**PATHOPHYSIOLOGY OF ENDOCRINE SYSTEM**

Depending on the causes and developmental mechanisms of the endocrine disorders, they are divided into the following groups:

1. Disorders in the central regulating mechanisms of the endocrine glands activity:

1. connected with disturbances in the hypothalamus;
2. connected with disturbances in the hypophysis.

2. Peripheral disorders:

1. connected with pathological processes in the endocrine glands;
2. disturbances in activity of hormones connected with extraglandular mechanisms.

Since hypothalamus connects the nervous and endocrine regulation systems of the organism, lesions and diseases of this area (inflammation, vascular disorders, trauma, tumors) influence functions of the endocrine glands by the parahypophysial and transhypophysial ways. The secondary changes in the activity of the endocrine system caused by the lesions of the reticular formation and the higher parts of the central nervous system are also realised through hypothalamus.

Disturbances in the parahypophysial regulation of the endocrine glands activity form the basis of a number of endocrine diseases (Icenko-Cushing disease, Simmonds’ disease, Addison’s syndrome, adiposogenital dystrophy, etc.).

Feedback mechanisms are important in the pathogenesis of some diseases of the endocrine glands. In a number of cases localization of disturbance causing the endocrine disease is ascertained, taking into consideration the feedback mechanism. For example, increased blood content of thyrotropic hormone in hypothyrosis witnesses localization of the pathological process in the thyroid gland (decreased blood content of thyroxin results in hypersecration of the thyrotropic hormone by the feedback principle).

One must take into account the feedback mechanism during therapeutic employment of the hormonal preparations (especially glucocorticoids). Because the hormone, when administered into the organism, inhibits activity of the corresponding glands; its long use causes atrophy of the gland. After cessation of the treatment the pathological process may develop connected with deficiency of this hormone.

Endocrinopathies connected with pathological processes in the endocrine glands are characterised by their hyperfunction or hypofunction. Usually endocrine disturbances of the hyperfunctional type are caused by the tumors of glands processing the secretory activity (adenoma), whereas those of hypofunctional type result from various lesions of glands (inflammation, allergy, removal of the gland by the operative way) and genetic disturbances of synthesis of the hormone.

Some tumors (the tumor developing from the chromophobic cells of the hypophysis or metastases into endocrine glands of tumors developing from other tissues of the organism) do not produce hormone; they compress the tissues and cause atrophy in the normal cells of the gland, resulting in its hypofunction.

In the endocrine glands hormone-synthesizing tumors are frequent which cause hyperfunction of the gland. For instance, eosinophilic adenoma of the hypophysis produces a large amount of somatotropic hormone. This causes giantism (in developing young organisms) or acromegaly (in adult persons). Adenoma of the pancreatic island is accompanied by hyperinsulinism which results in decreased blood sugar and fits of hypoglycemia (sometimes-loss of consciousness and comatous condition).

Rarely tumors may develop in several glands at the same time. One or all of them may possess hormonal activity. But since all the endocrine glands are interconnected, lesion of any gland is clinically manifested as pluriglandular (polyglandular) failure.

The endocrine glands, as well as any other tissues of the organism, may be affected by inflammatory processes and infectious diseases. Tuberculosis necrotizes the glandular tissue, syphilis resilts in syphylitic gumma. In adrenal glands these process cause Addison’s disease, in thyroid gland-hypothyrosis, etc. In orchits and gonorrhea male sexual glands may be affected (as a result of ascending infection). In some acute infectious diseases endocrine glands may be affected as a result of non-infectious complications (for example: the infection caused by meningococci may result in hemorrhage into the adrenal gland).

In thyroid, parathyroid, sexual glands, adrenal cortex the pathological processes connected with autoallergic mechanisms are observed, for instance, Hashimoto’s disease (autoimmune thyroiditis or lymphatic goiter).

Genetic disorders in biosynthesis of hormones are frequent in the pathology of the sexual glands, though hereditary defects may be observed also in the thyroid gland, adrenal cortex, etc. For instance, cretinism may be connected with hereditary deficiency of enzymes participating in the synthesis of thyroxin.

In the origin of some endocrinopathies exogenous factors (especially alimentary factors) play a decisive part. For example: endemic goiter develops as a result of iodine deficiency.

Under clinical conditions iatrogenic (resulting from the methods of treatment) endocrinopathies are observed, some of which are connected with surgical methods. For instance: if during strumectomy (removal of thyroid gland) the surgeon removes also parathyroid glands, then in patient hypoparathyrosis develops; sometimes after removal of chromophobic adenoma of hypophysis panhypopituitarism develops. Iatrogenic endocrinopathies may result also from drug theraphy. For instance: after treatment of non-endocrine diseases by large doses of corticoid preparations hypocorticoidism may develop.

Factors which influence hormones out of the glands, that is, after secretion into the blood, may increase or decrease their activity; these states manifest themselves clinically as hyperfunction of the corresponding gland. For example: 2 groups of patients with diabetes mellitus and hyperglycemia are distinguished:

1. with decreased blood content of insulin;
2. with increased blood content of insulin.

In both groups hyperglycemia results from insulin deficiency. But in the first group the disease is connected with absolute insulin deficiency, whereas in the second group insulin’s action is blocked up in periphery (extrapancreatic diabetes).

So, pathogenesis of endocrinopathies connected with extraglandular (peripheral) mechanisms depends on the further fate of the hormones in the blood:
1. Changes of ability of hormones to conjugate with plasma protein – results in increase (hyperfunction) or decrease (hypofunction) of free forms of hormones.

2. Breakdown of hormones by enzymes (for instance, insulin may be decomposed under the influence of unsulinase ).

3. Decrease of activity of the hormone in the blood – may result from synthesis of autoantibodies against certain hormone or changes in its molecular structure (active center of molecule). For instance, there are hypophysial dwarfs with high blood content of somatotropic hormone which cannot influence the growth, whereas administration of the exogenous somatotropic hormone stimulates the growth.
4. Blockade of the hormonal receptor is frequent type of endocrinopathies. Blood content of the hormone is normal or even higher, whereas symptoms of its hypersecretion are observed, and action of exogenous hormone is also weak.

5. Disturbance in permissive effect of steroid hormones –decreased blood content of glucocorticoids weakens action of the hormones of distant effect (adrenalin, somatotropic hormone, insulin, glucagon).

