posture, and palpation in the region of the tumor; patients with urinary bladder paragangliomas occasionally precipitate a paroxysm during micturition. The elevations of blood pressure are induced by the sudden release of catecholamines that may acutely precipitate congestive heart failure, pulmonary edema, myocardial infarction, ventricular fibrillation, and cerebrovascular accidents. The cardiac complications have been attributed to what has been called catecholamine cardiomyopathy, or catecholamine-induced myocardial instability and ventricular arrhythmias. Nonspecific myocardial changes, such as focal necrosis, mononuclear infiltrates, and interstitial fibrosis, have been attributed either to ischemic damage secondary to the catecholamine-induced vasomotor constriction of the myocardial circulation or to direct catecholamine toxicity. In some cases pheochromocytomas secrete other hormones, such as ACTH and somatostatin, and may therefore be associated with clinical features related to the secretion of these or other peptide hormones.

THYROID GLAND

Hyperthyroidism

The three most common causes of thyrotoxicosis are also associated with hyperfunction of the gland and include the following:

- Diffuse hyperplasia of the thyroid associated with Graves disease (accounts for 85% of cases)
- Hyperfunctional multinodular goiter
- Hyperfunctional adenoma of the thyroid

Effect of T3

- uncouples the OXPHOS → energy dissipation → ↑ basal metabolic rate
- ↑ metabolism of carbohydrates, ↑ tissue Gl utilization, ↑ glycogenolysis and ↓ tissue glycogen
- catabolic effect on protein metabolism → muscle atrophy and osteoporosis.
- mobilization of depot fat + ↑ oxidation of fats in the liver + inhibition of transition carbohydrates to fats → ↑ ketone bodies

Manifestation:

- ↑ excitability cortex
- in the cells of the cortex, brainstem and anterior horns of spinal cord develop toxic-degenerative changes
- persistent tachycardia, tendency to atrial fibrillation
- increased humidity and skin temperature
- exophthalmos
- change the skin of legs and hands (acropathy)

The clinical manifestations of hyperthyroidism are protean and include changes referable to the hypermetabolic state induced by excess thyroid hormone and to overactivity of the sympathetic nervous system (i.e., an increase in the β -adrenergic “tone”). Excessive levels of thyroid hormone result in an increase in the basal metabolic rate. The skin of thyrotoxic patients tends to be soft, warm, and flushed because of increased blood flow and peripheral vasodilation to increase heat loss. Heat intolerance is common. Sweating is increased because of higher levels of calorigenesis. Increased basal metabolic rate also results in characteristic weight loss despite increased appetite. Cardiac manifestations are among the earliest and most consistent features of hyperthyroidism. Individuals with hyperthyroidism can have an increase in cardiac output, due to both increased cardiac contractility and increased peripheral oxygen requirements. Tachycardia, palpitations, and cardiomegaly are common. Arrhythmias, particularly atrial fibrillation, occur frequently and are more common in older patients. Congestive heart failure may develop, particularly in elderly patients with preexisting cardiac disease. Myocardial changes, such as foci of lymphocytic and eosinophilic infiltration, mild fibrosis in the interstitium, fatty changes in myofibers, and an increase in size and number of mitochondria, have been described. Some individuals with thyrotoxicosis develop reversible left ventricular dysfunction and “low-output” heart failure, so-called thyrotoxic or hyperthyroid cardiomyopathy.

In the neuromuscular system, overactivity of the sympathetic nervous system produces tremor, hyperactivity, emotional lability, anxiety, inability to concentrate, and insomnia. Proximal muscle weakness and decreased muscle mass are common (thyroid myopathy).

Ocular changes often call attention to hyperthyroidism. A wide, staring gaze and lid lag are present because of sympathetic overstimulation of the levator palpebrae superioris. However, true thyroid ophthalmopathy associated with proptosis is seen only in Graves disease.

In the gastrointestinal system, sympathetic hyperstimulation of the gut results in hypermotility, malabsorption, and diarrhea.

