MINISTRY OF HEALTH OF REPUBLIC OF MOLDOVA
STATE UNIVERSITY OF MEDICINE AND PHARMACEUTICS
"NICOLAE TESTEMITANU"

A 56

Prof. Dr. Z. Anestiadi
Dr. V. Anestiadi

ENDOCRINOLOGY

Course of lectures

842868

UNIVERSITATEA DE STAT
DE MEDICINĂ ŞI FARMACIE
"NICOLAE TESTEMIŢEANU"
BIBLIOTECA

ed

Chisinau, 2003

CZU 616.43/.44(075.8)

A 65

Approved by Central Methodic Council at SMPU "Nicolae Testemitanu" under №2 of November 6th, 2003.

About the Authors

Zinaida Gh. Anestiadi – University Professor, Doctor –habilitat in Medicine, Chief of the Chair of Endocrinology.

Vasile V. Anestiadi – Doctor in Medicine, Superior Scientific Collaborator at the Centre for Pathology of the Academy of Sciences, Associate Lecturer.

Reviewers:

Vlada-Tatiana Dumbrava – University Professor, Doctor-habilitat in Medicine.

Constantin Babiuc – University Professor, Doctor in Medicine.

Description CIP of the National Book Chamber

Anestiadi Z.,

Endocrinology. Course of lectures. /Anestiadi Z., Anestiadi V.; State University of Medicine and Farmaceutics "Nicolae Testimitanu". - Ch.: S.n., 2003 (Tipogr. "Sinergie" SRL)/ 338 p.

ISBN 9975-907-66-0

100 ex.

616.43/.44(075.8)

This book appeared with the support of Novo Nordisk A/S

ISBN 9975-907-66-0

PREFACE

This is the first textbook in English on Endocrinology published in our Country, written by University Professor Z.G.Anestiadi together with Dr. V.V.Anestiadi.

Professor Z.G.Anestiadi is in charge of the Endocrinology Chair at the State University of Medicine and Pharmaceutics "Nicolae Testemitanu".

The book appears at the right time to fill a large gap in the literature in English for foreign students. It generalizes the wealth of experience gained by the authors in teaching Endocrinology at this higher medical establishment. The content of the book has been maintained at a high scientific level, it is distinguished by simple and concise presentation of an extensive range of topics.

It will be useful not only for medical students, but also for physicians in many different fields of medicine.

Rector

SUMP "N.Testemitanu",

Member of the Academy of Sciences of Moldova.

University Professor **Ion I. Ababii**

Contents

About Novo Nordisk

novo nordisk®

Novo Nordisk is a focused healthcare company. With the broadest diabetes product portfolio in the industry, including the most advanced products within the area of insulin delivery systems, Novo Nordisk is a world leader in diabetes care. In addition, Novo Nordisk has a leading position in areas such as haemostasis management, growth hormone therapy and hormone replacement therapy. Novo Nordisk manufactures and markets pharmaceutical products and services that make a significant difference to patients, the medical profession and society.

Lecture 1.

1.1. Introduction in Endocrinology.

Endocrinology is the study of the endocrine glands and of the hormones, they secret into the blood.

The term "endocrinology" comes from Greek words "endon" - within; "krinein"- to secrete and "logos"- teaching.

The term "hormone" comes from Greek "hormauo" - to set in motion. The term of "hormone" was suggested by Bayllis and Starling in 1905.

The hormones have the following particularities:

- they are secreted by specialized glandular structure;
- they are secreted directly into the blood;
- they have specific chemical structures;
- they exert the general influence on the organism, i.e. possess the distant action, not in the place of the production.

The Endocrine glands have the following particularities:

- they have the glandular structure;
- they produce hormones;
- they have not the excretorial channals;
- they secret the products of their activity directly into the blood.

The biological action of the hormones:

- They activize the permeability of the cells membranes for metabolites, thus they take part in all kinds of the metabolism.
- They participate in the regulation of the vital functions of the organism: respiration, circulation, digestion, reproduction.
- The hormones participate in providing (maintenance,

guarantee) the activity of the immune system, the resistance of the organism to the stress and provide the adaptation in the environment.

The other biologically active substances such as glucose, FFA, prostaglandins are named "parahormones" because they are produced in the diverse tissues which have no specific glandular structures.

The Endocrine system is represented by 8 glands with the internal (endogen, endocrine) secretion.

- The Hypophysis (Pituitary Gland) - the central endocrine gland
- The Thyroid Gland
- The Parathyroid Glands
- The Thymus
- The Pineal Gland (Epiphysis)
- The Islet Apparatus of the Pancreas
- The Adrenals (Cortex and Medulla)
- The Sexual Glands (Gonads)

The other glands of the endogen secretion are named, too, the peripheral endocrine glands because they are under the regulatory influence of the trophic hormones of the anterior pituitary.

It is established also the function of the secretion of the hormones of the Hypothalamus.

The hypothalamic region (hypophysotrophic) with following nuclei, which possess hormonal function included in the regulatory system, are named "the hypothalamo-hypophyseal region", that is:

- the arcuate nucleus;
- the ventro-medialis nucleus;
- periventricular nucleus;
- retrochiasmatic nucleus;

- supraoptic nucleus;
- paraventricular nucleus.

Together with hypophysis (with trop hormones of the hypophysis) this region constitutes the neuro-hormonal system, mutual system, whose function is maintenance within the specific mechanism (feed-back), which includes also the hypothalamic neuro-hormones-releasing factors: "liberins" and "statins".

The Hypophysis (Pituitary Gland) is situated in the sella turcica under the basal part of the brain. Hypophysis is named the central endocrine gland; according with its topography, anatomy and function. Other glands with internal secretion are named peripherical.

The dimensions of hypophysis are 10x12x6 mm and are practically identical with those of sella turcica. The hypophysis of an adult weighs about 0,7 g. The stalk of the hypophysis connects it with the hypothalamic part of the brain.

Stalk consists of nerve fibres passing from the base of the brain to the posterior pituitary; and of portal vessels system of the hypophysis.

The hypophysis consists of three parts:

- the anterior lobe
- the posterior lobe
- the intermediate part.

The anterior lobe (anterior pituitary) consists of: basophil, eosinophil and chromophobe cells.

Basophil cells, composing from 4 to 10% of the cellular composition of the adenohypophysis contain granules which are stained by the principal dyes. Cells are distinguished depending on the name the hormone produced: adenocorticotrophic (corticotrophocytes), follicle-stimulating (gonadotrophocytes), luteinizing (gonadotrophocytes) and thyrotrophic (thyrotrophocytes).

Eosinophil (acidophil) cells stain with acid dyes and around to 30-35% of the total number of glandular cell of the adenohypophysis. Red (fuchsinophil) eosinophil cells and orange cells can be distinguished by the number and colour of the granules in the protoplasm. For the most part red cells are located in the rostral zone of the anterior pituitary, while the orange cells are spread over the whole gland.

Among eosinophil cells somatotrophic cells (somatotrophocyte, the granules of which stain red and lactotrophic cells (lactotrophocytes) with orange granules of the cytoplasm, are distinguished in accordance with produced hormones. The chromophobe (principal) cells comprise from 50 to 60% of all the cells in the anterior pituitary. They lack the typical granulation and, under normal conditions, reveal no signs of incretory activity. The intermediate part of the hypophysis is underdeveloped in man. It consists of small follicles filled with colloid and of separate small cysts filled with a colloid-like substance. The small cysts are the remnants of the cavity of the hypophyseal pouch. The posterior lobe is represented by neuroglial cells with processes called pituicytes, connective-tissue stroma and Herring's bodies consisting of neurosecretion's accumulation.

The hypophysis produces a large number of different hormons:

1. formed in the basophil cells of the anterior pituitary:

- Adrenocorticotrophic hormone (ACTH)
- Follicle-stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Thyrotrophic hormone (TTH)

2. formed in the eosinophil cells of the anterior pituitary:

- Somatotrophic hormone (STH)
- Prolactin (PRL)

The exophthalmic factor and lipotrophic factor are also produced here. The cells of the intermediate part of the hypophysis are responsible for the incretion of melanocyte-stimulating hormone (MSH).

Vasopressin (antidiuretic hormone) and **oxytocin** are hormones of the posterior lobe. These hormones however, are not formed in the posterior lobe, but only accumulate and undergo transformations there. Vasopressin and oxytocin are formed in the neurosecretory cells of the supraoptic and paraventricular nuclei of the anterior hypothalamus.

In terms of chemical structure all the hormones of the anterior pituitary are proteins; STH and PRL are simple proteins, while ACTH is a polypeptide. TTH, FSH and LH are glycoproteins, i.e. protein complexes which include carbohydrates in their structure.

STH. The growth hormone has the maximum species specificity among the hormones of the hypophysis. STH stimulates anabolic processes in protein metabolism and exerts a substantial effect on carbohydrate metabolism; it possesses a fat-mobilizing effect (promoting activation of the fat oxidation) and influences calcium-phosphorus metabolism. Growth is mediated in large part by somatomedine-C also named insulin-like-growth-factor (IGF-1), whose synthesis is controlled by GH.

As distinct from other trophic hormones of the anterior lobe which produce their effect through the peripheral endocrine glands, the somatotrophic hormone exerts a direct influence on the metabolism of the tissues and cells of the organism.

ACTH. The adrenocorticotropic hormone (ACTH) on the one hand produces an effect on the adrenal cortex promoting the synthesis of glucocorticoids, oestrogen, androgen and partly aldosterone; on the other hand it also has an extra-adrenal effect (in experiment in vitro). The latter is displayed by the mobilisation of fat from the depot and its oxidation (experiments in vitro). Like MSH, ACTH has an effect on melanophores though to a considerably lesser degree.

TSH. The thyrotrophic hormone (TSH) intensifies the biosynthesis of the thyroid hormones (thyroxin and triiodthyronine) and their entry into the blood and is conductive to hyperplastic processes in the glandular tissue of the thyroid gland.

FSH. The follicle-stimulating (FSH) and luteinizing (LH) hormones stimulate the sexual glands and are called gonadotrophic hormones. The correlation of the concentration of FSH and LH in the hypophysis of adult males is approximately 3:1. In female this correlation may shift to 1:1. In females FSH activates the growth of ovarian follicles and in males the growth of the epithelium of seminiferous tubules.

LH. The luteinizing hormone (LH or HSIC) in females is conductive to ovulation and the development of the corpus luteum in the ovaries. In males it stimulates the growth and function of interstitial cells (Leydig's cells) in the testes.

PRL. The lactotrophic hormone (prolactin, PRL) also belongs to the group of gonadotrophic hormones because it stimulates the functioning of the corpus luteum (luteotrophic hormone). The main physiological effect of PRL, however, lies in its ability to activize the secretion of the mammary glands by its direct effect on them.

ADH. The antidiuretic hormone (ADH, vasopressin) and oxytocin, or neurohypophyseal hormones, are actually simple peptides. In physiological amounts ADH intensifies water reabsorbtion in the distal segments of the renal tubules which leads to a reduction in diuresis. With excessive incretion (in amounts greater than physiological), vasopressin (ADH) on the one hand increases arterial pressure by stimulating contractions of the vascular smooth muscles while on the other hand it stimulates the contraction of the intestinal smooth muscles.

Oxytocin stimulates contractions of the uterus and intensifies lactation. The stimulation of lactation in mainly due to the increased contraction of the lactic ductus under the effect of oxytocin.

The supply of blood to the anterior pituitary is accomplished through the portal system of the superior hypophyseal artery which is a branch of the internal carotid artery, the interlobular artery (a branch of the inferior hypophyseal artery) and the inferior capsular artery. The posterior pituitary is supplied with blood by the inferior hypophyseal artery. Blood in the portal venous system of the hypophysis flows from the hypothalamus to the hypophysis; this is of utmost importance because the releasing factors of the hypothalamus are transported with blood to the incretory elements of the anterior pituitary.

The hypophysis is innervated from the hypothalamus and the carotid plexus. From the supraoptic and paraventricular nuclei of the hypothalamus the bundles of the nerve fibres pass in the stalk of the hypophysis mainly to the posterior pituitary and only partially to the anterior pituitary and the intermediate part. The sympathetic nerve fibres which stem from the internal carotid plexus terminate in two lobes of the hypophysis and the intermediate part.

Regulation. The higher regulator of the neuro-endocrine system is the hypothalamus, which is a region of the brain located in its basal part within the limits of the middle cranial fossa. On the lateral side the hypothalamus is bounded by the optic tractus; in front by the cranial epithelial lamina, on the back by the cerebral peduncle, anterior pole of the red nucleus and substantia nigra; above, the medullary groove passing below the optic thalamus from the foramen of Monro to the aqueduct of Sylvius. The hypothalamus is connected with the cerebral cortex, the reticular formation, subcortical structures, the optic thalamus, the brain stem, cerebellum and spinal cord. There are 32 pairs of nuclei in the hypothalamus which participate in regulation of the most vital vegetative functions of the organism. The hypothalamus is the site of the higher centers of the sympathetic and parasympathetic parts of the vegetative nervous system regulating arterial pressure, vascular permeability, heat production and heat emission, appetite and several

metabolic processes. The hypothalamic centers are also involved in sleep and wakefulness and psychic activity regulation.

The hypothalamus regulates the activity of the peripheral endocrine glands both via the hypophysis (transhypophyseally) and by-passing the hypophysis (parahypophyseally). The activity of the hypothalamic centers is controlled by other parts of the central nervous system and particularly by the cerebral cortex. The hypothalamus and hypophysis constitute a single interconnected system of the organism. The hypothalamic nuclei are connected with the hypophysis by means of neurosecretory pathways.

The neurosecretory nuclei are following:

- the arcuate nucleus;
- the ventro-medialis nucleus;
- periventricular nucleus;
- retrochiasmatic nucleus;
- supra-optic nucleus;
- paraventricular nucleus.

This region of hypothalamus is named hypophysotrophic i.e. regulating the function of hypophysis.

The secretions of the neurons of hypothalamic nuclei move along the axons of the tracts separately of the posterior pituitary and the adenohypophysis. In regulating the activity of the peripheral glands, ("target" glands), the hypothalamo-hypophyseal system, in its turn, is subject to the strong influence of the former. The "feed-back" system or "plus-minus interaction" ensures the normal production of the hormones in the organism, thus maintaining the consistency of the internal medium and various functions of the organism. The incretion of trophic hormones of the adenohypophysis is regulated by the releasing factors (releasing hormones) of the hypothalamus. There are releasing factors for all the trophic hormones of the adenohypophysis.

Monoamines (dopamine, noradrenaline, serotonin) regulate the incretion of releasing factors and their entry into the circulation. These monoamines are produced by the nerve cells located in the mediobasal part of the hypothalamus. The supra-optic nuclei of the hypothalamus produce vasopressin (antidiuretic hormone) for the most part, while the paraventricular nuclei mostly produce oxytocin; these eventually accumulate in the posterior pituitary. Change in the osmotic pressure of plasma and its volume, as well as the state of the central and vegetative nervous system, regulate the incretion of vasopressin (ADH). Vasopressin incretion intensifies with a reduction in plasma volume and increase in its osmotic pressure. With reverse changes the incretion of vasopressin decreases.

Tabel 1

THE NORMAL CONTENT OF THE HYPOPHYSEAL HORMONES IN THE BLOOD

HORMONE	NORMAL CONTENT	METHOD
Adrenocorticotrophic hormone	10-150 ng/ml	Radioimmunoassay (RIA) using standard kit of the Amersham Association (Britain)
Thyrotrophic hormone	0,5-1,5 ng/ml	-//- kit Cea-IRE-Sorin Ass. (France)
Somatotrophic hormone	3,81±0,8 ng/ml	-//- kit Cea-IRE-Sorin Ass. (France)
Luteinizing hormone in males	5-25 mU/ml	-//-
Follicle-stimulating hormone in males	5-25 mU/ml	Institute of experimental Endocrinology and Chemistry of Hormones (AMS Russia) kit Cea-IRE-Sorin Ass. (France)

642868
UNIVERSITATEA DE STAT DE MEDICINĂ ŞI FARMACIE "NICOLAE TESTEMIŢEANU"
BIBLIOTECA

1.2. Acromegaly. Gigantism.

Acromegaly is a disease characterized by the disproportional growth in adult of the skeleton, soft tissues and internal organs, which occurs as a result of the augmented production of the growth hormone by eosinophil cells of the anterior pituitary. Acromegaly means large extremities (greek "acron"- extremity, "megas"- great). Acromegaly occurs in adult at the age of 20 to 40 years, just as frequently in males and in females.

Gigantism is a disease characterized by proportional intensified growth (height over 200cm) of the skeleton (although not corresponding to age) and of other organs and tissues as a result of the increased production of the growth hormone. Gigantism usually develops in the period of sexual maturation at the age of 17 to 25 years, more often in males.

Thus acromegaly and gigantism are variants of one and the same abnormal process.

History. The disease was first described by French neurologist Pierre Marie in 1886.

Aetiology. The aetiology of acromegaly and gigantism is unknown. The development of the acromegaly is promoted by:

- hypophyseal eosinophil adenoma or hyperplasia of the eosinophil cells;
- cranial trauma (contusion, head injury);
- pregnancy;
- acute and chronic infections (influenza, enteric fever and typhus, measles, syphilis);
- psychic trauma;
- inflammatory process in the hypothalamic area;
- lesion of the tuber cinereum;
- genetic factors;

BIBLIOTECA

- ectopic STH producing tumours (in the pharyngeal region, sphenoid sinuses).

Pathogenesis. Hyperproduction of the somatotrophic hormone (STH) leads to gigantism in open zones of growth, to increased dimensions of the internal organs (splanchnomegaly) and of muscular tissue and after the closure of epiphyseal zone, to disproportional enlargement and thickening of extremities and cranial bones together with the increase of the soft tissues.

Pathology. Pathological examination often reveals an eosinophil adenoma or the diffuse hyperplasia of eosinophil cells in the anterior pituitary, on rare occasions there is a malignant adenoma with metastases in the cranial bones or sella turcica. The sella turcica is widened and sections of the main bone adjoining it destroyed. The bones of the skeleton, joint, cartilages, capsules and tendons are thickened. Hypertrophy and hyperplasia of the endocrine glands and internal organs are noted.

Clinical picture. Patients suffering from acromegaly complain of headache, sexual disorders, changes in their outward appearance and voice, impairment of vision and memory, muscular pain.

Very characteristic are the patients' complaints of:

- headache ;
- changed appearance;
- a repeated change within a short period of time of the patient's size in hats, gloves, shoes, suits and other clothes.

During examination particularly noticeable is characteristic clinical picture (Acromegaloidic feature):

- tall stature;
- enlargement of the superciliary arches, zygomatic bones, the hollow of the auricles, nose, lips, tongue;

- prognathism (marked projection of the lower jaw);
- diastema (an increase in the space between teeth);
- enlargement of the head, hands, feet, heel bones at the cost of the thickening of the bones, including cranial.

The skin is coarse, with thick folds, particularly on the face, more rarely on the hairy part of the head. The skin is more sebaceous and moist than usual and intensified pigmentation often occurs. There is abundant growth of hair on the body and face (hypertrichosis). The thorax increases in volume making the patient barrel-chested. The intercostal spaces become widened. The sternum, clavicles and ribs thicken. In some cases kyphosis and scoliosis of the spine develop.

The internal organs are often enlarged (splanchnomegaly). The cardiovascular system reveals hypertrophy of the heart, predominantly the left ventricle, with subsequent dilatation and progressive cardiac insufficiency. A more frequent earlier and marked development of atherosclerosis is noticed. Arterial pressure is often elevated. The levogram is usually encountered in the ECG and the deformation of the QRS complex is revealed, testifying the disorders of intraventricular conductivity. The "T" wave is flattened or inverted.

The respiratory organs show a tendency to bronchopneumonia with frequently developing emphysema.

In some cases peptic ulcer disease and malignant tumour of the abdomen occur. Disturbance of the protein-forming function of the liver and a tendency of forming stones in gall bladder and developing dyskinesia of the bile ducts are frequent.

In gigantism the dimensions of the internal organs are increased in proportion to growth and there are no signs of their functions being disturbed.

Impairment of vision in acromegaly most often comes down to bilateral-hemianopsia (defective vision or blindness in the temporal half of the

field of vision in each eye), primarily to the red, white colours. This is observed in atrophic changes in the optic chiasm because of the compression of the optic nerves by the tumour during its extracellar growth. Sometimes a total blindness may develop.

Disorders of the central nervous system are usually manifested by symptoms of increased intracranial pressure (headache attended by nausea and vomiting, dizziness, epileptoid paroxysms, chocked disc, etc.). Functional disorders of the vegetative nervous system give rise to hyperhydrosis, instability of arterial pressure, hot flushes, tendency to tachycardia. Disorders of the higher nervous activity are revealed in apathy, flaccidity, sluggishness, lapses of memory, drowsiness. In the initial phase of the disease the endocrine glands (thyroid, parathyroid glands, pancreas and others) are usually subject to hyperplasia and their function is heightened. Eventually (at later period of the disease) hypoplasia of the endocrine glands often develops with a function's reduction.

Laboratory findings. The investigations used for the diagnostic aim are following;

- Growth hormone level in acromegaly is increased by 7-10 times;
- Glucose tolerance test has diabetic type in 25% of cases;
- Insulin-like-growth-factor (IGF-1) level is raised in acromegaly in about 80% of cases. It reflects mean 24hour growth hormone levels;
- Visual field defects are common (bitemporal hemianopsia);
- MRI of pituitary will almost always reveal the pituitary adenoma;
- CT (computer tomography) reveals the pituitary adenoma changes of the dimensions of the sella turcica;
- Pituitary function- partial or complete anterior hypopituitarism is common;

- Prolactin - mild to moderate hyperprolactinaemia occurs in 30% of patients.

There are usually no changes in the blood. In the severe progressive form of the disease, however, anaemia, leucopenia and eosinophilia are possible. Tolerance to carbohydrates is often lowered to the point of diabetes mellitus (in 15 to 25% of patients).

There is an increased amount of total protein, hypoalbuminaemia, and hyperglobulinaemia, mainly at the expense of alpha-1- and alpha-2-globulins. In the active phase of the disease the levels of STH, NEFA, inorganic phosphorus and immunoreactive insulin in the blood and excretion of inorganic phosphorus and calcium in the urine are increased.

Diagnostic test. The determination of the STH content in the blood serum after glucose loading may be used to show up the active phase of acromegaly. The test is based on changes in STH incretion by the hypophysis depending on the content of sugar in the blood. In case of hypoglycaemia STH incretion by the hypophysis is sharply increased whereas with hyperglycaemia it decreases. In healthy individuals the content of STH in the blood serum diminishes within three hours of glucose loading. After glucose loading the level of the growth hormone is paradoxically increased in the blood serum of patients with the active phase of acromegaly whereas in the inactive phase it does not change. This test, however, cannot always serve as a trustworthy diagnostic aid.

X-ray diagnosis. The sella turcica is enlarged with a widened entrance and deepened fundus. Destruction of its clinoid processes and posterior wall is often noted. The dimensions of the skull are enlarged with the thickening of the skullcap bones and their external protrusions. Heightened pneumatization of the paranasal sinuses is noticed.

Diagnosis and differential diagnosis. Acromegaly is diagnosed on the basis of complaints (headache, changed appearance, a repeated

change within a short period of time of the patient's size in hats, gloves, shoes, suit and other clothes), in the combination with a characteristic clinical picture (enlargement of supercilliary and zygomatic arches, nose, lips, tongue, prognathism, drastic thickening of the bones of extremities, etc.) and data obtained by other methods of examination, including first of all determination of the level of STH in the blood prior to and after glucose loading, and of inorganic phosphorus and X-ray diagnosis. The increasing of the IGF-1 level.

Hypophyseal gigantism is diagnosed on the basis of the more or less proportional growth of the skeleton (height over 200cm) and other organs and laboratory and X-ray data (a high level of STH, inorganic phosphorus, late ossification of epiphyseal cartilages, change in size of the sella turcica and so on).

Acromegaly is differentiated from Paget's disease, hypothyroidism and the pachydermoperiostosis syndrome. Evidence in favour of Paget's disease and against acromegaly is the lesion of only separate bones with severe trabecular reorganization and without changes in the sella turcica and the soft tissues.

Unlike acromegaly, in marked forms of hypothyroidism the enlargement of facial features and thickening of limbs take place at the cost of swelling soft tissues; this swelling is eliminated by treatment with thyroidin or triiodthyronine. One should not, however, neglect the main form of hypothyroidism, the cause of which is tumour of the hypophysis.

Evidence in favour of the pachydermoperiostosis syndrome and against acromegaly is the massive thickening and hardening of regional areas of the skin, the absence of changes in the cranial bones and the sella turcica.

Hypophyseal gigantism is differentiated from constitutional gigantism, partial gigantism, primary hypogonadism and Marfan's syndrome.

Constitutional gigantism is evidenced by the medical history (great height and body weight of the parents), normal sexual and physical development, the absence of abnormal changes judging from the results of additional methods of examinations (laboratory findings and X-ray diagnosis).

Marfan's syndrome is characterized by development defects (abnormal shape of the ears, congenital heart defects, dolichocephalic cranium, etc.).

Primary hypogonadism is marked by high disproportional growth (a relatively short trunk, a small head, long extremities) in combination with acute underdevelopment of sexual organs and the absence of secondary sex characters.

Prognosis. In cases of a benign tumour the prognosis is favourable (the disease lasts tens of years), but unfavourable in the case of malignant adenoma. Death may be caused by cardiac insufficiency, necrosis of the tumour or compression by it of vital brain centers, intercurrent infections or cerebral haemorrhages. With a benign tumour or simply hyperplasia of the eosinophil cells of the anterior pituitary, working capacity is preserved for many years.

In the mild form of acromegaly patients may be qualified as group III invalids.

The constant increase of intracranial pressure, diminution of muscular strength and impairment of vision (moderate degree of the disease) provide sufficient grounds for granting group III invalidity, while noticeable progress of the disease will call for granting group II invalidity.

In severe form of the disease (marked symptoms of increased intracranial pressure, adynamia, pronounced myalgia, considerable impairment of vision) leads patients to group II invalidity, while acute adynamia and sharply progressive impairment of vision - to group I invalidity.

Patients suffering from acromegaly must be kept under constant comprehensive medical surveillance by an endocrinologist, neurologist and ophthalmologist.

Treatment. The principal methods of treatment are X-ray or gamma-ray therapy, applied to the hypothalamo-hypophyseal region. In the absence of symptoms of tumour of the hypophysis X-ray therapy is applied on three fields (two temporal and one frontal). It is conducted by the fractional-intensive method in increasing doses (75-100-150-200R) with intervals of one-two days, and then 250R daily. The total dosage is 3000 to 5000R.

In a tumour of the hypophysis patients in the active phase of the disease are given X-ray treatment directed at the hypothalamo-hypophyseal region from four fields (two temporal, frontal and occipital). The single dose is from 200 to 250R. The total dosage is from 8000 to 12000R (10000R on the average).

In the event of the disease continuing to develop a course of X-ray therapy is repeated after 6 to 8 months.

Instead of X-ray therapy directed at the tumour gamma-ray therapy can be prescribed using radioactive cobalt (60Co). The skin and bone tissue is less damaged in gamma-ray therapy and increasing the depth dosage becomes possible. The total dose for the entire course is from 4000 to 5000 rads. To increase the healing effect it is expedient to combine radiation therapy with the use of female sex hormones (diethylstilbestrol, oestradiol propionate and others), which reduce the incretion of STH.

In some cases radioactive gold (98Au) or radioactive yttrium (90Y) is implanted in the tumour. The latter is used in the form of granules with an activity of 1 to 2 microCi. It is introduced into the hypophysis transnasally or transsphenoidally (nasal cavity, anterior wall of sphenoidal sinus, floor of sella turcica.

The treatment of acromegaly with heavy particles in the form of high-energy protons produced by a cyclotron is promising.

The criteria of the efficacy of radiation therapy are the cessation of headache, expansion of visual fields, stabilization of the dimension of the sella turcica, restoration of the function of the sexual glands and normalization of the content of STH and inorganic phosphorus in the blood, improvement in the index of carbohydrate metabolism, etc.

In the absence of any effect from radiation therapy and when the visual fields continue to narrow sharply, the surgical excision of the hypophysis's tumour or cryohypophysectomy is indicated.

Racking headache is relieved by dehydration and hypotensive therapy (magnesium sulphate, hydrochlorothiazide, euphylline, etc.)

To maintain the remission with normal level of the STH the treatment is often combined with medium term treatment by dopamine agonists or octreotide (synthetic analog of the somatostatine).

Agonists of the dopamine are known as preparations: bromcriptin, parlodel, bromergon and are administered per orally in dose of 2,5mg (in pills) from 1 pill 3 times per day till two pills 4 times per day during 2-6 months.

Octreotid, a synthetic analog of somatostatin (Sandostatin) inhibits the secretion of the STH. Somatostatin (Sandostatin) is given by subcutaneous injection in doses of 50-200 micrograms 8 hourly under the control of the STH level. But it is very expensive.

Complications such as diabetes mellitus and insipidus, toxic goitre, hypothyroidism, hypogonadism, hypocorticism, etc., require therapy relevant for these diseases.

In the necessity, substitution therapy with the thyroid preparations, corticosteroid and sexual hormones is administered. In males there is indicated an androgenic preparation: Sustenon-250 or Omnadren

intramuscularly 1 ml one time in the month. In females - feminine sex hormones: Sinestrol, Folliculin intramuscularly daily during 15-20 days or Microfolin per os; and after that Progesterone is associated intramuscularly or Pregnin per os, imitating the menstrual cycle. Nowadays there are the combined preparations including oestrogens and progestins. Diane-35, one pill daily - 21 days every month.

Lecture 2.

2.1. Simmonds' Syndrome (Hypothalamo-Hypophyseal Cachexia) and Sheehan's Syndrome (Postpartum Hypopituitarism)

Simmonds' Syndrome is a disease which develops as a result of extensive destructive changes in the adenohypophysis and the diencephalon, leading to insufficiency of the anterior pituitary (panhypopituitarism) and progressive emaciation. The disease occurs more often in females and usually begins at the age of 30 to 40 years.

History. The disease was first described by Glinsky in 1913 and by Simmonds in 1914.

Aetiology. Simmonds' Syndrome may develop as a result of damage to the hypothalamo-hypophyseal region by:

- inflammatory or infectious process (syphilis, tuberculosis, influenza, typhoid, etc.);
- cranial trauma with subsequent haemorrhage into the adenohypophysis;
- tumours of the hypophysis;
- hypophysectomy.

The Sheehan's Syndrome was described in 1939 by Sheehan and is the most frequent form of insufficiency of the anterior pituitary. Its aetiological factors are:

- necrosis of the hypophysis as a result of prolonged spasms of its arteries in profuse haemorrhages during childbirth, abortion;
- embolism of the hypophyseal vessels developing after childbirth or abortion with septic state;

- gastrorrhagia or other massive haemorrhage.
- multifoetation and frequent pregnancies predispose the organism to the development of Sheehan's Syndrome.

Pathogenesis. Extensive destructive changes of the hypothalamus and adenohypophysis lead to the loss of the incretion of trophic hormones of the anterior pituitary. This, in turn impairs the function of the peripheral endocrine glands, primarily of the thyroid gland, the adrenal cortex and sexual glands. The reduced production of the growth hormone by adenohypophysis leads to the development of the atrophic processes in the organs and tissues.

Pathology. Pathological examination most often reveals changes in the anterior pituitary: tumours, haemorrhges, necroses and inflammatory processes. Similar changes in the hypothalamus are noted more rarely. In some cases a tumour is found in other parts of the brain with compression and destruction of the hypothalamus. Marked atrophic changes are noted in all organs and tissues (skin, subcutaneous fat, skeletal muscles, internal organs, endocrine glands, external genitalia). Fatty degeneration of the bone marrow is often encountered.

Clinical picture

Complaints include:

- increasing general weakness;
- apathy, progressive weight loss;
- absence of appetite to the point of the aversion to food;
- constipation alternated by diarrhea;
- chilliness, drowsiness, headache;
- decreasing of sexual desire and potency;
- disorders of the menstrual cycle;
- diminishing of the resistance to infections.

During examination particularly noticeable are:

- acute emaciation and premature ageing;
- dryness of skin, atrophy;
- paleness with earthy hue or the remarkable alabaster paleness;
- hair thins and falls out;
- lack of hair under the armpits and the pubis;
- the subcutaneous fat is very thin or entirely wasted away;
- the lower jaw becomes atrophied;
- caries sets in and teeth fall out;
- The inner organs are reduced in size (splanchnomicria). The involvement of the cardiovascular system is manifested by a tendency to bradycardia, dull heart sounds, arterial hypotonia and to collapse at the smallest physical extension. The ECG shows low-voltage waves, bradycardia, and dystrophic changes of the myocardium.
- The disorders in the function of the gastro-intestinal tract (dyspeptic phenomena, nausea and vomiting) caused by a eduction of gastric secretion and external secretion of the ancreas. Ptosis and atonia of the intestine develop and the iver function is disturbed.
- The disorders of the nervous-psychic sphere are manifested by flaccidity severe apathy and loss of memory. The patient ecomes depressed, sleepy and suffers from hallucinations and at times from negativism. In the later period of the disease here may be symptoms resembling those of schizophrenia. In some cases there are polyradiculoneuritis and sometimes sharp pain of various localizations (the upper and lower extremities, the lumbar and abdominal regions). With affection of the hypothalamus and hypophysis diabetes insipidus occurs in some patients. In some cases, determined by adenomas, vision is impaired (atrophy of the optic nerve, narrowing of the field of vision).

- The affection of the endocrine system is manifested mainly by a diminution in the function of the thyroid gland (dryness of the skin, bradycardia, persistent constipation, hypothermia); the sex glands (disappearance of the secondary sex characters, disturbance of the menstrual cycle in females, impotence in males and hypoplasia of the genitalia); adrenal cortex (alabaster paleness of the skin, increasing general weakness, progressive weight loss, hypotonia).

In Sheehan's Syndrome the clinical picture is basically the same as in Simmonds' Syndrome. Unlike the latter, however, Sheehan's Syndrome

- develops stealthily acquiring a chronic course;
- emaciation is less severe;
- symptoms of the thyroid insufficiency often prevail in the clinical picture of this disease attended by pastiness and sometimes by the oedema of the face and extremities, which is not typical of Simmonds' Syndrome;
- psychic changes in Sheehan's Syndrome are less marked than in Simmonds' Syndrome and are mainly associated with hypothyroidism (apathy, depression).

Laboratory findings

- A low level of ACTH, TTH, FSH, LH, STH in the blood;
- normochromic or hypochromic anaemia are often noted, sometimes leucopenia with neutropenia and moderate eosinophilia;
- the content of sodium and chlorine in blood is diminished; there is a tendency for hyperkalaemia and hypoglycaemia;
- the sugar (content) curve after glucose loading is flat;
- hypoproteinaemia which is a consequence of the disintegration of the proteins and a decrease in their synthesis;
- hypercholesterolaemia;

- the decrease of the blood concentration of thyroid hormones, cortisol, oestrogen, etc.
- the sharply reducing of the daily discharge of 17-OCS, 17-CS, gonadotrophins and oestrogens in the urine;
- in diabetes insipidus the relative density of urine reduces to 1.005-1.000.

X-ray diagnosis. In tumour of the hypophysis the sella turcica is enlarged and its shape changes. In many cases there is marked osteoporosis of the bones.