6. Weak metabolism of hormones – may result from disturbed hepatic function (hepatitis, cirrhosis); some hormones accumulate in the organism and cause corresponding changes. For example, weakness of metabolism of aldosterone in hepatocirrhosis accelerates development of ascites and edema. In hepatic insufficiency on men inactivation of estradiol is slowed down. This causes hyposecration of gonadotropic hormone by feedback mechanism; the function of testicles is also weakened and impotency comes into being.

At the initial stages of the endocrinophathies connectsd with extraglandular (peripheral) mechanisms the function of the corresponding gland is normal, but then under the influence of the feedback mechanisms the changes occur also in the gland.

**Hypophysis (pituitary gland), though a tiny organ, is concerned with a variety of diverse functions in the body.** The hypophysis and hypothalamus are so closely interlinked (hypothalamohypophyseal system) that disfunctions of the hypothalamus cause secondary changes in the pituitary body and diseases of the pituitary involve the hypothalamus.

Hyperpituitarism, that is, oversecretion of one or more of the pituitary hormones , may be due to diseases of the anterir pituitary, posterior pituitary or hypothalamus. Hyperfunction of the anterior pituitary is due to the development of hormone – secreting pituitary adenoma or carcinoma (rarely).

Hypersecretion of growth hormone results in gigantism and acromegaly. Both these clinical syndromes result from sustained excess of somatotropic hormone, most commonly by somatotroph (somatotropin secreting) adenoma.

When somatotropin excess occurs prior to epiphyseal closure (ossification of epiphyseal cartilages), giantism is produced. So, gigantism occurs in prepubertal boys and girls. The main clinical feature of giantism is the excessive and propertionate growth of the child (enlargement as well, as thickening of the bones resulting in considerable increase in height and enlarged thoracic cage ) . The giants are very tall ( more than 2 metres in hight ).

Acromegaly arises as a result of hypersecration of somatotrophic hormone in adults following cessation of bone growth ; it is more common than gigantism . Acromegaly (Gr. akros extreme, related to extremity; megas – large) is characterized by enlargement of hands, feet, tongue and lips , coarseness of facial features with increase in soft tissue, thickening of the skin, prominent supraorbital ridges and more prominent lower jaw (prognathism), kyphosis. The volume of the internal organs also increases (splanchnomegaly). Sometimes, TSH (thyrotropin) excess (resulting in thyroxicosis) and gonadotropin insufficiency (causing amenorrhea in the females and impotance in the males) are observed.

 Rapid tissue growth in giantism and acromegaly is connected with metabolic changes. Somatotropin accelerated biosinthesis of proteins and inhibits their catabolism .Its anabolic action depends on content of insulin and glucocorticoids. Growth hormone acellerates the process of lipolysis in fatty tissue and formation of ketonic bodies.

In giantism and acromegaly carbohydrate metabolism is also disturbed. Acromegaly is frequently accompanied by diabetes mellitus.

Hypersecretion of adrenocortitropic hormone is the main pathogenetic factor of Icenko-Cushing disease (pituitary dependent Cushing’s syndrome). There are 4 major etiologic types of Cushing’s syndrome:

1. Pituitary Cushing’s syndrome (60-70% cases – is caused by excessive secretion of ACTH due to corticotroph (ACTH – secreting) adenoma . ACTH accelerates synthesis of hydrocortisone and corticosterone in adrenal cortex , causing secondary hypercorticoidism. This disease is characterised by adiposis of the face ("moon face"), neck and trunk ( but not the limbes), elevated blood pressure and increased erythrocyte count, hypogenitalism (phenomena of masculinization in women), hyperglycemia and glucosuria. The organism’s resistance against infections is decreased.
2. Adrenal Cushing’s syndrome.
3. Ectopic Cushing's syndrome – has an origin in ectopic ACTH elaboration by non- endocrine tumors (lung cancers, malignant thymoma, pancreatic tumors ). The plasma ACTH level is high and cortisol secretion is not suppressed by dexamethasone administration.
4. Iatrogenic Cushing’s syndrome – may result from prolonged therapeutic administration of high doses of glucocorticoids or ACTH, for example, in organ transplant recipients and in autoimmune diseases. These cases are generally associated with bilateral adrenocortical insufficiency.

Hypersecretion of thyrotropic hormone causes hyperfunction of thyroid gland; hyperthyroidism and thyrotoxicosis develop. Thyrotropin increases quantity of acid mucopolysaccharides in the skin, muscles and behind eyeballs. This is connected with increase of the number of mast cells in which acid mucopolysaccharides are synthesized. Accumulation of acid mucopolysaccharides behind eyeballs causes exophthalmos.

Hypersecretion of gonadotropic hormones (follicle – stimulating hormone and luteinizing hormone) results in hyperfunction of sexual glands. In childhood this causes precocious puberty. Frequently hypophyseal hypergonadoism is of familial character.

Hyperprolactinemia – is excessive production of prolactin most commonly by prolactinoma, that is , lactotroph ( prolactin – secreting ) adenoma. In the female hyperprolactinemia amenorrhea - galactorrhea syndrome is observed characterized by infertility and expression of drop or two of milk from breast not related to pregnancy or puerperium. In the male it may cause impotence or reduced libido. These features result either from associated inhibition of gonadotropin secretion or interference in gonadotropin effects.

Hypersecretion of antidiuretic hormone causes oliguria and accumulation of water in the organism. Secretion of antidiuretic hormone may be increased by reflex way (as a result of pain or emotional strain. Nicotine and acetylcholine also increase its secretion. Rarely pulmonary diseases (tuberculosis, lung abscess, pneumoconiosis, empyema, pneumonia) may cause overproduction of ADH. Inappropriate release of ADH occurs most often in paraneoplastic syndrome, for instance, in oat cell carcinoma of the lung, carcinoma of the pancreas, lymphoma and thymoma. Rarely lesions of the hypothalamus (trauma, hemorrhage, toxic, infectious allergic psychical factors) cause a disease, the main pathogenic factor of which is ADH hypersecration (hyperhydropexy or Parhon’s syndrome).

In hypopituitarism there is usually deficiency of one or more of the pituitary hormones affecting either anterior pituitary, or posterior pituitary and hypothalamus. The total anterior pituitary insufficiency is called panhypopituitarism. Its most common causes are: non-secretary (chromophobe) adenoma, Sheehan’s syndrome, Simmond’s disease and empty-sella syndrome.