The skeletal system is also affected. Thyroid hormone stimulates bone resorption, increasing porosity of cortical bone and reducing the volume of trabecular bone. The net effect is osteoporosis and an increased risk of fractures in patients with chronic hyperthyroidism.

Other findings include atrophy of skeletal muscle, with fatty infiltration and focal interstitial lymphocytic infiltrates; minimal liver enlargement due to fatty changes in the hepatocytes; and generalized lymphoid hyperplasia and lymphadenopathy in patients with Graves disease.

Hypothyroidism

Hypothyroidism is caused by any structural or functional derangement that interferes with the production of adequate levels of thyroid hormone. Hypothyroidism is a fairly common disorder, and by some estimates the population prevalence of overt hypothyroidism is 0.3%, while subclinical hypothyroidism can be found in greater than 4%.

Goiter

It is an enlargement of the thyroid gland.

Types:

- **thyrotoxic** (↑ function of thyroid gland)
- **hypothyroid** (↓ function of thyroid gland)
- **endemic** (with normal function of thyroid gland)

Hypothyroidism:

- Infantile hypothyroidism (cretinoid idiocy)
- Myxedema

Myxedema

- ↓ metabolism
- ↓ body t^0
- obesity
- edema of skin and subcutaneous tissue accumulation of hydrophilic mucous substances in face
- mental deficiency → dementia
- apathy and sleepiness
- brittleness of nails, hair falling
- sexual dysfunction

Infantile hypothyroidism (cretinoid idiocy, congenital hypothyroidism)

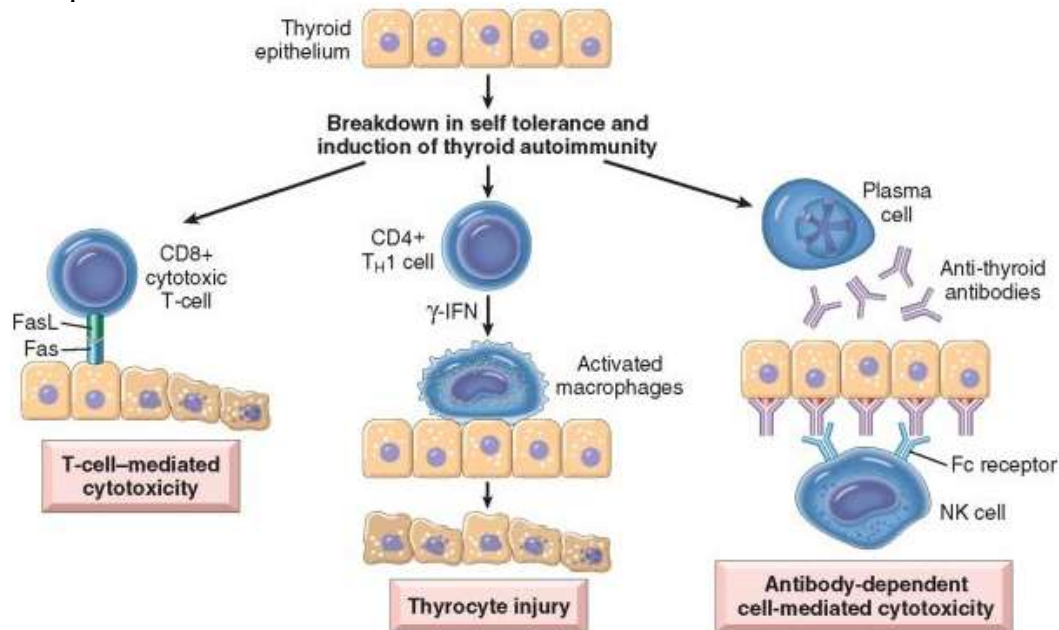
- excessive sleeping, reduced interest in nursing
- poor muscle tone
- low or hoarse cry
- infrequent bowel movements,
- exaggerated jaundice
- low body temperature.
- larger anterior fontanel, persistence of a posterior fontanel, umbilical hernia, and a large tongue (macroglossia)

Thyroiditis

Thyroiditis, or inflammation of the thyroid gland, encompasses a diverse group of disorders characterized by some form of thyroid inflammation. These diseases include conditions that result in acute illness with severe thyroid pain (e.g., infectious thyroiditis, subacute granulomatous thyroiditis) and disorders in which there is relatively little inflammation and the illness is manifested primarily by thyroid dysfunction—subacute lymphocytic thyroiditis and fibrous (Reidel) thyroiditis.