CT and MRI of the sella turcica sometimes reveal adenoma of the anterior pituitary.

Hormonal diagnostic tests. To confirm the secondary character of hypothyroidism the thyrotrophin test is done in the initial phase of the disease. A heightened uptake by more then 50% of radioactive iodine by the thyroid after the subcutaneous injection of 10 U of thyrotrophin testifies to the central (hypophyseal) genesis of hypothyroidism.

Diagnosis and differential diagnosis. The diagnosis of hypothalamo-hypophyseal cachexia is made on the grounds of progressive emaciation combined with premature ageing, the falling out of hair, symptoms of the simultaneous insufficiency of the thyroid, adrenal cortex and sexual glands, as well as data from the medical history (the appearance of symptoms of the disease soon after abnormal childbirth, complicated by massive haemorrhage and puerperal sepsis, etc.). Hypothalamo-hypophyseal cachexia is differentiated from diseases attended by acute emaciation such as malignant new growths, chronic infections (tuberculosis, etc.), Addison's disease, neurogenic anorexia (anorexia nervosa). In cases of malignant new growth and chronic infections body hair does not fall out while the laboratory findings are not characteristic of hypothalamo-hypophyseal cachexia. As distinct from Addison's disease, hypothalamo-hypophyseal cachexia is recognized by the

absence of a typical pigmentation of the skin and mucous membranes by the shedding out of hair and a remarkable "alabaster" paleness combined with symptoms of the thyroid and sexual gland insufficiency. Anorexia nervosa occurs mainly in young girls of 13 to 14 years old, but may also develop in young women. The data from the medical history and the incongruity of acute emaciation with a generally satisfactory condition, the absence of hair falling out and of the regression of secondary sex characters against the background of disorders of the menstrual cycle provide evidence in favour of anorexia nervosa and exclude the possibility of hypothalamo-hypophyseal cachexia (development of the disease after severe psychic trauma and conflicts which result in the loss of appetite to the extent of aversion to food or as a consequence of a strict diet observed for reducing weight).

Prognosis. The prognosis of the disease depends on the cause and dynamics of the main pathological process. In a disease caused by an inflammatory or a tumour process in the hypothalamo-hypophyseal region, radical treatment (removal of the tumour, cyst, etc.) arrests the further advancement of the disease and makes possible partial restoration of the function of the anterior pituitary.

In Sheehan's Syndrome prognosis in regard to recovery is unfavourable. When proper substitution therapy is applied the life of the patient may be prolonged for many years. Without correct treatment death occurs as a result of acute adrenal insufficiency, hypopituitary coma and from attendant acute infections. Most patients suffering from hypothalamo-hypophyseal cachexia are incapable of working (group I and II invalids). In cases of a relatively favourable course of the disease patients are sometimes qualified as group III invalids.

Prophylaxis. Prophylaxis consists in the prevention and immediate treatment of puerperal infections, sepsis, shock, haemorrhages, and childbirth injuries.

Treatment. Treatment is directed at removing the cause of the disease. Surgery or radiation therapy is undertaken when there is a tumour in the hypothalamo-hypophyseal region. Specific anti-inflammatory therapy is indicated when the hypothalamo-hypophyseal region is involved in an infectious process (syphilis, tuberculosis, etc). Whenever necessary, substitution hormonal therapy is applied in parallel irrespective of the cause of the disease: ACTH (20-100 U intramuscularly every day in the initial phase of the disease), corticosteroids (cortisone 25mg daily, DOCA (desoxycortone acetate) 5mg daily or every other day and others), gonadotrophic agents (chorionic gonadotrophin, 500-1000 U intramuscularly 2-3 times a week, and others).

Substitution therapy in males is conducted with androgenic preparation (testosterone propionate intramuscularly 10-25mg 2-3 times a week; or Sustenon-250, Omnadren 1ml intramuscularly every month and other agents); in females with female sex hormones (diethyestilbestrol per os or 1mg intramuscularly daily; progesterone intramuscularly or pregnin per os). Diane-35 one pill daily during 21 days every month.

In cases of hypothyroidism, treatment with thyroidin or triiodthyronine should be conducted with great caution, because these preparations intensify hypotension. In view of this they are prescribed in combinations with glucocorticoids (prednisolone, dexamethasone and others). Thyroidin is prescribed per os 0,03-0,05g twice a day and triiodthyronine hydrochloride 10-20microg daily with control maintained over the state of cardiac activity, pulse rate and arterial pressure.

Anabolic steroid preparations are prescribed, such as methandrostenolone (nerobol), 5mg given orally 2-3 times a day; methylandrostendiol sublingually 25mg 1-2 times a day; 1ml of a 2.5 or 5 per cent of a retabolil solution intramuscularly once every three weeks and other agents to augment protein synthesis in the body. Patients suffering from hypothalamo-hypophyseal cachexia need mental and

physical rest. They should be given a high-calorie diet rich in proteins, carbohydrates, vitamins (C, B complex and others) and also in sodium chloride.

In case of hypopituitary coma and precomatose status large doses of corticosteroids are prescribed (hydrocortisone by intravenous drip, 100-300mg daily or cortisone intramuscularly, 50mg every 4-6 hours. A physiological solution (500ml) with 250-300ml of 5% glucose solution is infused intravenously by drip to prevent dehydration of the organism.

Strophanthin, caffeine, cordiamin, mesatone (phenylepinephrine hydrochloride) and other drugs are prescribed to prevent cardiovascular insufficiency.

2.2. Hypophyseal nanism (Dwarfism, Microsomia)

Nanism (Gr. Nanos-dwarf) is characterized by deficient stature (adult males no higher than 130 cm and adult females below 120 cm). Nanism may be an independent disease (genetic nanism) or as a symptom of particular endocrine and non-endocrine diseases.

Hypophyseal nanism is a genetic disease caused by an absolute or relative deficiency of the growth hormone in the organism which leads to the retarding of the growth of the skeleton and other organs and tissues. In genetic nanism the sharp retardation of growth usually begins after two-three years of age.

History. The disease was first described by Paltauf in 1891.

Aetiology and Pathogenesis. Hypophyseal nanism is currently regarded to be a genetic disease which is inherited as an autosomal-recessive trait. Hypophyseal nanism may occur as a result of the isolated insufficiency of the growth hormone. In hypophyseal nanism together with insufficiency of the growth hormone a decrease in the production of gonadotrophic hormones is often observed, more rarely a decrease

of the thyrotrophic hormones of the anterior pituitary. This, in turn, leads to a decrease in the function of the peripheral endocrine glands (thyroid, sexual, adrenal cortex), hormones of which also have stimulating effects on growth (panhypopituitary form of dwarfism).

In some cases hypophyseal nanism may occur in people with a normal level of the growth hormone but when hormone is biologically not active.

Besides hypophyseal nanism, genetic nanism also includes a form of dwarfism arising when there is a normal level of growth hormone but the peripheral tissues are insensitive to it.

It is established that the pathogenesis of Laron's nanism is determined by the deficiency of the IGF-1 and IGF-2 but in the same time the level of the growth hormone is normal. Growth is mediated in large part by somatomedine-C (insulin-like-growth-factor IGF-1) and IGF-2 whose synthesis is controlled by GH.

Nanism may develop as a consequence of the lesion of the hypothalamo-hypophyseal region by traumatic, infectious, tumorous, vascular and other processes.

Multiple acute infectious diseases (pneumonia, influenza, tonsillitis and other) affect growth and development, just as chronic infections (tuberculosis, syphilis and others), hereditary factors (small height of parents or relatives, alcoholism etc.), insufficient or poor nutrition, particularly when lacking in proteins and vitamins, and unfavourable environmental conditions.

Pathology. The hypophysis is often merely hypoplastic. In many cases atrophic changes are revealed in its anterior lobe caused by a particular abnormal process (tumour, inflammatory process, haemorrhage, etc.). Sometimes there are no morphological changes in the hypophysis and hypothalamus.

Hypoplasia and atrophy are also revealed in the thyroid gland, sexual glands and rarely in the adrenals. The skeleton and internal organs are small in size.

Clinical picture. The constitution of parents with the genetic form of nanism is proportional. The skin is usually pale, at times with a yellowish shade, wrinkled and sometimes dry. The subcutaneous fat is poorly developed but obesity sometimes occurs with deposits of fat mainly over the abdomen, in the area of mammary glands, pubis and thighs. The muscular system is poorly developed. The skeleton's maturation lags behind registered age. The internal organs are small in size (splanchnomicria), but their function is usually not disturbed.

In the panhypopituitary form of dwarfism there is a tendency towards bradycardia and a lower arterial pressure. In this form of hypophyseal nanism the sexual system is sharply underdeveloped. Throughout the life-span the genitals remain of size that is characteristic for early childhood. Males sometimes have cryptorchidism (failure of the testis to descend into the scrotum). Females do not have menstruation. Secondary sex characters and sexual desire are absent.

In all types of genetic nanism the intellect is preserved. In nanism caused by organic lesion of the brain (tumour, hydrocephalus, etc.) general cerebral symptoms appear, mental retardation, quite often diabetes insipidus. In compression of the optic chiasm by a tumour, vision's fields become narrower (bitemporal hemianopsia).

Laboratory findings. A low level of the growth hormone in the blood serum is observed. The level of the IGF-1 and IGF-2 is diminished. There is a decrease in the alkaliphosphatase's activity and the level of inorganic phosphorus. In the panhypopituitary form of genetic nanism lymphocytosis, hypercholesterolaemia and a tendency towards hypoglycaemia are often noted. The sugar curve is sloping and is not high. The levels of thyroid hormones in the blood are at the lowest

limit of the norm and even lower. The level of the cortisol in the blood is diminished. The excretion of the 17-CS, 17-OCS and oestrogens in the urine is decreased.

Diagnostic tests. A test with intravenous infusion of insulin or arginine amino acid is performed in several instances to disclose the unused capacity of the somatotrophic function of the hypophysis. The test with the injection of insulin should be conducted with caution (there is a risk of a severe hypoglycaemic state). The test is based on stimulating incretion of the hypophyseal growth hormone by means of hypoglycaemia. Insulin is injected intravenously in a dose of 0,1 U/kg or 4 U per 1m2 of body surface. Investigation of the growth hormone in blood serum is conducted prior to and every 15-30 minutes for 1-2 hours after the administration of insulin. In healthy individuals with hypoglycaemia the hormone in the blood serum is more than tripled. In patients with hypophyseal or cerebral nanism the level of the growth hormone in the blood serum in the presence of hypoglycaemia either changes very slightly or not at all.

The biological mechanism of the arginine test is not very clear. Arginine is introduced intravenously in a dose of 0,5g/kg for a child or a patient with nanism and 30g of a dry substance for an adult. The arginine solution is injected intravenously for 30 minutes. Investigation of the growth hormone in the blood serum is carried out 15 minutes before arginine injection and every 15-30 minutes for one-two hours after the arginine was introduced. The response of healthy individuals to the arginine injection is marked by a sharp augmentation of the growth hormone in the blood serum (by eight and more times). In patients suffering from hypophyseal nanism the level of the growth hormone in the blood serum after arginine injection either does not change at all, or very slightly.

The endogenic reserve of the TH is revealed by the GHRH test. The preparation is administered in doses from 1 to 3 microg/kg body mass

of the patient. The increase of the STH is noted after 15-20 min. The positive test shows that the hypophysis is intact and the damage is on the hypothalamic level.

X-ray diagnosis. On a radiograph the cranium has the proportions typical of a child. The skull cap is thin. In genetic nanism the sella turcica is normal. The changes in it depend on the cause of the disease. In congenital underdevelopment of the hypophysis the sella turcica is diminished or normal. When there is a tumour in it, by CT and MRI it is revealed that sella turcica is enlarged, deformed and its walls are destroyed. In the panhypopituitary form of genetic nanism there is a delay in the ossification of the epiphyseal lines of bones. In untreated cases the zones of growth do not close throughout life.

Diagnosis and differential diagnosis. The diagnosis of genetic nanism (an independent disease) is made on the basis of the medical history (sharply retarded growth from the age of two-three years), and a typical clinical picture, particularly in combination with proportional retardation of growth acute underdevelopment of the sexual apparatus and with preserved intellect. Genetic nanism is differentiated from nanism occurring in hypothyroidism, chondrodystrophy, Shereshevsky-Turner Syndrome, Down's disease and somatogenic dystrophy. Unlike genetic nanism thyreogenous nanism is marked by the disproportional retarding of growth in combination with a considerably diminished intellect and symptoms of hypothyroidism (inertness, constipation, dryness of skin, a lower thyroid hormones content in the blood, the sharp reduction of the basal metabolism).

Symptoms favouring chondrodystrophy and against hypophyseal (genetic) nanism are the disproportional retardation of the growth but with sexual apparatus developing normally. The appearance of these patients is very typical: a large head with strongly developed frontal and parietal eminences, a normal-sized trunk with sharply shortened extremities mainly because of the drastic shortening of the humeral

and femoral bones. Very often there is saber deformity of the lower extremities and the buttocks protrude sharply.

The Shereshevsky-Turner Syndrome has several symptoms similar to those of hypophyseal nanism, i.e. proportional retardation of growth, sexual infantilism often a preserved intellect. As distinct from hypophyseal nanism, however, the Shereshevsky-Turner Syndrome is characterized by skin folds on the neck from head to shoulder, a low posterior hair link and low position of ears. The Shereshevsky-Turner Syndrome is usually attended by congenital developmental defects of the internal organs (coarctation of the aorta, etc) and the skeleton (syndactyly, a Madelung-type deformity of the radio-carpal articulation), negative sex chromatin, karyotype 45,X.

As distinct from hypophyseal nanism, congenital abnormality of growth in Down's disease is attended by mental retardation and a typical appearance: slanting eyes and an inanely joyful facial expression. A thickened tongue protrudes from the patient's mouth.

In cases of constitutionally delayed growth of the body and retarded physical development there is no progressive gap with the passing years between actual age and bone development. This distinguishes it from hypophyseal nanism. Sexual development in such children proceeds normally or is only slightly delayed. In puberty children with constitutionally delayed growth usually catch up with their coevals in height.

In some cases long-term dynamic observation is necessary for making a final diagnosis. Growth retardation due to somatogenic dystrophy is determined on the grounds of the medical history data (starvation, chronic metabolism disorders and diseases of the internal organs) and also of the abnormalities of the kidneys, heart, lungs, digestive system).

Laurence-Moon-Biedl Syndrome presents a combination of retarded growth and mental retardation, obesity, polydactyly, retinitis pigmentosa, atresia ani.

Prognosis. The prognosis of the disease depends on the cause and dynamics of the main pathological process (tumour of the hypophysis, an inflammatory process, etc). In hypophyseal nanism (genetic disease) timely therapy (anabolic steroids, substitution therapy) considerably improves prognosis of both life and working capacity. Patients may often perform any kind of work that does not involve physical and considerable neuro-psychic tension.

In many cases the working capacity of patients is limited and they become group II invalids. If the patient has a very short stature and is extremely weak physically, he is qualified a group II invalid.

Treatment. The treatment of the nanism depends on the cause of the disease. A hypophyseal tumour is removed surgically. In treating hypophyseal nanism, for stimulating growth and physical development, wide use is currently made of synthetic anabolic steroids (methylandrostenediol, methandrostenolone, retabolil).

It is most expedient to begin treatment with anabolic steroids from the age of five to seven years and not later than when the patients are 19 years old (in ossification of the skeleton corresponding to an age not older than 14 to 16 years). Anabolic steroids are prescribed in intermittent courses over a period of many years with the gradual substitution of the less active agents by more active ones (usually after two-three years). Methylandrostendiol is prescribed sublingually in a daily dose of 1,0-1,5 mg/kg or methandrostenolon (nerobol, dianabol) per os in a daily dose of 0,1-1,15 mg/kg or retabolil injected in a dose of 1mg/kg intramuscularly once a month and so on.

In some cases a preparation of the human growth hormone (somatotrophin) can be used to achieve an anabolic effect, but its

therapeutic action generally does not last longer than one and half to two years because of the formation of specific antibodies to the preparation. The growth hormone preparation is prescribed intramuscularly in a dose of 2-4 mg two-three times a week.

When symptoms of hypothyroidism are present, thyroid preparations are prescribed: thyroidin, 0,05-0,2 g daily; triiodthyronine hydrochloride, 5-20 microg daily; L-thyroxine 50 microg daily.

To stimulate and develop the sexual glands, chorionic gonadotrophin is prescribed from 16 years of age in dose from 1000 to 1500 U intramuscularly once or twice a week in courses of 10 to 15 injections. Treatment of males with chorionic gonadotrophin is often alternated by the prescription of small doses of androgens (methyltestosterone per 5 mg daily sublingually and other), and of female by prescribing oestrogenic preparations. After the closing of growth zones treatment with preparations of the sex hormones of the corresponding sex is conducted in ordinary therapeutic doses.

The diet of patients with nanism should be of full nutritious value with an increased content of animal proteins, vegetables, fruits and sufficient amount of vitamins (A, E, C, D and group B), calcium and phosphorus.

2.3. Adiposogenital Dystrophy

Adiposogenital dystrophy is a disease connected with affection of the hypothalamo-hypophyseal system; it is characterized by the underdevelopment of sexual glands and obesity.

The disease occurs most frequently in boys, usually aged from six to seven years, but quite often at the age of ten to thirteen years.

History. The first description of the disease was made by the Russian physician Pekhkrants in 1889, by Babinsky in 1900 and Froehlich in 1901.

Aetiology. The disease may be caused by intrauterine infection (toxoplasmosis), injury at birth, acute (scarlet fever, typhus, virus infections) and chronic (tuberculosis, syphilis) infections and traumatic lesions of the brain in early childhood. Adiposogenital dystrophy may be caused by tumours (craniopharyngeoma, chromophobe adenoma), dropsy of the third ventricle, thromboses, emboli and haemorrhage. Very often it is impossible to establish the cause of the disease.

Adiposogenital dystrophy should be regarded as an independent disease only if obesity and genital hypoplasia occur in childhood and their cause remains undisclosed. If the cause of the disease has been established, obesity and hypogonadism are regarded as symptoms of the main pathological process.

Pathogenesis. The lesion of the hypothalamus is attended by infection or stimulation of its paraventricular and ventromedial nuclei, which leads to a sharp increase in appetite with the resulting development of obesity. The affection of the hypothalamus also diminishes the gonadotrophic function of the hypophysis which in turn results in hypogonadism and subsequent changes in higher nervous activity and development of the characteristic obesity.

Pathology. The pathological changes in the central nervous system depend on the main morbid process (inflammatory and traumatic lesion of the hypothalamus, tumours, dropsy of the third ventricle, thromboses). There are often no morphological changes.

Clinical picture. Patients complain of fatiguability, drowsiness, a sharp gain of weight, loss of working capacity, etc. The skin is often dry and pale. The face is round. In boys fatty deposits are of the feminine type (on the neck, arms, breast, abdomen, the region of the pelvis, buttocks). There is no hair on the face and body. Gynaecomastia is noted and growth is frequently retarded. There are usually no changes in the internal organs. Boys have a small scrotum, penis and testis. Cryptorchidism is often observed. There are no secondary sex characters.

Menstruation does not occur in girls 14 to 15 years of age, their uterus and uterine appendages are underdeveloped.

Changes in the functioning of the nervous system depend on the main pathological process. Diabetes insipidus is a frequent occurrence.

X-ray, CT and MRI diagnosis. In tumour of the hypophysis the sella turcica is enlarged and deformed.

Diagnosis and differential diagnosis. The diagnosis of the disease is made on the grounds of progressive obesity with distribution of fat by the "feminine type" in combination with acute hypoplasia of the genital glands.

Adiposogenital dystrophy is differentiated from the exogenous-hereditary form of obesity, Cushing's, Laurence-Moon-Biedl, Morgagni-Stewart-Morel, Klinefelter's and Shereshevsky-Turner Syndromes.

As distinct from adiposogenital dystrophy sexual development in the exogenous-hereditary form of obesity is either normal or somewhat retarded, the excessive deposit of fat on the pubis of boys simply creating the impression that their penis is abnormally small. Later, during

intensive growth during puberty, the boys lose weight and genital organs develop normally.

As compared to adiposogenital dystrophy, Cushing's syndrome is attended by the selective localization of the fat, relatively thin extremities, plethoric colour of skin, wide reddish-purple striae over the abdomen, arms and thighs, high indices of arterial pressure, disorders of carbohydrate metabolism, etc.

Unlike adiposogenital dystrophy, Laurence-Moon-Biedl syndrome is characterized by dementia, retinitis pigmentosa leading to blindness and often by polydactyly and syndactyly.

In the differential diagnosis of adiposogenital dystrophy and Morgagni-Stewart-Morel syndrome, the latter is recognized by hirsutism of the masculine type, increased arterial pressure, disorders of the carbohydrate metabolism to the point of diabetes mellitus, thickening of the internal lamina of the frontal bone, etc.

The Morgagni-Stewart-Morel syndrome usually occurs only in females, most often during menopause.

Adiposogenital dystrophy differs from Klinefelter's syndrome in that obesity is either absent or slightly pronounced. The penis is of the usual size, as a rule. The sex chromatin is positive; the karyotype is most frequently 47, XXY.

The Shereshevsky-Turner Syndrome is indicated by a typical appearance, a short webbed neck with pterygoid skin folds, a low position of the ears, a low posterior hair line, absence of sex chromatin, karyotype 45, X.

Prognosis. The prognosis of the disease depends on the cause and the dynamics of the main pathological process. In adiposogenital dystrophy of undisclosed cause prognosis in regard to life-span is favourable. Timely and correct treatment makes it possible to arrest the development

of the disease. The working capacity of patients depends on the degree of obesity, the condition of the cardiovascular system, vision and the severity of neurological disorders. In complications (chronic coronary insufficiency, cerebral sclerosis, impairment of vision, etc.) patients may be qualified as group II invalids.

Treatment. Treatment is primarily aimed at removing the cause of the disease. Anti-inflammatory therapy (antibiotics, urotropine) is applied to inflammatory processes in the hypothalamic region; surgery is applied when there is a tumour. The treatment of obesity and hypogonadism is carried out according to generally accepted principles. Irrespective of the cause of the disease all patients are prescribed a diet limiting carbohydrates and fats. In cases of an abnormal increase of the feeling of hunger (bulimia), anorexic drugs (phepranon, desopimon and others) are prescribed.

Hypogonadism is treated by the long-term prescription of first chorionic gonadotrophine (choriogonin), 500-1000-1500 U intramuscularly 2-3 times a week, and later (during puberty) 1 ml of a 1-5% solution of testosterone propionate intramuscularly 2-3 times a week or 5-10 mg of methyltestosterone three times a day (sublingually); sustenon, omnadren 1 ml intramuscularly every month.

Substitution cyclic hormone therapy of women and girls beginning from 12-13 years of age entails the administration of oestrogenic drugs (sinestrol, folliculin and others) for 15 to 20 days, with the subsequent introduction of progesterone or pregnin (syn. ethisterone, progneninolone) for 8-10 days. Diane-35 one pill daily during 21 days every month.

Lecture 3.

3.1. Syndrome of Persistent Lactation (Galactorrhoea) and Amenorrhoea (Chiari-Frommel Syndrome)

Chiari-Frommel Syndrome is a pathological symptom complex resulting from damage to the hypothalamus with the subsequent (secondary) development of endocrine disorders. The disease occurs in women and girls.

History. The symptom complex of galactorrhoea and amenorrhoea with puerperal atrophy of the uterus and ovaries was first described by Chiari in 1855.

Aetiology and pathogenesis. The cause of the Chiari-Frommel Syndrome is often chromophobe adenoma or a tumour in the hypothalamic region. When the pathological process damages hypothalamic centres, normally inhibiting the formation of prolactin, its production increases with the eventual development of continuous lactation.

Pathology. Chromophobe adenoma of the hypophysis is often discovered during pathological examination. It is the most frequently occurring hormonally active tumour of the hypophysis, consisting of the main (chromophobe) cells. The chromophobe adenoma is usually benign but it may be sometimes (in 2-3% cases) prove to be malignant. In transitional forms of chromophobe adenoma (from benign to malignant) polymorphism of cellular elements is histologically observed and also mitoses, the impairment and abnormal structure of the adenohypophysis. In some cases compression occurs and the displacement or destruction of the optic chiasm by the tumour.

The uterus and ovaries are atrophied.

Clinical picture. Complaints of:

- headache;
- disturbance of the menstrual cycle;
- discharge of milk from the mammary glands not connected with pregnancy or breast feeding;
- impairment of vision acuity;
- thirst;
- gain or loss in body weight.

The patients are often stout with general or located accumulation of fat or they are emaciated. Hypertrichosis is sometimes noted.

Changes in the nervous system and of the vision's organs depend on the size of the tumour and the direction of its growth. Compression of the optic chiasm by the tumour leads to bitemporal hemianopsia (narrowing of the vision's fields). Penetration or compression of the hypothalamus by the tumour sometimes results in functional disorders of its vegetative centres. This, in turn, causes vasomotor and trophic disturbances, diabetes insipidus, etc.

Occasionally patient's condition does not change substantially and for several years the only pathological symptoms are persistent lactation and amenorrhoea.

The laboratory findings depend on the character of the pathological process in the hypothalamus.

X-ray, CT and MRI diagnosis. A hypophyseal tumour is attended by enlargement of the sella turcica, a change of its shape, etc.

Diagnosis and differential diagnosis. Chiari-Frommel Syndrome is established on the basis of a characteristic triad: amenorrhoea, galactorrhoea (sometimes for several years) not connected with pregnancy and breast feeding, disturbance of the hypothalamo-

hypophyseal function (obesity, or emaciation, diabetes insipidus and others).

Endocrine and metabolic disorders caused by chromophobe adenoma are also observed in craniopharyngioma, eosinophil and basophil adenoma of the hypophysis, aneurysm of the internal carotid and so on. Calcification of the tumour is evidence in favour of craniopharyngioma and against chromophobe adenoma. As distinct from eosinophil adenoma, chromophobe adenoma lacks the typical symptoms of acromegaly. The absence of symptoms of Itsenko-Cushing disease is evidence in favour of chromophobe adenoma and against basophil adenoma. Signs of the diminished function of other endocrine glands together with abnormalities of the sella turcica on X-ray of the skull exclude the possibility of primary hypogonadism. In some cases aneurysm of the internal carotid artery produces symptoms (bitemporal hemianopsia, hypopituitarism, changes in the size of the sella turcica) resembling those of chromophobe adenoma. In such cases arteriography is used for differential diagnosis.

Prognosis. With early diagnosis and timely treatment the prognosis is often favourable. Patients live many years. In cases of a rapidly growing benign tumour or its malignant degeneration the prognosis is unfavourable. The cause of death can be either hypophyseal coma as a result of the rupture of the cyst or acute haemorrhage into the tumour, adrenal insufficiency or compression of the vitally important brain centres by the tumour.

In cases of the slow growth of the tumour the working capacity is often only partially lost. Work involving physical loads and emotional stress is contraindicated.

When a tumour develops rapidly, progressive impairment of the vision and increase in the symptoms of an insufficiency of the endocrine glands lead to patients being qualified as group I invalids.

Treatment. Effective methods of treatment include radiation therapy (X-ray therapy, telecurietherapy, using radioactive cobalt (60 Co), implantation of radioactive gold (198 Au), or yttrium (90 Y) in the tumour), hypophysectomy or cryohypophysectomy. The total course dose of radiation therapy for the hypothalamo-hypophyseal area is usually from 5000 to 6000 rads.

Indications for surgical treatment are the sharp narrowing of the vision's fields and the absence of any effect after one or two courses of radiation therapy. To avoid the acute deficiency of the adrenal cortex during surgery, it is performed together with cortisone therapy. Radiation therapy is expedient to prevent postoperative recurrence.

To reduce galactorrhoea various preparations of female sex hormones are applied in some cases. Parlodel, which reduces the blood's level of prolactin is an effective agent in the treatment of the galactorrhoea-amenorrhoea syndrome. Parlodel is administered at the beginning 1,25 mg (0,5 tab.) one to three times a day at meal time with increasing dose till 2,5 mg (1 tab.) two to four times a day. If parlodel's treatment does not provide ovulation, combined treatment with gonadotrophins, clomiphene, Diane-35 is applied.

If the hypothalamo-hypophyseal region is affected by an infectious-toxic or rheumatic process, antibiotics, resolving and desensitizing agents are used.

3.2. Hyperhydropexis Syndrome (Parkhon's Syndrome)

The Hyperhydropexis Syndrome (antidiabetes insipidus) is characterized by oliguria, retention of liquids in the organism and the absence of thirst. Pronounced forms of the disease are rarely encountered.

History. The disease was first described by Parkhon in 1933.

Aetiology. The aetiology of the disease has not been sufficiently studied. Toxicoinfectious and allergic factors as well as psychic trauma have some significance in the development of the disease.

Pathogenesis. The principal link in the pathogenesis is the increased production of the antidiuretic hormone as a result of disturbed function of the hypothalamus.

It is known that the antidiuretic hormone (ADH) takes the lead in regulating osmotic pressure of the internal medium of the organism. An increase in osmotic pressure leads to increased incretion of the ADH, which by decreasing diuresis retains water in the organism. The secondary disturbance of the functioning of the endocrine glands involved in regulation of water metabolism (increased incretion of aldosterone, decreased function of the thyroid gland, etc.) plays a definitive role in the pathogenesis of the disease.

Clinical picture. Patients complain of:

- weakness;
- headache;
- gain in body weight;
- reduction of diuresis and intake of the liquids.

The skin of patients is pale and dry. There is uniform obesity. Oedemas of various localizations are noted. Amenorrhoea often occurs in females; in males, decrease in the sexual functioning, to the point of impotency.

Laboratory findings. Hypercholesterolaemia, hypernatraemia, hyperchloraemia and an increased content of the neutral fats are revealed in the blood. There are constantly high relative density of the urine and an increasing discharge of the antidiuretic hormone and aldosterone in the urine.

Treatment is basically symptomatic. A diet is prescribed with limited sodium chloride and a reduction in the total calorie count of food at the

expense of carbohydrate. A large amount of vegetables and fruits is included in the food ration. Diuretic agents are used in large doses: Furosemide (Lasix) 40-80 mg daily and Spironolactone (Verospiron) from 200 to 300 mg a day. In some cases attempts are made to use the antagonists of ADH production, such as Oxytocin (alpha-hypophamine), Phenamine (amphetamine) and glucocorticoids. In the absence of contraindications remedial exercises and balneotherapy are prescribed.

3.3. Diabetes Insipidus

The hypothalamic and renal forms of **diabetes insipidus** should be distinguished: the former is caused by an absolute deficiency of the **antidiuretic hormone** (ADH). Hypothalamic diabetes insipidus may be either an independent disease or a symptom of certain endocrine and non-endocrine disease. It is encountered in patients of all ages but most often in young people from 18 to 25 years of age.

Renal (nephrogenic) diabetes insipidus is a genetic pathology of the ADH receptors of the tubules of the kidney (relative deficiency of ADH) inherited as a recessive sex-bond trait. The disease is only encountered in males.

Aetiology. The main causes of the disease are neurotrophic virus infections (influenza, etc.) other acute and chronic diseases (scarlet fever, whooping cough, sepsis, typhoid, relapsing fever, typhus, tuberculosis, syphilis). Diabetes insipidus may occur as a result of craniocerebral traumas, tumours of the hypophysis (craniopharyngioma, chromophobe adenomas) and hypothalamus, and also of metastases of other tumours in the hypophysis or hypothalamus. In some cases diabetes insipidus develops in endocrine diseases of hypothalamo-hypophyseal genesis (adiposogenital dystrophy, Simmonds' syndrome, hypophyseal nanism, acromegaly, gigantism, Itsenko-Cushing disease). Diabetes insipidus often occurs in bony xanthomatosis (Hand-Schueller-Christian's

syndrome). The disease is sometimes of hereditary origin. In some cases it is not possible to reveal the cause of the disease.

Pathogenesis. Damage of the supraoptic and paraventricular nuclei of the hypothalamus and in some cases of the hypothalamo-hypophyseal tract along whose nerve fibres neurosecretion passes to the posterior pituitary, leads to an absolute deficiency of the antidiuretic hormone (ADH). In some cases the ADH deficiency may be relative as a result of its excessive disintegration on the periphery (an increase in its inactivation in the liver and kidneys).

Diabetes insipidus may also occur as a result of the congenital pathology of the receptors of the kidneys' tubular apparatus. This is manifested by the inability of the kidneys to react positively to ADH circulating in normal amounts (renal form of the disease). The lack of ADH leads to a reduced reabsorbtion of water in the distal segments of the convoluted tubules of the kidneys, which causes an increase in diuresis (polyuria). Dehydration of the organism is attended by stimulation of the "thirst centre" in the hypothalamus resulting in thirst (polydipsia).

Pathology. Pathological examination reveals tumours, inflammatory lesion, traumas of the hypothalamus, the hypothalamo-hypophyseal tract and the posterior pituitary. Degenerative changes in the supraoptic nuclei and the supraoptic-hypophyseal tract are found in histological examination. In some cases severe morphological changes are not found.

Classification. The following forms of the diabetes insipidus are distinguished according to their pathogenesis:

1. Diabetes insipidus, caused by an absolute deficiency of ADH
   - connected with organic injuries to the hypothalamo-neurohypophyseal endocrine complex;
   - idiopathic (spontaneous).

2. Diabetes insipidus, caused by a relative deficiency of ADH:

- Connected with increased inactivation of ADH at the periphery;
- Renal diabetes insipidus (total or considerable insensitivity of the distal part of the kidney tubules to ADH).

Clinical picture. The disease usually appears abruptly, developing gradually only rarely. Patients complain of:

- constant thirst (polydipsia);
- excessive urination (polyuria);
- frequent urination (pollakiuria);
- loss of appetite;
- weakness;
- headache;
- insomnia;
- chills;
- constipation.

During examination the dryness of the skin and absence of perspiration are particularly noticeable. Patient's appearance is not changed although in some cases they might be thinner. Obesity occurs in cases of hypothalamic polyphagia. As a rule, no substantial deviations from the norm are seen in the internal organs. Hypoacid gastritis and colitis occur in some cases. The intake of large amount of liquids leads to distention and downward displacement of the stomach. Disorders of the menstrual cycle occur in females, sometimes to the point of amenorrhea, as well as sterility, a tendency to spontaneous abortion while males suffer diminution of libido and potency. In children diabetes insipidus is usually attended by retarding growth and delayed puberty. An early symptom of diabetes insipidus in children is urinary incontinence at night.

In the secondary (symptomatic) diabetes insipidus the clinical picture is caused by the main disease, i.e. acromegaly, adiposogenital dystrophy etc.

Laboratory findings. Total blood count and biochemical blood tests reveal no abnormalities. The urine is colourless, transparent, with a weak acid reaction; it does not contain sugar or abnormal admixtures. The relative density of the urine is low: 1.001 to 1.005; daily diuresis is up to 40 l.

Diagnosis and differential diagnosis. The diagnosis of diabetes insipidus is made on the grounds of polydipsia and polyuria with a low relative density of the urine. Diabetes insipidus is differentiated from diseases which have poluria as a symptom, namely, diabetes mellitus, psychogenic polydipsia and chronic renal insufficiency at the stage of "forced" polyuria.