Pituitary insufficiency occurring due to postpartum ischemic pituitary necroses is called Sheehan’s syndrome whereas occurrence of similar process without preceding pregnancy as well as its occurrence in males is termed Simmond’s disease.

Sheehan’s syndrome results from spasm of hypophyseal blood vessels during hemmorhages after labour or abortion as well as sepsis (septic embolism) also developing after labour or abortion. The clinical manifaestations of Sheehan’s syndrome include failure of lactation following delivery (due to deficiency of prolactin), loss of axillary and pubic hair, amenorrhea, sterility and loss of libido. Concomitant deficiency of TSH and ACTH may result in hypothyroidism and adrenocortical insufficiency.

Both in Sheehan’s syndrome and Symmond’s disease the symptoms of panhypopituitarism appear when 90-95% of adenohypophyseal cells are destructed. Synthesis of adenohypophyseal tropic hormones is sharply decreased. General weakness, anorexia, dentition, shedding of hairs, atrophy of organs and tissues, decreased resistance of the organs and tissues, decreased resistance of the organs against infectious diseases, disturbances in sexual functions and functions of the central nervous system, hypophyseal cachexia are observed.

Empty – sella syndrome is characterized by the appearance of an empty sella (Turkish saddle) and features of panhypopituitarism. It results from herniation of subarachnoid space into the sella due to an incomplete diaphragma sella creating an empty sella. Less common causes are Sheehan’s syndrome, infarction and scarring in an adenoma, irradiation damage or surgical removal of the gland.

In experiment panhypopituitarism is reproduced by the way of hypophysectomy the outcome of which depends on the age of the animal. In hypophysectomized young animals the growth is delayed, sexual glands do not develop, secondary sexual characters and sexual instincts do not come into being, thyroid gland and adrenal cortex are small, involution of the thymus gland does not occur, deciduous dentition is not replaced. The animals become flabby and inactive, the basal metabolism and body temperature are low. In adult animals energy metabolism becomes weaker, protein , fat and carbohydrate metabolism are disturbed , thyroid gland , adrenal cortex and sexual glands decrease, functions of ovaries are disturbed.

Severe deficiency of growth hormone in children before growth is completed, results in retarded growth and pituitary dwarfism. Frequently it is the result of an inherited autosomal recessive disorder, but may also result from pituitary adenoma or craniopharyngioma, infarction and trauma to the pituitary gland. The clinical features of inherited cases of pituitary dwarfism, which appear after one year of age, include proportionate retardation in growth of bones, normal mental state for age, poorly –developed genitalia, delayed puberty and episodes of hypoglycemia. The height of adult male dwarf is less than 130 cm and that of female dwarf less than 120 cm. Predisposition to obesity is observed.

One must distinguish pituitary dwarf from hypothyroid dwarf (cretinism) in which there is achondroplasia and mental retardation.

Hyposecretion of adrenocorticotropic hormone causes secondary weakness of the adrenal cortex function (secretion of glucocorticoids is changed more markedly) which is called Addison’s syndrome. Addison’s syndrome must be distinguished from Addison’s disease (primary insufficiency of the adrenal cortex ) in which pigmentation of the skin is increased (hence its other name –bronze disease). Because the primary hypofunction of the adrenal cortex causes hypersecretion of ACTH ( by the feedback mechanism) some products of fermentative hydrolysis of which possess melanotropic action.

Insufficiency of the thyrotropic hormone causes hypofunction of the thyroid gland.

Hyposecretion of gonadotropic hormones before the period of puberty causes infantilism which is frequently accompanied by growth inhibition. Usually secondary sexual characters do not develop, development of the genital organs is delayed. In girls menstruations are absent or irregular.

In hypophyseal hypogenitalism which develops after puberty, in men eunuchoidism, impotency, azoospermia or hypospermia are observed. Frequently sexual glands are atrophied, gradually some secondary sexual characteristics disappear. Changes in the person’s appearance (baldness, premature senility, obesity) occur. In women early cessation of menstruations, spontaneous abortion and infertility, further- atrophy of mammary glands, premature senility and predisposition to obesity are observed.

One of the frequent variants of the gonadotropic hormones hyposecretion is adiposogenital dystrophy which results from lesion of the hypothalamohypophyseal system (toxoplasmosis, birth injury, scarlet fever, tuberculosis, syphilis, cranicocerebral injury, tumors of hypothalamus, chromophobe adenoma of hypophysis, thrombosis and embolism of cerebral vessels). The first symptoms of the adiposogenital dystrophy are observed at the age of 6-7 years (in boys) or 10-13 years (in girls): hyperorexia and obesity, arrest of development of the genital organs, changes in the higher nervous activity. In boys obesity develops which is characteristic of female body structure (increased subcutaneous fat in neck, arms, chest, abdomen, pelvis, thighs, buttocks). Hairs on face and body do not develop.

Insufficiency of the posterior pituitary is uncommon. Removal of the posterior lobe of the hypophysis causes polyuria.

The significant clinical syndrome due to hypofunction of the neurohypophysis and hypothalamus is diabetes insipidus which results from deficient secretion of antidiuretic hormone (inflammatory and neoplastic lesions of the neurohypophysis due to surgery, radiation, head injury and idiopathic cases). The main features of the diabetes insipidus are excretion of a very large volume of dilute urine of low specific gravity (< 1.010), polyuria and polydipsia.

In certain group of women with atony of uterus during labour, changes witnessing lesion of hyphothalamus (obesity, slight diabetes insipidus) are observed. Evidently, some forms of atony of uterus are connected with hyposecretion of oxytocin.

**According to the origin of the pathological processes which cause hypercorticoidism (hyperadrenalism), that is, hyperfunction of the adrenal cortex, its 3 types are distinguished:**

1. Central (secondary) hypercorticoidism-results from changes in the activity of the hypothalamus or hypophysis (Icenko-Cushing disease).
2. Ectopic hypercorticoidism – is caused by some non-endocrine tumor cells (some types of pulmonary carcinoma) which synthesize ACTH.
3. Peripheral hypercorticoidism-results from changes in the gland (primary hypercorticoidism) or extraglandular increase of activity of hormones (disturbance in ability of plasma proteins to conjugate steroids). Primary hypercorticoidism is caused by adrenal tumors (adenoma, carcinoma), hyperplasia or hypertrophy of adrenal cortex which results in hypersecretion of glucocorticoids, mineralocorticoids, androgens and estrogens.