Hashimoto thyroiditis

Hashimoto thyroiditis is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient. Akin to other autoimmune diseases, Hashimoto thyroiditis has a strong genetic component.



Pathogenesis.

Hashimoto thyroiditis is caused by a breakdown in self-tolerance to thyroid auto-antigens. This is exemplified by the presence of circulating autoantibodies against thyroglobulin and thyroid peroxidase in the vast majority of Hashimoto patients. The inciting events leading to breakdown in self-tolerance in Hashimoto patients have not been fully elucidated, but possibilities include abnormalities of regulatory T cells (Tregs), or exposure of normally sequestered thyroid antigens. Induction of thyroid autoimmunity is accompanied by a progressive depletion of thyrocytes by apoptosis and replacement of the thyroid parenchyma by mononuclear cell infiltration and fibrosis. Multiple immunologic mechanisms may contribute to thyroid cell death, including:

- CD8+ cytotoxic T cell-mediated cell death: CD8+ cytotoxic T cells may cause thyrocyte destruction.
- Cytokine-mediated cell death: Excessive T-cell activation leads to the production of TH1 inflammatory cytokines such as interferon- γ in the thyroid gland, with resultant recruitment and activation of macrophages and damage to follicles.
- Binding of anti-thyroid antibodies (anti-thyroglobulin, and anti-thyroid peroxidase antibodies) followed by antibody-dependent cell-mediated cytotoxicity.

Subacute (granulomatous) thyroiditis

Subacute thyroiditis, which is also referred to as granulomatous thyroiditis or De Quervain thyroiditis, occurs much less frequently than does Hashimoto disease. The disorder is most common between the ages of 40 and 50 and, like other forms of thyroiditis, affects women considerably more often than men (4 : 1).

Pathogenesis.

Subacute thyroiditis is believed to be triggered by a viral infection. The majority of patients have a history of an upper respiratory infection just before the onset of thyroiditis. The disease has a seasonal incidence, with occurrences peaking in the summer, and clusters of cases have been reported in association with coxsackievirus, mumps, measles, adenovirus, and other viral illnesses. Although the pathogenesis of the disease is unclear, one model suggests that it results from a viral infection that leads to exposure to a viral or thyroid antigen, which is released secondary to virus-induced host tissue damage. This antigen stimulates cytotoxic T lymphocytes, which then damage thyroid follicular cells. In contrast to autoimmune thyroid disease, the immune response is virus-initiated and not self-perpetuating, so the process is limited.

Graves Disease

Graves disease has a peak incidence between 20 and 40 years of age. Women are affected as much as 10 times more frequently than men.

Pathogenesis.

Graves disease is characterized by a breakdown in self-tolerance to thyroid auto-antigens, most importantly the TSH receptor. The result is the production of multiple autoantibodies, including:

- **Thyroid-stimulating immunoglobulin:** This IgG antibody binds to the TSH receptor and mimics the action of TSH, stimulating adenyl cyclase and increasing the release of thyroid hormones. Almost all individuals with Graves disease have detectable levels of this autoantibody. Thyroid-stimulating immunoglobulin is relatively specific for Graves disease, in contrast to thyroglobulin and thyroid peroxidase antibodies.
- **Thyroid growth-stimulating immunoglobulins:** Also directed against the TSH receptor, thyroid growth-stimulating immunoglobulins have been implicated in the proliferation of thyroid follicular epithelium.
- **TSH-binding inhibitor immunoglobulins:** These anti-TSH receptor antibodies prevent TSH from binding normally to its receptor on thyroid epithelial cells. In so doing, some forms of TSH-binding inhibitor immunoglobulins mimic the action of TSH, resulting in the stimulation of thyroid epithelial cell activity, whereas other forms may actually inhibit thyroid cell function. It is not unusual to find the coexistence of stimulating and inhibiting immunoglobulins in the serum of the same patient, a finding that could explain why some patients with Graves disease have episodes of hypothyroidism.