Diabetes mellitus is attended by hyperglycaema, glucosuria and polyuria with a high relative density of the urine. In differential diagnosis with psychogenic (polyuria) polydipsia tests are made with deprivation of liquid, with pituitrin in a free water regimen, with a sodium chloride load etc. In psychogenic polydipsia a test with dry food (devoid of liquid) results in a reduction in diuresis and a raising of the relative density of the urine to indices typical of healthy people without any signs that the patient is suffering or any symptoms of dehydration. Depriving diabetes insipidus patients of liquid does not increase the relative density of urine above 1.010 and leads to the rapid development of the symptoms of the dehydration (a reduction in body weight, increase in the content of erythrocytes, haemoglobin and proteins in the blood) with deterioration of the patient's condition (nausea, vomiting, diarrhea, muscle spasm, headache, tachycardia, psychic excitation, collapse). In view of this patients should not be deprived of liquids for more than six to eight hours. The data of the medical history are also in favour of the psychogenic polydipsia, with polydipsia and polyuria prevailing in daytime.

In differential diagnosis to distinguish diabetes insipidus from chronic renal insufficiency the medical history (indications in the case history

that there have already been kidney and hypertensive diseases) and laboratory findings are of major importance. Renal insufficiency is characterized by polyuria not exceeding three- to four litres a day, hypoisosthenuria, proteinuria, hyperazotaemia combined with high arterial pressure, changes in the fundus of the eye.

In differential diagnosis of the hypothalamic and renal forms of the disease the pituitrin test is applied: after pituitrin is infused the amount of the urine decreases in hypothalamic diabetes insipidus while its relative density increases. The use of pituitrin in neurogenic diabetes insipidus is ineffective.

Prognosis. For most patients suffering from diabetes insipidus the prognosis with regard to life is favourable but it is doubtful that they will ever be cured. In symptomatic diabetes insipidus, prognosis and working capacity are determined by main disease. Patients with pronounced diabetes insipidus are mostly qualified as group III invalids.

Treatment. The diet should include a large amount of vegetables, fruits and dairy products. Treatment is primarily directed at eliminating the cause of the disease. In neuroinfection antibiotics and biioquinol (quinine iodobismuthate) are prescribed; in tumour of the hypothalamo-hypophyseal system radiation therapy or surgical treatment. When diabetes insipidus develops as a result of syphilis, anti-syphilitic therapy is undertaken. The principal method for treating hypothalamic diabetes insipidus is substitution therapy aimed at increasing the reabsorbtion of the water.

Adiurecrin (a powder extract of the posterior pituitaty of cattle) is introduced intranasally for this purpose in doses of 0,03 to 0,05 g two or three times a day. The duration of the antidiuretic effect of adiurecrin is from six to eight hours. When adiurecrin is insufficiently effective or contraindicated (diseases of the upper respiratory tracts or of the paranasal sinuses) pituitrin is prescribed.

Pituitrin is the aqueous extract of the posterior pituitary; its effect lasts from four to five hours. The preparation is introduced subcutaneously in a dose of 1 ml (5U) three to four times a day. Sometimes the diuretic dichlothiazid is used in a dose of 100 mg daily, which has paradoxal effect on diuresis and thirst in patients with diabetes insipidus. In recent times combined treatment with adiurecrin and chlorpropamide has been used in compensation of the hypothalamic form of diabetes insipidus (particularly when it is combined with diabetes mellitus). Chlorpropramide is prescribed per os in a dose from 250 mg to 750 mg daily.

The therapeutic effect is usually manifest on the second to fourth day. It is essential to watch over the sugar level in the blood because of possible hypoglycaemia.

There is a new preparation for diabetes insipidus treatment. Adiuretin is the synthetic analog of the vasopressin without vasopressor effect. Adiuretin solution is administered intranasally one to four drops in each nostril two - three times a day.

Lecture 4.

4.1 Itsenko-Cushing Disease.

The **Itsenko - Cushing**'s disease results from the initial affection of subcortical and brain-stem formations (hypothalamus, thalamus and reticular formation) with the subsequent involvement in the pathological process of the hypophysis and adrenal cortex.

The disease occurs more frequently in females particularly those from 20 to 40 years of age.

History. The disease was first described by the Russian neurologist Itsenko in 1924. He was the first to point out that the initial factor in this disease is affection of the diencephalon with the secondary involvement in the pathological process of the hypophysis and the entire system of endocrine glands, especially adrenal cortex with hypercortisolism. In 1932 a similar symptom complex was described by American neurosurgeon Cushing, who linked the origin of the disease with a basophil adenoma of the anterior pituitary with consequent stimulation of the adrenal cortex with development of hypercortisolism.

Aetiology. It is often impossible to discover the cause of disease. It is linked with:

- craniocerebral or psychic trauma;
- infectious diseases (particularly neuroinfections: encephalitis, meningitis, arachnoencephalitis);
- intoxications;
- basophil adenomas (tumours of the hypophysis);
- childbirth.

It is considered that in some cases these factors may cause the disease and in other may merely provoke it; the third opinion is that they attend the process without contributing to its origin.

Pathogenesis. Under the influence of the increased production of corticotrophin-releasing factor, as a result of the affection of the hypothalamus, there is an excess incretion of ACTH which is the main pathogenetic factor in the disease. The hyperproduction of ACTH mainly intensifies the function of the fascicular and reticular zones of the adrenal cortex. The increase in the production of the glucocorticoids (caused by the intensifications in the functioning of the fasciculate zone of the adrenal cortex- hypercortisolism) leads to:

- arterial hypertension;
- osteoporosis;
- the appearance of wide striae of the stretched skin;
- obesity;
- reduced resistance to infections;
- disturbance of carbohydrate metabolism to the point of the development of diabetes mellitus (steroid).

The increased function of the reticular zone of the adrenal cortex results in the hyperproduction of the steroids with androgenic properties. This is manifested by disorders of the ovaries (acne and sometimes hypertrichosis).

Pathology. The anterior pituitary is most often the site of the:

- basophil adenoma;
- hyperplasia of the basophil cells;
- adenocarcinoma (more rarely);
- eosinophil adenoma;
- chromophobe adenoma.

Acute degeneration of the hypothalamic nerve cells is revealed histologically, the lesion being most pronounced in the supraoptic, paraventricular and tuberal nuclei with the complete or practically complete lack of neurosecretion in the posterior pituitary.

Hyperplasia and hypertrophy of the adrenal cortex and of the islet apparatus are noted and the hypofunction of the thyroid gland and of the sexual glands.

There are atherosclerotic changes in the cardiovascular system; in the liver are seen fatty infiltration and dystrophic changes.

Classification. The Itsenko-Cushing disease according to form and development, may take a:

- mild form;
- moderate form;
- severe form.

Depending on the course, it may be progressive or torpid. In the progressive form the symptoms grow rapidly (several months).

Clinical picture. Most frequently the disease develops gradually. Patients complain of:

- general weakness;
- headache;
- pain in the back and limbs;
- disturbance of the menstrual cycle;
- diminution of the libido and potency;
- change in appearance and colour of face;
- obesity;
- hypertrichosis by the masculine type (in females);
- drowsiness;
- apathy;
- slow thinking.

On examination is noted selective localization of the fat on the face ("moon face" - purplish-red), chest, abdomen, neck (over the seventh cervical vertebra - "buffalo hump") combined with relatively thin limbs.

The skin is usually affected by acne and furuncles, is dry, desquamating, with a purplish-marble pattern. There are wide dystrophic bands of stretched skin purple in colour (striae) over the abdomen, arms, mammary glands, the flanks of the thighs and other parts of the body. Haemorrhages in the skin easily occur. Hirsutism by the masculine type often occurs in females but with loss of the hair on the head. Downy hair prevails on the face. A certain feminization is evident in males: less growth of hair on the face and loss of the hair on the body.

The bone and muscle system. Deformations and fractures of the bones often occur accompanied by pain of various intensity and duration. Bone changes do not usually conform to the degree of pain reaction. There is sometimes no pain at all in cases of multiple fractures, such changes in the bones are connected with osteoporosis which is often the main symptom of the disease. Osteoporosis most often occurs in the spine, skull, ribs, the bones of the feet and hands. Its development is linked with excess production of glucocorticoids which leads to disorders in the formation of the protein frame of the bone tissue, resulting in insufficient deposits of calcium salts. Attempts have been made to explain the diminution of the pain sensitivity in fractures by the analgesic effect of excess glucocorticoids.

In childhood Itsenko-Cushing disease, besides giving rise to osteoporosis, also causes retardation of the growth and of differentiation of the skeleton.

The cardiovascular system. Tachycardia, expansion of the heart border to the left, systolic murmur at the apex and accentuation of the second sound over the aorta are noted. Arterial hypertension with a high systolic and diastolic pressure and high venous pressure are observed. Arterial hypertension and metabolic disorders in the heart muscle often result in the development of chronic circulatory insufficiency. Focal changes in the myocardium are mostly linked with excess production of corticosteroids, primarily glucocorticoids and with systemic

hypertension leading to hypertrophy of the left ventricle and relative coronary insufficiency. The deficit of potassium which occurs with excess production of the cortisol and sometimes of aldosterone in combination with an increased cortisol content, is the basis of the development of electrolyte-steroid cardiopathy with necrosis. The ECG changes are the same as those at the corresponding phases and stages of hypertensive disease: levogram, decrease of the T wave, increase of the Q-T interval, decrease of the S-T segment.

The respiratory organs. Bronchitis, pneumonia, tuberculosis often develop as a result of the lower reactivity of the organism since the cortisol suppresses the production of the antibodies. Disorders of the carbohydrate metabolism are also conducive to pathology of the respiratory organs.

The digestive organs. Heartburn, pain in the epigastric region and chronic hyperacidic gastritis may occur. In many cases gastroduodenal ulcers, "steroid ulcers" appear. There is sometimes gastric haemorrhage. Disturbance of the antitoxic synthetic, galactose-fixing and cholesterol-oesterizing function of the liver is noted.

The kidneys and urinary tract. Glomerular filtration and the rate of renal blood flow are reduced. In some cases stones appear, the origin of which is linked with hypercalciuria, the reduced secretion of citric acid. Prolonged arterial hypertension gives rise to the nephrosclerosis which in far-advanced cases is complicated by renal insufficiency to the extent of the development of anuria.

The nervous system and psyche. In the development of psychic disorders the following syndromes are distinguished:

- the neuroasthenic syndrome, typical of the prodromal period;
- the astheno-adynamic syndrome which is the main syndrome throughout the course of the disease;
- the depressive syndrome;

- the epileptiform syndrome;
- the hypochondriac-coenaesthopathic syndromes, which may occur at any period of the disease.

Patients suffer from loss of the memory, slow thinking, there is impairment of intellect, they become flaccid and slow. There are reduced emotional reactions to external stimuli and persistent suicidal thoughts appear.

An unfavourable course of the disease gives rise to the syndrome of impaired intellect and memory (marked slowness, difficulties in orientation under new conditions, apathy or euphoria, reduced critical attitude to one's own condition). Psychic disorders are mainly linked with the disturbance of cortical-subcortical relationships and excessive ACTH, glucocorticoid and serotonin levels.

The endocrine system. As a rule the function of the thyroid gland is clinically undisturbed. However, the absorbtion of radioactive iodine by the thyroid gland, protein-bound iodine (PBI) of the blood and basal metabolism are often below or at the lowest limit of the norm.

The sexual function is depressed to the point of impotence in males. Libido is reduced in females, the menstrual cycle is disturbed and amenorrhoea sometimes occurs.

Atrophy of the uterus, ovaries and mammary glands is observed. In childhood growth is arrested and sexual development is retarded.

Laboratory findings. Hyperhaemoglobinaemia, erythrocytosis, neutrophilic leucocytosis, eosinopenia and lymphocytopenia are often found in the blood. During the active stage of the disease there is an increased concentration of fibrinogen and reduced fibrinolytic activity in the blood with simultaneous hyperheparinaemia, which is one of the causes of the development of haemorrhagic complications.

Hypercholesterolaemia, hypoalbuminaemia, hyperglobulinaemia, hypernatriaemia, hyperchloraemia and hypokalaemia often occur. Hypophosphataemia and a decrease of the activity of alkaline phosphatase are also noted, these both being factors in the development of osteoporosis.

Frequently, there is low tolerance of carbohydrates and hyperglycaemia and glucosuria (steroid diabetes mellitus), quite often the content of ACTH and cortisol of total 17-OCS and of free and protein-bounded 11-OCS in the blood plasma is raised.

There is an increased excretion of 17-OCS, 17-CS and cortisol in the urine. In chromatography of 17-OCS excreted in the urine, tetrahydrocortisol predominates over tetrahydrocortisone. In the active stage of Itsenko-Cushing disease the excretion of 17-OCS in the urine at night is stronger than their excretion in the morning hours.

X-ray diagnosis. Osteoporosis of the cranial bones is recorded on the craniogram. The dimensions of the sella turcica are usually unchanged and osteoporosis is seen in the region of its back.

Marked osteoporosis of the vertebral bodies ("fish" vertebrae) is very characteristic. X-ray examination of the adrenals by means of US, CT, MRI and pneumosuprarenography (the introduction of the oxygen into the peripheric space or the retroperitoneal technique with the introduction of the oxygen into the presacral region) reveals hyperplasia of both adrenals (which often have a heterogenous structure) on the tomogram. The adrenals are considered to be enlarged if the area of the right adrenal is 7.8 cm2 and at the left 8.7cm2 .

Diagnostic tests. Tests with metopirone (metyrapone) and dexamethasone are used in the differential diagnosis of Itsenko-Cushing disease and Cushing's Syndrome. Metopirone is prescribed per os in a dose of 750 mg every six hours for 48 hours. On the eve of the administration of the metopirone and during the second 24 hours, urine

is collected for determining 17-OCS. Metopirone selectively blocks the enzyme-11-beta-hydroxylase in the adrenal cortex as a result of which disorders of the biosynthesis of cortisol aldosterone and corticosterone occur. The decrease in the level of cortisol in the blood leads to an increase in the ACTH incretion (according to the feedback principle). ACTH stimulates the production of the 17-oxy-11-deoxycorticosterone, which does not inhibit the incretion of ACTH by the hypophysis, but is excreted in the urine in the form of 17-OCS .

In cases of Itsenko-Cushing disease the excretion of 17-OCS in the urine doubles and triples after the intake of metopirone due to the activity of the hypothalamo-hypophyseal system. This is connected with the ACTH that stimulates the adrenal cortex function. In Cushing's syndrome caused by a tumour of the adrenal cortex, there is no increase of 17-OCS excretion following the administration of metopirone.

The test with dexamethasone is based on suppressing the production of endogenic ACTH according to the feedback principle.

In Itsenko-Cushing disease the per os administration of dexamethasone (2mg every six hours for 48 hours) is attended by a decreased 17-OCS excretion in the urine by more than 50%, whereas in Cushing's Syndrome the excretion of 17-OCS in the urine does not change.

Diagnosis and differential diagnosis

Itsenko-Cushing disease is diagnosed mainly on the basis of a physical examination: selective localization of fat in combination with relatively thin extremities and atrophied buttocks, a purplish-red "moonface", hirsutism, a marble hue of the skin on the arms and legs, broad purple striae located mainly over the abdomen, arms, mammary glands, the flanks of the thighs; high indices of both systolic and diastolic arterial pressure.

Auxiliary methods of examination help to make the diagnosis exact. These include, above all, X-ray diagnosis (marked osteoporosis of the cranial bones, particularly of the back of the sella turcica and of the

vertebral bodies, mainly of the thoraco-lumbar segment; also hyperplasia of both adrenals).

Itsenko-Cushing disease is differentiated from Cushing's Syndrome which is caused either by a hormonally active tumour of the adrenal cortex (glucosteroma) or by tumour producing ACTH-like substances (bronchogenic cancer, carcinoma of the lungs, the thymus gland, thyroid gland, pancreas, uterus, ovaries). Itsenko-Cushing disease is differentiated from juvenile dyspituitarism, obesity developing with arterial hypertension, disorders of carbohydrate metabolism and, in females, disorders of the menstrual cycle.

In some instances Itsenko-Cushing disease is differenciated from Cushing's Syndrome caused by the prolonged intake of glucocorticoids.

As distinct from Itsenko-Cushing disease the radiography in the case of a glucosteroma shows a unilateral tumour of the adrenal with simultaneous hypoplasia of the other adrenal. Glucosteroma develops more rapidly with osteoporosis less pronounced but hirsutism more pronounced. The test with dexamethasone and metopirone produces a negative result.

As distinct from Itsenko-Cushing disease the Syndrome of juvenile dyspituitarism is characterized by a benign course, accelerated growth and differentiation of the skeleton, absence of changes in bone structure, many narrow striae pinkish red in colour on the skin, lability of arterial pressure and carbohydrate metabolism and the absence, as a rule, of changes in the size of the adrenals, increase in the size of the ovaries and changes in their shape. In the Syndrome of youth dyspituitarism there are often calcification of the dura mater and hyperostoses on the bones of the skullcap.

In some cases it is essential to make a differential diagnosis to distinguish Itsenko-Cushing disease from obesity combined with high arterial pressure, disturbance of the menstrual cycle and moderate hypertrichosis.

The possibility of Itsenko-Cushing disease is rejected in case of normal colour of skin, absence of selective fatty deposits in the regions of the face and trunk and normal hormonal indices.

Prognosis. The prognosis of the disease is doubtful and if no treatment is undertaken the outlook is unfavourable. Marked forms of Itsenko-Cushing disease end in death because of such complications as erysipelas, sepsis, phlegmon, pneumonia, cerebral haemorrhage, renal insufficiency.

Working capacity is reduced. Work that involves regular moderate physical and neuro-psychic tension is contraindicated. In the mild form of the disease patients are qualified as group III invalids, in the moderate form with slow progression of the disease, group III is also indicated but if the disease develops rapidly, patients receive group II invalidity. The moderate form of the disease permits work which involves no more than slight physical and nervous-psychic tension. In the severe form of the disease patients are rated as group II invalids while complications (haemorrhages, marked cardiovascular insufficiency, osteoporosis, spine fractures) rate them as group I invalids.

4.2 Treatment of the Itsenko-Cushing Disease

Treatment. A diet is recommended with a limited amount of fats, carbohydrate, sodium and liquids. Methods of treatment include exposure of the hypothalamo-hypophyseal area to the radiation at a distance (X-ray and gamma-ray therapy), surgery and drug therapy.

It is recommended irradiation of the hypothalamo-hypophyseal region in the mild and moderate forms of the disease and in cases of the growth of the adenoma of the hypophysis after adrenalectomy.

The X-ray therapy is best for patients with a mild form of the disease and also for patients with the moderate form when circumstances do not allow gamma-ray therapy. X-ray therapy is applied according to the fractional-intensive method, with increasing doses of 75-100-150-200R

with intervals of one-two days and then 250R daily. Irradiation of the hypothalamo-hypophyseal redion is carried out alternately from four fields (two temporal, frontal and occipital). The total X-ray dose for the entire course is 6000-8000R. A repeated course of X-ray therapy of the same dosage is prescribed eight to ten months later to attain stable remission.

Compared to X-ray therapy, gamma-ray therapy is more effective. It is usually prescribed for patients with the moderate form of the disease and also when the clinical picture is that of Itsenko-Cushing disease with a X-ray revealed tumour of the hypophysis. The total gamma-ray dosage for the entire course is 4500-5000R.

In some cases radiation therapy can take the form of implantation of Y90 or Au198 in the region of the adenohypophysis by the stereotaxic method. To prevent alopecia, the toxic effect of radiation therapy on the central nervous system, anabolic steroids, vitamin C and of the B group and stimulators of leucopoiesis are prescribed.

Clinical remission after radiation therapy is usually in evidence after six to eight months. This is seen in body weight returning to normal in the diminution of trophic changes of the skin, the normalization of the menstrual cycle, a decrease in arterial pressure and hyperglycaemia and the normalization of bone tissue. Despite full clinical remission, however, excretion of 17-OCS in the urine remains high in most patients. On the severe forms of Itsenko-Cushing disease with a rapidly progressing course, as well as the absence of stable remission following radiation therapy of the hypothalamo-hypophyseal region are indications for surgery. The operation consists of bilateral total adrenalectomy combined with autotransplantartion of sections of the adrenal cortex into the subcutaneous tissue which allows for a diminution of the substitution dosage of corticosteroids and increasing the tolerance to their deficit in the organism.

Bilateral total adrenalectomy is performed in two stages with an interval of three to four weeks and is followed by the regular administration of supporting doses of glucocorticoids (25-50mg of cortisone daily, 5-10mg of prednisolone daily). In cases of a developing tumour of the hypophysis which is damaging the optic tracts (Nelson's Syndrome) hypophysectomy, electrocoagulation or section of the hypophyseal stalk are indicated. There is great promise in using chemical preparation to block the synthesis of corticosteroids (o'p'-DDD,metopirone,elipten; chloditan o'p'-DDD (orto, para,prim-isomer-dichlor-diphenyl-dichlor-ethane) brings about the destruction of the adrenal cortex and suppresses the incretion of corticosteroids.

These preparations can be prescribed only in cases of mild or moderate forms of the disease. Chloditan is administered in a dose of 6 to 8g per os daily. When phenomena of secondary hyperaldosteronism (very acute muscular weakness, spasms, electrolyte disorders and arterial hypertension) are evident, spironolactone (aldactone-A) is prescribed which normalizes electrolyte metabolism.

Anabolic steroids are applied in cases of osteoporosis: 5-10mg of methandrostenolone daily, 25-50mg of methylandrostenediol daily sublingually, 25mg of nerobolil, retabolil intramuscularly once a week.

Parlodel, a drug that has a modulatory effect upon the trope function of the hypophysis, is also used.

Complications of the cardiovascular system are treated with the normal therapy applied to chronic cardiovascular insufficiency.

Lecture 5.

5.1 Brief Anatomo-Physiological Data of the Thyroid Gland.

The thyroid gland (glandula thyroidea) is situated in the anterior surface of the neck at the region of the 2nd - 4th tracheal rings. It consists of two lateral lobes (right and left) and one intermediary part between them called the isthmus. In an adult the thyroid gland weighs from 25 to 30g on the average.

The structural and functional unit of the thyroid gland is the follicle. The follicle's walls are lined with one layer of cubical epithelium. The cavity of the follicle is filled with a homogenous viscous yellowish mass - colloid, a product of the epithelial cells of the follicles. In the hyperfunction the epithelium becomes columnar, multilayer and filled with colloid fluid. In the hypofunction it is thickened and epithelium is flattened.

Colloid mainly consists of thyroglobulin, which is iodinized glycoprotein. The thyroglobulin molecule consists of iodothyrosines (monoiodothyrosine and diiodothyrosine) and iodothyronines (mono-, di-, triiodothyronine and thyroxine) and practically all the amino acids of the organism. There are clear cells which increte non-iodized hormone thyreocalcitonine. In blood supply the thyroid gland takes first place in the organism.

The thyroid gland is innervated by sympathetic and parasympathetic nerves. Iodized hormones (thyroxine and triiodothyronine) and the non-iodized hormone (thyrocalcitonine) are the products of the endocrine activity of the thyroid gland.

There are four stages of the synthesis of the thyroid iodized hormones with the participation of the iodine:

1. the including uptake of the iodine in the thyroid gland;

2. organification (oxidation) of the iodine or iodination of the thyrosine with thyroglobulin;

3. the process of the condensation of the iodo-thyrosines (MIT and DIT) into the iodo-thyronines;

4. releasing (secretion) of the thyroid hormones.

The process of the passage of iodides into the thyroid gland and their oxidation into molecular iodine stimulate the thyrotrophic hormone of the hypophysis. Under the effect of enzyme deiodase and iodothyrosinase, stimulated by the thyrotrophic hormone, a deiodizing process develops in parallel which consists in the splitting of molecular iodine from mono- and diiodothyrosine. All the stages of synthesis of thyroid hormones take place in the follicular epithelium on the apical part, and then they are reserved in the thyroglobulin molecule. The thyroglobulin molecule under the action of the proteolytic enzymes (protease) is split and the active hormone gets in the blood through the basal part of the follicle cells where capillars pass.

On reaching the tissues the iodine-containing hormones are deiodized under the effect of the enzyme of tissue deiodase as a result of which triiodothyroacetic acid is formed. It is considered that the tissue physiological effect inherent in thyroxine and triiodothyronine is connected with this acid. Excess iodine is excreted from the organism with the urine (98%), bile (2%) and a very small amount with sweat, saliva and the expired air.

The activities of the thyroid and the adenohypophysis are under mutual control and under control of the hypothalamus, the higher regulator of the neuro-endocrine system. The hypothalamus contains the

thyrotrophine releasing factor (TRF) which stimulates the thyrotrophic function of the anterior pituitary. The relative equilibrium in the adenohypophysis - thyroid gland system is attended according to the principle "plus-minus interaction" of the trophic hormones of the hypophysis and the effector endocrine glands. Whenever there is an excess of iodine-containing hormones, the thyrotrophic function of the hypophysis diminishes, and with their deficit it increases.

An increase in the production of the TTH not only leads to intensification of the processes of biosynthesis of the iodine-containing hormones, it also leads to the diffuse or nodular hyperplasia of the thyroid tissue.

The clear cells of the thyroid gland increte the thyrocalcitonine (TCT). Thyrocalcitonine is a hormone which reduces considerably the blood calcium content because it blocks bone resorption and increases the absorption of the calcium by bone tissue.

The biological actions of the thyroid hormones are following:

- intensify all kinds of the metabolism;
- intensify the growth process in small doses;
- provide the differentiation of the tissues including nervous;
- exert the "calorigenic" effect (increase the production and expense of the energy);
- in toxic doses they cause the disturbance of the oxidative phosphorylation, thus decrease energy accumulation in form of adenosin triphosphate (ATP);
- in physiological doses thyroid hormones stimulate the synthesis of the proteins but in toxic doses they possess a catabolic effect;
- influence the carbohydrate metabolism: increase the absorption of glucose in the intestine, increase the glycogenolytic effect of the epinephrine thus diminish the content of glycogen in the muscles and liver, as a result, the

level of the glucose in the blood arises - hyperglycaemic effect;

- stimulate cholesterol's synthesis but in the same time intensify its disintegration and excretion by bile, thus they decrease the blood content of the cholesterol;
- increase the lipolytic effect of other hormones (STH, adrenalin);
- thyroid hormone deficiency caused by iodine insufficiency determines the development of the congenital hypothyroidism and cretinism with the mental underdevelopment.

5.2 Diffuse Toxic Goitre

Definition. Diffuse Toxic Goitre is an endocrine disease which includes the hyperplasia and hypertrophia of the thyroid gland and its hyperfunction (hyperthyroidism), that determines the development of the thyrotoxicosis (intoxication by thyroid hormones) and causes the metabolic disturbances and pathological changes in all organs, systems and tissues of the organism.

Diffuse toxic goitre is caused by the heightened incretion of thyroxine and triiodothyronine by the thyroid gland. It is characterized first of all by changes in the cardiovascular and nervous system. Diffuse toxic goitre is encountered everywhere, most commonly between the ages of 20 to 50, women being affected more frequently than men.

History. The disease was described by Ivez (1722); Perry (1786); Flajani (1802); Graves (1835); Moebius (1886). In 1840 Basedow pointed three basic signs (triad) in the clinical picture of this disease, namely:

- goitre
- exophthalmos
- tachycardia.

Aetiology

The hereditary factors predispose to the development of the disease. The predisposition to this disease may display in various manners:

- the deviation of the TRH - test;
- the appearance of the antibody to the thyroglobulin;
- the impairment of the test with T3 of the suppression of the uptake of the radioactive I131 by thyroid gland;
- increased frequency of the HLA-B8 antigens in the patients and their relatives.

The female sex determines the neuroendocrine incitement of the organism (pregnancy, lactation, menstrual period, climax) and makes is susceptible to this disease.

The pubertal period, as well as a neuropathic constitution, particularly neurocirculatory dystonia developing with marked vegetative phenomena, also predispose to this disease. Neurocirculatory dystonia is a prestage of the diffuse toxic goitre.

The disease is provoked by: psychic trauma (acute or chronic), acute and chronic infections (influenza, rheumatism, acute and chronic tonsillitis, tuberculosis, etc.), diseases of the hypothalamo-hypophyseal system, a cerebral trauma with the resultant development of encephalitis, affection of the peripheral nerves, overheating of the organism (excessive insolation, etc.), pregnancy, intake of large doses of iodine (basedowian); among children the disease is mostly provoked by infection, such as influenza, tonsillitis, measles, whooping cough, scarlet fever, rheumatism.

Pathogenesis of the diffuse toxic goitre is not yet sufficiently clear. It is presumed that the main role in the pathogenesis of the disease is played by following mechanisms:

- the long-acting thyroid stimulator (LATS) formed in the thymus and lymphocytes;

- disturbance of immunological processes;
- increased sensitivity of adrenoreceptors of the tissues to catecholamines.

Nowadays the diffuse toxic goitre is considered as a genetic autoimmune disease. It is presumed that toxic goitre may develop in a congenital defect in the system of immunological survival. As a result forbidden lymphocyte clones are not suppressed and interact with the organ specific antigen of the thyroid. This mutual action is accomplished both directly and through the T-lymphocytes (T-helpers). As a consequence of this mutual action beta-lymphocytes which produce thyroidstimulating immunoglobulins (antibodies) are involved into an immunological process. These immunoglobulins react in turn with the TSH-receptors which are found on the plasma membrane of the thyroid cells. The specific immunoglobulins stimulating the thyroid function are joined under the common name "Thyrostimulating immunoglobulins" - TSI. The most studied among them is "Long-Acting Thyroid-Stimulator" - LATS.

It has been established that in the thyroid these sympathetic nerve impulses give rise to intensified formation and secretion of biosynthesis of the more active hormone triiodthyronine over the less active hormone tetraiodthyronine is characteristic.

The symptoms of thyrotoxicosis (hyperhydrosis, tremor, tachycardia, exophthalmos) occur when the thyroid gland is functioning normally as a result of the increased sensitivity of adrenoreceptors to catecholamines. A definite role in the pathogenesis of the disease obviously belongs to tissue deiodase, whose increased activity accelerates the tissue actions of thyroid hormones.

Disorders of metabolism of thyroid hormones in peripheral tissues (liver, kidneys, and muscles) obviously also play a certain role in the pathogenesis of the disease. This leads to the formation and to the

insufficiently rapid disintegration of such active metabolites as triiodthyroacetic acid.

Change in the ion composition of the medium in which the action of these hormones is revealed in the effector tissues also influences the intensity and direction of the effect produced by thyroid hormones. An increase in potassium concentration in the medium of thyroxine action intensifies hormone's effect, whereas an increase in calcium concentration reduces it.

The clinical manifestations of toxic goitre are brought out by the biological effect of thyroid hormones and catecholamines. The excess production of thyroid hormones or heightened sensitivity to them of the peripheral tissues results in the activation of protein catabolism. Carbohydrate metabolism is disturbed, under the influence of the excess production of thyroid hormones the transition of carbohydrates into fats is inhibited while sensitivity of the sympathetic nerve endings in fatty tissue to the effect of adrenaline is increased. The latter circumstance and a reduced content of glycogen in the liver lead to the intensified mobilization of fat from its depots and the loss in weight of the patient. The excess of thyroid hormones causes disorders of the water-salt metabolism, increasing the discharge of water, sodium chloride, calcium, phosphorus and potassium to a lesser degree; the content of bound magnesium in the blood serum increases.

The excess of thyroid hormones and the products of their metabolism (triiodothyroacetic acid) result in disturbance of oxidative phosphorylation. This is revealed in disturbance of energy accumulation in the cell in the form of adenosine triphosphate (ATP). Due to the excess of thyroid hormones the monoamines oxydase activity is inhibited. As a result its sensitivity to catecholamines increases which leads to tachycardia, degenerative lesions of the heart muscle.

Pathology. The thyroid is enlarged and sometimes very big in size. Its consistency varies from soft to moderate. Histologically the follicles are lined with columnar epithelium and contain a small amount of liquid colloid. The connective tissue of the thyroid is infiltrated by lymphoid cells. The heart is usually enlarged at the expense of the left ventricle. Histological investigation at first reveals focal necrotic and necrobiotic changes in myocardium. The liver shows a picture of serous hepatitis and later sometimes a picture of chronic thyrotoxic hepatitis or cirrhosis. In some cases hyperplasia of the thymus, tonsils and lymphatic nodes is encountered. Sometimes there is hypoplasia of the adrenals.

Classification

The term of **thyrotoxicosis** it used to characterize the degree of the thyroid intoxication in toxic goitre and other pathological states (acute thyroiditis, carcinoma of the thyroid gland, some infections).

The term of hyperthyroidism is permissible only for the definition of physiological temporary conditions (in menstruation, pregnancy etc.).

In toxic goitre three stages of the **thyrotoxicosis** are distinguished:

- mild form - the clinical symptoms are less pronounced and tachycardia no more than 100 beats per minute;
- moderate form - the clinical symptoms are well manifested and tachycardia from 100 to 120 beats per minute;
- severe form - the clinical symptoms significantly pronounced and as a rule there are complications, the tachycardia more than 120 beats per minute, extrasystolia, cardiac fibrillation.

There are five degrees of the **enlargement** of the thyroid gland:

- Stage I - the enlarged isthmus of the gland is palpated, the lateral lobes are slightly palpated; the thyroid gland is not outlined when the neck is examined.
- Stage II - the thyroid gland is easily palpated and seen when the patient makes swallowing movements.

- Stage III - is called thick neck (the enlarged thyroid gland is easily seen on examination); the configuration of the neck is unchanged.
- Stage IV - pronounced goitre sharply changing the configuration of the neck.
- Stage V - the goitre grows very large and the configuration of the neck changes sharply.
- Stage "0" - at this stage the thyroid gland is not palpable or only slightly palpable but not enlarged.

Last years the WHO recommended using three degrees of the "Goitre".

- 1. palpated goitre;
- 2. seen goitre;
- 3. large goitre.

Clinical picture

Complaints:

- weakness, fatigability, irritability, tearfulness;
- sensation of pressure in the region of the neck;
- increased perspiration;
- trembling of the limbs and of the whole body;
- palpitation;
- disturbance of sleep, insomnia;
- considerable and rapid loss of body weight;
- thickening of the anterior surface of the neck;
- exophthalmos;
- frequent and unstable stool with a tendency for diarrhea;
- disturbance of menstrual cycle.

During the examination of patients it is noted:

- patients are fussy; they make a lot of rapid unnecessary movements and are verbose;
- facial expression with angry frightened look;

- exophthalm;
- goitre;
- skin is usually warm, thin, transparent and moist;
- hands and feet are usually warm;
- subcutaneous fatty layer is often diminished.

The thyroid gland is enlarged diffusely, although in some cases the increase of one lobe may be greater than of another. In palpation of the thyroid gland attention is paid to its size, shape, consistency, the presence or absence of nodes, sensitivity, and the degree of displacement. The thyroid is usually of soft or moderately firm consistency, mobile and not fused with underlying tissues. It may be localized retrosternally or in the form of the ring around the trachea and oesophagus (ring goitre). The goitre may also develop from an accessory lobe or the ectopic tissue of the gland.

Ocular symptoms are inconstant. One of the most characteristic ocular symptoms is ophthalmopathy. There are distinguished three stages of ophthalmopathy depending on subjective symptoms, exophthalm's expression, oedema of the eyelids and disorders of the function of the oculomotor muscles.

- I degree (mild form), exophthalmos (15,9 ± 0,2 mm);
- II degree (moderate form), exophthalmos (17,9 ± 0,2 mm);
- III degree (severe form), exophthalmos (22,8 ± 1,1 mm), disturbance of closure of the eyelids with ulceration of the cornea, stable diplopia, sharply pronounced functional disorders of extraocular muscles, signs of atrophy of the optic nerves. Normal protrusion of the eyes is 12-14 mm.