Hypersecretion of each of the three types of corticoids produced by the adrenal cortex causes distinct clinical syndrome, mixed forms of which may also occur:

1. Cushing’s **syndrome** (chronic hypercorticoidism) caused by excess of glucocorticoids (cortisol);
2. Conn's syndrome (primary hyperaldosteronoism) caused by hypersecretion of mineralocorticoids (aldosterone);
3. adrenogenital syndrome (adrenal virilism) caused by excessive production of adrenal sex steroids (androgens).

The following tumors may cause primary hypercoprticoidism (each of them may be benign or malignant):

1. glucosteroma (adrenal cortex tumor , producing glucocorticoids )-causes Cushing's syndrome;
2. aldosteroma (aldosterone – producing tumor ) causes Cinn's syndrome;
3. androsteroma ( androgen- producing tumor ) causes adrenogenital syndrome;
4. corticoestroma ( estrogen –producing tumor )- causes adrenogenital syndrome;
5. mixed tumors ( glucoaldosteroma , glucoandrosteroma) – produce different hormones; for instance , glucoandrosteroma produces glucocorticoids and androgens, causing Cushing's syndrome and adrenal virilism.

Adrenal Cushing's syndrome (primary hypercorticoidism) is caused by disease in one or both adrenal glands (adrenal cortical adenoma, carcinoma, cortical hyperplasia). Though similar to Icenko-Cushing disease by its clinical course, this type of Cushing's syndrome is characterised by low serum ACTH levels. To distinguish them, dexamethasone test is used. During 2 days, every 6 hours 2 mg of dexamethasome is administered which suppresses ACTH secretion. In the presence of sound adrenal glands this causes decreased glucocorticoid secretion. Therefore, Icenko – Cushing's disease content of 17- ketosteroids (metabolic products of adrenal cortex hormones and androgens) in urine (normally 10-25 mg daily in men and 5-15 mg in women) is decreased. If the disease is connected with adrenal gland tumor , dexamethasone does not influence the 17 – ketosteroids content.

Hypercortisolism results in disturbances in all types of metabolism. Acceleration of gluconeogenesis, hyperglycemia , hypersecretion of insulin cause weakness in β-cells (as a result of strenous activity), and diabetes mellitus (steroid diabetes) may develop.

The process of lipolysis is slowed down, which causes obesity. Fat is accumulated mainly in subcutaneous layer of face, neck, chest and abdomen, whereas extremities seem comparatively thin.

Proteins break down rapidly, whereas their synthesis, as well as synthesis of antibodies is disturbed, organism’s resistibility against infections decreases.

A large amount of calcium is excreted in urine, and its absorption in intestines is disturbed. Decreased blood content of calcium results in increased activity of parathyroid glands; the secondary hyperparathyroidism develops. Osteporosis, deformations and fractures in bones are observed.

Hydrocortisone accelerates erythropoiesis and causes neutrophilic leukocytosis accompanied by eosinopenia and lymphopenia.

Increased reabsorbtion of sodium results in accumulation of water in the organism. Intercellular fluid and blood volume are increased. Besides, vascular wall sensibility to the influence of catecholamines is increased. Blood content of ammonia rises, which excites the central nervous system ; its action on the vasomotor center increases vascular tension. So, hypercortisolism is accompanied by increased arterial pressure.

Primary hyperaldosteronism (Conn’s syndrome) results due to adrenocortical diseases:

1) aldosterone-producing adrenocortical adenoma:

2) bilateral adrenal hyperplasia , especially in children (congenital hyperaldosteronism);

3) adrenal carcinoma(rarely).

Conn’s syndrome is more frequent in adult females.Its principal features are the following:

1. hypertension ( usually mild to moderate diastolic hypertension);
2. hypokalemia and associated muscular weakness, peripheral neuropathy and cardiac arrhythmias;
3. retention of sodium and water;
4. polyuria and polidipsia due to reduced concentrating power of the renal tubules;
5. metabolic alkalosis.

Primary hyperaldosteronism is associated with adenoma of the adrenal cortex zona glomerulosa, whereas secondary hyperaldosteronism occurs in response to high plasma renin level. Secondary hyperaldosteronism results from pathological processes out of adrenal glands:

1. hypersecretion of renin by kidneys (renal ischemia, reninoma);
2. hyperosmotic or isoosmotic dehydration;
3. decreased inactivation of aldosterone in liver ( renal, cardiac, hepatic edemas).

Although adrenal cortex secretes a smaller amount of sex steroids , than the gonads , but adrenocortical hyperfunction may occasionally cause sexual disturbances. The following factors cause hypersecretion of sex steroids(mainly androgens):

1. in children-congential adrenal hyperplasia in which there is congenital deficiency of a specific enzyme;
2. in adults-adrenocortical adenoma or carcinoma; Cushing’s syndrome is often present as well.

The clinical features also depend on the age and sex of patients:

1. in children-distortion of the external genitalia (in girls) and precocious (early) puberty (in boys);
2. in adults –virilization (hirsutism, oligomenorrhea, deepening of voice, hypertrophy of the clitoris) in females and feminization in males (rarely);
3. increased excretion of 17-ketosteroids in the urine.

Three types of adrenocortical hypofunction (hypoadrenalism or hypocorticoidism) are distinguished:

1. primary hypocorticoidism –is caused by the disease of the adrenal glands; acute (adrenal crisis) and chronic (Addison’s disease) forms are described;
2. secondary hypocorticoidism – results from diminished secretion of ACTH;
3. hypoaldosteronism.

Hypocorticoidism may be total (hyposecretion of all adrenocortical hormones) or partial (hyposecretion of one of the hormones).

In experiment acute total hypocorticoidism is reproduced by the way of adrenalectomy. After such operation adynamia and fatigue, hyporexia, decreased basal metabolism and body temperature are observed. If forced to run, the animal dies. Complete removal of both glands also causes death.

Causes of adrenal crisis (sudden loss of adrenocortical function) are the following:

1. bilateral adrenalectomy ( in the treatment of cortical hyperfunction, hypertension and selected cases of breast cancer);
2. Waterhouse-Fridericksen syndrome – results from septicemia (in endotoxic shock and meningococcal infection) producing grossly hemorrhagic and necrotic adrenal cortex (adrenal apoplexy);
3. rapid withdrawal of steroids;
4. any form of acute stress in a case of chronic hypocorticoidism (Addison’s disease).