The key role of anti-TSH receptor antibodies in the pathogenesis of hyperthyroidism is supported by animal models of Graves disease. Immunization of mice with the TSH receptor results in generation of antibodies that cause thyroid stimulation, thyroid enlargement with lymphocytic infiltration, elevated thyroxine levels, and, in a subset of mice, ocular signs reminiscent of Graves ophthalmopathy.

Autoimmunity also plays a role in the development of the infiltrative ophthalmopathy that is characteristic of Graves disease. In Graves ophthalmopathy, the volume of the retro-orbital connective tissues and extraocular muscles is increased for several reasons, including (1) marked infiltration of the retro-orbital space by mononuclear cells, predominantly T cells; (2) inflammatory edema and swelling of extraocular muscles; (3) accumulation of extracellular matrix components, specifically hydrophilic glycosaminoglycans such as hyaluronic acid and chondroitin sulfate; and (4) increased numbers of adipocytes (fatty infiltration). These changes displace the eyeball forward and can interfere with the function of the extraocular muscles. Recent evidence suggests that orbital preadipocyte fibroblasts express the TSH receptor and thus become targets of an autoimmune attack. T cells reactive against these fibroblasts secrete cytokines, which stimulate fibroblast proliferation and synthesis of extracellular matrix proteins (glycosaminoglycans) and increase surface TSH receptor expression, perpetuating the autoimmune response. The result is progressive infiltration of the retro-orbital space and ophthalmopathy.

The clinical findings in Graves disease include changes referable to thyrotoxicosis as well as those associated uniquely with Graves disease, diffuse hyperplasia of the thyroid, ophthalmopathy, and dermopathy.

Hyperparathyroidism

- **Primary** – pathology of parathyroid gland
- **Secondary** – compensatory increase in production of parathyroid hormone in response to long-term hypocalcemia.
- **Tertiary** – development of autonomously functioning parathyroid adenoma on the background of long-existing secondary hyperparathyroidism
- \uparrow serum Ca: \uparrow bone resorption, \downarrow renal clearance of Ca, \uparrow intestinal Ca absorption
- Serum Ph : in primary \downarrow (\downarrow renal tubular Ph reabsorption); in secondary generally \uparrow (because of renal disease)

Manifestations: 50% of patients have no symptoms

Malignant hypercalcaemia:

- bone pain, muscle soreness (myalgias)
- kidney stones and osteoporosis
- weakness and fatigue, depression

- ↓ appetite, nausea, vomiting, constipation
- polyuria, polydipsia
- cognitive impairment

Hypoparathyroidism

- neuromuscular irritability, paresthesia, tetany (hands and feet), seizures, parkinsonism like effects
- mental status change, fatigue, headaches, insomnia
- widened QT interval
- defective, carious, teeth
- bone pain, abdominal pain

SEX HORMONES

Sex hormones are synthesized in testicles, ovaries. Smaller amount of sex hormones are produced in adrenal cortex and placenta. Small amount of male sex hormones are produced in ovaries and female sex hormones - in testicles.

Male sex hormones are called androgens and female - estrogens.

Chemical structure - steroids. Synthesis and secretion of the sex hormones are controlled by the pituitary gonadotropic hormones. Sex hormones act by means of the activation of gene apparatus of cells. Catabolism of sex hormones takes place in liver. The time half-life is 70-90 min.

The main estrogens: estradiol, estrole, estriole (are produced by follicles) and progesterone (is produced by yellow body and placenta). The main biological role of estrogens - conditioning for the reproductive female function (possibility of ovum fertilization). Estradiol results in the proliferation of endometrium and progesterone stimulates the conversion of endometrium in decidual tissue which is ready for ovum implantation. Estrogens also cause the development of secondary sexual features. Its synthesis is regulated by the luteinizing hormone. Testosterone forms the secondary sexual features in males.