Ophthalmopathy. The pathogenesis of the ophthalmopathy is determined by long-acting thyroid-stimulating factor (LATS) and by ophthalmic factor. In the base of ophthalmopathy are: the oedema and the proliferation of the retrobulbar and the connective tissue of the

extraocular muscles. This is caused by the accumulation in these muscles of acid mucopolysaccharides containing hyaluronic and chondroitinsulfuric acids, possessing marked hydrophily, by a block of venous orbital circulation and by proliferation of the connective tissue of the orbit and its infiltration by lymphocytes and plasma cells.

Pathological changes in the severe form of ophthalmopathy are often combined with local (pretibial) myxoedema manifested in the thickening of the skin on the anterior surface of the shins and feet.

Diffuse toxic goitre may be attended by several other ocular symptoms which are mainly connected with the enhanced activity of the sympathoadrenal system. The symptoms of Krause, Graefe, Kocher, Moebius, Stellwag, Dalrymple, Zenger, Ellineck are most frequently encountered.

Graefe's sign consists in lagging of the upper lid behind the globe when the person fixes his gaze on some slowly descending object; as a result a white strip of the sclera is seen between the upper lid and the iris. The mechanism of this symptom is linked with the increased tonus of the muscle raising the upper eyelid. Graefe's sign can be observed in healthy myopic people.

Moebius symptom consists in the weakness of convergence.

Stellwag's symptom is infrequent (normal rate of 6 to 8 times a minute) and incomplete blinking.

Pigmentation around the eyes (Ellineck's symptom) is considered to be one of the manifestations of adrenal insufficiency.

The cardiovascular system. Cardiovascular disturbances are the main clinical symptoms of toxic goitre. The subjective and objective signs of cardiac disorders attending diffuse toxic goitre at all stages of development are combined under the general term "goitre heart".

Patients suffer from palpitation; dyspnoea ("dissatisfaction with inhalation"). The pulse is rapid (90 beats per minute and more). Tachycardia is one of the most constant and early symptoms of the disease. It is not relieved at rest or during sleep. The systolic pressure elevates while the diastolic pressure goes down which results in the elevation of the pulse pressure. The elevation of systolic pressure is mainly connected with a considerable increase of the stroke volume and the minute volume. The diminution of diastolic pressure is caused by the enlargement of the microcirculatory bed under the effect of thyroid hormones.

The apex beat is often diffuse and resistant. Mitral configuration imitating rheumatic heart disease is often observed. On auscultation the heart sounds are long and the first sound is often amplified at the apex. A functional systolic sound may be heard at the heart apex.

Functional vascular sounds may be heard over the pulmonary artery, on the carotids (systolic murmur), as well as over the jugular vein ("humming - top murmur"). The pathogenesis of systolic murmur is explained by the intensified rate of blood flow and the relative distension of the left venous orifice.

Disorders of the cardiac rhythm may occur in some patients with toxic goitre: sinus (respiratory) arrhythmia, sometimes extrasystole.

Cardiac fibrillation often occurs in the severe form of toxic goitre. It occurs at the beginning of the disease and usually has a paroxysmal character. It may eventually become constant as toxic goitre progresses. The pathogenesis of cardiac fibrillation is considered to be fundamentally linked with the augmented excitability. As a result, heterotopic foci of excitability appear in it, and also with the unfavourable effect of thyroid hormones on metabolic processes in the myocardium. Cardiac insufficiency in toxic goitre is mainly caused by overstrain of the heart as a result of disturbed haemodynamics and

reduced contractile capacity of the myocardium. Myocardial infarction, however, occurs very rarely as a result of a lesser tendency for thrombus formation.

Respiratory organs. There are no essential disorders of respiration.

Digestive organs. Many patients complain of an increase of appetite. There may be frequent stool (2-3 times a day) and a tendency to diarrhea. In severe forms there is vomiting and gastro-intestinal crises due to spasm of the pylorus and spastic contractions of the intestine.

The liver in toxic goitre is affected quite often; this is explained mainly by the intense inactivation in it of the excess of thyroid hormones, their binding with glucuronic and sulphuric acids. As a result of intoxication by thyroid hormones the permeability of capillaries is disturbed and serous hepatitis thus develops. In the severe form of the disease the liver is enlarged and tender and in some cases there is jaundice. All the basic functions of the liver are disturbed to a certain degree in toxic goitre, namely, antitoxic, glycogen - synthesizing, glycogen - fixing, albumin -, cholesterol-, prothrombin- forming and pigment - regulating functions. More often functional disorders of the liver in toxic goitre are reversible.

The kidneys and urinary tract are not affected as a rule. In some cases, however, there can be disorders in the reabsorption of calcium and phosphorus. These disorders are functional.

The neuro-muscular system and psyche. Disorders of the central and peripheral nervous system are among the foremost in the clinical picture of the disease. The trembling of the whole body (the "telegraph - post" symptom) and of parts of the body (tongue, closed eyelids, etc) is very characteristic. Tremor of the extended fingers of a relaxed hand (Marie's sign) is also typical. As a rule, dermography is rapid, sharply pronounced, stable and red.

As a result of the increase of the catabolic processes in the muscular tissue the following myopathic syndromes appear: chronic thyrotoxic myopathy, exophthalmic ophthalmoplegia (exophthalmic ophthalmopathy) (see section on ocular symptoms), myasthenia gravis and periodic paralysis.

Trophic disorders are also observed: shedding of hair and brittleness of nails.

The endocrine system. The menstrual cycle in females is disturbed. In girls there are delay of menstruation and of the appearance of secondary sex characters. In severe forms of the disease libido and potency in males are diminished, gynaecomastia is noted in males.

Changes in the functional state of the adrenal cortex come down to a certain intensification of its function in mild forms of the disease and the gradual decrease to the point of exhaustion in severe forms.

Hyperplasia of the thymus and of the entire lymphatic system (spleen, lymphatic nodes, papillae of the lingual root) is noted.

These clinical symptoms are incorporated under the general name "thymicolymphatic status" which is most often encountered in the severe form of the disease in children and elderly people.

The insufficiency of the adrenal cortex function which forms the basis of this condition serves as the principal cause of the inability of such patients to develop adaptation reactions in response to stress. Without adequate preparation of the patient for surgery, this may lead to sudden death of the patient on the operating table or immediately after surgery.

The peculiarities of the clinical course of diffuse toxic goitre.

Children as a rule have a marked enlargement of the thyroid gland.

Growth and processes of ossification are accelerated in childhood, particularly marked in adolescents of 13 to 15 years of age. It is observed

the retardation of sexual development. In children with diffuse toxic goitre signs of thymicolymphatic status are more frequent.

Tremor of the hands in children may be sweeping. In same cases choreiform movements occur; they are less marked than in chorea; not jerky and are usually coordinated, lymphocytosis is common in the blood.

In elderly patients the clinical course of toxic goitre is primarily characterized by changes in the cardiovascular system. Cardiac fibrillation and insufficiency of circulation quite often develop.

Diffuse toxic goitre and pregnancy. Diffuse toxic goitre in women predisposes to spontaneous abortion, stillbirth and premature delivery. Pregnancy in its turn affects the course of diffuse toxic goitre. Diffuse toxic goitre may be aggravated not only in pregnancy but also in lactation, in view of which it is best to reduce it as much as possible.

Thyrotoxic crisis. Thyrotoxic crisis is a severe complication of diffuse toxic goitre; it develops mainly in patients with a severe or moderate form of the disease. One of the causes of thyrotoxic crisis is partial thyroidectomy, intercurrent infections, intoxications, toxiinfections, after various surgical interventions, in the absence of treatment due to late diagnosis of toxic goitre, and sometimes as a result of the therapeutic application of I131.

The pathogenesis of thyrotoxic crisis is caused by a sharp increase of thyroid hormone incretion and a sharp diminution of adrenocortical function.

Thyrotoxic crisis is attended by the turbulent aggravation of the clinical symptoms of diffuse toxic goitre. Nausea, uncontrollable vomiting, diarrhea and sometimes profuse sweating develop, which result in the dehydration of the patient's organism. Extreme nervous agitation to the point of acute psychosis and insomnia set in. As a rule, acute muscular weakness develops later to the extent of total adynamia and prostration.

Body temperature elevates considerably (up to 40 grades Celsius and higher). The skin is very warm to the touch and often moist. Acute tachycardia (up to 200 beats a minute) develops.

Arrhythmia frequently occurs (paroxysmal form of cardiac fibrillation, extrasystole) and acute cardiac insufficiency develops. Arterial pressure is often very low. Jaundice occurs in some cases. There is a typically sharp rise in the level of thyroid hormones (T3, T4) in the blood.

Fatality rate without treatment reaches 75% and in elderly people even 100%. Death usually occurs within the first 48 hours.

Laboratory findings in the diffuse toxic goitre.

There are following pathological changes: leucopenia, relative and absolute, lymphocytosis and monocytosis, a tendency towards thrombocytopenia, considerably more rarely towards eosinophilia; increased erythrocyte sedimentation rate (ESR).

Hypocholesterolaemia;

Hypoalbuminaemia;

Hyperglycaemia, a lower tolerance of glucose and the development of diabetes mellitus are observed;

Prothrombin content in blood is often reduced;

Hyperbilirubinaemia is the result of a disturbance in the pigment-regulating function of the liver.

Diagnostic tests:

- determination of PBI;
- basal metabolism;
- radioisotope tests;
- the radioimmune assay of total and free thyroxine and triiodthyronine in the blood.

Determination of protein - bound iodine (PBI). The content of PBI in blood plasma considerably increases (normal level from 40 to 80 microg/l).

Radioisotope tests. In diffuse toxic goitre the I131 uptake by the thyroid is increased more than 50% after 24 hours with contact method.

Triiodthyronine (suppression) test shows the lack of the suppressor effect on the uptake of I131 by thyroid gland after 24 hours less than 50% comparing to initial.

Radioimmune assay of the thyroid hormones T3, T4 free and total shows their sharp increase in the blood. TSH is normal or low.

Lecture 6.

6.1 Treatment of Diffuse Toxic Goitre.

Two principal methods of treatment are applied to diminish the thyroid function: drug therapy using thyreostatic agents (mercazolil, potassium perchlorate, methylthiouracil) and radical therapy, i. e. treatment with radioidine (I131), surgical treatment (subtotal subfascial resection of the thyroid).

Treatment with thyreostatic agents. Some of the most effective agents applied in the treatment of diffuse toxic goitre as an independent method are antithyroid preparations of the imidazole group, including carbimazole (neomercazole) and 1-methyl-2-mercaptoimidazole, 1-M-2-M (mercazole, methothyrin), potassium perchlorate and thiouracil derivatives (methylthiouracil, propylthiouracil). With the use of these agents euthyroidism is produced in 50 to 75 per cent of cases.

Antithyroid preparations of the imidazole group most widely used are mercazolil and its analog methothyrin (1-M-2-M). Diffuse forms of toxic goitre with enlargement of the thyroid not exceeding the third degree and by any severity of the disease serve as indications for prescribing the above-mentioned agents as the principal method of treatment irrespective to age. Antithyroid preparations may be used in temporary treatment of patients with cardiac fibrillation, marked cardiac insufficiency, psychoses (in preparations for operation or for treatment with radioiodine). In diffuse toxic goitre complicated by severe dystrophy of the liver with marked jaundice, treatment with mercazolil is not contraindicated.

Contraindications are substernal goitre (the hazard of a goitrogenic effect and compression of the upper respiratory tract and blood vessels), the

period of pregnancy and lactation, leucopenia and neurotropenia (the neutrophil count is 35% and less).

Iodine preparations are indicated only in preparation for an operation and in the treatment of thyrotoxic crisis.

The mechanism of action of agents of the imidazole and thiouracil group is thought to be mainly linked with blocking the transformation of iodothyrosines into iodthyronines.

In view of the toxicity of antithyroid drugs their use during treatment is paralleled by systematic control over the state of the leukocytes at least once every 7-10 days.

Antithyroid drugs may cause nausea, vomiting, diarrhea, pain in the epigastric region, elevation of body temperature, skin rashes, and in long-term application hypothyroidism and enlargement of the thyroid gland.

Treatment with antithyroid drugs should be individual. In the mild form of the disease mercazolil (methothyrin, imidazole) is prescribed in doses of approximately 0.01 g two or three times a day (20 to 30 mg in 24 hours), potassium perchlorate in a dose of 0.25 g two - three times a day. The combination of potassium perchlorate with iodine preparations is impermissible because they increase the concentration of iodine in the blood, thus blocking the therapeutic effect of potassium perchlorate. In the moderate and severe form of toxic goitre mercazolil (methothyrin, imidazole) is prescribed in doses of approximately 0.01 g four times a day (40 - 50 mg a day). In some cases the daily dose of mercazolil (methothyrin) can be used in doses that do not exceed 1 g per day. The dosage of antithyroid drugs is gradually reduced and the patient is transferred to maintenance doses seven to ten days after achieving an euthyroid state (remission). The largest maintenance dose of mercazolil (methothyrin) is 0.01 g once a day, the smallest is 0.005 g once every three to four days. After attaining the euthyroid effect the maintenance doses are prescribed over long periods of time (up to a year and more).

The criteria of the euthyroid condition (remission) are a normalized pulse, stabilized body weight or gain in weight, and the disappearance of nervous disorders. The stability of the therapeutic effect is evaluated on the basis of the indices of thyroid hormones in the blood and PBI, basal metabolic rate, radioiodine diagnosis, and the dimension of the goitre.

Indications for discontinuing antithyroid drugs on achieving stable clinical remission can be the results of radioiodine diagnosis (normalization of I131 uptake by the thyroid: marked suppression of I131 uptake by the thyroid in a test with triiodthyronine hydrochloride), and the reduced dimensions of the goitre, normal level of the T3, T4 in the blood.

On achieving a stable clinical effect and to avoid a recurrence of the disease antithyroid agents are discontinued only after the thyroid has returned to the dimensions corresponding to about the I-II degree of enlargement.

To prevent the goitrogenic effect of antithyroid drugs it is expedient to apply them in combination with small doses of thyroidine or triiodthyronine hydrochloride after the euthyroid state is attained. In the absence of contraindications (hyperacidic gastritis, peptic ulcer disease, bronchial asthma) treatment with antithyroid drugs is usually also combined with reserpin, beta-adrenoblockers (anaprilin), which block the increased activity of catecholamines or reduce the sensitivity of adrenoreceptors and thus augment the efficacy of antithyroid drugs. This makes it possible to achieve clinical remission more rapidly and reduce the daily dosage of the drugs mentioned. The dosage of the drugs is selected individually. Reserpin can be prescribed in a dose of 0.25 mg twice and anaprilin (obsidan, inderal) in a dose of 30 mg two to three times a day until tachycardia is relieved.

The dosage of preparations is gradually reduced 10 to 14 days after the complete relief of tachycardia. Among the complex of measures applied

in the treatment of diffuse toxic goitre neuroleptic agents (elenium) are used. Chlordiasepoxid, seduxen (diazepam), phrenolon (methophenazin) are also used.

Preparations of digitalis (digoxin syn. oxydigitoxin, isolamid syn. lantosid) are prescribed in cardiovascular insufficiency. Anabolic steroids are used in malnutrition: nerabol (syn. dianabol) in a dose of 5 mg twice a day or retabolil (syn. eubolin) in a dose of 1.0 ml of a 5% solution intramuscularly once a month, or nerabolil (syn. norstenol) in a dose of 1 ml of a 2.5% solution intramuscularly once a week. In diminished function of the adrenal cortex in patients with the severe form of the disease, especially at an elderly age, glucocorticoids (prednisolone in a dose of 5-20 mg a day) and other drugs are prescribed.

Treatment with I131

Treatment with I131 is very effective. The indications for using I131 in treatment are the following:

- diffuse toxic goitre in the moderate and severe form, especially in the absence of a stable euthyroid state resulting from treatment with antithyroid preparations;
- diffuse toxic goitre in the severe form with grave irreparable changes in the internal organs particularly in the cardiovascular system, which make doubtful a favourable outcome of the operation; relapses of toxic goitre after subtotal recession of the thyroid;
- thyrotoxic psychosis:
- diffuse toxic goitre with severe attendant disease (stage II hypertensive disease, ischaemic heart disease, severe chronic diseases of the lungs, etc) in the absence of a stable euthyroid condition due to treatment by thyreostatic preparations, diffuse toxic goitre with marked ophthalmopathy in the absence of a stable euthyroid condition.

Contraindications for treatment with I131 are the following: a mild form of toxic goitre; nodular forms of toxic goitre (relative contraindication), retrosternal form of toxic goitre (relative contraindication); a period of pregnancy and lactation; stable leucopenia; young age (under 40) because of danger of an hereditary effect.

In the severe form of the disease complicated by cardiac fibrillation, cardiac insufficiency, lesions of the liver, psychoses, in severe attendant diseases as well as in the refusal to be operated, it is possible to apply I131 treatment to patients 30-39 years of age.

The principal therapeutic effect of large doses of I131 consists in the ability of its beta-rays to cause the death of follicular epithelial cells of the thyroid with their subsequent replacement by connective tissue. The therapeutic effect of small doses of I131 (up to 6 milliCurie) is evidently connected only with disturbance of enzyme systems, because specific histological changes are absent in the cells of the follicular epithelium. Total therapeutic doses are 6 - 12 milliCurie.

Before the treatment with I131 it is necessary to reach euthyroid state to avoid the thyrotoxic crises.

Surgocal treatment

One of the widely used methods for treating diffuse toxic goitre is surgery: subtotal subfascial thyroidectomy leaving 5 to 6 g of the thyroid gland.

Indications for surgery are the moderate and severe forms of diffuse toxic goitre in the absence of a stable euthyroid condition after drug therapy, a large diffuse toxic goitre; nodular and retrosternal forms of toxic goitre; diffuse toxic goitre in children and adolescents in the absence of a stable euthyroid condition resulting from drug therapy; pregnancy (3rd - 6th months) and lactation; diffuse toxic goitre complicated by cardiac fibrillation.

Contraindications for surgery are diffuse toxic goitre in the severe form with grave irreparable changes in the internal organs, particularly of the cardiovascular system (III degree circulatory insufficiency, anasarca, ascites, etc.), which make a favourable outcome of the operation doubtful; temporary contraindications are acute infectious diseases (influenza, tonsillitis and others). In such cases patients are usually operated in one month after convalescence.

To prevent postoperative thyrotoxic crisis, patients with toxic goitre should be operated on only after the euthyroid state has been produced. The euthyroid state is achieved by using mercazolil (methothyrin). Two to three weeks before the operation mercazolil treatment is supplemented with preparations containing iodine.

In reduced adrenocortical function with clinical symptoms of the thymicolymphatic state treatment with glucocorticoid preparations (prednisolone 10-30 mg or hydrocortisone 25-50 mg a day) is applied as preoperative management for two to three weeks prior to surgery.

On the day of the operation 50 to 100 mg of cortisone or hydrocortisone are injected intramuscularly to prevent acute insufficiency of the adrenal cortex.

Treatment of thyrogenic ophthalmopathy

On attaining the euthyroid state it is essential to begin treatment immediately with thyroidin or triiodthyronine hydrochloride (in the absence of coronary pathology) increasing the doses to maximum tolerance. Dehydration therapy includes treatment with diuretics (furosemide in a dose of 40 mg twice a week), diet with a restriction on liquids, spicy and salty foods. It is presumed that the mechanism of the favourable effect of prednisolone in these cases is mainly connected with inhibition of the synthesis of mucopolysaccharides in orbital tissues. Antibiotics are prescribed both independently and in combination with X-ray therapy. Since X-rays are capable of increasing the penetrability

of the haematoencephalic barrier, it is expedient to prescribe antibiotics after the second session of X-ray therapy.

X-ray therapy in thyrogenic ophthalmopathy is needed.

In the first variant X-ray therapy is applied to the hypothalamo-hypophyseal region in small doses (initial dose 50 rad, subsequent doses 75 rad, and the total dose is 450-600-800 rad).

If there is no stable positive effect after half of the course of X-ray therapy in small doses, a variant is applied with higher total doses (3000-6000 rad).

Sometimes (in turbulently progressive thyrogenic ophthalmopathy with the hazard of dislocating the eyeball) the second variant is used, which consists in irradiating the orbital field of the eye socket (single dose 75-200 rad, total dose up to 1000 rad).

Treatment of thyrotoxic crisis. In thyrotoxic crisis the patients must have complete psychic and physical rest.

To inhibit the incretion of thyroid hormones it is recommended intravenous drip of 1 per cent Lugol's solution, prepared with sodium iodide instead of potassium iodide in amounts of 100-250 drops in 1 litre of a 5% glucose solution in an isotonic solution of sodium chloride.

If there is no vomiting the infusion of Lugol's solution is paralleled by the prescription of mercazolil in a dose of 0.01 g. Every eight hours with the simultaneous intake of reserpin per os (0.25-1.0 mg every 4 hours) or intramuscularly (1 ml of a 0.25 per cent solution every 4-5 hours). Beta-adrenoblockers (anaprilin, in a dose of 30-50 mg per os) are used for blocking the peripheral effects of catecholamines (tachycardia).

Intravenous drip, subcutaneous or rectal infusion of 2-3 l of isotonic solution of sodium chloride with a 5% glucose solution are prescribed to prevent dehydration of the organism. In repeated vomiting 10 ml of

a 10 per cent solution of sodium chloride is injected intravenously, as well as rectal drip of 500 ml of a 2.5% solution of sodium hydrocarbonate. Acute insufficiency of the adrenal cortex is treated by intravenous drip of hydrocortisone (100 - 600 mg) or the intramuscular injection of hydrocortisone or cortisone in a dose of 100 to 300 mg a day. A 0.5% solution of DOCA (deoxycorticosterone acetate) is injected intramuscularly in doses of 5-10 mg a day.

The cardiotonic and vasotonic therapy (caffeine, cordiamine, strophanthin or corglycon, etc.) in common doses are used to relieve cardiovascular insufficiency. Hyperthermia can be reduced by cooling the patient's body with electric fans, maintaining a low temperature of air in the room and also by prescribing acetylsalicylic acid.

6.2 Toxic Adenoma

Toxic adenoma is characterized by the presence of nodule (adenoma) which independently produces thyroid hormones at an increased rate, by hypoplasia and a decreased function of the remaining tissue of the thyroid. As a rule, toxic adenoma occurs in women and more often at an age over forty.

History (see Diffuse Toxic Goitre)

Aetiology and pathogenesis. The aetiology of toxic adenoma, just as of other adenomas, is not very clear. As distinct from diffuse toxic goitre, the long-acting thyroid-stimulating factor (LATS) does not participate in the pathogenesis of toxic adenoma. The toxic adenoma produces thyroid hormones autonomously irrespective of the action of the thyrotrophic hormone of the hypophysis. As a result of the increased production of thyroid hormones the production of TSH may be inhibited with the subsequent decrease of the function of the remaining tissue of the thyroid gland. It is presumed that the principal role in the

pathogenesis of toxic adenoma belongs to local disorders of nerve pulsation received by different segments of the thyroid tissue.

Pathology. The adenoma has a smooth surface. Histologically it is more often of a homogeneous structure with microfollicular structure and high cuboidal or columnar epithelium and liquid vacuolized colloid. In some cases toxic adenoma may have a macrofollicular structure and pronounced proliferation of the epithelium.

Clinical picture. The clinical picture of toxic adenoma is mainly the same as in diffuse toxic goitre. As distinct from diffuse toxic goitre toxic adenoma is often marked by a few symptoms with a moderately pronounced clinical picture (mild weakness, slight loss of weight, moderate tachycardia, etc.), absence of ophthalmopathy and pretibial myxoedema. In palpating the thyroid an elastic node is determined with clear-cut boundaries and a smooth surface of various firmness, moving easily in swallowing.

Diagnostic tests. Among the diagnostic tests decisive importance belongs to radioisotope scanning of the thyroid. The scan shows the high uptake of radioiodine by the node ("hot nodule") with reduced uptake by the remainder of the gland.

Diagnosis and differential diagnosis. See "Diffuse Toxic Goitre" and "Carcinoma of Thyroid Gland".

Prognosis. See "Diffuse Toxic Goitre".

Treatment. The treatment of toxic adenoma is most often surgical, subtotal resection of the affected lobe of the thyroid and adenoma. Surgery is permissible only when producing the euthyroid state by means of preoperative preparation (see "Diffuse Toxic Goitre"). When there are contraindications for surgery, treatment with radioiodine may be applied.

Lecture 7.

7.1 Hypothyroidism.

Hypothyroidism is caused by insufficiency in creation of thyroid hormones by the thyroid gland or by the complete loss of its function. The share of hypothyroidism among other endocrine diseases is gradually increasing. Hypothyroidism is encountered in females more often than in males. The idiopathic form of hypothyroidism occurs mainly in females older than forty years.

History. The disease was first described in 1873 by Gall. The term myxoedema (mucous swelling) was introduced in 1878 by Ord. On the autopsy of two patients Ord discovered mucous swelling of the skin and subcutaneous fat and linked these changes with the thyroid. The most complete clinical characteristic of hypothyroidism (myxoedema) was given by S.P.Botkin in his clinical lectures (1883 - 1887).

Aetiology. In the mechanism of origin primary and secondary hypothyroidisms are distinguished. In primary (thyrogenic) hypothyroidism the pathological process is localized in the thyroid, whereas in secondary hypothyroidism in the hypothalamo-hypophyseal system.

Primary hypothyroidism may occur as a result of hereditary defects in the biosynthesis of thyroid hormones (defect in accumulation of iodine by the thyroid, defects at the level of the transformation of monoiodthyrosine and diiodothyrosine into triiodothyronine and thyroxine). The latter are caused by the autosomal recessive gene.

Primary hypothyroidism may also be caused by hypoplasia and aplasia of the thyroid as a result of its embryonal developmental defect, degenerative changes in the thyroid consequent upon infectious-inflammatory processes (thyroiditis, strumitis), subtotal or total

thyroidectomy. Hypothyroidism may develop after treatment with radioiodine. The temporary diminution of the thyroid function may occur in treatment by antithyroid agents (mercazolil, potassium perchlorate) of diffuse toxic goitre. Primary hypothyroidism may occur as a result of the insufficient introduction of iodine into the organism (endemic goitre). The cause of primary hypothyroidism may sometimes be cancerous metastases, chronic infections (tuberculosis, syphilis).

Secondary hypothyroidism is most often caused by affection of the hypothalamo-hypophyseal system (Sheehan's syndrome, congenital underdevelopment of the hypophysis, chromophobe adenoma, craniopharyngioma). In some instances it has not been possible to establish the aetiology of hypothyroidism.

Pathogenesis. The pathogenesis of primary hypothyroidism is caused by the reduction in mass of the glandular tissue of the thyroid, inhibition of the synthesis of thyroid hormones under the effect of antithyroid drugs or lack of iodine in the organism.

In secondary hypothyroidism as a result of reduced incretion of TSH or thyrotrophin-releasing factor not only is synthesis disturbed, but the entrance of the thyroid hormones from the thyroid gland into the blood is also disturbed.

The pathogenesis of the late forms of hypothyroidism appearing several years after subtotal thyroidectomy or treatment with I131 is now regarded as the result of autoaggression. Injury to the thyroid tissue after surgical intervention or treatment with I131 is attended by the tissue proteins of the thyroid (thyroglobulin, etc.) getting into the blood. Since these tissue proteins are antigens, they lead to a response consisting in a considerable rise in the autoantibody titre.

As a result of autoimmune processes taking place in thyroid stroma, lymphoplasmocytic infiltrates appear and destructive processes in the

thyroid parenchyma develop. This eventually leads to a decrease in the functional activity of the thyroid.

The pathogenesis of congenital hypothyroidism and of hypothyroidism in women older than 40 against the background of the age involution of sexual glands is currently regarded from positions of autoimmune processes.

A deficit of thyroid hormones leads to disorders in all kinds of metabolism: protein (reduction of synthesis and disintegration of proteins); carbohydrate (heightened tolerance of carbohydrates, tendency to hypoglycaemia); lipid (increase of alpha- and beta-lipoproteins and particularly of cholesterol in the blood); water-salt (retention of water and sodium chloride in the tissues). Retention of water and sodium chloride, accumulation in the connective tissues of mucoproteins possessing pronounced hydrophilic properties lead to the development of mucous swelling.

The sharp decrease in oxidation processes and diminution of protein synthesis cause retardation of growth in children (myxoedematous nanism).

Disturbance of the function of the vegetative nervous system (inhibition of its sympathetic part) leads to functional changes in the activity of various organs (bradycardia, diminished motor activity of the gastro-intestinal tract, reduced perspiration).

Pathology. The pathomorphology of the thyroid is connected with the character of its lesion (thyroiditis, strumitis). Proliferation of connective tissue and decrease in parenchymatous tissue are noted. In hypothyroidism of congenital origin there is underdevelopment or lack of thyroid tissue. Morphopathological changes in the thyroid resulting from genetic defects in the biosynthesis of thyroid hormones are expressed in the development of hyperplasia and hypertrophy of thyroid tissue.

In secondary hypothyroidism there is atrophy of the parenchyma of the organ and the replacement of the glandular tissue by fat. The

configuration of the follicles is irregular, their diameter is shortened. The colloid within them is dense and practically unvacuolized.

Pathomorphological changes in the thyroid as a consequence of treatment with I131 or X-ray therapy are characterized by destruction of its tissue, phenomena of atrophy and fibrosis.

Histological study of the skin reveals hyperkeratosis, degenerative changes in the epidermis, accumulation of mucin in the connective-tissue layer. Mucin consists of mucopolysaccharides, hyaluronic and chondroitinsulphuric acids. There is pronounced atherosclerosis not corresponding to the patient's age. The cardiac cavities are usually distended. Degenerative changes and proliferation of connective tissue are seen in the heart muscle.

Classification. By the degree of severity, hypothyroidism is classified as mild, moderate and severe (myxoedema).

Clinical picture. The disease usually develops gradually. There are complaints of lassitude, somnolence, apathy, slowness, chilliness, weakening of memory, constipation.

General examination. The patient's face is large, yellowish-pale, sometimes with blushing cheeks, puffy, old-looking, with poor expression. The palpebral fissures are narrow, in rare cases the eyeballs are deep set. The eyes have lost the sparkle. A puffy swelling of the upper and lower eyelids, swollen lips and cheeks are noted. In some cases there is oedema in the supraclavicular region, on the back surface of the hands and feet.

As distinct from other disease in hypothyroidism no indentation remains on the oedematous tissues after pressure is applied. It is presumed that mucin mainly accumulates in the upper papillary layers of the skin. When the swelling spreads to the subcutaneous fat a dimple remains in pressure. Changes of the skin occur more often in hypothyroidism in the moderate and severe forms. The skin is thick, rough, cold to the

touch, dry, peeling, pale, with a yellowish hue, which is due to insufficient blood supply and hypercarotenaemia as result of the slow transformation of carotine into vitamin A. Gross trophic disorders also occur in skin appendages.

The hair is brittle, dry and is shed intensively. The shedding of hairs in the outer part of the eyebrows, is characteristic. The nails are brittle, dull and with lines on the surface.

The cardiovascular system. Bradycardia is a common occurrence (the pulse rate is 60 beats per minute and rarer). The boundaries of the heart are distended, more often uniformly. The heart sounds are dull. Arterial pressure is reduced at the cost of systolic pressure. Pulse pressure is low. There is a diminution of the minute and systolic blood volume, of the amount of circulating blood and the rate of blood flow.

Disorders of the cardiovascular system are linked with interstitial oedema of the heart muscle and reduction in the content of potassium which plays a major role in the metabolic processes of the myocardium.

The ECG shows sinus bradycardia, a small voltage of waves, mildly pronounced "T" and "P" waves, a decrease of the S - T interval below the isoelectric line, enlongation of the P - Q interval.

In the hypothyroidism marked atherosclerosis with development of ischaemic heart disease often occurs, particularly in middle-aged and elderly patients.

Respiratory organs. There are no essential disorders in the respiratory function. The voice is changed (swelling of the vocal chords in the larynx) and simultaneously there is oedema of the tongue and lips which makes speech incoherent. In moderate and severe forms of hypothyroidism speech is usually slow with long pauses between words. Patients have a tendency to catarrhal states of the upper respiratory tract and focal pneumonias.

This is connected with change in the function of respiratory organs and diminished resistance of the organism to infections.

The gastro-intestinal tract. Nausea and persistent constipation attended by meteorism are noted which is caused by weakening of the motor function of the intestine. As a result of mucinous changes the tongue thickens so that there is not enough room for it in the mouth. Periodontosis and increased tendency for dental caries are often encountered. The secretory and motor activity of the stomach is diminished, hypo- and achlorhydria occur with a considerable decrease in the content of pepsin in the gastric juice. The changes in the liver are usually very mild and only pertain to hepatic structure.

Kidneys. A reduction in glomerular filtration, blood flow and the secretory capacity of the tubules is noted, but there are no clinical manifestations of renal insufficiency.

Nervous system and phychics. The changes in the central nervous system are most constant. The disease is manifested in lassitude, apathy, somnolence, a deterioration of intellect which grows with the advancement of the disease. Sometimes in severe protracted course of hypothyroidism a serious disturbance of psychics may develop to the point of psychosis (persecution mania, acute and chronic maniacal state). In many cases there are headache and dizziness which, are linked with oedema of the cerebral tissue. Hearing is impaired as a result of oedema of the acoustic nerve. The tendon reflexes are diminished.

In some cases severe pain of the type of radiculitis in the upper and lower extremities occurs, there are paraesthesias, cramps, unsteady gait, and severe polyneurotic, pseudotabetic or funicular disorders. Thermoregulation is disturbed and body temperature drops. The EEG reveals low voltage, the slowing down or absence of the alpha-rhythm, an increase of beta-activity. Changes both in the central and peripheral

nervous system are reparable in character and may completely disappear after timely treatment with thyroid agents.

Endocrine system. The thyroid is not palpated and in some cases (in primary hypothyroidism) it is enlarged. This occurs in a hereditary defect of the biosynthesis of thyroid hormones, in endemic goitre. In the latter case dense nodules may be palpated in the thyroid. There is sometimes a decrease in the adrenal function. Quite often the function of the sexual glands is disturbed.

In men there may be a diminution of potency to the point of impotence, disturbance of spermatogenesis. Women may suffer from primary or secondary amenorrhoea, menometrorrhagia, and sometimes hypermastia. Often, particularly, in severe form of hypothyroidism, sterility develops; there are miscarriages and stillbirths. In patients of both sexes there is diminution or disappearance of libido, the shedding of hair on the pubis, and axillae.

Particuliarities of the clinical course of hypothyroidism in children. In children hypothyroidism is one of the frequent endocrine diseases. In congenital hypothyroidism the symptoms of the disease usually begin to appear when the infant is given the breast less frequently (approximately from the 6th month of life). Retardation of the physical, sexual and mental development is characteristic of the clinical picture of this disease in children. Without substitution therapy by thyroid preparations these symptoms are the more pronounced the earlier hypothyroidism originated. Children begin to hold the head properly, to sit and to walk at a later age. The eruption of teeth is delayed. As a result of retarded growth of the facial skeleton a saddle nose sometimes forms. The abdomen is big bulging with an umbilical hernia which is caused by chronic constipation. As a rule, the disease is attended by growth retardation and disorders in the development of the bone system. The tubular bones are wide and short. The proportions of the skeleton are almost chondrodystrophic. There is a delay in the appearance of

ossification nuclei. Epiphyseal dysgenesis is manifested by the ossification of epiphyseal cartilage's beginning from numerous irregular foci spread over the whole zone of the changed cartilage. The fontanels ossify late. Sometimes large fontanels may remain open even to the age of eight to ten years.