Clinical features of acute hypocorticoidism are due to deficiency of mineralocorticoids (aldosterone) and glucocorticoids (cortisol);

1. deficiency of mineralocorticoids results in salt deficiency, hyperkalemia and dehydration;
2. deficiency of glucocorticoids causes hypoglycemia, increased insulin sensitivity and vomiting.

Headache, dyspnea, diarrhea, nervous excitement, convulsions, cyanosis, subcutaneous hemorrhages are observed. Adrenal pressure falls sharply. The causes of death (within 1-2 days) are collapse, pulmonary edema and dehydration.

Addison’s disease or bronze disease results from progressive chronic destruction of more than 90% of adrenal cortex on both sides.

Any condition which causes marked chronic adrenal destruction may produce Addison’s disease: tuberculosis, autoimmune or idiopathic adrenalitis, histoplasmosis, amyloidosis, metastatic cancer, sarcoidosis , hemochromatosis. Regardless of the cause , the adrenal glands are bilaterally small and irregularly shrunken. Clinical manifestations develop slowly and insidiously:

1. asthenia(progressive weakness), weight loss and lethargy;
2. hyperpigmentation-initially is more marked on exposed areas, but later involves also unexposed parts and mucous membranes (hence the name-bronze disease);
3. arterial hypotension;
4. upper gastrointestinal symptoms (mild loss of appetite, nausea, vomiting, upper abdominal pain);
5. episodes of hyperglycemia;
6. biochemical changes (acidosis, hyperkalemia, low levels of serum sodium, chloride and bicarbonate).

Corticosteroid deficiency results in changes in cardiovascular system activity (decreased cardiac muscle contractility, bradycardia, arrhythmia).

The clinical features of primary (Addison’s disease) and secondary (Addison’s syndrome) adrenocortical insufficiency are alike except the following:

1. cases of Addison’s syndrome lack hyperpigmentation because of suppressed melanocyte- stimulating hormone production from the pituitary body;
2. plasma ACTH levels are elevated in Addison’s disease and low-to-absent in Addison’s syndrome;
3. in Addison’s syndrome aldosterone levels are normal owing to stimulation by renin.

Isolated deficiency of aldosterone with normal cortisol level may occur in association with reduced renin secretion (hyporeninism) in the following cases:

1. congenital defect due to deficiency of an enzyme required for its synthesis;
2. prolonged administration of heparin;
3. certain diseases of the brain;
4. excision of an aldosterone-secreting tumor.

Isolated hypoaldosteronism is observed in adults with mild renal failure and diabetes mellitus. Its predominant features are hyperkalemia and metabolic acidosis.

Adrenal medulla hyperfunction is caused by tumors developing from adrenal gland chromaffin tissue. They are called pheochromocytoma which means “dusky brown tumor”. Most pheochromocytomas are slow-growing and benign, but 5-10% of tumors are malignant, invasive and metastatic. Content of catecholamines in pheochromocytoma reaches 300 mg, whereas the adrenal gland of healthy person contains only 4-8 mg of catecholamines. Epinephrine and norepinephrine periodically pass into the blood and cause hypertensive crisis. Other cholamines are congestive heart failure, myocardial infarction, pulmonary edema, cerebral hemorrhage and even death. Headache, dizziness, temporary disturbance in vision, hallucinations, convulsions, nausea and vomiting are observed.

Blood content of cholesterol in such patients is high, which leads to atherosclerosis. Rarely the disease is accompanied by constant hypertension and takes a course of malignant hypertension. In 10% of such patients diabetes mellitus is revealed.

Adrenal medulla hypofunction has no severe consequences. Evidently, it is one of the pathogenetic factors of the arterial hypotension.

**Hyperfunction (hyperthyroidism) as well as hypofunction (hypothyroidism) of the thyroid gland are characterized by distinct clinical syndromes.**

Most common causes of hyperthyroidism are diffuse toxic goiter, toxic multinodular goiter and toxic adenoma. Less frequent causes include hypersecretion of hypophyseal TSH (thyrotropin) by a pituitary tumor, hypersecretion of TRH (thyroliberin) in hypothalamus, thyroiditis, metastatic tumors of the thyroid gland, congenital hyperthyroidism in the newborn of mother with Basedow’s disease, excessive doses of thyroid hormones or iodine (jodbasedow disease).

Depending on the developmental features, some disease may be accompanied either by hyperthyroidism or hypothyroidism. The severe clinical forms of the hypothyroidism are called thyrotoxicosis.

The usual symptoms of hyperthyroidism are emotional instability, nervousness, fatigue, weight loss (in spite of good appetite), heat intolerance, perspiration, menstrual disturbances, tremor of the outstretched hands, cardiac manifestations (tachycardia, palpitations, cardiomegaly). The skin is warm, moist and flushed. Weakness of skeletal muscles and osteoporosis are common. Typical eye changes (exophtalmos) are a common feature in Basedow’s disease.

“Thyroid storm” or “thyroid crisis” may occur in persons who have undergone subtotal thyroidectomy before adequate control of hyperthyroid state, or in hyperthyroid persons under acute stress, trauma and with severe infection. These patients develop high grade fever, tachycardia, cardiac arrhythmias,and coma, and may die of congestive heart failure or hyperpyrexia.

The most frequent disease which is accompanied by thyrotoxicosis is Basedow’s or Graves’ disease (diffuse toxic goiter or exophthalmic goiter). Triad of features characterizing this disease was first described by Basedow (1840): 1) diffuse thyroid enlargement, 2) exophthalmos, 3) tachycardia. The disease is more frequent between the age of 30 and 40 years and has five-fold increased prevalence among females.

In the etiology of Basedow’s disease psychical factors are of great importance. Frequently onset of the disease is put in touch with psychical trauma. But a number of researches consider that psychical trauma may cause thyrotoxicosis only in persons with constitutional hyperthyroidism. It is also assumed that predisposition to Basedow’s disease is inherited. Thyrotoxicosis may arise after acute and chronic infectious diseases, craniocerebral trauma, pregnancy, intake of a large amount of iodine.