Effect of sex hormones on protein metabolism: stimulate the processes of protein, DNA, RNA synthesis; cause the positive nitrogenous equilibrium.

Effect of sex hormones on carbohydrate metabolism: activate the Krebs cycle; activate the synthesis of glycogen in liver.

Effect of sex hormones on lipid metabolism: enhance the oxidation of lipids; inhibit the synthesis of cholesterol.

Effect of sex hormones on energy metabolism: stimulate the Krebs cycle, tissue respiration and ATP production.

Sex hormones are used for treatment of variety diseases. For example, testosterone and its analogs are used as anabolic remedies; male sex hormones are used for the treatment of malignant tumor of female sex organs and vice versa.

Male sex hormones

Testosterone deficiency syndromes

Testosterone has a role in the development of fetus and its absence will result in female phenotype. A lack of testosterone at the expected time of pubescence is manifest by delayed closure of epiphysis and eunuchoidal skeletal proportions, no deepening of the voice, delayed and scanty growth of pubic and axillary hair, absence of beard and mustache growth, small prostate, small penis and a nonpigmented, nonrugated scrotum, low testicular volume with absent spermatogenesis, poor muscular development, and usually, psychosocial immaturity. The patients are usually brought to the physician by their parents, who are worried about poor growth and development.

Classification:

Primary hypogonadism (due to Leydig cell dysfunction. GnRHs in serum or urine are elevated because of decreased feedback at the pituitary – hypothalamic unit).

Secondary (due to disorders of the hypothalamic – pituitary unit. Pituitary and hypothalamic hypogonadism may be differentiated by appropriate testing with GnRH)

Primary hypogonadism

Leydig cell function is depressed in malnutrition, in renal failure, myotonic dystrophy, in chronic disease, to a variable extent with aging, and by certain toxins such as lead and alcohol.

Klinefelter's syndrome

This most frequent cause of primary hypogonadism is defined as the presence of one or more extra X chromosomes in at least one tissue. The hallmark of the Klinefelter's syndrome is the presence of small and firm testes, containing sclerosed tubules with only rare sertoli cells, and there is thus usually azoospermia. Eunuchoidal habitus, gynecomastia, female distribution of body fat, particularly around the hips, and female distribution of pubic hair, lack of temporal recession of the hairline, arched palate, mental retardation constitute the typical findings. Many of these clinical findings may be absent and the disease manifests itself only by infertility or decreased fertility.

Sertoli-cell-only syndrome (germinal aplasia).

These patients present as essentially normal men with slightly reduced testicular volume and infertility. There is an absence of germinal cells in the tubules. Plasma testosterone is normal, and elevated serum FSH concentrations. There are no chromosomal abnormalities in this syndrome, and the buccal smear is negative.

Secondary hypogonadism.

Delayed pubescence.

The prepubertal male is hypogonadotropic. FSH stimulation of tubular development is the first evidence of pubescence. At the present, there is no reliable test to distinguish between delayed puberty and hypogonadotropic hypogonadism.

Kallman's syndrome (hypogonadotropic hypogonadism).

It is the most frequent cause of secondary hypogonadism. It is inherited as an autosomal dominant with variable penetrance and is characterized by low FSH, LH levels, anosmia or hyposmia, and the variable occurrence of short fourth metacarpals, syndactyly, midline skeletal defects, and mental retardation. Inadequate secretion of FSH and LH may occur as an isolated defect as well. In both cases the disease can be shown to be hypothalamic in origin, since repeated injections of GnRH will eventually elicit a normal gonadotropin response. Boys remain sexually prepubescent until either testosterone secretion is induced by HCG (chorionic gonadotropin) or androgen is given.

Isolated LH deficiency (fertile eunuch syndrome).

This is a rare syndrome, the boys having pubertal testicular size and some spermatogenesis in the absence of signs of androgen effect. The deficiency of LH is not complete and HCG will virilize and increase sperm counts.

Syndromes of androgen resistance.