Retarded mental development is manifested by the delayed development of speech, a poor vocabulary and impairment of intellect. Disorders of the sexual glands are displayed by the late development of the genitals and secondary sex characters. Dysfunction of the ovaries, hypoplasia of the uterus and testes are observed.

Hypothyroid (hypothermic) coma. Hypothyroid coma is a formidable complication of hypothyroidism. It may develop in patients with a severe form of hypothyroidism that had not been treated with thyroid preparations for a long time. Infections, physical traumas, overcooling are conducive to the development of hypothyroid coma.

Hypothyroid coma is clinically manifested in the drastic deterioration of the patient's condition, a sharp drop in body temperature, sometimes to 23 grades C, the intensification of sinus bradycardia and hypotonia.

Laboratory findings. Anaemia is often observed in the blood. It may be normochromic (more rarely hypochromic, with a deficit of iron), or pernicious-like, which results from the diminished absorption of vitamin B12 in the intestine. Leucopenia with relative lymphocytosis appears in some cases. Quite often there is a heightened ESR. Hypercholesterolaemia usually occurs as a result of the diminution of metabolism and the discharge of cholesterol in the bile. The content of beta- and alpha-lipoproteins in the blood is often increased. Hypoalbuminaenia and hyperglobulinaemia (at the expense of beta- and alpha-2-globulins, and in hypothyroidism of autoimmune genesis also at the expense of gamma-globulins) are a frequent occurrence. These changes occur as a result of the diminution of protein synthesis

and catabolism. The content of sugar in the blood is often determined at the lower limit of the normal level. In some cases a high titre of auto-antibodies to thyroglobulin or the thyroid tissue is registered in the blood. Sometimes the excretion of 17-CS and 17-OCS in the urine is reduced.

Diagnostic tests. To diagnose hypothyroidism TTH, PBI, total thyroxine (T4) in the blood, and basal metabolism are determined and radioisotope tests are used. In hypothyroidism PBI is lower than 40 microg/l. As a rule, I131 uptake in the thyroid is reduced.

Thyrotrophine test. The test is based on the ability of thyrotrophin to augment the thyroid function and is used for the differential diagnosis of primary and secondary hypothyroidism. Prior to conducting the test, the uptake of I131 by the thyroid is determined. On the next day 10 U of thyrotrophin are injected subcutaneously after which the investigation of I131 uptake is repeated. In primary hypothyroidism the value of I131 is not changed, but in secondary hypothyroidism it increases by more than 50%. In atrophy of the thyroid the uptake of I131, however, is not changed even in secondary hypothyroidism.

Basal metabolism in hypothyroidism is reduced (it is usually lower than 10%). Indices of basal metabolism are not of decisive significance for the diagnosis of hypothyroidism. The decrease of basal metabolism occurs not only in hypothyroidism, but also in obesity, hypopituitarism, neurogenetic cases, anorexia, nephroses, cardiac insufficiency, anaemia, prolonged intake of sedatives, in a diet lacking in proteins.

Diagnosis and differential diagnosis. The diagnosis of hypothyroidism is made on the basis of a characteristic clinical picture of the disease, the findings of diagnostic test (TSH, T4 of the blood, radioactive diagnosis and basal metabolism) and hypercholesterolaemia. Hypothyroidism is differentiated from Down's disease, diseases attended by growth retardation (rickets, hypophyseal nanism, chondrodystrophy), chronic nephritis.

As distinct from hypothyroidism, in Down's disease the patients have slanting eyes. The outer corners of the eyes are slightly raised. There is no oedema of skin.

In growth retardation caused by rickets, there are rachitis changes in the bones. The intellect is preserved and sexual development is also normal. There are no pathological changes in the skin. As distinct from hypothyroidism, in hypophyseal nanism the proportion of different parts of the body is preserved despite the sharp delay of growth. The intellect remains normal.

In chondrodystrophy mental development is normal, there are no abnormalities of the skin and sexual glands, but the appearance of the patient is very characteristic: a large head with well-developed frontal and parietal tubers, a disproportionally large trunk and small extremities in combination with a sharp delay in growth.

In chronic nephritis the case history shows indications of renal diseases. In chronic nephritis oedema is soft and in hypothyroidism it is firm. Diagnosis is assisted by changes in the urinary sediment (proteinuria, microhaematuria, cylindruria), arterial hypertension and changes in the fundus of the eye (constriction of arterioles, haemorrhages, exudation and oedema of retina). In some cases changes in the cardiovascular system require differential diagnosis between rheumatism and congenital valvular diseases in children.

Primary hypothyroidism is differential from secondary. In secondary hypothyroidism after the subcutaneous injection of 10 U of thyrotrophin, the uptake of I131 is usually increased by more than 50%, while in primary hypothyroidism it is not changed. In primary hypothyroidism of autoimmune genesis, as distinct from secondary hypothyroidism, a high titre of auto-antibodies to thyroglobulin or the thyroid tissue is noted in the blood.

Prognosis. In correct substitution therapy by thyroid preparations in uncomplicated cases the prognosis in adults is favourable both in regard to life and working capacity. In complicated cases prognosis is determined by the character and severity of complications. Prognosis of hypothyroidism in children depends mainly on whether the disease had been treated in good time.

When treatment with thyroid preparations had been delayed (begun later than the first year of life) prognosis in children with congenital hypothyroidism is unfavourable as their mental development is concerned. In hypothyroid coma the prognosis is usually unfavourable. The outcome is fatal in 90% of patients.

Prognosis in regard to working capacity depends on the degree of severity of hypothyroidism. In hypothyroidism of the mild form patients can perform any work not involving considerable physical or nervous-psychic stress. In hypothyroidism of the moderate form work involving slight physical and neuro-psychic tension is indicated, such patients may be qualified III group invalids. Patients with the severe form of hypothyroidism are incapable of work. They are II group invalids, and only in rare cases can perform work at home.

7.2 Treatment of the Hypothyroidism.

Treatment. Patients with hypothyroidism must receive a full value diet with a restriction on food stuffs rich in cholesterol and sodium chloride. In opposite the total calories in the daily diet must be reduced. The principal method of treating hypothyroidism is substitution therapy with thyroid preparation such as thyroidine and triiodothyronine hydrochloride.

The effect of thyroidine (a hormonal agent of the desiccated thyroid of animals) depends on the presence in it of thyroid hormones, mainly of thyroxine and small amount of triiodothyronine.

In view of the possible heightened sensitivity to thyroid preparations it is expedient to begin per oral treatment with thyroidine with small doses (0,025 g twice a day), gradually increasing the dosage every 5 - 10 days by 0,025 g a day till the euthyroid effect is attained.

The effect of thyroidine begins two - three days after the beginning of treatment, and the final effect is produced in three - four weeks.

Under conditions of the euthyroid state the required optimum dose of thyroid preparations is prescribed individually either continuously or, to avoid overdosage, with intervals of 1 - 4 days (the dose is taken for 2 or 3 days after which a day's interval is made). The daily dose of thyroidine usually does not exceed 0,3 g. To avoid overdosage in treatment with triiodothyronine hydrochloride, administration is begun with a dose of 5 - 10 microg which is then gradually increased depending on the need to 25 - 100 microg a day. Triiodothyronine hydrochloride is more active than thyroidine (0,1 g of thyroidine corresponds to approximately 25 - 30 microg of triiodothyronine hydrochloride and 0,1 mg of thyroxine).

In using triiodothyronine hydrochloride the clinical effect is produced in 24 hours, and the euthyroid state usually in 7 to 12 days. If signs of overdosage with thyroid preparations appear (tachycardia, loss in body weight, increase of arterial pressure, nervous-psychic excitability, insomnia, pain in the heart region, perspiration), they must be discontinued for a few days (usually 1 or 2 days) and then prescribed again, but in smaller doses. Phenomena of overdosage with thyroid preparations occur more rarely if analogs of anaprilin (inderal, obsidan in a dose of 20 - 80 mg a day) are added.

Indications of the efficacy of treatment with thyroid preparations are evident in the restoration of the patient's working capacity, the increased rate of growth (in children), the normalization of the pulse, of the level of cholesterol, PBI of blood plasma and the value of basal metabolism.

Under conditions of a euthyroid state the value of basal metabolism is usually within the limits of ±10%.

It is essential to show the greatest caution in applying treatment with preparations of the thyroid gland to patients suffering from ischaemic(coronary) heart disease and the hypertensive disease. To avoid frequent paroxysms of angina pectoris thyroid preparations in such cases are prescribed in subcompensation doses in combination with cardiovascular agents.

The initial dose of thyroidine should not exceed 0,01 - 0,02 g once or twice a day, and of triiodothyronine hydrochloride 5 microg daily. Later the dosage of thyroidine may be increased by no more than 0,015 g daily with intervals of 10 days, and of triodothyronine hydrochloride by not more than 5 microg daily with intervals of 14 days.

The initial dose of L-thyroxine is 50 - 100 microg daily or triiodothyronine hydrochloride 10 to 25 microg daily.

Treatment is applied under control of arterial pressure, electrocardiogram (recorded every week), blood serum cholesterol and the value of basal metabolism. Hypothyroidism is usually treated by the combined prescription of thyroidine and triiodothyronine hydrochloride. This is regarded as the most physiological method, because it ensures the entry of both thyroid hormones into the organism.

In hypothyroidism of autoimmune genesis glucocorticoids (prednisolone) are prescribed together with thyroid preparations. Glucocorticoids inhibit the antigen-antibody reaction and diminish the synthesis of antibodies. Prednisolone is prescribed in courses for two months. During the first month prednisolone is prescribed in a dose of 20 - 40 mg a day, while during the second month this dose is gradually reduced. Whenever necessary (increase of the titre of auto-antibodies), treatment with prednisolon is repeated.

At the age of 12 to 18 months treatment with thyroidine is usually begun with a single dose of 0,01 - 0,015 g increasing it by 0,01 - 0,015 g every week. Usually the optimum daily dose of thyroidine at this age is 0,045 to 0,06 g. For the older children the initial dose of thyroidine is 0,03 to 0,04 g, the maintenance dose is 0,075 to 0,15 g a day.

In children with severe congenital hypothyroidism or hypothyrodism acquired in early childhood retardation in physical and mental development is corrected by prescribing thyroidine in a dose of 0,1 to 0,3 g a day with the gradual reduction of dosage and the subseguent prescription of a maintenance dose. The treatment of secondary hypothyroidism does not differ from that of primary hypothyroidism.

Patients with hypothyroidism are also treated by vitamins (of group A and C). In anaemia (depending on its genesis) iron preparations, hydrochloric acid, vitamin B12 and antianaemia are prescribed.

Among the physiotherapeutic procedures carbon dioxide or narzan mineral water baths, shower, sea and river bathing are applied.

In hypothyroid coma triiodothyronine hydrochloride is prescribed intravenously in a dose of 100 microg every 12 hours or 25 microg every 4 hours with the subsequent reduction of the dosage of triiodothyronine hydrochloride after the rise in rectal temperature. To control collapse hydrocortisone is administered in a dose of 50 - 100 mg every 6 - 12 hours till all symptoms disappear.

Lecture 8.

8.1 Auto-Immune Thyroiditis (Hashimoto's Thyroiditis).

Auto-immune thyroiditis is encountered everywhere. Women contract auto-immune thyroiditis 17 times as frequently as males. In women the disease usually develops at the age over 40. The prevalence of auto-immune thyroiditis is about 5 per cent of all diseases of the thyroid.

History. The disease was first described in 1912 by the Japanese surgeon Hashimoto. The auto-immnune genesis of struma lymphomatosa was first established in 1956 by Denich and Routh.

Aetiology. The aetiology of the disease has not been fully clarified. Any effect on the thyroid resulting in a disturbance of the physiological isolation of the antigens may create prerequisites for the origin of an auto-immune process (injury to the thyroid in bacterial and virus infection, surgery, treatment with radioiodine, etc.). It has been noted that in some cases chronic auto-immune thyroiditis is familial in character, which is possibly connected with genetic predisposition.

In some patients suffering from Hashimoto's thyroiditis there exists a congenital tendency to the formation of antibodies. Thus, for example, auto-immune thyroiditis often combines with rheumatoid arthritis, with acquired haemolytic and pernicious anaemia, myasthenia and other diseases, in the pathogenesis of which the auto-immune mechanism is not excluded.

Pathogenesis. As a result of damage (rupture) to or the increased permeability of walls of thyroid follicles occurring under the effect of various factors (infection, operation). substances possessing auto-antigenic properties enter the bloodstream. Thyroglobulin and microsomal particles are the main among them. When they penetrate the interparenchymatous spaces of the thyroid these substances cause

an inflammatory reaction with infiltrates consisting of giant and plasmatic cells. Auto-antibodies form in relation to these auto-antigens.

The antigen-antibody reaction destroys the thyroid tissues. This in turn, releases into the blood new substances possessing auto-antigenic properties, which results in further growth of the titre of circulating antibodies. Progressive cytolysis is conducive to the gradual destruction of the thyroid parenchyma and its secondary replacement with cicatricial connective tissue and the increase of symptoms of hypothyroidism.

The degree to which the auto-immune process is manifested depends not only on the duration of the disease and the amount of the antigen produced, but to a great extent on the immune reactivity of the organism which is possibily caused by genetic factors.

Pathology. The thyroid is usually enlarged and of hard consistency. Histological examination shows diffuse infiltration of the connective tissue by lymphoid and plasmatic cells, the destruction in such places of the basic membrane and the epithelial wall of the follicles. In some places the basic membrane is destroyed without the presence of inflammatory cells.

The amount of colloid in the follicles is diminished or it is entirely absent. The hyperplastic process is attended by proliferation of the fibrous tissue of various degree.

Clinical picture. Usually the disease develops gradually. There are no complaints or the patients complain of general weakness and fatigue.

In some cases, however, the onset of the disease may be acute with pain in the thyroid referred to the ear and back of the head. The beginning of auto-immune thyroiditis is sometimes attended by thyrotoxicosis. When the thyroid is very firm and enlarged the patient complains of a sensation of thickening, of pressure in the area of the anterior surface of the neck and sometimes of difficulty in swallowing.

In palpation the thyroid is not painful, it is mobile (is not adhered to the surrounding tissues), of moderate firmness, with a smooth and more rarely tuberous surface because of indurations due to local auto-immune thyroiditis.

When the disease is of long duration (of several years after enlargement of the thyroid gland has been noted) symptoms of hypothyroidism appear, which usually cause changes in the organs and systems. In the acute onset of Hashimoto's thyroiditis the clinical picture of marked hypothyroidism can develop in 2 to 3 months from the beginning of the disease. Compression symptoms appear rarely.

Laboratory data. Moderately heightened ESR, lymphocytosis and leucopenia sometimes occur. The content of gamma-globulins in the blood serum is often increased; this is connected with the presence of auto-immune antibodies in the blood. The content of albumins and alpha-1- globulin in the blood is reduced.

In the acute period of the disease the blood alpha-2- globulin content is sometimes increased. In hypothyroidism the blood plasma protein-bound iodine (PBI) content is reduced.

Diagnostic tests. The method of passive haemagglutination of Boyden's tannin treated erythrocytes in Stavitsky's modification is used in the diagnosis of auto-immune thyroiditis.

The method is based on the agglutination of tannintreated erythrocytes sensitized by the specific antigen, thyroglobulin, with thyroglobulin antibodies freely circulating in the blood serum. The presence of auto-antibodies and their titre are determined by this method. In auto-immune thyroiditis the titre of auto-antibodies is usually heightened.

The I131 uptake by the thyroid at the beginning of the disease may be normal or even increased but later (with the advancement of hypothyroidism) it decreases. In hypothyroidism basal metabolism is reduced.

X-ray diagnosis. When there is a large and firm goitre, constriction of the trachea and oesophagus may be revealed by X-ray.

Diagnosis and differential diagnosis. The diagnosis of auto-immune thyroiditis is made on the grounds of a typical clinical picture, which shows diffuse enlargement of the thyroid of moderate firmness, with no adhesions with the surrounding tissues, mobile in palpation in combination with phenomena of hypothyroidism and heightened titre of circulating antithyroid auto-antibodies.

Auto-immune thyroiditis is differentiated from chronic Riedel's struma, nodular and mixed sporadic goitre and carcinoma of the thyroid.

As distinct from auto-immune thyroiditis in chronic Riedel's struma the goitre is of very firm (ligneous) consistency and in adhesion with the surrounding tissues. The titre of antithyroid antibodies is usually not increased.

The normal titre of antithyroid antibodies, the data of puncture biopsy of the thyroid without a morphological picture typical of auto-immune thyroiditis, and the absence of symptoms of disturbed thyroid function are evidence of nodular or mixed sporadic goitre.

Unlike auto-immune thyroiditis, in carcinoma of the thyroid the mobility of the gland is reduced, the regional lymph nodes are enlarged, there is a marked loss in body weight and metastases in other organs.

Evidence of auto-immune thyroiditis and against carcinoma of the thyroid is a reduction in size and firmness of the thyroid tissue after tentative treatment with thyroid agents or prednisolone; of decisive importance, however, are the results of histological studies of the removed thyroid tissue.

Subacute thyroiditis (de Quervain - Crile) is characterized by an acute onset, attended by pain in the region of the thyroid, elevation of body

temperature, more frequently a normal titre of circulating antithyroid antibodies.

Prognosis. Auto-immune thyroiditis usually progresses slowly aften developing into hypothyroidism in a few years. If the treatment is begun in good time when the thyroid is only firm, particularly in local Hashimoto's thyroiditis, auto-immune thyroiditis may be complectely cured.

Treatment. Auto-immune thyroiditis can be treated by medicinal preparations and by surgery. In drug therapy synthetic analogs of glucocorticosteroids (prednisolone and others) are prescribed. In the presence of hypothyroidism thyroid agents (thyroidin, triiodothyronine hydrochloride) are prescribed.

The daily dose of prednisolone is usually 20 to 40 mg. Treatment with glucocorticoid preparations is conducted in courses of six to eight weeks with the gradual reduction of the dose during the last two weeks of treatment.

The dosage of thyroid preparations is selected individually under the control over the general condition of the patient, body weight, pulse rate, the level of cholesterol in the blood serum.

The approximate daily dose of thyroidine is usually 0,1 to 0,3 g.

The reduced size of the thyroid and the disappearance of its hardness, the normalization of the titre of antithyroid auto-antibodies are the criteria for the efficacy of treatment.

When malignant degeneration of the thyroid is suspected and if there are compression phenomena (compression of the oesophagus of trachea) because of the large size of the goitre, operative treatment is indicated.

8.2 Subacute Thyroiditis (de Quervain's Thyroiditis).

The prevalence of subacute thyroiditis is 1 to 2 per cent of all the diseases of the thyroid.

In women it is encountered four to six times more frequently than in men. The disease occurs most often from 30 to 50 years of age.

History. Subacute thyroiditis was first described in 1904 by de Quervain.

Aetiology and Pathogenesis. The disease is caused most probably by a virus infection (epidemic parotitis, an acute respiratory disease, measles, etc).

The infammatory process in the thyroid causes the destruction of follicular cells and follicles, the loss of colloid by the follicles. The destructive process in the thyroid leads to the increase of the content of T3 and T4 in the blood which results in phenomena of thyrotoxicosis. The heightened level of non-hormonal iodine compounds in the blood blocks the mechanism of iodine uptake by the thyroid.

With the eventual diminution of destructive processes there is a decrease of non - hormonal iodine compounds in the blood and restoration of the mechanism of iodine uptake by the gland.

Pathology. A histological examination of the inflammated parts of the thyroid gland reveals desquamation degeneration and proliferation of follicles. Polymorphonuclear and round - cell infiltration is noted in the stroma of the gland and inside the damaged follicles. The presence of giant multinuclear cells and granulomas resembling tubercles as in tuberculosis is a characteristic feature.

Clinical picture. The disease usually has an acute onset. Severe pain occurs in the region of the anterior surface of the neck, which intensifies with the turn of the head, swallowing, and cough and is referred to the head, ears and neck.

Body temperature rises to 39-40 grades Celsius, chills, headache, weakness and ringing in the ears appear. During the primary stage of subacute thyroiditis thyrotoxicosis (tearfulness, irritation, increased perspiration, tachycardia, etc.), may appear; it is commonly of a transient character.

The thyroid is enlarged, unchanged or subject to hyperaemia, which is the result of the reflex dilatation of skin vessels.

Laboratory findings. The blood often shows lymphocytosis and heightened ESR. The total leucocyte and differential counts are often unchanged. The content of alpha-2-globulins and fibrinogen is increased. In the initial period of the disease the level of T3 and T4, and PBI in the blood is increased, while the heightened titre of circulating antithyroid antibodies is registered inconstantly, the uptake of I131 by the thyroid is reduced, but when the acute inflammatory phenomena subside it is restored.

Diagnosis and differential diagnosis. The diagnosis of subacute thyroiditis is made on the grounds of the acute onset of the disease with the appearance of tenderness in the thyroid tissue, an increase in the functional activity of the thyroid and the low uptake of I131 by the gland.

Subacute thyroiditis is differentiated from acute purulent thyroiditis, haemorrhage into the nodular goitre, mediastinitis, and acute pharyngitis (see Acute Purulent Thyroiditis).

In some cases differential dignosis has to be made with toxic goitre, malignant lesion of the thyroid (pseudoinflammatory form).

Evidence for toxic goitre and against subacute thyroiditis are the absence of tenderness of thyroid tissue, limited movements of the neck, symptoms typical of an inflammatory process and the high uptake of I131 by the thyroid. Carcinoma of the thyroid is diagnosed on the basis of a nodule in the gland that tends to grow rapidly, localization of

metastases, scanning data and the results of the histological study of glandular tissue removed by surgery.

Prognosis. The disease lasts from several weeks to two years. Subacute thyroiditis usually ends in recovery. In the absence of correct and timely treatment subacute thyroiditis is characterized by wave - like recurrent course. In some cases subacute thyroiditis may ultimately develop into stable hypothyroidism.

Treatment. Synthetic analogs of the adrenocortical hormones (prednisolone, dexamethasone and others) are prescribed in 10 to 14 days after the onset of the disease.

Prednisolone is administred in a dose of 40 to 50 mg daily with a gradual reduction of the dose by 5,0 to 2,5 mg every 10 days under the control of blood tests and tests for antibody titre.

After the inflammatory process subsides in hypothyroidism or in the presence of thickened areas in the thyroid tissue thyroidin in a dose of 0,1 to 0,5 g or triiodothyronine hydrochloride in a dose of 20 to 100 microg a day is prescribed. Treatment with antibiotics and sulphanilamide preparations is not effective.

They are nonetheless prescribed in the first 10 days of the acute period of the disease to prevent purulent lesions of the thyroid.

In repeated relapses of the disease X-ray therapy may be applied in the region of the thyroid in a total dose of 400 - 600 rad.

If glucocorticoids are not contraindicated their combination with X-ray therapy is effective. Thyroid preparations are prescribed in the presence of hypothyroidism.

8.3 Acute Purulent Thyroiditis.

Acute purulent thyroiditis is characterized by a purulent inflammatory process in the thyroid caused by infection brought in by the haematogenic or lymphogenic route. The disease is rarely encountered.

Aetiology and Pathogenesis. The disease may be caused by any acute or chronic infection (tonsillitis, pneumonia, typhoid fever, sepsis, etc).

The infection penetrates the thyroid by the haematogenous route, with the lymph or by contact with neighbouring organs affected by the infectious process.

In some cases the inflammatory process is localized only in the thyroid, without affecting other organs. The inflammatory process can spread to any one of the lobes of the thyroid or to the whole gland.

An acute inflammatory reaction occurs (hyperaemia of the skin over the thyroid, severe pain in the region of the affected lobe, high body temperature, etc.).

Pathology. Oedema develops in the affected thyroid tissue, as well as infiltration by polymorphonuclear leucocytes and lymphocytes with the eventual (when the process advances) formation of an abscess in it.

Clinical picture. The disease begins acutely. Severe pain appears in the region of the affected lobe, which intensifies in swallowing, when the head is turned to the side, in coughing with pain referred to the lower jaw, ears and back of the head.

Symptoms typical of any acute infectious disease develop: rise of body temperature to 39-40 grades Celsius, chills, headache, weakness, ringing in the ears, etc. Progressive oedema of the submucosa and mucosa of the trachea and larynx often develops and disturbs the function of external respiration.

The affected thyroid lobe is enlarged and very tender to palpation.

The skin over it is hot to the touch. In palpation of the thyroid a softened area with fluctuation can be found (formed abscess).

Regional lymph nodes are often enlarged.

Laboratory findings. Neutrophil leucocytosis and increased ESR in the blood. The blood level of thyroid hormones is not changed. The uptake of I131 by the thyroid is not disturbed.

Diagnosis and differential diagnosis. The diagnosis of acute purulent thyroiditis is made on the basis of the acute onset of the disease, sharp local tenderness in the region of the thyroid, neutrophil leucocytosis, increased ESR and also the normal indices of the functional state of the thyroid.

Acute purulent thyroiditis is differentiated from subacute thyroiditis, haemorrhage into the nodular goitre, mediastinitis and acute pharyngitis.

The presence of neutrophil leucocytosis, the absence of disorders in the functional state of the thyroid, are evidence in favour of acute purulent thyroiditis but against subacute thyroiditis. As distinct from acute purulent thyroiditis haemorrhage into the nodular goitre is not attended by symptoms characteristic of an inflammatory process (absence of high body temperature, changes in blood, etc).

Unlike acute purulent thyroiditis in mediastinitis there is no local tenderness or consolidation of the thyroid tissue.

Prognosis. Acute purulent thyroiditis usually lasts from one to two months. If the diagnosis is made in time and treatment is correctly applied the disease usually ends in recovery.

The criterion of recovery is total relief from all inflammatory phenomena (normalization of leucocytes, ESR, body temperature, etc.).

If there is an abscess in the thyroid it can open externally or into the mediastinum, trachea or lungs with the eventual development of

mediastinitis, aspiration pneumonia or pulmonary abscess. In some cases acute purulent thyroiditis may end in hypothyroidism.

Treatment. A strict regimen of bed rest in an in-patient clinic is indicated.

Antibiotics (penicillin with streptomycin, oletetrin and other) are prescribed in combination with sulphanilamide drugs.

In the first 10 days penicillin is usually prescribed in a dose of 1.000.000 U daily (250.000 U intramuscular 4 times a day), streptomycin in dose of 500.000 - 1.000.000 U daily (250.000 U or 500.000 U twice a day), oletetrin in a dose of 1,5 g daily after which the dosage of antibiotics is reduced.

A 50 per cent alcohol warming compress is placed on the area of the thyroid gland. In progressive inflammatory phenomena and the appearance of fluctuation, opening of the abscess is indicated with subsequent drainage of the wound or the removal of the entire affected lobe of the gland.

8.4 Chronic Fibrous Thyroiditis (Riedel's Struma).

Chronic fibrous thyroiditis is characterized by proliferation of connective tissue in the thyroid with replacement of its parenchyma and growth into the capsule and adjoining muscles, vessels and nerves.

Riedel's struma is encountered rather rarely. According to the data of the Mayo Clinic (USA), there were only 0,05 per cent of cases of Riedel's struma among 42.000 operations on the thyroid.

The disease has been noted more frequently in women than in men, and particularly in individuals over 50.

History. The disease was first described in 1896 by Swiss surgeon Riedel.

Aetiology and Pathogenesis. The aetiology of this disease has not been established.

The chronic inflammatory process in the thyroid is attended by primary proliferation of connective tissue, which grows into the fibrous sheath and surrounding tissues. The proliferation of connective tissue in the thyroid is usually local, but in some cases it is not total, with atrophy of the parenchyma of the organ and development of hypothyroidism.

Pathology. The thyroid is usually enlarged and adheres to its capsule, the adjacent muscles, vessels and nerves; it is ligneous in consistency.

In section the thyroid is greyish-white in colour. The pathohistological changes are manifested in the proliferation of connective tissue in which there are atrophied follicles of irregular shape, groups of thyroid cells, occasional lymphocytes and giant multinuclear cells.

In the central part of the thyroid there are numerous nodules, consisting mainly of enlarged follicles filled with colloid.

Clinical picture. The disease usually begins insidiously with no subjective complaints, but in many instances the patients are distressed by a sensation of 'lump' and pressure in the region of the thyroid.

Eventually, as the goitre grows and adheres to the adjacent organs (larynx, oesophagus, vessels and nerves) difficulties in breathing, pain during swallowing, a dry cough, a hoarse voice even to the extent of aphonia, disorders of circulation appear. The thyroid is usually enlarged, painless, hard as stone and with the smooth surface.

Its mobility is limited or completely lost because of adhesions with surrounding tissues. The skin covering the thyroid gland does not adhere to it and is therefore easily folded by the fingers. The lymph nodes are not enlarged. Body temperature is not elevated.

Laboratory findings. There are no changes in the peripheral blood. The ESR is sometimes increased. The uptake of radioiodine by the

thyroid as well as the indices of basal metabolism are normal, or somewhat decreased X-ray diagnosis. Displacement or contraction of the oesophagus or trachea is often revealed by X-ray examination.

Diagnosis and differential diagnosis. The diagnosis of the disease is made on the grounds of a goitre that is hard as stone and in adhesion with surrounding tissues.

Differential diagnosis is made with auto-immune thyroiditis and carcinoma of the thyroid. Moderate density of the thyroid, its mobility in palpation and the heightened titre of circulating antithyroid antibodies testify to auto-immune thyroiditis.

The differential diagnosis of carcinoma of the thyroid and Riedel's goitre is often rather difficult.

Quite frequently carcinoma of the thyroid can only be excluded after the histological examination of the affected lobe of the thyroid.

Prognosis. The disease lasts for years and may end in hypothyroidism. In phenomena of compression the prognosis depends on timely surgical intervention.

Treatment. In the absence of compression the patient may be treated with thyroidine over a long period of time (6 to 12 months). In phenomena of compression surgery is indicated, partial or total resection of the affected part of the thyroid with the dissection of adhesions. Sometimes the pathological process undergoes involution after surgical intervention.

Lecture 9.

9.1 Malignant New Growths of the Thyroid.

Carcinoma of the thyroid accounts for 0,5 to 2,2 per cent of all tumours of different localization.

In relation to other diseases of the thyroid the incidence of carcinoma of this organ varies from 1 to 21 per cent. Malignant new growths of the thyroid occur more frequently in women than in men.

They account for 0,5 per cent and 0,2 per cent of the total mortality from malignant tumours among women and men, respectively.

History. The first reports on carcinoma of the thyroid date back to the end of the 18th century. Lebert was the first to describe histological changes in malignant goitre in 1862.

In Russia the first description of the clinical picture of carcinoma of the thyroid was made by Zege Von Monteifeul and Gernet in 1893. The first operation in Russia for tumours of the thyroid was performed in 1893 by Subbotin.

Aetiology and Pathogenesis. The aetiology of carcinoma of the thyroid has been established. The predisposing factors are iodine deficience, hyperplastic processes in the gland, age (older than 40 year), sex an so on.

Malignant tumours of the thyroid most frequently develop in a gland changed by goitre, particularly in regions of endemic goitre, and more rarely in a normal thyroid.

According to Nikolaev, nodular parenchymatous and microfollicular colloid goitres have a greater tendency to malignization in an endemic locality, while hormonally active macrofollicular adenomas are less so.

Carcinoma originates most often in a nodular goitre with a normal or reduced function and very rarely in a diffuse toxic goitre. The condition of the nervous system is of major importance in the development of malignant new growths of the thyroid.

Among the factors conductive for the development of carcinoma of the thyroid is also injury to the gland, chronic inflammatory processes in it, roentgen irradiation of the region of the thymus, tonsils and adenoids carried out in childhood or adolescence.

The more frequent development of carcinoma of the thyroid in women is believed to be connected with substantial hormonal changes taking place in their organism in childbirth, lactation and the menstrual - ovarian cycle.

Pathology. Malignant new growths of the thyroid are divided into three groups:

- differentiated tumours (papillary and follicular carcinomas);
- non-differentiated tumours (small - and giant - cell carcinoma);
- other forms of malignant tumourous (carcinoma consisting of Huerthle's cells, epidermoid carcinoma, fibrosarcoma).

Among malignant new growths of the thyroid various forms of cancer are most frequently encountered, of which papillarly carcinoma is most common.

In section papillary carcinoma is dark brown in colour. The tumourous tissue is usually not incapsulated.

Histologically, papillary cancer is characterized by branching papillary proliferations possessing a vascularized connective tissue basis and covered with cuboidal and columnar epithelium. Nuclear polymorphisim of follicular cells is noted. Mitoses are occasionally observed. Papillary carcinoma metastasized along the lymphatic ducts (mainly to the cervical

lymph nodes, less frequently to other parts of the gland and rarely to the bones and lungs).

Papillary carcinoma is most often of papillary - follicular structure.

Its metastases are only of papillary structure and do not possess hormonal activity.

Follicular carcinoma in section is usually grayish or light pink in colour.

It is usually encapsulated. Histological examination reveals preserved normal tissue of the thyroid with areas of large amounts of small and medium follicles of irregular shape, containing dense, intensively coloured colloid.

The cells lining the follicular walls are usually larger than normal ones and contain large nuclei. Their mitoses are often encountered. Follicular carcinoma metastasizes haematogenically (to the bones, lungs and rarely to the brain), and along the lymphatics (to the opposite lobe of the thyroid, to the cervical lymph nodes). Follicular carcinoma and its metastases possess hormonal activity.

In the giant-cell type of non-differentiated tumour of the thyroid gland there are giant spindle cells often containing several nuclei.

The cells of the tumour and its metastases are hormonally inactive. Small-cells carcinoma is characterized by compact accumulation of small cells no bigger than a large macrophage.

This type of cancer is distinguished by a tendency to invasion and metastatic spread.

Huerthle cell carcinoma is characterized by the presence of large acidophilic cells (Huerthle's cells) with vesicle-like nuclei and eosinophilic granules. Metastasis occurs in the lymph nodes and bones.

Fibrosarcoma consists of elongated cells with hyperchromatically stained nuclei and connective - tissue fibrils.

Clinical picture. The clinical picture of the disease depends on the morphological structure of the tumour. Papillary carcinoma of the thyroid has a more favourable course than non-differentiated forms of cancer which are known for a more malignant course and early metastasis.

Among the earliest symptoms of malignant new growth in the thyroid are the rapid growth of nodular goitre with an increase in its firmness, change in contour, complaints on sensation of the tumour.

When the tumour grows into the capsule of the thyroid and adheres with the surrounding tissues, the mobility of the affected part of the gland is reduced. It becomes dense and tuberous in consistency.

The sound of the voice changes when the recurrent nerve is compressed.

Hoarseness may develop; this results from paresis of the true vocal cords as the tumour grows into the surrounding tissues.

Dyspnoea and palpitation sometimes occur. Carcinoma of the thyroid metastasizes first to the cervical lymph nodes, the retrosternal space, then on the lungs, bones, skin, liver, kidneys and other organs.

In affection of the lungs by metastases dyspnoea is common and sometimes cough.