Basedow’s disease is considered an autoimmune disease; there are many immunogenic similarities between this condition and Hashimoto’s thyroiditis. The pathogenesis of ophthalmopathy in this disease is also regarded as of autoimmune origin. In the blood of persons with diffuse toxic goiter immunoglobulin was found stimulating the function of the thyroid gland. It was named LATS (long acting thyroid stimulator).

Activity of the sympathoadrenal system is also of great significance in the pathogenesis of Basedow’s disease (sympathetic nerve impulses increase secretion of the thyroid gland hormones). Sometimes owing to the increased sensibility of the adrenoreceptors in the thyroid gland to the action of catecholamines, its activity may be accelerated regardless of other stimulating factors.

Interstitial transformation of the thyroid hormones also play a part in the development of the thyrotoxicosis.

In thyrotoxicosis processes of dissimilation are accelerated, loss of energy, as well as basal metabolism and body temperature increase, nitrogen balance becomes negative. Glycogen and fat reserves rapidly decrease, cachexia is observed. Hyperglycemia, hyperketonemia and ketonuria come into being, diabetes mellitus develops.

Toxic influence of the thyroid hormones on the cardiac muscle causes disturbances in the activity of the cardiovascular system: tachycardia, increased systolic and pulse pressures (diastolic pressure is slightly decreased), in severe cases-cardiac fibrillation.

Changes in the higher nervous activity are observed: irritability, anxiety, sleeplessness. Disturbances in the vegetative centers of the hypothalamus cause disorders in the activity of internal organs.

Hypothyroidism is hypometabolic clinical state resulting from inadequate production of thyroid hormones for prolonged periods, or rarely from resistance of the peripheral tissues to effects of thyroid hormones. Deficiency of the thyroid hormones may be connected with lesion and diseases of the thyroid gland (peripheral or primary hypothyroidism) or hyposecretion of the thyrotropic hormone (central hypothyroidism). Usually the cases of primary hypothyroidism are more severe. Some forms of the peripheral hypothyroidism are hereditary, others arise as a result of autoimmune thyroiditis, iodine deficiency or strumectomy (complete removal of the thyroid gland). The main clinical mainfestations of hypothyroidism are the following:

1. Cretinism or congenital hypothyroidism (development of severe hypothyroidism during infancy and childhood).
2. Myxedema (adulthood hypothyroidism).
3. Hashimoto’s disease or autoimmune (lymphocytic) thyroiditis.
4. Endemic goiter.

Hypothyroidism causes disturbances in the metabolic processes, functional changes, and then morphological changes come into being.

Regardless of the causes of hypothyroidism, its physiological effects are the same: fatigue and extreme somnolence (with sleeping up to 14-16 hours a day), extreme muscular sluggishness, failure of many trophic functions in the body (evidenced by scaliness of the skin, depressed growth and fragility of hairs), frog-like husky voice and edematous appearance throughout the body called myxedema (Lat. - mucous edema).

Hereditary forms of hypothyroidism (cretinism) arise frequently as a rasult of hereditary deficiency of one of the enzymes participating in the synthesis of the thyroid hormones, and rarely-sensitivity of tissues to the thyroid hormones is decreased, although thyroid gland activity is normal.

The causes of congetinal hypothyroidism are the following:

1. developmental anomalies (thyroid agenesia, ectopic thyroid);
2. genetic defect in thyroid hormone synthesis ( defect in iodine trapping, oxidation, iodination, coupling and thyroglobulin synthesis);
3. fetal exposure to antithyroid drugs;
4. endemic cretinism in regions with endemic goiter due to dietary lack of iodine (sporadic cretinism, on the other hand, is due to developmental anomalies and genetic defects in thyroid hormones synthesis described above).

Cretin is a child with severe hypothyroidism present at birth or developing within the first two years of postnatal life. This is the period when brain development is taking place, so that in the absence of treatment the child is both physically and mentally retarded. The word “cretin” is derived from the French, meaning Christ-like, because these children are so mentally retarded that they are incapable of committing sins.

The clinical features of a cretin are: slow to thrive, poor feeding, constipation, dry scaly skin, hoarse cry, bradycardia. As the child ages, clinical picture of fully-developed cretinism emerges characterized by impaired skeletal growth and consequent dwarfism, round face, narrow forehead, widely-set eyes, flat and broad nose.

Skeletal growth in cretin is characteristically more inhibited than is soft tissue growth. Therefore, the soft tissues are likely to enlarge excessively giving the cretin the appearance of an obese and stocky, short child. A gaping mouth with the tongue constantly hanging out is characteristic of the appearance; it is due to an extreme enlargement of the tongue which does not fit into the mouth. Occasionally the tongue becomes so large in relation to the skeletal growth that it obstructs swallowing and breathing, inducing a characteristic guttural breathing that sometimes chokes the baby.

Neurlogical features such as deaf- mutism, spasticity and mental deficiency are more evident in sporadic cretinism due to developmental anomalies and dyshormonogenetic defects.

In cretinism the functions of other endocrine glands (especially that of the sexual glands) are also disturbed; amenorrhea, oligospermia, azoospermia are observed.

The adult-onset severe hypothyroidism causes myxedema-edema due to accumulation of hydrophilic mucopolysaccharides in the ground substance of dermis and other tissues.

Ablation of the thyroid gland, antoimmune thyroiditis, endemic or sporadic goiter, hypothalamohypophyseal lesions, thyroid cancer, prolonged administration of antithyroid drugs, mild developmental anomalies and dyshormonogenesis may cause myxedema.

The clinical features of myxedema are: mucous edema, mental and physical lethargy, slowing of speech and intellectual function, puffiness of face, loss of hair and altered texture of the skin, constipation, cold intolerance. Basal metabolism and body temperature are decreased. Bradycardia and arterial hypotension are observed.

Autoimmune (lymphocytic) thyroiditis is a group of thyroiditis which includes Hashimoto’s thyroiditis or Hashimoto’s disease. Hashimoto’s disease (diffuse lymphocytic thyroiditis or goitrous autoimmune thyroiditis) is characterized by principal features: diffuse enlargement and lymphocytic infiltration of the thyroid gland and occurrence of thyroid autoantibodies.

It is assumed that this disease results from lesion of thyroid gland by infectious factors. Proteins of the thyroid follicles (especially thyroglobulins) pass into the blood and result in formation of autoantibodies which cause inflammation of allergic character in thyroid gland. Sometimes at first activity of the gland may be increased, but then fibrosis occurs, and hypothyroidism comes into being.