Syndromes manifested by feminine habitus and the presence of testes, and is characterized by an absolute or varying degrees of resistance to androgen action as a result of absent or decreased amounts of intracellular receptor for dihydrotestosterone.

Patients present in their teenage years as girls with primary amenorrhea, this pseudohermaphroditism is inherited, with transmission as an X-linked recessive or autosomal dominant trait. In the most extreme form, testicular feminization, the women have well-developed breasts, absent pubic and axillary hair, normal external genitalia, a short blind vaginal pouch, an absent uterus, and testes (palpable "masses") present either in the labial folds or inguinal canal. The tests have small tubules and lack germ cells.

Precocious puberty -is activation of the hypothalamic-pituitary axis with a consequent enlargement and maturation of the gonads, and the development of the secondary sexual characteristics, adult serum testosterone levels, and spermatogenesis (the onset of sexual maturation before age 10 in males).

The incidence of true precocious puberty is greater in females (2:1), and about 80 % of female cases have no identifiable abnormality. In contrast, 60 % of male cases have underlying organic disease.

Boys exhibit facial, axillary, and pubic hair, penile growth, and increased masculinity. Linear growth is initially rapid in both sexes, but the adult height is shortened by premature closure of the epiphysis.

Female sex hormones

The changes that occur in normal menstrual cycles depend on cyclical variations in the output of FSH and LH, influenced by the output of Gn-Rh on LH, influenced by the output of Gn-RH. The effects of Gn-RH on LH and FSH release, in terms of the amounts secreted at different stages of the menstrual cycle, are strongly influenced by negative feedback control effects exerted by oestradiol-17 β and progesterone.

The developing Graafian follicles in the ovaries respond to the cyclical stimulus of gonadotrophins by secreting two oestrogens, oestradiol-17 β and oestrone; these are metabolised to a third oestrogen,

oestriol. After ovulation, the corpus luteum secretes progesterone as well as oestrogens. The changes in the uterus are determined by the ovarian steroid output at each stage. These changes are modified if pregnancy occurs.

Oestrogens act on several target tissues, including the uterus, vagina and breast; progesterone mainly acts on the uterus, and is essential for the maintenance of early pregnancy. Both oestrogens and progesterone are important in the control of the hypothalamio-pituitary-ovarian axis. Oestradiol-17 β may stimulate or inhibit the secretion of gonadotrophins, depending on its concentration in plasma; the stimulating effect of oestradiol-17 β can be prevented by high plasma [progesterone]. Inhibins and activins also play a role in regulating ovarian function and they change during the cycle; however, their measurement is not performed as part of routine investigation. Inhibin B originates from developing follicles while inhibin A is derived from the dominant follicle and corpus luteum.

Sexual disorders in the female are often presented with menstrual abnormalities such as primary (Turner's syndrome, congenital adrenal hypoplasia) and secondary amenorrhea.

Oligomenorrhoea and amenorrhoea

Women with oligomenorrhoea or amenorrhoea may present because of concerns they have regarding their bleeding pattern, infertility, hirsutism, virilism or a combination of these.

Physiological causes of amenorrhoea (pregnancy, lactation) and anatomical abnormalities should first be excluded as the possible cause. Amenorrhoea may be primary, that is, the patient has never menstruated, in which case abnormal development is a likely cause, or secondary to various causes. Investigation of primary amenorrhoea is required if the patient has reached the age of 16 and has undergone normal secondary sexual development or at the age of 14 if the patient has no breast development.

Measurements of plasma concentrations of prolactin, FSH, LH, oestradiol-17 β TSH and free T4 are required. In addition, plasma testosterone, androstenedione and dehydroepiandrosterone sulphate (DHAS) concentrations may need to be measured if there is hirsutism or virilisation.