Obturation of the bronchi by metastases leads to inflammatory phenomena in the lung tissue which is manifested by the elevation of body temperature, the increase of general weakness, cough with purulent sputum.

The first bones to be affected by metastases are cranial bones, the spinal column, sternum, ribs, the long bones of the extremities, shoulder blades and pelvic bones.

Laboratory findings. The changes in the peripheral blood are non-specific. In some cases a small leucocytosis is noted.

ESR is usually normal or slightly increased. A considerable increase of ESR is only observed in far-advanced forms of cancer. Marked leucocytosis in the pseudoinflammatory form of carcinoma of the thyroid, and in rare cases a shift of the differential leucocyte count to the left.

Diagnostic tests. Scanning of the gland, biopsy of the lymph nodes and of glandular tissue removed in operation are used in diagnosis of carcinoma of the thyroid. The scanning of the thyroid gland (tissue) reveals a small I131 uptake by the tumourous tissue and its metastases is increased. Radiography, pneumomediastinography and tomography are used to localize the metastases of the tumour of the thyroid more exactly.

Diagnosis and differential diagnosis. The diagnosis of the malignant new growth of the thyroid is based on the clinical picture of the disease (rapid growth of the nodular goitre, the increase of its firmness, change of contours, limitation of mobility, localization of metastases, etc) and on the data of auxiliary methods of investigation (scanning of the thyroid which detects a small I131 uptake by the tumour's tissue with the exception of follicular carcinoma, biopsy of the lymph nodes, emergency biopsy of the thyroid tissue removed during surgery, radiography, pneumomedistinography and tomography).

The differential diagnosis of a malignant tumour of the thyroid should be made with nodular goitre, acute and chronic thyroiditis (Riedel's struma, auto-immune thyroiditis; see corresponding sections of the lecture), tuberculosis and syphilis of the thyroid.

Unlike acute thyroiditis, malignant new growths of the thyroid gland usually have no symptoms of an acute inflammatory process. Tuberculosis of the thyroid is confirmed by the presence of tuberculosis of the lungs or lymph nodes, positive Pirquet's and Mantoux's tests,

and tuberculous nodules revealed in histological examination of the affected thyroid tissue.

In syphilitic affection of the thyroid there are positive serological reactions (Wassermann, Meinicke tests and other), and also characteristic histological changes of the thyroid tissue manifested in interstitial and diffuse inflammation in congenital syphilis and the formation of gummas in acquired syphilis.

Metastases of malignant tumour of the thyroid into the lymph nodes should be differentiated from tuberculosis of the cervical lymph nodes and lymphogranulomatosis.

In such cases decisive importance belongs to the results of histological examination of a bioptate material of a lymph node.

Prognosis. The course of papillary carcinoma of the thyroid is more favourable than that of follicular carcinoma (of the thyroid) since the latter produces distant metastases more frequently.

Carcinoma of the thyroid takes a more favourable course in children and young people than in adults even when there are metastases in the cervical lymph nodes and in the lungs. This is connected with the fact that carcinoma of the thyroid in young people is most often papillary in structure.

Patients with this form of cancer may live for a long time, and if the tumour is sensitive to radiation the patient may be completely cured. Prognosis is relatively favourable also in follicular carcinoma and its metastases which possess hormonal activity, because in treatment with radioactive iodine the metastases regress and disappear.

The prognosis in unfavourable in non-differentiated forms of cancer distinguished by a malignant course, rapid growth and early metastases.

Treatment. For treating malignant new growths of the thyroid early surgical intervention is recently used in combination with X-ray therapy,

telegamma therapy with I131, as well as hormonal therapy with thyroidine and triiodothyronine.

The extent of operative intervention is determined by the limits to which the tumour has spread.

In early stages of carcinoma of the thyroid (differentiated and in some cases non-differentiated) enucleation or enucleation with resection of the glandular lobe is performed. If carcinoma has grown into the surrounding tissues and organs, extirpation of the tumour is performed within the limits of the healthy tissues with removal of the regional lymph nodes when there are metastases in them. In multifocal primary tumour involving both lobes of the thyroid total thyroidectomy is performed with bilateral dissection of the lymph nodes.

In the postoperative period X-ray therapy is prescribed in the region of the thyroid in a total dose of 4.000 - 6.000 rad for the course of treatment.

Telegamma therapy with Co60 has advantages over X-ray therapy, particularly in treating cancer metastases.

This is connected with the fact that gamma rays possess greater hardness and penetrate deeper into the tissues causing less damage to the skin, trachea and oesophagus.

Irradiation is conducted from three or four fields. The total dose per field is 3000 to 4000 rad.

In hormonally active tumour of the thyroid and its metastases, and also to prevent their development in the postoperative period, treatment with radioactive iodine is conducted.

Rokhlin and Zadvornova recomend single I131 doses of 2-5 and rarer 10 mCi.

Total doses by the end of the year do not usually exceed 30-50 mCi, and in the duration of several years 100 - 200 mCi.

In inoperable carcinoma of the thyroid the principal methods of treatment are X-ray and telegamma therapy.

Thyroid preparations are prescribed to inhibit production of the thyrotrophic hormone of the hypophysis.

They are applied over long periods of time before and after operation. Thyroidine is prescribed in a dose of up to 2-3 g daily, and triiodothyronine hydrochloride in a dose of 200 - 600 microg/24 hrs.

9.2 Endemic and Sporadic Goitre.

The main symptom of endemic goitre is progressive enlargement of the thyroid gland.

This disease affects many people in geographic areas with a deficit of iodine in the environment.

Sporadic goitre is attended by enlargement of the thyroid in persons living outside the regions of endemic goitre.

Sporadic goitre occurs as consequence of certain unfavourable endogenous factors, mainly of genetic nature.

History. Endemic goitre was first mentioned by physicians of Ancient China, India and Greece. In 1275 Marco Polo was the first to report on goitre in Russia. In the 16th century Paracelsus in Switzerland established a link existing between goitre and cretinism. In 1849 - 1850 Prevost and Chatin pointed out for the first time the link between endemic goitre and iodine deficiency in nature and unfavourable social and living conditions.

Epidemiology. There are about 200 million people affected by endemic goitre in the world. Large foci of endemic goitre are found in the United States, Egypt, Brazil, Switzerland, Congo, India, the western regions of China and other countries.

In the former USSR endemic goitre is encounted mainly in Western Ukraine, Byelorussia and Karelia, in the upper reaches of the Volga river, in the Mari Autonomous SSR, in the Urals, in Central and Northen Caucasus, Uzbekistan, Kirghizia, Tajikistan; in some regions beyond Lake Baikal and in the valleys of the great Siberian rivers.

Endemic goitre is most prevalent in high mountainous regions, in woody localities with podzol soil. In the black soil regions endemic goitre is not encounted, as a rule.

Aetiology and Pathogenesis. The main cause of endemic goitre is the lack of iodine in foodstuffs due to the deficiency of iodine in the soil and water.

In areas of endemic goitre the daily uptake of iodine by the organism is only 20 to 80 microg instead of the required 200 to 220 microg under normal conditions.

Unfavourable social and living conditions, improper diet (food with excess of calcium and fluorine salts, derivatives of thiourea and thyourates, and poor in vitamins) and infections - toxic efffects are conducive to the development of endemic goitre.

The etiology of sporadic goitre has not been finally established. The development of sporadic goitre is linked with the action of certain endogenic factors, mainly of genetic character (defect of the enzyme systems leading to a lesser uptake and assimilation of iodine by the thyroid and disturbance of the biosynthesis of thyroid hormones; disorders in the use of thyroid hormones at the periphery). Excessive food rich in goitrogens such as thiocyanates (cabbage, turnip, soya) is conducive to the development of sporadic goitre. Under their effect the iodine uptake by the thyroid and the biosynthesis of thyroid hormones are reduced.

The deficiency in thyroid hormones both in endemic and sporadic goitre results in the augmented incretion of the thyrotrophic hormone of the

hypophysis, causing hyperplasia of the thyroid tissue with the development of goitre.

Pathology. Pathomorphological examination reveals diffuse, nodular (adenomatous) and mixed types of goitre, which, in turn, are histologically separated into parenchymatous and calloid forms.

In the nodular goitre there are often hemorrhages, fibrosis, cysts, foci of calcification and malignant regeneration.

Classification. Endemic and sporadic goitre are differentiated according to the extent to which the thyroid is enlarged (0, I, II, III, IV, V), to the form (diffuse, nodular, mixed), and to functional manifestations (euthyroid, hypothyroid and with signs of cretinism).

The nodular goitre with marked phenomena of thyrotoxicosis is separated as a special form, namely, 'toxic adenoma of the thyroid'. Goitre is classified according to localization as retrosternal, partially retrosternal, ring goitre and goitre that had been malpositioned from the embryonal buds (goitre of the root of the tongue, of the accessory thyroid lobe, etc).

Goitre is enlargement of the thyroid beginning with III degree.

In I and II degree of enlargement of the thyroid the term "goitre" is applicable only is there is a node in the gland.

Clinical picture. The clinical picture of the disease depends on the functional condition of the thyroid, the size and localization of the goitre. In euthyroid goitre of small size patients usually have no complaints. In a large euthyroid goitre as a result of compression of the trachea by the enlarged thyroid, bouts of asphyxia and dry cough develop; in compression of the oesophagus there are dysphagic phenomena.

Stimulation of the inferior laryngeal nerve makes the voice hoarse to the extent of aphonia, etc.

The hypothyroid goitre is attended by clinical phenomena of hypothyroidism (see "Hypothyroidism").

In the combination of iodine deficiency, poor social and living conditions and unsatisfactory sanitary and hygienic situation in sites of endemic goitre hypothyroid forms of goitre and cretinism prevail.

Cretinism is characterized by dementia, a severe form of hypothyroidism, retarded growth and disproportionate development of different parts of the trunk, inarticulate speech and deaf - mutism.

The existence of endemia is confirmed by the mass incidence of the disease, large number of hyperplasias of the thyroid of I and II degree and of patients with goitre of III - V degree, the spread of struma endemia among children and adolescents. Cases of cretinism in places of endemic goitre testify to the severity of endemia.

A large percentage of nodular and mixed forms of goitre (10 per cent of all cases and higher), the wide spread of enlargement of the thyroid of III - V degree, a decrease in the ratio of male to female patients (1:1 - 1:3), the prevalence of goitre among domestic animals also show the severity of endemia. The Lenz-Bauer coefficient in foci of severe endemia (the ratio of male to female patients) is 1:1 - 1:3; in foci of moderate severity 1:4 - 1:6 and in foci of mild endemia 1:7 - 1:9.

As a result of the well - organized system of the prevention of endemic goitre in the former USSR, the number of foci of endemic goitre has been drastically reduced and endemic cretinism has disappeared.

Diagnosis and differential diagnosis. The diagnosis of endemic goitre is based on the clinical picture of the disease and the date of case history (the prevalence of disease, place of residence of patients, etc).

It is made when the thyroid begins growing larger in individuals living outside the regions of endemic goitre.

Together with other clinical symptoms, the functional condition of the thyroid is also assessed on the basis of indices of radioiodine diagnosis, T3, T4, PBI and basal metabolism.

Differential diagnosis of endemic and sporadic goitre is made with auto-immune thyroiditis, diffuse toxic goitre and carcinoma of the thyroid.

Auto-immune thyroiditis is confirmed by the case history (development of the disease after the thyroid is damaged by bacterial and virus infections, operation, etc), as well as the heightening of the titre of circulating anti-thyroid auto-antibodies.

Unlike diffuse toxic goitre, in endemic or sporadic goitre combined with neuro-circulatory dystonia there is no constant tachycardia or general perspiration, the levels of T4 and the blood PBI are either normal or reduced, and so on.

The diagnosis of a malignant new growth of the thyroid is made on the basis of the rapid growth of the nodular goitre, the increase of its firmness, change in its outlines, limitation of mobility, the enlargement of regional lymph nodes, and the data of scanning which often detect the small I131 uptake by the tumour's tissue, etc.

Prognosis. A large goitre may compress the trachea, oesophagus and blood vessels. The nodules in the thyroid tissue may undergo malignant generation.

In a small euthyroid goitre patients are capable of working, whereas in goitre of IV and V degree working capacity is limited.

In this case it is not advisable to perform work requiring great physical tension, long walks or standing for a considerable length of time, or if it is necessary to keep the body, particularly the neck, in some unusually strained position. Patients are disabled in compression by the goitre of vitally important organs, in its retrosternal position and in malignant

degeneration of the thyroid. In some cases the working capacity of such patients is restored after surgery.

Prevention. Mass prophylaxis is carried out in the areas threatened with endemic goitre.

Special iodinized bread is baked or the population is supplied with iodized salt (25 g of potassium iodide per 1 ton of table salt).

Antistrumin is prescribed for children at children's establishments, for expectant and nursing mothers (0,001 mg of potassium iodide) in a dose of 1 tablet once or twice a week (group iodine prophylaxis). Individual iodine prophylaxis is carried out in patients after thyroidectomy, in cases when operative or hormonal treatment is inexpedient for patients with endemic goitre or when they refuse surgery. This is likewise indicated for persons living temporarily in a region of endemic goitre.

Treatment. The treatment of endemic and sporadic goitre depends on its size and functional condition (see "Hypothyroidism").

In hypothyroid and euthyroid goitre, particularly in its diffuse forms, in some forms of polycystic or soft conglomerate nodular goitre without great destructive changes thyroidine may be prescribed in the initial period in a dose of 0,05 to 0,1 g daily or every other day or triiodothyronine hydrochloride up to 75 microg every day.

Besides this, antistrumin is given in euthyroid goitre.

Treatment is conducted over a considerable period of time, from six to twelve months and longer.

Indications for surgery are nodular or mixed goitre, a large goitre, particularly one causing mechanical compression of the respiratory tract, oesophagus, vessels and nerves; suspected malignant degeneration of the goitre. To prevent relapses of goitre in the postoperative period either antistrumin is prescribed in a dose of 1 tablet once a week or 0,05 g thyroidine once a week within a year.

Lecture 10.

10.1 Brief Anatomo-Physiological Data of the Parathyroid Glands.

The parathyroid glands (epithelial bodies) are small endocrine glands of reddish or yellowish - brown colour. In man they are usually represented by two pairs. The dimensions of each of them are usually approximately 0,6 x 0,3 x 0,15 cm and the total weight is about 0,05 to 0,3 g.

The parathyroid glands lie closely to the posterior surface of the thyroid.

The superior pair of parathyroid glands, adjoining the capsule of the lateral lobes of the thyroid, is located on the borderline between the superior and median third of the thyroid at the level of the cricoid cartilage.

The inferior pair of parathyroid glands is located at the inferior pole of the thyroid. In some cases the parathyroid glands may be located in the tissue of the thyroid, the thymus, and also in the region of the pericardium.

The parathyroid glands are supplied with blood by the branches of the inferior thyroid artery, and innervated by the fibres of the sympathetic nervous system from the recurrent and superior laryngeal nerve.

The parathyroid glands consist of the parenchyma divided into lobules by connective - tissue membranes with vessels. Two types of cells are distinguished in the parenchyma of the parathyroid glands:

- Principal cells;
- Oxyphil cells.

The most numerous among the former are round small cells: containing a small amount of watery light cytoplasm and a nucleus that stains

well. This type of principal cells indicates the increased function of the parathyroid glands. Together with them dark principal cells are distinguished which indicate that the parathyroid glands are in a state of rest.

The oxyphil cells are regarded as the involutionary stage of the principal cells. They are usually large in size with a small compact nucleus. The parathyroid glands are vitally necessary formations.

The removal of all of the parathyroid glands results in death.

The product of the internal secretory activity of the parathyroid glands is the parathormone, which, together with thyrocalcitonine, a hormone of the thyroid, maintains the constant content of calcium in the blood. In healthy people the parathormone and thyrocalcitonine are in a state of dynamic equilibrium.

Under the influence of the parathormone the blood calcium content rises, and under the effect of the thyrocalcitonine diminishes.

The hypocalcaemic effect of thyrocalcitonine is linked with its direct action of bone tissue and the inhibition of resorptive processes in the bones.

ACTH, glucocorticoids, the growth hormone, thyroxine, androgens, oestrogens and Vitamin D also participate in the regulation of phosphorus - calcium metabolism. Unlike the parathormone these hormones produce a hypocalcaemic effect.

Vitamin D mainly intensifies the absorption of calcium and phosphorus in the intestine and also augments the reabsorption of phosphorus in the kidneys. The mobilizing effect of vitamin D of the escape of calcium and phosphorus from the bones is weakly pronounced.

The functional activity of the parathyroid glands is mainly of autoregulating character and depends on the content of calcium in the

COURSE OF LECTURES IN CLINICAL ENDOCRINOLOGY
Lecture 10

blood serum: in hypocalcaemia the incretion of parathormone increases, whereas in hypercalcaemia it diminishes.

Calcium plays an important role in the vital activity of the organism. It reduces the excitability of the peripheral nervous system and the permeability of cellular membranes; it is an important plastic material for the formation of bone tissue and participates in regulating blood coagulation.

The principal calcium and phosphorus reserves are contained in the bone tissue. The amount of calcium in the bone tissue is about 95 to 99% of its content in the organism, and of phosphorus - 66 per cent of the entire amount. The organism of a man weighing 70 kg contains approximately 1120 g of calcium.

The daily requirement of calcium in adults is 0,5 to 1,0 g.

Calcium in the bones exists in the form of phosphorus - calcium compounds forming crystals of hydroxyl apatite. The total content of calcium in the blood of healthy people is 0,095 to 0,115 g/l (9,5 to 11,5 mg/100 ml).

Only ionized calcium possesses biological activity, the content of which in blood serum is 0,05 g/l (5 mg/100 ml), 0,04 g/l (4 mg/100 ml) of calcium in the blood is bound with protein, 0,02 g/l (2 mg/100 ml) of calcium is not ionized.

The amount of protein - bound calcium increases with the shift of the pH of the medium in the alkaline direction.

It has been established that the parathormone regulates the content of ionized calcium and phosphorus in the blood by controlling its component fraction, i.e. inorganic phosphorus.

The content of the phosphorus in the blood serum of the healthy people is 0,1 to 0,15 g/l (10 to 15 mg/100 ml), including inorganic phosphorus

0.03 to 0,15 g/l (3 to 5 mg/100 ml), lipid phosphorus 0,08 g/l (8 mg/100 ml), ester phosphorus 0,01 g/l (1 mg/100 ml).

In excess production of the parathormone hypercalcaemia occurs caused mainly by washing calcium out of the bones. The escape of calcium from the bones into the blood occurs as a consequence of the destruction of bone tissue by proteolytic enzymes which are discharged by osteoclasts when they are activated by parathormone. The latter also disturbs the metabolism of the osteoblasts depriving their ability to synthesize the protein matrix of bone and turning them into osteoclasts.

Together with hypercalcaemia the parathormone simultaneously reduces the phosphorus content in the blood by inhibiting its reabsorption in the proximal segments of the renal tubules. As a result the excretion of phosphorus in the urine is intensified.

The parathormone also increases the excretion in the urine of chlorides, sodium, potassium, water, citrates and sulphates and causes alkalinization of the urine.

10.2 Hypoparathyroidism.

Hypoparathyroidism (tetany) is caused by the intensified production of the parathormone and is characterized as a result by bouts of tonic spasm.

Hyroparathyroidism may occur at any age.

History. Tetany was first described in 1830 by Steinheim. The term "tetany" was introduced in 1852 by Corvisart. Cohn was the first to point out the independent role of the parathyroid glands in 1895. In 1906 Erdheim established the connection of tetany with the removal of parathyroid glands.

In 1908 Mac Callum first detected the diminution of calcium content in the blood after the removal of the parathyroid glands.

The parathyroid hormone (parathormone) was discovered in 1925 by Collip.

Aetiology and Pathogenesis. The disease may be caused by the accidental removal of the parathyroid glands in resection of the thyroid, in removal of the parathyroadenoma, of the other parathyroid glands are atrophied.

Hypoparathyroidism may also be caused by inflammatory processes in the parathyroid glands, haemorrhage in them as a result of a trauma and their congenital insufficiency. In latent insufficiency of the parathyroid glands the disease may be manifested as a result of infection, intoxication (lead poisoning, carbon monoxide or ergot poisoning), D-hypovitaminosis, alkalosis, pregnancy, lactation, in insufficient absorption of calcium by the intestine.

The parathormone deficiency leads to the reduced calcium content in the blood serum, which in turn causes a sharp increase in nervous - muscular excitation.

Pathology. Phenomena of atrophy or dystrophy, sometimes foci of inflammatory infiltrates in the parathyroid glands are found in the pathological examination. In some cases there are no histological changes in the parathyroid glands. Haemorrhages and erosive ulcers are often found on the mucous membrane of the stomach and duodenum. Inflammatory and dystrophic changes are also found in the liver and kidneys.

Classification. The generally accepted classification includes the following subdivisions. Hypoparathyroidism:

- postoperative tetany;
- secondary tetany depending on bleeding, tuberculosis, amyloidosis, syphilis, and infarction;
- idiopathic hypoparathyroidism connected with congenital absence of the glands;

- primary hypoparathyroidism - atrophy;
- pseudohypoparathyroidism caused by genetic disorders.

Classification of Hypoparathyroidism according to Nicolaev and Tarkaeva (1974) is following:

- postoperative tetany;
- secondary tetany in haemorrhage;
- alkalosis;
- amyloidosis;
- infarction;
- tuberculosis;
- idiopathic hypoparathyroidism;
- pseudohypoparathyroidism;
- pseudopseudohypoparathyroidism.

Clinical picture. According to the clinical course, acute, chronic and subclinical forms of hypoparathyroidism are distinguished.

In congenital deficiency of the parathyroid glands or when they are affected by an unknown factor the idiopathic form of tetany develops which usually has a chronic course with exacerbation in the spring and autumn. Quite often the bout of tetany is heralded by such symptoms as cold hands and feet, numbness, a prickly sensation of the skin, gooseflesh, paraesthesia, and a feeling of spasm.

The precursory signs are followed by painful tonic spasm which affect symmetrical groups of muscles and are selective in character. Spasm begins most often in the muscles of the upper extremities and more rarely in the lower extremities. The flexor muscles suffer most of all. Because of the spasm of the facial muscles the sardonic smile appears. The lips take the shape "fish's mouth". A convulsive clenching of the jaws is caused by spasm of the masticatory muscles (trismus). Spasms in the muscles of the upper extremities lead to a characteristic position of the hand: the fingers are flexed and bent to the palm slightly, the

thumb is flexed, the hand is bent at the wrist joint (accoucheur's hand). In spasm of the muscles of the lower extremities the thighs and shins are stretched out, the feet turned inward, the toes flexed. Spasm of the muscles of the back causes the trunk to be bowed forward (opisthotonus).

Sharp disorders or respiration occur as a result of the convulsive contractions of the intercostal muscles of the abdomen and diaphragm.

There can also be pain in the region of the abdomen caused by spasm of the muscles of the abdominal wall and the smooth muscles of the intestine.

Children often have spasm of the laryngeal muscles which causes laryngospasm. Protracted laryngospasm results in asphyxia and a fatal outcome.

The bout of spasm may last from several minutes to several hours.

In the mild form of the disease the bouts occur rarely (once or twice a week) and they last not more than a few minutes. Tonic spasms in this form of the disease are usually limited and occur most often in the hands.

In the severe form of hypoparathyroidism bouts are frequent (sometimes several times a day); they last for hours and are easily provoked by external stimuli. In the chronic course of the disease trophic disorders result in dryness of the skin, brittle and reedy nails, defects in the enamel of the teeth, cataract. On the part of the cardiovascular system tachycardia and disturbances of the cardiac rhythm often occur.

The ECG shows an elongation of the Q-T interval which is connected with hypocalcaemia.

Disorders of the gastro-intestinal tract are often manifested in the intensification of its motor and secretory functions. Patients suffer from pylorospasm and diarrhea. Quite often the secretion and activity of the

gastric juice are increased. In some cases gastric or duodenal ulcer develops.

The heightened excitability of the vegetative nervous system leads to tachycardia, excessive perspiration, a tendency to vasomotor reactions.

The acute form of hypoparathyroidism follows a very severe course. The bouts of tonic spasm occur frequently and can be protracted.

In the chronic form of the disease the course is less severe. Bouts of spasm occur rarely, usually under the influence of provoking factors such as infections, psychic traumas, overcooling, overheating, etc.

Seasonal exacerbations in spring and in autumn are characteristic of this form of the disease. The concealed form of hypoparathyroidism is displayed by bouts of tonic spasm occurring only under the influence of provoking factors.

Laboratory findings. Hypocalcaemia and hyperphosphataemia are typical of hypoparathyroidism. The content of calcium in blood usually corresponds to the severity of the disease.

In the severe form of tetany the blood calcium content diminishes to 0.06 - 0,05 g/l (6-5 mg /100 ml) and lower, whereas in its latent form the level may by normal. Hypocalciuria and hypophosphaturia are noted.

Diagnostic tests. Tests based on increased mechanical, thermal and electrical excitability of the neuro-muscular apparatus are used to detect the latent form of hypoparathyroidism.

Chvostek's sign is manifested by tapping the facial nerve in front of the tragus of the concha auriculae with a finger or percussion hammer.

This sign may by the I, II, or III degree.

Muscle contraction of the entire region innervated by the facial nerve is characteristic of obvious tetany and is designated as Chvostek-I.

In "Chvostek-II" muscular contraction occurs in the region of the wing of the nose and the corner of the mouth; and in "Chvostek-III" contraction of just the muscle of the corner of the mouth.

"Chvostek-II" and "Chvostek-III" are usually detected in the latent form of the disease.

Trousseau's twitching is detected by applying a rubber tourniquet or a rubber cuff compressing the patient's arm till the pulse disappears for two to three minutes. In latent tetany a convulsive reaction of the hand in the form of accoucheur's hand occurs in the compressed limb at the end of the time mentioned. Schlesinger's sign is demonstrated by the rapid passive flexing of the patient's leg at the hip joint when it is extended at the knee joint. In latent tetany the extensor muscles of the hip contract convulsively with extreme supination of the foot. Contraction of the muscles of the limbs under the effect of galvanic current even of the small intensity (0,7 mA) is known as Erb's sign.

Sulkowitch's test is used for the approximate assessment of calcium content in the blood (see "Hyperparathyroidism").

Diagnosis and differential diagnosis. The diagnosis of hypoparathyroidism is made on the basis of the characteristic clinical symptoms (tonic spasm affecting the symmetrical groups of muscles), laboratory findings (hypocalcaemia, hyperphosphataemia) and positive diagnostic tests.

The bouts of spasm in hypoparathyroidism are differentiated from tetany caused by alkalosis (gastric, hyperventilation tetany), insufficient absorption of calcium by the intestine (intestinal tetany), affection of the central nervous system (infections, intoxication tetany), negative balance of calcium (tetany of pregnant and nursing women), insufficient renal function (renal tetany).

In differential diagnosis the case history is of substantial importance.

Gastric tetany develops after a long bout of uncontrollable vomiting; hyperventilation tetany occurs after frequent deep breathing movements (in hysteria); intestinal tetany develops in protracted diarrhea and also in rickets, etc.

As distinct from tetany in hypoparathyroidism in these form of tetany, except for the renal and intestinal forms, there are no disorders of phosphorus - calcium metabolism.

Spasms in hypoparathyroidism are also differentiated from those of epilepsy, hypoglycaemia, the tetany syndrome caused by organic diseases of the central nervous system (rheumatism, cerebral tumour, etc.).

Unlike parathyroidal forms of tetany the convulsions in epilepsy are attended by loss of consciousness, biting of the tongue, involuntary urination and defecation. There are no disorders of phosphorus - calcium metabolism. The case history confirms the hypoglycaemic genesis of the convulsions, the characteristic feeling of hunger, and the normal content of calcium in the blood in the presence of hypoglycaemia.

In the tetany syndrome caused by organic disease of the central nervous system, as distinct from tetany in hypoparathyroidism, there are no disorders of the phosphorus - calcium metabolism and changes in the acid-alkaline equilibrium.

Prognosis. In tetany and correct substitution therapy prognosis for life is usually favourable. In the occurrence of laryngospasm the prognosis is very serious (death may result from asphyxia). An untreated patient with hypoparathyroidism may develop cachexia with a fatal outcome from intercurrent diseases. The working capacity of patients depends on the severity of the disease. In the mild form of hypoparathyroidism patients are usually capable of working. In hypoparathyroidism of moderate severity the patient is often given II group invalidity, in the severe form II or even I group. The work performed by patients should not be attended by overdue physical and nervous-physic tension. Work

connected with any considerable mechanical, thermal or electrical effects on the neuro - muscular apparatus, and work close to moving mechanisms and under conditions that are dangerous to life are contraindicated.

Prophylaxis. The prophylaxis of hypoparathyroidism consists in the maximum preservation of the parathyroid glands during operations on the thyroid and also in the prevention of postoperational complications (adhesions, infiltrates) disturbing blood supply to these glands.

To avoid the development of hypoparathyroidism in patients with relapsing toxic goiter it is preferable to treat them with radioactive iodine instead of surgery.

Treatment. To arrest an acute paroxysm of tetany 10 to 50 ml of a 10 per cent calcium chloride solution is injected intravenously depending on the severity of the attack. The effect of the agent is already seen by the end of the injection.

Sedatives and spasmolytic agents (bromides, phenobarbital chloralhydrate per os or in a rectal injection, papaverin, etc.) are also prescribed.

Calcium salts (chloride, lactate and gluconate) are prescribed per os two hours after meals in the interval between paroxysms of spasm, 45 ml of an officinal solution of aluminium hydroxide is prescribed 20 minutes before meals to increase calcium content in the blood and reduce the level of phosphorus in it.

This preparation intensifies the function of the parathyroid glands.

For better absorption of calcium it is advisable to administer it together with gastric juice, ammonium chloride or diluted hydrochloric acids.

If treatment with calcium preparations is not sufficiently effective, it is recommended to additionally prescribe ergocalciferol (vitamin D2) and dihydrotachisterol (tachystin, AT-10), maintaining calcium content

in the blood at normal level. To relieve the paroxysms of tetany vitamin D2 (alcoholic solution) is prescribed in doses of 200 000 to 400 000 U daily with the subsequent gradual diminution of the dose to 25000 - 50000 U daily after cessation of attacks.

Dihydrotachisterol (AT-10) which has a stronger therapeutic effect is prescribed in an oil solution when needed in a dose of 1 -10 mg daily. Treatment with vitamin D2 and dihydrotachisterol is conducted under the regular control of calcium level in the blood and its excretion in the urine (Sulkowitch's test).

To prevent bouts of tetany from 40 to 100 U of parathyroidine are injected subcutaneously or intramuscularly depending on the need. Parathyroidine is an extract from the parathyroid glands of cattle; 1 ml contains 20 U of the effective factor. Its therapeutic effect after injection occurs in four to six hours and lasts 20 to 24 hours. The maximum level of calcium in the blood after the administration of the preparation is attained in 18 hours. In long - term administration of parathyroidine, an anaphylactic reaction and resistance may develop as a result of the formation of immune antibodies to the parathormone, which restrict the possibilities of its use.

The diet of patients with hypoparathyroidism should include a large amount of calcium and a limited amount of phosphorus.

Meat intensifies the manifestation of tetany and it must be completely excluded from the diet in periods of exacerbation.

To intensify the biosynthesis of vitamin D in the organism, moderate ultraviolet irradiation or short periods of sun bathing should be recommended for patients with the chronic form of hypoparathyroidism.

10.3 Hyperparathyroidism.

Primary hyperparathyroidism (Recklinghausen's disease, osteitis fibrosa generalizata, osteodystrophia fibrosa) is caused by an excessive production of the parathormone and characterized by pathological changes first of all of the bones and kidneys.

Recklinghausen's disease is encountered most frequently between the ages of 20 to 50. Women are affected more frequently than men.

History. The disease was described in 1891 by Recklinghausen. In 1942 Rusakov proved for the first time that hyperparathyroidism is caused by tumour of the parathyroid glands.

Aetiology. The disease occurs more frequently in the presence of a single and more rarely in multiple adenomas or hyperplasia of the parathyroid glands. The causes of the formation of adenomas remain unknown.

Pathogenesis. The excessive production of parathyroid hormone has a direct effect on the bones and results in the increased activity of osteoclasts which discharge citric acid. The resultant local acidosis causes mobilization of phosphate and calcium from the bones and their passage into the blood. The impoverishment of bone tissue in calcium and phosphate (phosphorus and calcium compounds) causes its cystic reorganization, replacement of destroyed bone tissue with fibrous tissue, osteomalacia, distortion and fractures of the bones.

In affecting the kidneys directly, parathormone inhibits the reabsorption of phosphorus in the renal tubules which results in its intensified excretion in the urine and a lower concentration in the blood. By inhibiting the secretion of calcium by the kidneys the parathormone induces hypercalcaemia. The latter reduces neuro-muscular excitability with the development of muscular hypotonia.

Hypercalcaemia and subsequement hypercalciuria inhibit the effect of the antidiuretic hormone on renal tubules, which results in polyuria with eventual polydipsia.

The heightened concentration of calcium in the blood and urine promotes nephrocalcinosis which leads to the development of severe renal pathology.

Pathology. A single adenoma is often found in pathological examination ana more rarely multiple adenomas or hyperplasia of all parathyroid glands. Adenomas are most frequently found in the lower parathyroid glands, more often in the left one.

The adenoma is usually yellowish - pink, more rarely brownish - yellow or cherry - red in colour. Histological examination demonstrates the predomination of principal or light cells in the adenoma. Sometimes haemorrhages, cysts, calcifications and deposits of cholesterol are found in the adenoma.

The bones are marked by diffuse osteoporosis, cysts filled with dark brown pigment (brown tumours or giant-cell tumours, epulides). The thinning out of the cortical layer and distention of the bone - marrow cavities are noted; there are pathological fractures and static deformations. The bones are easily cut with the knife. Histological study demonstrates the resorption of bone tissue and fibrosis of the bone marrow.

Stones, more often oxalate stones, form in the kidneys and in the urinary tract. Nephrocalcinosis occurs less frequently (deposition of calcium salts in the renal parenchyma). Calcium salts are sometimes detected in the heart, lungs, the gastro-intestinal tract and other internal organs.

Classification. The generally accepted classification is as follows.

1. Primary hyperparathyroidism arising on the basis of one or several hyperfunctioning adenomas; diffuse parathyroid hyperplasia.

2. Carcinoma of the parathyroid glands: hormonally active (primary hyperparathyroidism); non-functioning.

3. Secondary parathyroid hyperplasia caused by chronic renal failure; insufficiency of vitamin D; rickets; multiple myeloma; osteomalacia; Paget's disease; insufficient absorption of calcium in the intestine.

4. Cysts of the parathyroid glands. Non-functioning parathyroid adenoma.

There is a somewhat modified classification according to Nikolaev and Tarkaeva (1974).

I. Primary hyperparathyroidism

1. Visceropathic forms with the prevalent affection of:

- renal parenchyma;
- gastro-intestinal tract;
- neurological and psychic spheres.

2. Bone form:

- fibrous - cystic osteitis;
- pagetoid form.

3. Mixed form.

II. Secondary hyperparathyroidism

1. Renal form:

- renal rickets;
- tubulopathies (Lightwood's type; Albright's type; Fanconi's type).

2. Intestinal form.

III. Tertiary hyperparathyroidism.

- Hormonally inactive tumours.

According to clinical course, chronic and acute hyperparathyroidism is distinquished.