Endemic goiter is the special form of hypothyroidism. The term goiter is defined as thyroid enlargement caused by compensatory hyperplasia and hypertrophy of the follicular epithelium in response to thyroid hormone deficiency. The end-result of this hyperplasia is generally euthyroid state (in contrast to thyrotoxicosis in diffuse toxic goiter), though at some stages hyperthyroidism may be observed.

Epidemiologically, goiter occurs in 2 forms:

1. endemic;
2. non-endemic or sporadic.

Prevalence of goiter in a geographic area in more than 10% of the population is termed endemic goiter. Such endemic areas are several high mountainous regions far from the sea (Swiss, Alps, Ands, Pamirs, Tien Shan, Caucasis, Urals) where iodine content of soil, drinking water and food is insufficient for the formation of adequate quantities of thyroid hormone.

Frequently enlarged thyroid gland occurs in persons who do not have iodine deficiency (idiopathic nontoxic colloid goiter). Some foods (certain varieties of turnips and cabbages) contain goitrogenic substances that have antithyroid activity, thus also leading to TSH-stimulated enlargement of the thyroid gland.

Usually endemic goitre develops slowly, the level of thyroid hormones does not come down critically, and the signs of hypothyroidism are mild.

Decreased secretion of thyroid hormones resulted from iodine deficiency, cause hypersecretion of the hypophyseal thyrotropin (by the feedback principle) which results in thyroid hyperplasia. Hyperplastic gland can assimilate more iodine. But gradually even the compensatory enlargement of the thyroid gland cannot provide the organism with sufficient amount of thyroid hormones.

In order to prevent the endemic goiter 0.002% of iodine compounds are mixed to the table salt.

Hyperthyroidism and hypothyroidism result in also changes in the secretion of thyrocalcitonin. Owing to rapid destruction of bone tissue proteins in hyperthyroidism, a large amount of calcium compounds pass from bones into the blood. By the feedback principle, this causes inhibition of parathormone secretion, whereas secretion of thyrocalcitonin is accelerated. So development of osteoporosis is delayed. But in prolonged hyperthyroidism the function of C cells is disturbed.

Owing to increased calcium content in bone tissue during hypothyroidism, secretion of thyrocalcitonin is accelerated.

Besides, adenoma, developing from C cells of thyroid gland, causes hypersecretion of thyrocalcitonin.

**Hyperparathyroidism (excessive production of parathyroid hormone) is classified into 3 types:**

1. primary hyperparathyroidism-occurs from over secretion of parathyroid hormone due to disease of the parathyroid glands (parathyroid adenoma, carcinoma or primary hyperplasia);
2. secondary hyperparathyroidism- is caused by diseases in other parts of the body (any condition that causes hypocalcemia, including chronic renal insufficiency and intestinal malabsorption, vitamin D deficiency and consequent rickets);
3. tertiary hyperparathyroidism- is a complication of secondary hyperparathyroidism in which the hyperfunction persists in spite of removal of the cause of secondary hyperplasia (partially autonomous hyperplastic nodule continues to secrete large quantities of parathyroid hormone regardless of the needs of the body).

Adenoma and hyperplasia of the parathyroid gland cause Recklinghausen’s disease (osteodystrophia fibrosa cyctica). Activity of osteoclasts is increased which secrete citric acid; calcium and phosphorus compounds are dissolved and pass into the blood. In bone tissue cysts are formed, it is converted into fibrous tissue. Bones are softened, become twisted, and fractures occur. Hypercalcemia results in decrease of neuromuscular excitability and muscular tension. Calcium is deposited in tissues. As a result of hypercalcemia secretion of antidiuretic hormone is decreased; polyuria and polydipsia occur. Calcification of the epithelial cells of renal tubules result in severe disturbances in renal function (anuria, uremia).

Hypoparathyroidism (deficiency or absence of parathyroid hormone) is of 3 types:

1. Primary hypoparathyroidism-is caused by disease of the parathyroid glands (surgical procedures involving thyroid or parathyroid glands, idiopathic hypoparahtyroidism of autoimmune origin in children and sporadic or familial cases).

The main biochemical disorders are hypocalcemia, hyperphosphatemia and hypocalciuria. Their clinical manifestations are:

1. increased neuromuscular irritability and tetany;
2. calcification of the lens and cataract formation;
3. abnormalities in cardiac conduction;
4. disorders in the central nervous system activity (due to intracranial calcification);
5. abnormalities of the teeth.

2. Pseudo- hypoparathyroidism- is a rare inherited condition in which the tissue fail to respond to parathyroid hormone though parathyroid glands are normal.

3. Pseudopseudo- hypoparathyroidism (incomplete form of pseudo- hypoparathyroidism) –is rare familial disorder in which all the clinical features of pseudo- hypoparathyroidism are present except that these patients have no hypocalcemia or hyperphosphatemia, and the tissues respond normally to parathyroid hormone.

**Pathology of the sexual glands result in changes characteristic of each sex, as well as severe disorders in the higher nervous activity.**

Hyperfunction (hypergenitalism) and hypofunction (hypogenitalism) of sexual glands, that is, testicular or ovarian hypergonadism and hypogonadism, are distinguished.

Experimental investigation of sexual glands mainly is based on the method of castration, that is, removal of testes (testectomy) or ovaries (ovariectomy). After castration the small amounts of androgens and estrogens continue to enter from adrenal cortex.

Castration of young animals causes arrest of development of internal and external genital organs. Sexual maturation and development of the secondary sexual characteristics (for instance, the comb and spurs in cocks) are retarded. Sexual reflexes do not come into being. The distinctive properties of males and females are somewhat obliterated and a kind of intermediate (intersexual) type develops. Energy metabolism is reduced. The skeleton becomes elongated (ossification and closure of epiphyseal sutures is retarded). Development of the larynx is impeded, and the voice loses its sonorousness and strength.

Castration of adult animals (after the period of sexual maturity) causes atrophy of the sexual apparatus, involution or weakness of the secondary sexual characteristics. The sexual instinct perceptibly weakens. In females the uterus and mammary glands undergo retrograde development. Higher nervous activity is impaired, the inhibitory reactions are weakened, and the processes of excitation are intensified. Metabolism is affected: the oxidative processes diminish and deposition of fat is observed.