Turner's syndrome (ovarian dysgenesis) is characterized by 45,X karyotype and chromatin-negative buccal smear, streak gonads, infertility, primary amenorrhea, short stature, sexual infantilism, a variety of phenotypic abnormalities (webbing of the neck, high-arched palate, low posterior hairline, low-set ears, cubitus valgus, chest deformities, shortening of metacarpal, metatarsal, and phalangeal bones, hypoplastic nails, pigmented nevi, small mandible, epicanthol folds, lymphedema of the hands and feet, tendency for keloid formation) plasma gonadotropins are usually elevated.

True hermaphroditism

It is the presence of male and female gonads in the same individual.

The exact origin of true hermaphroditism is not known.

The external genitalia are ambiguous, with either male or female predominance. A penis with hypospadias and cryptorchism is often present. Breast development and menses occur in about 70 % of the patients ovulation and spermatogenesis are uncommon most patients are raised as males. 2/3 of patients are chromatin-positive, and the most common karyotype is 46,XX. Mosaic patterns such as XX/XY and XY/XXY are often found.

The menopause.

It is discontinuation of menstruation. It may be natural (results from age-related declining ovarian function and usually occurs between ages 40 and 50. As the ovary becomes atrophic and ceases to respond to gonadotropin stimulation, the few remaining follicles undergo atresia and urinary gonadotropin excretion increases sharply), premature (refers to cessation of ovarian function before the age 40, and must be distinguished from gonadal dysgenesis and hypopituitarism), artificial (follows ovariectomy, irradiation of the ovaries).

Menopause may be asymptomatic or symptoms primarily due to estrogen deficiency and autonomic nervous system responses may be severe and last a few months or year.

Menopausal symptoms:

- 1) early: vasomotor effects (hot flushes and sweating); psychological (anxiety, emotional lability, irritability);
- 2) middle: genitourinary (dyspareunia (senile vaginitis), vaginal infections, urgency of micturition); changes of the skin and hair (dryness, hair loss);
- 3) late: osteoporosis; cardiovascular disorders.

Questions for self-control of knowledge:

1. What is the violation of feedbacks and mechanisms of self-regulation in neuroendocrine system.
2. Main types of endocrine disorders: classification principles, general characteristics, general mechanisms.
3. Pathology of hypothalamic-pituitary system.
4. Typical forms of adrenal gland pathology, their manifestations.
5. Thyroid gland disorders etiology, pathogenesis.
6. Main manifestation of violations of parathyroid glands.
7. Main manifestation of dysfunction of sex glands.
8. General characteristics of detection methods and principles of therapy of endocrine disorders.

Tasks for self-managed student work:

1. Role of adrenal cortex hormones in formation of protective-adaptive reactions of the body.
2. Role of autoimmune processes in development of thyroid diseases.
3. Pathology of thymus. Lymphoid toxemia
4. Role of endocrine disorders in etiology and pathogenesis of non-endocrine diseases

Literature

Basis literature:

1. Литвицкий, П. Ф. Патопфизиология = Pathophysiology: лекции, тесты, задачи : учеб. Пособие / П. Ф. Литвицкий, С. В. Пирожков, Е. Б. Тезиков. – М. : ГЭОТАР-Медиа, 2016.– 432 с.

Additional literature:

2. Kumar, V. Robbins and Cotran Pathologic basis of disease, 7th Edition / V.Kumar, A.K. Abbas, N. Fausto. — Philadelphia: Elsevier Inc., 2005. – 1629 p. Режим доступа: <http://www.rkmyat.in/up1/34/1629.pdf>. – Дата доступа: 30.08.2016.
3. Кидун, К. А. Тестовые задания по патологической физиологии = Test tasks on pathological physiology : в 3-х ч. Ч. 3, Частная патофизиология : учеб.-метод. пособие для студ. 3 курса фак. по подг. спец. для зарубеж. стран, обуч. на англ. яз. по спец. «Лечебное дело», мед. вузов / А. К. Кидун. – Гомель : ГомГМУ, 2015. – 113 с.
4. Научная электронная библиотека eLIBRARY.RU [Электронный ресурс] / Научная электронная библиотека. – М., 2005. – Режим доступа: <http://www.elibrary.ru>. – Дата доступа: 26.08.2017.

Compiler:

senior lector

_____ K.A. Kidun