Clinical picture. The disease usually develops gradually. Acute weakness, polydipsia and polyuria, sharp emaciation, pain in the bones, particularly the bones of the feet, are often early complaints of patients; teeth that are seemingly healthy become loose and fall; there are often spontaneous, repeated, not very painful, but long - healing fractures, loss of appetite, nausea, vomiting that does not result from the intake of food, constipation or diarrhea.

Examination reveals acute emaciation. The skin is often greyishearthen in colour and dry. Due to osteoporosis of the bones, primarily of the vertebral bodies, and deformation of the extremities patients become shorter in stature. They develop a waddling gait (goose gait) and stumble which is the result of muscular weakness and disorders of coordination. In some cases patients are bedridden because of extreme weakness. They are often barrel - chested with thick ribs (signs of former multiple fractures). Cysts are found during palpation of bones. There is often no union of bones and false joints form.

Percussion of the cranial bones containing cysts produces a characteristic tympanic sound ("the sound of ripe water-melon").

Cysts - epulides in the visceral cranium are an early characteristic sign of the disease. Nikolaev claims that the formation of osteoporosis and cysts are stages of one and the same process and that the process always begins with osteoporosis.

Tachycardia and disturbance of the cardiac rhythm are manifestations of the disease in the cardiovascular system. Arterial pressure is often high. The ECG registers shortening of the Q-T interval which is considered to be linked with hypercalcaemia.

Dysfunction of the gastro-intestinal tract, besides dyspeptic disorders, is manifested in abdominal pain. The acidity of gastric juice is often

heightened. Peptic ulcer of various localization often occurs: this primarily concerns the duodenum, then the stomach, oesophagus and intestine.

In hyperparathyroidism the kidneys are always involved in the pathological process. Polyuria, polydipsia and hyposthenuria are the early manifestations of renal pathology. The most frequent symptom of hyperparathyroidism is the formation of stones in the kidneys, usually bilateral and recurrent. According to the data of various authors, parathyroid stones in nephrolithiasis account for 6 to 15 % of cases. In the event of stones and concurrent infection cystitis, pyelitis, pyelonephtitis, hydronephrosis and urosepsis may occur. Nephrocalcinosis is attended by degenerative changes of the parenchyma with subsequent azotaemia and uraemia.

Changes in the nervous system are manifested by pain, paresis, dysfunction of the pelvis organs due to the compression of the roots or of the spinal cord itself. In some cases psychic disorders occur: depression, suspicion, fear, weakening of memory and more rarely agitation.

In some instances chronic hyperparathyroidism takes an acute course with the development of parathyroid crisis.

The body temperature rises, there are nausea, uncontrollable vomiting not resulting from the intake of food, anorexia, spastic pain in the abdomen, constipation, sharp muscular weakness, and somnolence. The content of calcium in the blood serum rises sharply to 0,17 - 0,2 g/l (17 -20 mg/100 ml).

Hypocalcaemia develops, as well as oliguria, collapse, coma, often with a fatal outcome.

Laboratory findings. Anaemia occurs in some cases. As a rule there are hypercalcaemia, hypophosphataemia, increased activity of alkaline phosphatase to 20 Bodansky units (the normal level is 1 to 5 units). In far advanced cases (in pronounced renal insufficiency)

hyperphosphataemia sets in, the calcium content in the blood decreases and azotaemia develops. The urine usually produces an alkaline reaction: hyperphosphaturia and hypercalcaemia are registered. Isohyposthenuria often occurs. The relative density of urine in this case reaches 1000. Proteinuria is common. Hyaline and granulate casts are usually found in the urinary sediment. The daily excretion in the urine of 17-CS and 17-OCS is usually considerably reduced.

X-ray diagnosis. The radiograph of bones usually reveals diffuse osteoporosis (long tubular bones, cranium, rarely the spinal column) with areas of more intensive rarefaction, the thinning of the cortical layer of tubular bones, cystic (giant - cell tumours) .

Cysts are more often located near the epiphyses of long tubular bones. Typical subperiostal resorption (resolution of the proximal and middle phalanges of the hands is established, sometimes of the tibia, the elbow or collar bones). An early symptom is the moth-eaten appearance of the distal phalanges of the hands.

Diagnosis tests. Sulkowitch's test is used to determine approximately the calcium content in the blood serum: 2,5 ml of Sulkowitch reagent (oxalic acid 2,5 g, ammonium oxalate 2,5g; glacial acetic acid 2,5 g, and distilled water to make 150 ml) is added to 5 ml of urine obtained in the morning on an empty stomach.

The precipitate in the urine of healthy individuals turns milky-white 30 seconds after the reagent has been added. A considerable milk precipitate is evidence of hypercalcaemia, whereas the absence of turbidity indicates hypocalcaemia.

The diagnosis of hyperparathyroidism makes it necessary to determine the tubular reabsorption of phosphorus, to apply a test with a 5 per cent sodium chloride solution load, cortisone and determine the arterial - venous difference of calcium level.

The tubular reabsorption of phosphorus is calculated from the formula:

% reabsorption = 100*(urine phosphorus * plasma creatinine)/ (urine creatinine x plasma phosphorus).

In healthy persons the index of tubular reabsorption of phosphorus is within the limits of 82 to 92 per cent, in patients with hyperparathyroidism it diminishes and is 26 to 78 per cent.

Determination of the arterio-venous difference in calcium level may be used in the early diagnosis of hyperparathyroidism. In the osseous form of hyperparathyroidism the calcium context in the arterial blood is higher than in the venous blood by 3 to 10 per cent (Nikolaev, Tarkaeva). In osteoporoses of non-parathyroid aetiology the calcium content in the venous blood is higher than in arterial blood.

Exceptions to this rule are patients with osteogenesis imperfecta and Paget's disease whose indices of the arterio-venous difference in calcium level are the same as in hyperparathyroidism.

In healthy people the calcium content in arterial blood is either the same as in venous blood, or lower.

The test with a 5 per cent sodium chloride solution load is based on the fact that without changing the content of calcium in the blood, calcium chloride increases calciuria in hyperparathyroidism patients as distinct from healthy people.

The absence of increased calciuria testifies against hyperparathyroidism.

Besides hyperparathyroidism, hypercalciuria may occur after loading with a 5 per cent sodium chloride solution in patients with Paget's disease, renal and intestinal osteodystrophy, Itsenko-Cushing's disease, which reduces the diagnostic value of the test.

The test is conducted in the following way: the patient is given an intravenous injection of a 5 per cent solution of sodium chloride in a dose of 0,125 ml/kg per minute for 45 minutes. The daily amount of

urine, in which calcium content is determined, is collected before and after the test.

The test with a prednisolone load is used to differentiate hyperparathyroidism from hypercalcaemia of different aeliology. The test is based on the ability of glucocorticoids to diminish the intestinal absorption of calcium because of which its content in the blood serum in healthy individuals is reduced also in hypercalcaemia of non-parathyroid origin.

In conducting this test prednisolone is prescribed in a dose of 30 mg daily for five days. The reduction of calcium content in blood serum (positive test) testifies against hyperparathyroidism.

In order to locate parathyroid adenomas more exactly, pneumo-mediastinography and pneumoparathyroidography are conducted in some cases in combination with the simultaneous introduction into the oesophagus of the thick barium suspension.

Recently the parathyroid glands are scanned by means of Se75 (Selen - methionine) for the same purpose.

Diagnosis and differential diagnosis. The diagnosis of hyperparathyroidism is made on the basis of the case history (gastric or intestinal ulcer), characteristic clinical symptoms (muscular weakness, substantial loss in body weight, diffuse, often aching and straining pain in the bones, polyuria, polydipsia, a goose gait, stumbling when walking, etc.), laboratory data (hypercalcaemia, hypophosphataemia, increased level of alkaline phosphatase in the blood, alkaline reaction of urine, hypercalciuria, etc.), X-ray data (diffuse osteoporosis, cysts, subperiostal resorption of the proximal and middle finger phalanges, nephro - calcinosis, etc.), as well as the results of diagnostic tests.

Primary hyperparathyroidism (Recklinghausen's disease) is differentiated from Paget's disease, myeloma, fibrous dysplasia,

osteogenesis imperfecta (Van der Hoeve's syndrome), renal osteodystrophy and other diseases.

The onset of the disease at an early age (older than 60), normal content of phosphorus in the blood serum and urine, high indices of the activity of alkaline phosphatase (more than 20 units), preserved concentration of capacity of kidneys, absence of systemic osteoporosis, combination of cysts with hyperostosis and osteosclerosis, absence of abnormalities in the bones of the hands and feet are evidence of Paget's disease.

The diagnosis of myeloma is made on the basis of hyperproteinaemia (sometimes to 140 - 180 g/l), the presence of myeloma cells in the bone marrow punctate and at times in the peripheral blood, normal activity of alkaline phosphatase, the presence in the urine of Bence-Jones bodies, typical X-ray data (round openings in the cranial bones - "perforated skull").

Unlike hyperparathyroidism, fibrous dysplasia is a disease of children and young age, which subsides by the time of sexual maturation.

In contrast to hyperparathyroidism, the general condition of patients with fibrous dysplasia is quite satisfactory.

Fibrous dysplasia usually develops without biochemical shifts and with normal excretion of 17-CS and 17-OCS, without systemic osteoporosis and stones in the kidneys.

Fibrous dysplasia combined with pigmentation of the skin (light-brown spots), a precocious sexual and physical development (Albright's syndrome) helps in the diagnosis.

Osteogenesis imperfecta (Van der Hoeve's syndrome) usually occurs in childhood.

The general condition of patients is good. In osteogenesis imperfecta the sclerae are blue and often combined with progressive dullness of hearing, malformations and developmental defects (syndactyly, polydactyly, tip foot), the rapid healing of fractures with the formation

of excessive bone callus, normal indices of phosphorus - calcium metabolism, normal excretion of 17-CS and 17-OCS.

Unlike hyperparathyroidism, renal osteodystrophy develops in childhood on the grounds of pyelonephritis, chronic glomerulonephritis, polycystosis or hypoplasia of the kidneys.

In renal osteodystrophy physical and sexual underdevelopment, a reduction or normal content of calcium in the blood serum, aminoaciduria, a higher content of calcium in the venous blood than in arterial blood are noted.

Intestinal osteodystrophy (insufficiency of calcium absorption) is confirmed by the case history (colitis, gastroenterocolitis, sprue, chronic pancreatitis, obstruction of bile ducts), absence of stones in the kidneys, normal or reduced calcium content in the blood serum in the urine, and the higher content of calcium in the venous blood than in arterial blood.

In the differential diagnosis of hyperparathyroidism and nephrolithiasis not complicated by renal insufficiency, the latter condition is confirmed by the absence of functional disorders of the kidneys, a constant acid reaction of the urine, etc.).

In some cases primary hyperparathyroidism has to be distinguished from hormonal spondylopathy, sarcoidosis, Burnett's milk-alkali syndrome, and from hyperparathyroidism caused by a non-parathyroid tumour with metastases to the skeleton or without them.

Hormonal spondylopathy develops mainly in women in the postclimacteric period.

Polydipsia and polyuria do not occur in this disease. Osteoporosis is usually not generalized and is more often localized in the spinal column (the lumbar or thoracic segments and more rarely the cervical segment).

The phosphorus content in the blood serum of these patients is normal, the activity of alkaline phosphatase is also not heightened. There is no renal pathology.

As distinct from hyperparathyroidism, in sarcoidosis the lymphatic nodes are usually affected. The skin of sarcoidosis patients has a bluish hue. Nodules, indurations and thickenings form in the subcutaneous tissue. After cortisone loading there is a sharp drop in the calcium level in the blood serum.

The diagnosis of Burnett's milk - alkali syndrome is made on the basis of case history (the intake of a large amount of alkalies and milk in treating an ulcer of long duration), of calcium content in the blood serum after the discontinuation of alkalies and milk, and absence of bone pathology, the presence of generalized pruritus.

In hyperparathyroidism as a consequence of a tumour of extraparathyroidial localization the primary tumour is revealed (carcinoma of the bronchi, lungs, ovaries, thyroid, etc.). There are no stones in the kidneys. The calcium content in venous blood is higher than in arterial blood. Excretion of 17-CS and 17-OCS in the urine remains within normal limits. If there are metastases into the skeleton, they are mainly located in the spinal column and flat bones. The destructive process is noted only in the foci of affection. The structure of the intact areas is not disturbed.

Prognosis. Prognosis in hyperparathyroidism is dependent to a large degree on early diagnosis and timely treatment. In operative treatment of the osseous form of hyperparathyroidism the prognosis is usually favourable.

The restoration of the working capacity of patients with this form of the disease depends on the degree to which the bone system has been affected. In moderate cases of the disease the working capacity of patients is restored after operation, usually within 3 to 4 months, and in case of a severe

course during the first two years. In the renal form of hyperparathyroidism the prognosis is less favourable. The restoration of the working capacity of patients with this form of the disease greatly depends on the degree to which the kidneys had been affected prior to operation. Without operative treatment patients with primary hyperparathyroidism become invalids and usually die from mounting cachexia and renal failure.

Treatment. The only method of treatment is surgery. Recovery takes place only after the parathyroadenoma has been removed.

Operative treatment in hyperplasia of the parathyroid glands (removal of three parathyroid glands with resection of the fourth) does not provide for stable recovery.

According to Nikolaev and Tarkaeva, there are no absolute contraindications for resection of parathyroadenoma. Relative contraindications are perforation of gastric ulcer and haemorrhage from it, acute renal failure, and exacerbation of pancreatitis.

Parathyroid crisis is an absolute indication for an emergency operation.

To prevent tetany in the postoperative period, up to 50 ml of a 10 per cent calcium chloride solution is injected intravenously and up to 100 U of parathyroidine intramuscularly or subcutaneously. In some cases (in mildly pronounced tetany) calcium drugs can be prescribed per os.

Vitamin D2 and dihydrotachisterol are used for better assimilation of calcium and its deposition in the bones.

Such treatment is conducted one to three months after operation under the control of the content of calcium, phosphorus and potassium in the blood.

To avoid overdosage of vitamin D2 and hypercalcaemia, insolation should be prevented.

The diet of patients should include a large amount of calcium and phosphorus (cottage cheese, milk, cheese, and so on).

Lecture 11.

11.1. Brief Anatomo-Physiological Data of the Islet Apparatus of the Pancreas.

The pancreas (Gr. Pankreas - the sweetbread; From pan - all, kreas - flesh) is situated behind the stomach, usually at the level of the first and second lumbar vertebrae and occupies the space from the duodenum to the hilus of the spleen.

The pancreas is 10-23 cm long, 3-9 cm wide, 2-3 cm thick and weighs from 70 to 100 g.

The pancreas consists of three parts: head (caput), body (corpus) and tail (cauda).

The head is located in the concavity of the duodenum.

The anterior surface of the body is turned to the posterior surface of the stomach, while the posterior surface adjoins the retraperitoneal fat, the upper pole of the left kidney and adrenal; the lower surface of the body adjoins the small intestine. The tail of the pancreas is situated retroperitoneally reaching to the hilus of the spleen.

The external secretory apparatus occupies the greater part of the pancreatic parenchyma.

It produces various components of the pancreatic juice.

Endocrine tissue making up the Langerhans' islets (accumulations of special cells) accounts for about 1 to 2 per cent of the gland in weight.

The main pancreatic duct passes through the thickness of the tissue along the entire length of the pancreas.

Together with the common bile duct it drains into the duodenum. The pancreas is supplied with blood by the pancreatic-duodenal artery and

by branches of the splenic artery. The Langerhans' islets are supplied with blood more abundantly than other parts of the pancreas.

The veins of the pancreas open into the portal vein either directly, or enter it through the splenic or superior mesenteric vein. The pancreas is innervated by branches of the vagus and sympathetic nerves.

The pancreas of a human adult contains 208000 to 1760000 islets, moreover there are more of them in the tail and body than in the head of the gland.

Three kinds of cells are distinguished in Langerhans' islets: beta-cells, located nearer to the centre of the island and comprising 60 to 70 per cent of all its cells; delta-cells, which are predecessors of other cells of the island (2 to 8 per cent); alpha-cells are located nearer to the periphery of the islet. These last account for all the remaining number of cells.

Alpha- and beta-cells contain granules in the protoplasm, while the delta-cells are non-granulated. Glucagon is formed in the alpha-cells (non-argyrophil); insulin - in the beta-cells; somatostatin - in the delta-cells; lipocain forms in the epithelium of the small drainage ducts of the pancreas.

Insulin is a protein substance possessing a molecular weight of 6000. The insulin molecule includes 51 amino acid residues of 16 different amino acids.

The amino acids in the insulin molecule are interconnected in the form of peptides composing two polypeptide chains: a short chain A (21 amino acid residues) and a long chain B (30 amino acid residues).

The polypeptide chains A and B are joined by two disulphide (-S-S-) bridges.

There is also a disulphide bridge within chain A.

Insulin is formed from its predecessor proinsulin under the effect of proteases.

The biological activity of proinsulin is not great; it is equal to appoximately 5 per cent of the insulin activity. It is presumed that proinsulin is synthesized in the microsomal fraction of beta-cells of the Langerhans' islets. Proinsulin transforms into insulin in the Golgi complex and in the newly formed secretory granules.

Proinsulin circulates in the blood in small amouts.

The specific effect of insulin is connected with the amino acid cystein, the activity of which, in turn, dipends on disulphide groups (S-S).

Normally, the daily requirement in insulin is about 40 U, while its content in the pancreas of a heathy adult is approximately 150-250 U. In healthy people the blood level of immunoreactive insulin is 19,8±1,01 mU/ml (obtained by means of the diagnostic kit CEA-IRE-Sorin association).

Insulin enters the liver with the blood draining from the portal vein where about half of it is inactivated under the effect of the enzyme insulinase.

Part of the insulin that is not destroyed in the liver binds with proteins, while another part remains free.

The insulin passes from the liver into the bloodstream where it circulates in a free state and bound with proteins. The correlation between these forms of insulin is determined by the level of glycaemia; when the sugar content in the blood is reduced, the bound insulin fraction predominates, and in hyperglycaemia free insulin is predominant.

Free insulin has an effect on all insulin-sensitive tissues, whereas the bound fraction has an effect only on fatty tissue, because the latter contains peptidases releasing insulin from its bound state.

The half-life period of insulin is 30 minutes. Besides the liver, insulin is inactevated in the fatty tissue, muscles, kidneys and placenta.

Glucose is the main biological stimulant of insulin incretion. Under the effect of the influx of a large amount of glucose to the pancreas the

synthesis of insulin is intensified, but under the effect of a small amount of glucose it is reduced. The synthesis of insulin is also increased under the effect of ACTH, STH, thyroid hormones, glucagon, secretin, ribose, arginine and leucine.

Somatostatin is one of the regulators of insulin incretion. It is a fourteen-member peptide found in the hypothalamus.

It is presumed that somatostatin is also formed in the delta-cells of Langerhans's islets, thyroid, stomach and lymphoid organs. Somatostatin inhibits the incretion of insulin and glucagon, depending on the level of glycaemia.

Somatostatin exerts a more pronounced inhibiting effect on the incretion of glucagon.

Insulin is conducive to the transport of sugar through the cellular membrane of muscular, hepatic and fatty tissue; it intensifies processes connected with the transformations of glucose, namely phosphorylation, oxydation, its transformation into glycogen and fats; it weakens the activity of glucose-6-phosphatase; intensifies the formation of energy-rich phosphorous compounds and weakens gluconeogenesis from protein, facilitating its synthesis from amino acids.

All the tissues of the organism are sensitive to insulin, except the nerves and erythrocytes in which glucose is utilized in the absence of insulin.

Glucagon, the antagonist of insulin, is a polypeptide consisting of 29 amino acid residues. Its molecular weight is 3485. Glucagon intensifies the disintegration of glycogen in the liver (glycogenolysis) and inhibits glycogen synthesis in the liver; it intensifies lipolysis, stimulates gluconeogenesis and the biosynthesis of glucose from amino acids. It exerts an insulinotrophic effect which increases in hyperglycaemia and decreases in the heightened activity of the sympathetic nervous system, starvation, the administration of adrenaline or noradrenaline.

Glucagon incretion diminishes in hyperglycaemia, with the increased concentration of free fatty acids in the blood. With the increased concentration of amino acids in the blood the incretion of glucagon is augmented.

The mechanism of action of lipocaine consists in that it activates the formation of phospholipids in the liver and stimulates the action of lipotrophic food factors thus aiding the exit of fat from the liver on the one hand, and, on the other, it activates the oxydation of fatty acids in the liver.

Carbohydrate metabolism

The carbohydrates that enter the organism with food are mainly used as energy material. The immediate source of energy is glucose and its oxydation.

The main splitting of carbohydrates occurs in the small intestine where, under the effect of pancreatic enzymes (such as diastase, maltase, lactase and saccharase) they are transformed into monosaccharides. The greater part of the monosaccharides (about 88 per cent) is transformed into glucose in the small intestine, and the smaller part (12 to 15 per cent) in the cells of the liver.

During phosphorylation glucose becomes the source for all transformations of carbohydrates, i.e. oxydation, the synthesis of glycogen and fat from it.

The phosphorylation process is a must for activating the glucose molecule, after which it becomes capable of further transformation: oxydation, and the transformation into glycogen and fat. The first stage of glucose phosphorylation takes place in the intestinal wall as a result of wich hexose-monophosphate is formed.

This process may be represented schematically in the following way:

$$\text{Glucose} + \xrightarrow[\text{Hexokinase}]{\text{Adenosine triphosphate (ATP)}} \text{hexose-monophosphate} + \text{adenosine diphosphate}$$

The specific feature of phosphorylation is that not a simple, i.e. inorganic acid, is added to the glucose molecule, but an energy-enriched phosphoric acid. As a result of such a compound of macroergic phosphate bond is formed, making glucose physiologically active.

Insulin is the activator of hexokinase in the reaction of glucose phosphorylation.

Having become enriched by this macroergic phosphate bond glucose can penetrate the intestinal wall.

Under the effect of the phosphatase glucose phosphorylates and passes through the intestinal wall into the portal circulation losing its physiological activity. In order to penetrate the hepatic cells from portal circulation glucose undergoes secondary phosphorylation. As a result of repeated phosphorylation taking place under the effect of hexokinase, glucose-6-phosphate is formed, which again makes glucose physiologically active. In repeated phosphorylation, as in the first stage, hexokinase activity is intensified by insulin. In the liver 18 per cent of the glucose-6-phosphate is transformed into glycogen; 2 per cent of the glucose-6-phosphate is oxydized in the pentose cycle.

The pentose cycle develops most intensively in the liver, fatty tissue, adrenals and the lens of the eye.

The importance of the pentose cycle in metabolism is very great because this cycle represents the sole source of ribose-5-phosphate, which is used for the synthesis of RNA.

In oxydation of glucose during the pentose cycle a large part of restored nicotinamide-adenine-dinucleotide (NADP-H2) is formed which is essential for the synthesis of fatty acids. Without the participation of free oxygen 25 per cent of glucose-6-phosphate is oxydized; this is anaerobic glycolisis (the Embden-Meyerhof pathway). Under the influence of liver enzyme glucose-6-phosphatase, the greater part of glucose-6-phosphate (55 per cent) is released from the compound with phosphoric acid and passes from the liver into the general circulation.

Of this amount of glucose which passes into the blood a small part is transformed into glycogen and is deposited in muscle cells (9 of 55 per cent, accepted as 100 per cent) and is partially transformed in the fatty tissue into fat (30 per cent). The greater part of the glucose (61 per cent) is oxydized in the tissues, providing for the energy requirements of the organism.

The process of glucose oxydation has two stages: anaerobic glycolysis (the Embden-Meyerhof pathway) and aerobic glycolysis.

The first stage does not require the participation of oxygen (liver, myocardium, skeletal muscles under conditions of rest). As a result glucose is transformed into pyroracemic acid, and in the skeletal muscles during work into lactic acid.

The second stage is accomplished in the presence of oxygen (lungs, muscles, kidneys, partly the liver).

At this stage glucose is oxydized to CO2 and H2O.

The lactic acid formed in the process of anaerobic glycolysis may resynthesize in the liver and muscles into glycogen, while the pyroracemic acid produced as a result of anaerobic glycolysis is completely transformed into lactic acid. During aerobic glycolysis the pyroracemic acid undergoes decarboxylation under the effect of enzyme carboxylase with the formation of acetylcoenzyme A.

The activator of the enzyme carboxylase is the coenzyme of co-carboxylase (phosphorylated vitamin B1). Acetylcoenzyme A is essential for the further synthesis of fatty acids, cholesterol and ketonic bodies.

Acetylcoenzyme A, on entering the cycle of di- and tricarbonic acids (Krebs' cycle exists in the lungs, mucsles, kidneys and partly in the liver), is subject to final oxydation in it to CO2 and H2O.

Insulin is the catalyser of this process. From the standpoint of energy the most favourable way for glucose oxydation is aerobic glycolysis because 36 molecules of adenosine triphosphoric acid (ATP) form in this process, whereas in oxydation of glucose without the participation of oxygen only two ATP molecules are produced.

Lipid metabolism

Fats are the principal source of energy stored by the organism in depot.

When needed they enter the blood from the fatty tissue in the form of non-esterized (free) fatty acids (NEFA), and then to the liver. After they disintegrate in the liver the fats are used by tissues as energy material. NEFA are an easily and rapidly utilized source of energy.

They supply about 50 per cent of the total amount of energy calories under conditions of basal metabolism.

The triglycerides which pass into the blood from the fatty depot form complexes in the liver with alpha- and beta-globulins and are secreted by the liver as components of alpha- and beta-lipoproteins. Normally the fat is not stored in the liver, but is discharged from it and is stored in the fatty depot.

The exit of fat from the liver and the oxydation of fatty acids in the liver is accomplished by means of lipocain.

It has been established that the factor accelerating the release of triglycerides from the complex with proteins is lipoprotein lipase, known

as the "clearing factor". Heparin produced by the mast cells activates the lipoprotein lipase in the blood. The normal intermediate products of NEFA metabolism are ketonic bodies (normally 0,05 - 0,1 g/l).

Ketonic bodies include beta-oxybutiric acid, acetoacetic acid and acetone. About 65 per cent of the ketonic bodies fall to the share of beta-oxybutiric acid, and the remaining 35 per cent to acetoacetic acid and acetone.

The liver is the principal organ where ketonic bodies form. The end result of the disintegration of NEFA is the formation of acetylcoenzyme A which condenses in the liver into acetoacetylcoenzyme A.

Under the effect of enzyme diacilase, acetoacetylcoenzyme A transforms in the liver into free acetoacetic acid which reduces reversibly into beta-oxybutiric acid.

The oxydation of acetoacetic acid to CO2 and H2O takes place in Krebs' cycle not in the liver, but in other organs (muscles, lungs, kidneys).

Phospholipids directly participate in the metabolism of fats. They are conducive to the oxydation of fat via the stage of lecithine and also increase the stability of cholesterol in blood serum preventing its deposition in the vascular wall.

Protein metabolism

The normal protein content in the plasma is 65-75 g/l, of which more than half falls to the share of albumins, while the remainder is a mixture of globulins.

The globulins, in turn, are separated into alpha-1, alpha-2, beta- and gamma-fractions.

The albumins are synthesized in the parenchymatous cells of the liver, and the globulins in the elements of the reticulo-histiocytic system.

In the metabolism between blood and cell all the nutritious substances and products of vital activity pass through the basic substance of the connective tissue. Two types of fibres: collagen and elastic fibres are the most important elements of the connective tissue.

Collagen and elastin have a protein nature. This makes it possible to presume that any factor or condition exerting an effect on protein metabolism will also have an effect on metabolic processes in these substances.

The high-molecular linear polyelectrolytes of the connective tissue are called acid mucopolysaccharides which in combination with proteins are known as mucopolysaccharide - protein complexes or mucoproteins.

Normally, besides mucoproteins the blood also contains glycoproteins: proteins containing an excess of glucose amine (4 per cent). Insulin increases protein synthesis because it makes the transfer of aminoacids into the cells easier, activates enzymes of peptide synthesis and intensifies the utilization of glucose with the provision of a corresponding source of energy.

Besides insulin, protein synthesis is also augmented by the somatotrophic hormone of the hypophysis (STH). ACTH, TSH, glucocorticoids and thyroid hormones, on the contrary, stimulate disintegration of protein to amino acids.

Under normal conditions the number of carbohydrates formed from proteins is not great.

11.2. Diabetes Mellitus.

Diabetes mellitus is an endocrine - metabolic disease. The essential factor in its pathogenesis is the absolute or relative insulin deficiency in the organism. This causes impairment in all kinds of metabolism - especially in the carbohydrate metabolism and leads to pathological modifications in all tissues, organs and systems.

Besides clinical manifestations for the diabetes mellitus are obligatory the biochemical "symptoms", such as hyperglycaemia and glucosuria.

Hyperglycaemia is the excess of glycaemia in fasting state more than 6,1 mmol/l and during 24 h more than 8,8 mmol/l. Normal range is: 3,3 - 5,5 mmol/l. The range of hyperglycaemia from 8,8 mmol/l till 9,9 mmol/l is called "the renal threshold" to the permeability for glucose, and in these conditions glucosuria appears.

Also for diabetes are characteristic the vascular affections to the small vessels (microangiopathy) and to the big vessels of big caliber (macroangiopathy).

Classification of Diabetes Mellitus

(WHO, 1998 - 99); (1980, 1985)

A. CLINICAL CLASSES

I Diabetes mellitus includes

Type 1.

Autoimmune
Idiopatic

Type 2.

Predominantly insulin resistance
Predominantly insulin secretory defects

Other specific types of diabetes:

Genetic defects of beta-cell function;
Genetic defects in insulin actions;
Diseases of the exocrine pancreas;
Diabetes in other endocrinopathies;
Uncommon forms of immune-mediated diabetes;
Drug or chemically - induced diabetes;
Other genetic syndromes associated with diabetes

Gestational Diabetes

Malnutritional Diabetes

II Impaired glucose tolerance (IGT)

B. CLASSES OF STATISTICALLY SIGNIFICANT RISK

Preceding impaired glucose tolerance

Potential impaired glucose tolerance (potential diabetes).

The clinical classes can be installed in quality of the diagnosis.

Type 1 diabetes constitutes 10 - 20% from all patients.

Diabetes type 1, insulin-dependent (juvenile) has the brutal beginning with the major clinical symptoms: polydipsia, polyuria, polyfagia, loss of weight, weakness. The type 1 of diabetes as a rule appears in children, adolescents and adults before 25 years old, more rarely - before 40 years old.

The patients need treatment with insulin for survival. There is insulinopenia, i.e. the insulin deficiency is absolute.

The type 1 diabetes has "acute" beginning, labile evolution, prone to ketoacidosis. For late complications there are characteristic microangiopathies especially nephropathy, which is the main cause (till 75%) of the mortality for this category of patients.

Diabetes mellitus type 2, constitutes 80% from all patients with diabetes, non-insulindependent, adult, in the obese and non-obese persons. It appears gradually.The small signs are characteristic: retarded (delayed) wound healing, parodontosis, furunculosis, neurodermitis (cutaneous itch), periodical thirst, dryness in the mouth. This form of diabetes is as a rule disclosed by the other, than endocrinologists, specialists.

The evolution of this form of diabetes is stable. It does not need the treatment with insulin, or need it for control. It appears at the age after 40 years old, on the background of the obesity. From late diabetic complications there are macroangiopathies, which in following (in the 80%) cause the mortality of the majority of the patients.

The macroangiopathies are the generalized process of atherosclerosis (coronary, cerebral, lower limbs vessels), i.e. generalized affections with such consequences as myocardial infarction, cerebral stroke, which are the main cause of death in the type 2 diabetes. The type 2 diabetes may be in the persons with normal weight and in the obese ones. There is the relative insulin deficiency, both insulin resistance and defect of its secretion.

The type 1 and type 2 diabetes constitute the main mass (amount) of diabetic patients, this is that form of disease, which is named "idiopatic, essential diabetes", with polyfactorial etiopathogenesis.

In my future lecture I will elucidate these types of diabetes mellitus.

II. Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycaemia (IFG) - are prestages of diabetes and disclosing by oral glucose tolerance test, and also by determining fasting glycaemia.

B. The classes of RISK statistically significant for diabetes includes:

1. Preceding IGT / IFG;

2. Potential IGT / IFG.

Potential IGT includes the following categories of persons:

- the twins of diabetic patients;
- the persons, whose parents or one of them have diabetes (are diabetic);
- the women which give birth to children with the weight more than 4 - 4,5 kg at birth (potential diabetes);
- persons with "android" obesity.

Epidemiology. Diabetes is wide - spread in all countries and embraces 2 - 6% of the population. There are groups among which diabetes is encountered 7 - 10 times more frequent, than in other groups of population, such as:

- the relatives of the patients with diabetes;
- the persons with obesity;
- the persons more than 40 - 50 years old;
- the patients with CVD (cardiovascular diseases): arterial hypertension, atherosclerotic affections in the young age, hepatic pathology;
- all groups with "potential diabetes".

Stages of the development of the diabetes are following:

1. Prediabetes (potential diabetes) - this state is considered when the glucose tolerance test is normal, but there (are) is the statistically significant risk for diabetes.

2. Impaired glucose tolerance (IGT) (IFG) - this stage is disclosed by oral glucose tolerance test (OGTT) and (or) by determination of the level of glucose in the fasting state (IFG).

3. Manifest (obvious) diabetes with:

- 1. clinical symptoms (major and (or) minor (small);
- 2. hyperglycaemia;
- 3. glucosuria.

In other cases of the hyperglycaemia without clinical symptoms oral glucose tolerance test must be performed.

Method of realizing (performing) the Oral Glucose Tolerance Test (OGTT). In the morning in fasting state (after 8 h past the last meal) the capillary blood is collected from finger and the glucose level is determined. The glucose load is administered per orally.

The load of glucose, as a rule, is equal to 75 g in adult without obesity. In children the quantity of glucose is counted according to 1,75 g per 1 kg body weight, but not less than 10 g, and not more than 50 g (for children).

In obese persons (adults) the load of glucose is counted as 1 g per 1 kg body weight, but not more than 100 g (for 1 time).

Table 2

The result of the OGTT will be appreciated (mmol/l / or mg/dl according to following criteria:

	NORMAL test	LATENT (subclinic asymptomatic diabetes)	MANIFEST (obvious diabetes)
Fasting state	5,5 (100)	5,5 (100)	6,1 (110)
At the 1 h after glucose load	8,8 (160)	≥ 9,9 (180)	≥9,9 (180)
At the 2 h after glucose load	6,1 (110)	≥ 7,15 (130)	≥7,15 (130)

The levels of glycaemia between normal and diabetic are included into test suspect for diabetes (borderline diabetes).

Values of the glucose concentration, mmol/l (mg/100ml), for diagnosis of diabets mellitus and other categories of hyperglycaemia, accepted by WHO, 1999 are following:

Diabetes mellitus:

Fasting glucose - ≥ 6,1 (≥ 110)

2 h past glucose ≥ 11,1 (≥ 200)

Impaired glucose tolerance IGT

Fasting < 6,1 (< 110)

2 h past glucose load ≥ 7,8 (≥ 140) and < 11,1 (< 200)

Impaired Fasting Glycaemia (IFG)

Fasting ≥ 5,6 (≥ 100) and < 6,1 (< 110)

2 h past glucose load if measured < 7,8 (< 140).