Evidently, all of these fenomena develop not only because of absence of the gonads, but also because of resultant hypofunction of the thyroid and pituitary glands.

Consequences of castration in human beings are similar. Men and women are castrated (gelt) because of some diseases or with religious end in view (eunuchs- guardians of harems or singing in church chorus of Roman Pope).

If the castration is performed before puberty, the sexual maturity stops, penis, prostate, vagina, uterus do not reach the maturity and even retrogress. The secondary sexual characteristics do not develop. When the castration is performed after the puberty, the sexual apparatus is retrogressed in lesser degree, and the secondary sexual characteristics are partly preserved. The secondary sexual characteristics which are preserved after the castration of the puberal organism (structure of the skeleton), are called independent sexual characteristics, and those that are lost (beard, moustache, deep voice in men, developed mammary glands, sloping forms of the body in women, character of distribution of hairs on the body of men and women) – are dependent sexual characteristics.

Testicular hypergonadism may be of 2 types:

1. Central (hypothalamo- hypophyseal) hypergonadism-is observed in cases of inflammation or tumor in the area of the grey (ashen) tuber: stimulation of secretory hypothalamic nuclei results in hypersecretion of liberins which cause accelerated synthesis of gonadotropic hormones. But such a tumor, when excessively developed, may squeeze the hypothalamus, and in these cases synthesis of testosterone is decreased.
2. Peripheral (glandular) hypergonadism-is connected with tumors of interstitial cells of Leydig

Hypertestoidism in the initial period of the individual life causes precocious puberty; growth is delayed (premature ossification of epiphyseal cartilages), but skeletal muscles develop well (anabolic influence of androgens). In hypothalamo- hypophyseal hypertestoidism synthesis of androgens, as well as spermatogenesis, are stimulated, whereas in the tumors developing from the intestinal cells synthesis of androgens is accelerated, but mature spermatozoon does not come into being. Because hypertestoidism connected with such tumors inhibits secretion of gonadotropic hormones ( by the feedback mechanism), including follicle – stimulating hormone which controls maturation of spermatozoons.

Testicular hypogonadism also may be primary and secondary:

1. Primary testicular hypogonadism may be connected with dysgenesis and atrophy of spermatic cord or hyposecretion of sex hormones ( hypotestoidism); both changes may be observed at the same time. They may be congenital or acquired. Congenital hypogonadism results from Klinefelter syndrome (dysgenesis of spermatic cord) and aplasia of the sexual glands, acquired hypogonadism may be caused by trauma, tuberculosis, acute infectious diseases ( epidemic parotiditis), orchitis (as complication of syphilis or gonorrhea), ionizing radiation.
2. Secondary hypogonadism results from diseases of the hypothalamo- hypophyseal system, and secretion of androgens is disturbed as a result of gonadotropic hormone insufficiency. As distinct from primary hypogonadism, symptoms of the secondary hypogonadism appear only after puberty.

Ovarian hypergonadism may be primary and secondary:

1. primary hypergonadism is caused by cysts and tumors of ovaries;
2. secondary hypergonadism is connected with hypersecretion of gonadotropic hormones.

Ovarian hypergonadism in early childhood causes premature development of genital organs and secondary sexual characteristics. At the beginning of the disease growth is accelerated, but soon arrest of development occurs (as a result of ossification of epiphyseal cartilages), and patients are short. Menstruations begin earlier (under 9 years of age) and cease later. Uterine bleeding is frequent.

Two forms of the ovarian hypogonadism are distinguished:

1. primary hypogonadism- results from dysgenesis, lesion by infections (epidemic parotiditis, tuberculosis, syphilis) or removal of ovaries;
2. secondary ( hypothalamo- hypophyseal) hypogonadism-results from epidemic encephalitis, tumors of the basis cerebri, meningitis, craniocerebral injury, dysfunction of thyroid and adrenal glands also may cause the secondary ovarian hypogonadism.

Deficiency of estrogens causes atrophy of genital organs and mammary glands; menstruations are absent or rare. As a result of hypogonadism before puberty development of uterus, vagina and ovaria is disturbed, the secondary sexual characteristics do not develop or are weak. The body becomes disproportionate (short lower extremities and narrow pelvis).

Progesterone deficiency causes loss of a large amount of blood during menstruations which become protracted; spontaneous abortion and infertility are observed.

There is the common feature of epiphysis (pineal gland) and thymus gland: they prevent the early puberty. When the child is 15-16 years old, these glands regress and the puberty sets in. But in spite of age involution, both pineal gland and thymus performs the most important vital functions in the organism throughout the life.

 Dysfunction of the pineal body is observed mainly in childhood. Rapid development of the primary and secondary sexual characteristics is one of the early symptoms of the epiphyseal syndrome which is explained by hypopinealism.

Tumors in the region of hypothalamus or the pineal gland (which destroy the pineal gland) may result in premature release of gonadotropins causing onset of pubertal changes prior to the age of 9 years. The features of the early puberty include premature development of genitalia both in the male and female, growth of pubic and axillary hair, in the female- breast growth and onset of menstruation.

Extirpation of pineal body in young cocks produces signs of early sexual maturation.

The thymus has to do with the cell- mediated immunity by T cells, processes of growth, development and sexual maturation. The antagonism between the thymus and gonads is attested by the fact that castration often impedes the normal involution of the thymus. Extirpation of thymus (in dogs, cats, rabbits) several days or weeks after birth in a number of cases results in accelerated development of the gonads.

Lesions of the thymus gland may result in diverse conditions of immunogenic, hematogenic or neoplastic character (thymic agenesis, hypoplasia or hyperplasia, thymoma, thymus in myasthenia gravis).

Thymic agenesia and hypoplasia are disorders in which the gland is unusually small or absent. These conditions include different types of hereditary immunodeficiency diseases (Di George’s syndrome, severe combined immunodeficiency, reticular dysgenesis). Acquired hypoplasia occurs as an aging phenomenon or may occur in the young due to severe stress, malnutrition, therapy with cytotoxic drugs and glucocorticoids.

Thymic hyperplasia (enlargement of the thymus or failure to involute) is usually connected with appearance of lymphoid follicles in the medulla of the thymus (thymic follicular hyperplasia). It is caused by myasthenia gravis (most commonly), Addison’s disease, Graves’ disease, rheumatoid arthritis, systemic lupus erythematosus, sclerodermia, hepatocirrhosis.