Aetiology. On the first plan among aetiological factors there are:

I. The hereditary factor - predisposing to diabetes. The familial forms of diabetes are found in 12 - 47% of relatives of patients with this disease. The following speaks in favour of the role which may be played by genetic factors in the development of type 1 diabetes: the presence of the HLA - antigens especially HLA - B8 and HLA - B15 in the blood of the patients with type 1 diabetes, more frequently than in other group of population. Also these antigens were detected in the blood of the relatives of patients with type 1 diabetes. Those of them who have both antigens B8 and B15, as a rule are revealing the more expressive (significant) insulin insufficiency.

II. The external factors of environment, especially viral infections Coxsachie - B4, measles, rubeola, mumps have pancreatotropic effect with the damaging action on the beta-cells. It is considered that HLA antigens in case of genetic predisposition can serve in quality of receptors for viruses.

It is established also that the development of Diabetes Mellitus in the persons with genetic predisposition takes place when the process of beta-cells replication is genetically changed. The other action of the external environment factors (viruses) with their damaging effect on the beta-cells may be considered the beginning of the autoimmune process, which is followed by the destruction of the beta-cells.

III. The discovering of the "insulitis" with the lymphoid infiltration of the Langerhans islets in the persons which were dead because of diabetes, right after the detection of this disease.

Conclusion on the Aetiology of Diabetes Mellitus. Among the aetiological factors it needs to be mentioned:

- Genetic predisposition for diabetes;
- The evidence (proof) for it may be the detection of diabetes in - 12 - 47% of relatives, along with presence of HLA antigens in blood;
- Viral infections factor, which possesses pancreatotropic action with destruction of Beta-Cells.
- Auto-immune process (insulitis), possibly initiated by viruses with the destruction of beta-cells;
- The external environmental factors (other than viral infections):
    1. over - eating with the food rich in carbogydrates;
    2. sedentary lifestyle, urbanization, aging of population;
    3. physic, psychic traumas;
    4. hepatic affections.
- The factors which can provoke disorder in the biosynthesis of insulin by hypoxy such as: atherosclerosis, arterial hypertension etc.
- Local processes in pancreas.

Pathogenesis. Insulin is produced in the beta-cells of the endocrine pancreas (Langerhans islets). Insulin decreases the glucose concentration in the blood (hypoglycaemic effect). Glucose stimulates (physiologically) the production of insulin by the beta-cells. It is established that in the Langerhans islets besides of beta-cells are present also alpha-cells and delta-cells.

The alpha-cells secrete a hormone glucagon, with the major action to increase the concentration of glucose in the circulation. It is the hyperglycaemic effect. Glucagon is called the main hyperglycaemic factor. Glucagon has the following mechanism of realization of its action by:

- Intensification of glycogenolysis in the liver, i.e. it augments the splitting (disintegration) of the hepatic glycogen.
- Glucagon augments gluconeogenesis - this is the formation (production) of glucose from proteins.

The delta-cells produce somatostatin, which has the regulatory action both on the secretion of insulin and glucagon, depending on the level of the glucose in the circulation.

The Langerhans islets are considered to be a whole "autonomic system" for maintaining the "homeostasis" of glucose. The absolute insulin deficiency in the patients with diabetes mellitus is appreciated (considered) when after the glucose load the increase of insulin level in blood does not take place. The relative insulin deficiency is appreciated when after the glucose load the insulin level increases, even more than the normal range, but it is insufficient to provide (guarantee) normoglycaemia.

Some physiological data

I. The action of insulin on the carbohydrate metabolism

All the tissues of the organism are sensitive to insulin except the nerves and erythrocytes in which glucose is utilized in the absence of insulin.

1. Insulin augments the activity of the enzyme hexokinase providing the phosphorylation of glucose and promotes all the stages of its assimilation beginning with the penetration through intestinal wall and further its penetration through the cellular membranes and intracellular transformations. Insulin augments the permeability of the cellular membranes for glucose;

2. Insulin intensifies the intracellular metabolism of glucose: both anaerobic glycolysis and aerobic oxidation:

a) Thus, during the anaerobic glycolysis of glucose (with the participation of insulin) are forming pyruvic acid and lactic acid, which are oxidated in Krebs cycle, with further their oxidation in the tissues till CO2 and H2O, in this way providing the energetic expenses of the organism. During the anaerobic glycolysis there are formed the key-compounds required (needed) for the synthesis of the lipids, such as: alpha-glycerophosphate, acetyl-coenzyme-A, and energetic compound, adenosine - triphosphate (adenosine triphosphoric acid (ATP)).

b) Insulin augments the aerobic oxidation of the glucose in the pentose cycle (more intensively in the liver, fatty tissue, adrenals and eye lens). The pentose cycle represents the sole source of ribose-5-phosphate, which is used for the synthesis of RNA.

In oxidation of glucose during the pentose cycle a large part of restored nicotinamid-adenine-dinucleotide (NADP-H2) is formed, which is essential for the synthesis of fatty acids.

3. The other action of insulin is providing the transformation of the glucose into glycogen in the liver as reserve (stock).

In the condition of insulin deficiency all these actions are absent and disorders of carbohydrate metabolism appear, such as hyperglycaemia, glucosuria, hyperlactacidaemia.

II. The action of insulin on the lipid metabolism:

- Insulin inhibits (stops) lipolysis, it stops splitting (disintegration) of the fat from depots (reserve, stock);
- Insulin intensifies liposynthesis;
- Insulin intensifies synthesis of the NEFA, from key-compounds which are formed during the oxidation of glucose. The raw - material serves acetyl - coenzyme A; and

in quality of source of energy serves the phosphoric compounds and restored NADP-H2.

It is known that NEFA are the main transport form of the lipids (fat).

NEFA by condensation with alpha-glycerophosphate form triglycerides, which are the neutral lipids from reserve - depots.

In the normal state NEFA in the liver are disintegrated in the Ketonic bodies, which include:

1. Beta-oxybutiric acid;

2. Aceto-acetic acid;

3. Acetone.

These compounds are oxidated in the tissues in the conditions when Krebs' cycle works normally, with the participation of insulin. In case when the concentration of the ketone bodies is higher and exceeds the oxidation capacity of the Krebs' cycle, the state of the diabetic ketoacidosis is developing. The higher concentration of the ketone bodies has toxic action on the function of the central nervous system (CNS), that as a result leads to the development of the diabetic coma.

III. The action of insulin on the protein metabolism

1. Insulin increases the permeability of the cellular membrane for amino-acids.

2. Insulin increases the inclusion (insertion) of the amino acids into the protein molecules (anabolic effect).

3. Insulin is necessary for the realization of the stimulatory action under protein synthesis by the other hormones, especially growth hormone.

Metabolic disorders in diabetes

Thus in the absence of insulin actions there are the following metabolic disturbances:

1. Hyperglycaemia. The concentration of glucose in the blood increases, and when it exceeds 8,8 - 9,9 mmol/l glucosuria appears.

2. Glucosuria. This is the presence of the glucose in the urine.

3. Hyperlactacidaemia due to increased glycogenolysis.

4. Hyperlipidaemia. This is the increase of the levels of all lipids in the circulation, higher level of:

- Non - estheirified (free) fatty acids (NEFA);
- Hypertriglyceridaemia;
- Dyslipoproteinaemia;
- Hypercholesterolaemia, especially increased LDL-cholesterol and decreased HDL-cholesterol.

5. There is fatty infiltration of the liver as a result of augmented depositing of triglycerides in conditions of its impoverishment of glycogen. Fatty infiltration of liver is the main prerequisite for ketosis. In the decompensated diabetes the concentration of ketone bodies in the blood increases, there is hyperketonaemia and ketonuria.

6. In the absence of insulin there is a decreased process of the synthesis of proteins and an increased process of protein splitting (breakdown) (catabolism). This is accompanied by an increase of hyperglycaemia and the accumulation of the products of their destruction.

7. There is the intensification of glycolization of proteins (binding of proteins with the glucose). The evidence is the increasing of the level of the glycosilated haemoglobin HbA1c. Normal range is equal to approximately 6%, in decompensated diabetes it increases up to 10% and more. Also there is the intensive process of forming of glucoproteins

(mucopolysaccharides).There is an increase in the blood of the level of creatinine, ammonia, urea, residual nitrogen (hyperazotaemia, hyperazoturia); that causes together with the hyperketonaemia a growing of the intoxication of the organism, leading to the development of the diabetic coma.

8. The discharge from organism of all these metabolites is accompanied by an increased osmolarity of the urine with the loss of liquid, dehydration of about 10% of body weight.

9. There are disturbances of the water - salt metabolism. The loss of electrolytes especially (K, Cl), hypokalaemia (hypopotassaemia), which causes muscular weakness, intestinal occlusion.

Other than insulin factors in the pathogenesis of the diabetes.

There are distinguished two groups of factors with the antiinsulinic effects called "antagonists of insulin":

- I. Non-hormonal antagonists of insulin, namely: Synalbumin, the excess of NEFA in the blood, lipotropin inhibitor, antibodies to insulin, Field's factor.
- II. Hormonal antagonists of insulin, namely: STH, ACTH, glucocorticoids, catecholamines, thyroid hormones, estrogens, glucagon.

It was shown that excess of NEFA impairs the permeability of cellular membranes for glucose and stops the use of glucose in the cells, thus leads to an increased insulin resistance (Randle).

Contrainsulinic hormones have the direct action on the lipolysis in fatty tissue, which promotes (conducts to) the increase of the concentration of NEFA, and in this way their diabetogenic effect is realized.

Besides the hypothesis about the role of insulin deficiency in the pathogenesis of Diabetes, there is the "Bihormonal Hypothesis" (theory) of the development of diabetes mellitus.

According to this hypothesis in diabetes the disturbance of the glucose homeostasis is determined not only by the deficiency of one hormone (insulin), but by the relative or absolute surplus of another hormone - glucagon.

Conclusion

Diabetes mellitus most often occurs as a consequence of relative insulin deficiency, and more rarely of absolute deficiency. Irrespectively of the genesis of the insulin deficiency, absolute or relative, the metabolic disturbances are the same in obvious, overt onset diabetes and their expression depends on the degree of decompensation. This has its reflection on the clinical manifestation of the disease, named "Clinical picture of Diabetes mellitus".

11.3 Clinical picture of diabetes mellitus

Later Diabetic Complications

The clinical manifestations of diabetes are the result of the metabolic changes that set in as the result of insulin insufficiency. The diagnosis of diabetes is based on the clinical symptoms and biochemical criteria, from which the main are hyperglycaemia and glucosuria.

The complaints for the type 1 diabetes are very characteristic, named the "major symptoms": thirst (polydipsia), polyuria (abundant urination), polyphagia (increased appetite), or loss of appetite, loss in weight, weakness.

The small symptoms are: pruritus of the skin (sometimes in the region of the genitals), connected with the effect produced by the glucose on nerve endings, tendency for purulent diseases (furunculosis, carbunculosis), retardation of the healing of wounds, parodontosis, alveolar pyorrhea.

The onset of the disease in children and adolescents with type 1 diabetes is extremely rapid, as a rule quite often devastating.

It may even be marked by diabetic Coma. Diabetes follows a severe course, a labile evolution and a tendency (prone) to ketoacidosis.

In patients with type 2 diabetes the symptoms of diabetes mellitus commonly develop gradually and diabetes is revealed by chance during some regular medical examination, or in case of the development of complications.

Polyuria appears as a result of osmotic diuresis, caused by glucosuria, ketonouria, azotouria.

Polydipsia (thirst) is determined by dehydration, which is caused by the osmotic diuresis with glucosuria, ketonuria, azoturia.

Polyphagia is provoked by "cellular hunger" due to the disturbance of assimilation of glucose. Because of the absence of insulin the energetic expenses are not provided.

Loss in weight is caused by glucosuria and lipolysis and by predominance of processes of catabolism of proteins. Weakness (general, muscular) is determined by hypokaliaemia and disintegration of the protein base of the muscular system.

Predisposition to the infections is determined by the diminution of the immunological resistance because of decreased capacity of the antibodies - production in the conditions of the profound disturbances of the metabolism.

Simultaneously glucose serves as the nutritional medium for microbes and promotes joining of the infections.

Presence of clinical features, the objective modifications:

- in patients with type 1 - there is the deficiency in the body weight, they are lean;
- in the patients with type 2 - there is the overweight, obesity of various degrees.

Dermatopathy - skin lesions in diabetes mellitus are not specific. The increased concentration of glucose in the skin often causes its affection by yeast microorganism. The skin is dry (as a result of dehydration) and wrinkled, with diminished turgor and the slow healing of skin wounds. There are on the skin the traces of scratches as a result of the itch, caused by irritative action of glucose on the nerve endings. The skin shows an obvious tendency for purulent processes: furunculosis, carbunculosis and mycosis (epidermophyty).

The face (facies). In the children there is the "rubeosis diabetica" - rosy colour of the skin of cheeks, forehead, upper eyelids, chin; this is caused by the dilation of the capillary network of the skin under the action of acetone (ketone bodies).

The physic and sexual development is retarded in the children, with the installation of the specific Syndrome of Mauriac, described in 1930.

In the adult patients on the skin there is xanthomatosis (accumulation of histiocytes imbibed mostly by triglycerides), with the most frequent localization in the form of papules and yellowish nodules on the palms, soles, buttocks, the back surfaces of elbow joints. The palms of the hands and soles of the feet become yellowish, which is connected with disorders of conversion in the liver of carotin (provitamin A) into vitamin A.

There are intensive hyperkeratosis of the skin of the feet, thickening of nails, these changes of the skin with concomitant infection may develop into moist form of the diabetic gangrene.

The muscle system becomes flabby and atrophic, since catabolic processes prevail over anabolic. In the type 1 lipoatrophic diabetes there are generalized lipoatrophy, associated with cirrhosis of the liver and insulin activity.

The bone system. There may be metabolic arthritis, osteoporosis of the bones of the limbs and vertebrae. Sometimes appears osteolysis of the small bones of the foot (Charcot joints).

The late diabetic complications. Specific for diabetes are the following late complications:

1. Angiopathy (micro- and macroangiopathy);

2. Mauriac Syndome;

3. Fatty infiltration of the liver ("Diabetic liver");

4. Urinary tract infections associated with diabetes, provoked by glucosuria.

Modifications on the part of the cardiovascular system. The generalized affection of the vascular system (Diabetic angiopathy) is characteristic of diabetes mellitus.

Diabetic angiopathy, in turn, can be subdivided into diabetic **microangiopathy**, and diabetic **macroangiopathy** (atherosclerosis combined with diabetic microangiopathies).

Microangiopathy is most characteristic of diabetes mellitus. This is a generalized degenerative affection of the small vessels, primarily of the capillaries, and of the arterioles and venules.

The capillaries and arterioles are affected most intensively in particularly predisposed places:

- the renal glomeruli (Nephropathy);
- the retina of the eye (Retinopathy);
- the distal parts of the lower limbs (peripheral angiopathy);

- degenerative affection of the small vessels in the striated muscles, skin, placenta;
- nerve trunks (Neuropathy).

All capillaries that have a basal membrane are involved in the pathological process, designated (called) - "Universal capillaropathy". In the microangiopathy (in Diabetes mellitus) the main changes take place in the basal membrane of capillaries. The common features of microangiopathies are:

- aneurysms;
- changes of the capillaries;
- thickening of the vascular basal membrane;
- deposition in it of glycoproteins, lipids, glycogen.

Diabetic nephropathy includes all clinical manifestations of renal pathology due to diabetes. A pathognomonic symptom of diabetes mellitus is nodular intracapillary glomerulosclerosis known as the Kimmelstiel - Wilson syndrome (1936). Three stages are distinguished in the clinical picture of diabetic nephropathy:

- 1. prenephrotic;
- 2. nephrotic;
- 3. nephrosclerotic.

1. The first stage (prenephrotic) is characterized by a period of mild proteinuria. In the urine precipitate there are no abnormalities. The duration of this stage varies from 1 to 8 years.

2. The second stage (nephrotic) is accompanied by stable proteinuria of up to 1-2 g/l. In the urine precipitate there are found erythrocytes, hyaline and granular casts. The relative urine density is reduced despite glucosuria. The renal filtration function and renal blood flow are reduced. The arterial pressure is increased and intermittent oedema is present; diabetic retinopathy may also be found.

3. The third stage (nephrosclerotic) corresponds to the clinical picture of contracted (wrinkled) kidney, it is Kimmelstiel-Wilson syndrome characterized by renal insufficiency (uraemia) (is the main cause of deceases in type I diabetes).

Diabetic retinopathy. Retinopathy is observed in 30-90% of diabetes patients. In diabetic retinopathy takes place a progressive loss of vision, even to the point of full blindness.

According to the modern classification, the following stages of diabetic retinopathy are distinguished:

- The stage one - retinal angiopathy (dilation and irregular pattern of the retinal vessels;
- The second stage - simple diabetic retinopathy (punctate haemorrhages and foci, retinal opacification around the optic papilla in the region of the yellow spot and between the superior and inferior temporal arteries). There are no proliferative changes;
- The third stage - proliferating diabetic retinopathy (new growth of vessels and proliferation changes in the retinal tissue, sometimes preretinal haemorrhanges, detachment of the retina, its rupture, against the background of changes inherent to the first two stages. In this stage appear newly grown vessels (neovascularization) and also proliferation of the connective tissue takes place, causing loss of vision or full blindness. Usually the retinopathy and nephropathy are developing simultaneously.

Diabetic macroangiopathy (atherosclerosis combined with diabetic microangiopathies). Combined angiopathy, i.e. the combination of micro- and macroangiopathies, with the prevalence of this or that vascular syndrome is most characteristic of diabetes mellitus.

The macroangiopathies predominate at the age of 40 years and more. The macroangipathies are manifested by rapidly progressive, generalized

atherosclerosis. The main importance in the origin of diabetic angiopathy is attached to disorders of protein, lipid and carbohydrate metabolism.

This leads to an increase in the blood of large glucoproteins, mucopolysaccharides, cholesterol, lipoproteins, triglycerides - and deposition of these substances in the vascular wall. The development of macroangiopathy (atherosclerosis) in diabetes depends on the duration of diabetes and the patient age. Most commonly there are observed sclerotic lesions of the:

- coronary arteries;
- lower limb arteries;
- cerebral arteries.

The lesion of the coronary arteries is the cause of death of 50,0% of patients with diabetes mellitus; lesion of the cerebral vessels - in 12,0%; lesion of the renal vessels - in 11,0%; lesion of the lower limb arteries accompanied by gangrene - in 2,3% of patients.

Coronary arteries atherosclerosis determines the development of coronary heart disease (angina pectoris, myocardial infarction and cardiosclerosis), develops earlier and more frequently in patients with diabetes mellitus, particularly in the elderly and obese. It is caused by:

- 1. Deficient nutrition of the heart muscle as a result of the constricted coronary artery;
- 2. Disorders of metabolic processes in the myocardium;
- 3. Microangiopathy in the heart muscle. Myocardial infarction in the patients with diabetes varies from 4 to 18% of cases.

The evolution of the myocardial infarction in diabetes is atypical:

- 1. often sets in without pain;
- 2. it is more severe and has a high fatality rate;
- 3. there may be transmural myocardial infarctions,

complicated by severe collapse, cardiac insufficiency, acute aneurysm; thromboembolic complications are also more frequent;

- 4. is more frequent the affection of the posterior wall of the left ventricle.

Myocardial infarction, in turn, often complicates the course of diabetes, even to the development of Diabetes Coma. The sclerotic lesions of lower limb arteries are rather frequent complications of diabetes mellitus.

There is the endarteritis obliterans, which may lead to gangrene; it develops in patients over 50 years of age 15 - 20 times more frequently, than in groups of population of the same age, but without diabetes.

Gangrene usually develops in the lower limbs; in case of the predominant involvement of the small vessels it rarely spreads higher.

Diabetic gangrene most commonly develops when atherosclerosis of the lower limb vessels is combined with diabetic microangiopthy.

The clinical manifestations of sclerotic affection of the lower limb vessels are pain, paraesthesia, numbness, intermittent claudication.

The feet are pale and cold to the touch and the pulse on the a.dorsalis pedis and a.tibialis post. is not palpated.

Dry gangrene develops subsequently, particularly after injury.

With concomitant infection it may develop into the moist form and if no measures of control are applied, it may terminate in sepsis.

The excess of proteolytic enzymes in sepsis inactivates insulin and may lead to diabetic coma.

Cerebral ischaemic disease. In affection by atherosclerosis of the brain vessels and base of skull vessels, there may develop:

- cerebral circulatory disorders;
- vascular thrombosis;

- focal or diffuse hemorrhages;
- these lead to the development of apoplexy coma (pseudocoma) and the death of patients.

The course of diabetes mellitus in adults over 40 years of age frequently is aggravated by cerebral circulatory disorders, cerebral stroke, myocardial infarction, infection; and gangrene of the lower limbs.

Thus macroangiopathy prevails in the elderly and is manifested by rapidly advancing atherosclerosis.

Respiratory organs

1. Diabetes mellitus is often combined with tuberculosis. The organism's resistance is reduced and the diabetic develops pulmonary tuberculosis at a young age. The course of pulmonary tuberculosis is characterized:

- by central localization of the focus;
- frequent development of disseminated, effusion forms (48%);
- asymptomatic course in many cases;
- rapid advancement;
- frequent formation of "silent caverns";
- prevalence of the abacillary forms in the patients with "newly onset diabetes".

2. Patients suffering from diabetes mellitus are highly predisposed to pneumonia.

3. Pneumonia has tendency to develop into an abscess or gangrene of lungs.

4. Dryness of the mucous membranes of the upper respiratory tract (determined by the negative water balance) causes a tendency to:

- pharyngitis;
- laryngitis;
- bronchitis.

Digestive organs (Diabetic enteropathy). Gastrointestinal complications are observed rather often; cavity of the mouth: the loosing and early loss of teeth, gingivitis, alveolar pyorrhea (parodontosis) and ulcerative (aphthous) stomatites.

Chronic gastritis is caused by gastric microangiopathies and atrophy of the gastric glands.

In the intestine there is observed the intensification of the motor activity, with "diabetic diarrhea" as a result of both the autonomic vegetative neuropathy and pancreatites.

The liver. In many cases the liver is enlarged, "diabetic liver", because of its fatty infiltration. The fatty infiltration of the liver is manifested clinically by its enlargement and a relatively soft and smooth surface revealed by palpation.

Tests for the liver function usually show normal values. Persisting fatty infiltration (by triglycerides) may lead to cirrhosis of the liver.

Urinary and genital systems. Diabetes mellitus is often accompanied by cystitis, pyelitis, pyelonephritis, caused in 90% by Escherichia coli, resistant to antibiotics. Urinary tract infections in diabetic patients are marked by latent course and pyuria and bacteriuria are most frequently observed in women after the age of 50.

Stable infections of the urinary tract (acute pyelonephritis, exacerbation of chronic pyelonephritis) often result in a septic condition which leads to decompensation of diabetes and even the development of Diabetic Coma.

The "severity" of patient's state is caused by:

- decompensation of diabetes;
- toxicosis associated with infection;
- pyelonephritis in diabetes patients (with ketoacidosis) may be complicated by necrosis of the renal papillae (necrotic papillitis), which follows an extremely severe course even

with the development of acute renal insufficiency, purulent toxicosis and diabetic coma.

Organs of vision. Complications on the part of organs of vision develop in diabetes mellitus. Disease of vascular coat of the eye (bilateral irites, iridocyclites) are observed quite frequently. Rubeosis iridis appears in severe diabetes as a consequence of growth of new vessels, cataract is a frequent pathology in the patients with diabetes mellitus. Among the causes which provoke its installation is disturbance of carbohydrate metabolism with the subsequent decrease of energy processes in the chrystalline lens.

Bilateral rapidly advancing cataract, "metabolic cataract", in a young person is evidence of the severity of diabetes mellitus. This is determined by depositing of the sorbitol in the chrystalline lens.

Nervous system. Diabetic neuropathy is the most frequent specific affection of the nervous system in diabetes.

Diabetic neuropathy is regarded to be a manifestation of the general metabolic and vascular disturbances, one of the main causes of which is absolute or relative insulin deficiency. As a result, a variety of metabolic disorders appear first of all in the nervous system.

The involvement of vessels supplying the nerves (vasa nervorum), plays an essential role in the development of neuropathy. It leads to disorders in the nutrition of the nerve trunks, disintegration of myelin and development of connective tissue. The nerves of the limbs suffer most frequently. The clinical picture of neuropathy is determined by the localization and type of the lesions. Polyneuritis, neuritis and neuralgia of the lower limbs in particular are the most common occurrences in the diabetes mellitus.

The central nervous system also is affected in diabetes. There are:

- Acute neuropsychic disorders (neuroasthenia, psychasthenia, hysteria),

- Encephalopathy,
- and rarely myelopathy.

The vegetative nervous system may be affected in diabetes with such manifestations as the motor dysfunction of the gastrointestinal tract and gall bladder, chronic constipation or diarrhea; loss of sexual potency.

The Mauriac's Syndrome (1930) - usually develops in children who had been ill with diabetes mellitus from a young age. This syndrome is characterized by:

- marked hepatomegaly;
- retardation of growth (even to nanism);
- retardation of the sexual development;
- the lagging of bone growth from the actual age.

Selective deposits of the fat usually occur in the Mauriac's syndrome, especially on the face (moon face with a marked diabetic flush), chest, abdomen and the seventh cervical vertebra; striae form in some cases.

The main symptoms of Mauriac's syndrome are believed to be associated

- with increased production of glucocorticoids which possess a catabolic effect;
- with insulin deficiency;
- with diminished incretion of the growth hormone;
- with diminished incretion of the gonadotrophic hormones;
- with impaired effect of the growth hormone on the cellular level because of insulin deficiency.

The Mauriac's syndrome serves as evidence of "bad" (improperly) treatment of diabetes with protracted long-term decompensation.

Lecture 12.

12.1 Acute Diabetic Complications.

Among the acute complications of diabetes mellitus there are distinguished:

- 1. ketoacidosis;
- 2. ketoacidotic coma;
- 3. hyperosmolar coma;
- 4. hyperlactacidaemic coma;
- 5. primary cerebral coma;
- 6. hypoglycaemic coma.

Ketoacidotic coma

May appear because of:

- late diagnosis of diabetes;
- faults in its treatment (discontinuation or inadequate dosage of insulin);
- stress, operation, pregnancy, concomitant diseases (influenza, pneumonia, food poisoning, myocardial infarction);
- gross faults in the diet;
- traumas: physic, psychic.

Pathogenesis of the ketoacidotic coma. The sharp insulin deficiency in the organism results in:

- the glycogen impoverishment in the liver;
- the increase (infiltraction) of fat in the liver;
- the increase of gluconeogenesis;
- diminished utilization of glucose by the tissues.

This leads to considerable hyperglycaemia and glucosuria. As the result of hyperglycaemia the osmotic pressure in the extracellular fluid increases and cell dehydration develops because water and cell electrolytes (potassium, phosphorus) pass from the cells into the intercellular spaces.

Decrease of the glycogen content in the liver causes intensified mobilization of fat from the depot and its subsequent entry into the liver. In the long run this results in fatty infiltration of the liver and eventual ketosis.

The consequence of hyperketonaemia and ketonuria is disturbed water - salt metabolism, i.e. reduced content of sodium, phosphorus, potassium and chlorides in the blood.

This, in turn, leads to dehydration of the organism and a shift in the acid - base equilibrium in the direction of acidosis. The latter is aggravated as the result of accumulation of hydrogen ions. The volume of extracellular fluid decreases. Renal blood flow and glomerular filtration are diminished.

Renal function in the secretion of nitrogen metabolites is disturbed. Increased disintegration of tissue proteins and their impaired resynthesis from amino acids aggravate the intoxication.

Ketoacidotic coma is the result of poisoning intoxication of the organism and creates conditions for oxygen deficiency (hypoxia) for the brain tissues. This leads to respiratory disorders, vascular collapse, reduced muscles tone and disturbance of higher nervous activity.

Ketoacidotic coma is the result of poisoning intoxication of the organism (the central nervous system before all) , with ketone bodies, dehydration and a shift of the acid - base equilibrum in the direction of acidosis.

Ketoacodotic coma usually develops gradually from 12-24 hours to a few days. Several stages may be distingnished in the development of ketoacidotic coma:

- 1. precoma;
- 2. beginning coma;
- 3. complete coma.

I. The precoma is characterized by drastic weakness, lassitude, somnolence, anorexia, nausea, vomiting, gastro-intestinal pain, dizziness and headache; polydipsia and polyuria are sharply intensified in this period.

- The blood sugar content exceeds 300 mg% (16.6 mmol/l);
- glucosuria increases sharply;
- acetonuria develops and the breath has an odor of acetone.

II. Beginning coma is marked by sharp adynamia even to the point of complete prostration. Consciousness is not lost but sometimes, confused.

- Acidosis causes noisy deep breathing with prolonged inspiration and short expiration.
- Each inspiration is preceded by a long pause (Kussmaul respiration).
- The breath has a sharp smell of acetone.
- The face is pale, but there is no cyanosis.
- The skin is dry, cold, inelastic.
- The tone of the ocular muscles is sharply decreased.
- The pupils are contracted.
- The muscles are flabby and relaxed.
- The tendon and periosteal reflexes are diminished.
- Temperature of the body is normal or below par.
- The tongue is dry and hyperaemic.
- Acute abdomen is simulated in some cases: there are nausea, vomiting.

- Acute abdominal pain, caused by pyloric spasm and spastic contractions of the intestine.
- The pulse is small and rapid.
- The arterial pressure and body temperature fall.
- Arterial flutter and fibrillation and extrasystolia may occur in ketoacidotic coma.
- The ECG demonstrates a lowered T wave and elongated QRST complex as the result of disturbed conduction of the heart muscle (hypokaliaemia).

Laboratory findings

- 1. glucose usually exceeds 350 mg% (19.4 mmol/l) and sometimes reaches 2000 mg% - blood osmolarity is elevated.
- 2. Hypercholesterolaemia, hyperbilirubinaemia.
- 3. Increased content of residual nitrogen.
- 4. Ketone bodies in some cases to 100 mg% (Normal = 16 mg%).
- 5. Hypokaliaemia.

Because of acidosis the reserve alkalinity of blood is reduced to 9-15 mmol/l, blood pH to 7,3 - 6,8, the ESR (Erythrocyte sedimentation rate) often is increased, the amount of haemoglobin and red cell count are increased.

III. Total ketoacidotic coma is accompanied by complete loss of consciousness in combination with further advancement of the symptoms. Oliguria and even anuria develop. The arterial pressure and body temperature fall.

Hyperosmolar coma - usually occurs after the age of 50. In half of the cases it develops in patients with unrecognized or improperly treated diabetes mellitus and sometimes in the mild form of the disease. Hyperosmolar coma may be consequence of drastic dehydration of the organism by: vomiting, diarrhea and burns, long-term treatment with diuretics and steroid drugs (glucocorticoids may be among the causes of hyperosmolar coma).

Pathogenesis of the hyperosmolar coma. The principal role in the pathogenesis of hyperosmolar coma is attributed to: hyperglycaemia developing against the background of pronounced insulin deficiency.

Very high hyperglycaemia and hypernatriaemia lead to hyperosmolarity of blood serum. The latter, in turn, causes sharply pronounced intracellular dehydration. Disorders of water and electrolyte balance in the brain cells cause severe neurological symptoms and loss of consciousness. Glucosuria promotes dehydration. The blood thickens. The minute volume is reduced. The filtration capacity of the kidney is disturbed. Oliguria and anuria develop.

Potassium, chlorides, urea and residual nitrogen accumulate in the blood. Coma develops in periods ranging from a few hours to several days. Rapid dehydration following polyuria is very characteristic. The patient becomes somnolent and soporose state or deep coma ensues.

The skin and visible mucous membranes become extremely dry. The eyeball tonus is diminished. The pupils are contracted and react feebly to light. Tachycardia, arrhythmia and arterial hypotension are observed.

Respiration is shallow and accelerated (tachypnoea), and the breath has no smell of acetone. Oliguria and even anurua occur. A focal functional neurological complex of symptoms is noted. Bilateral, spontaneous nystagmus and muscular hypertonus are particularly characteristic signs.

Among other possible symptoms are:

- Aphasia,
- Hemiparesis,
- Babinsky's pathological sign,
- Central - type hyperthermia,
- Hemianopsia.

The tendon reflexes are lost.

Changes in the biochemical blood composition consist in:

- High hyperglycaemia - 26 mmol/l;
- Increased blood osmotic pressure to 460 mosm/l (normal= 290-310);
- Hyperchloraemia;
- Hyperazotaemia 200 mg% in the absence of ketoacidosis;
- High haemoglobin content;
- Leucocytosis.

Hyperlactacidaemic coma is a very rare occurrence. As the result of hypoxia (and also against the background of medication with high doses of biguanides) conditions may be created in the organism of diabetes patients for a high expenditure disintegration of glycogen with excess production of lactic acid.

The resynthesis of lactic acid into glycogen and pyruvic acid is inhibited. The concentration of lactic acid in the blood increases considerably while that of pyruvic acid is reduced. This alters the normal ratio between lactate and pyruvate (normal ratio 12:1) in the direction of marked prevalence of lactate. Lactic acid acidosis develops. Nausea, vomiting, motor excitement, Kussmaul's respiration develop as result of acidosis.

Relatively mild hyperglycaemia and glucosuria are found, but no hyperketonaemia or ketonuria, considerable fall of reserve alkalinity and a decrease in pH of the blood are characteristic findings.

Cerebral coma (primary cerebral coma) may occur in elderly diabetes patients who also have hypertensive disease or atherosclerosis of the cerebral vessels. It may develop when large doses of insulin are injected for ketoacidosis coma. Oedema of the brain and punctate haemorrhages into its tissue are found on autopsy.

It is believed that these punctate haemorrhages in the brain occur as the result of a parasympathicotropic effect of large doses of insulin. This leads to sharp dilation and increased permeability of the cerebral vessels.

The clinical picture is characterized by a complex of neurological symptoms caused by oedema of the brain. Respiration is shallow. Arterial pressure is reduced. The blood sugar content may be slightly increased. The acid - base equilibrium is not disturbed. The urine test for acetone is usually negative.

Hypoglycaemic coma states and hypoglycaemic coma in diabetes mellitus may occur from overdosage of insulin or some sugar - reducing sulphanylamides, insufficient intake of carbohydrates in administration of the usual dose of insulin, increased insulin sensitivity, particularly in childhood and adolescence.

Besides exogenous, there may be endogenous hypoglycaemic states in diabetes mellitus. Hypoglycaemic states may also occur in the diabetes patients when the insulin inactivation ability of the liver is reduced (deficient production of insulin or activation of its inhibitors).

A reduced blood sugar content caused by intensified fixation of glycogen in the liver and muscles leads to disturbed nutrition of the central nervous system, the brain in the first place.

Deficient supply of the brain with glucose is marked by hypoxia and consequent disturbance of higher nervous activity and later of other functions of the brain (a sensation of hunger, psychoneurological phenomena, etc.).

Depending on the sensibility of the central nervous system to the lack of glucose, in some patients it occurs when the blood sugar content is reduced to 70-60 mg%, in other - when it is reduced to more than 50-40 mg% and lower.

In some cases hypoglycaemic states may occur when a very high blood sugar content falls rapidly and sharply (200 mg% to 100 mg%).

The attacks of hypoglycaemia occur suddenly, as a rule. Mild hypoglycaemic states are accompanied by a sensation of hunger, a slight chill, sweating, general weakness and pallor, or flushing of the face.

In more severe cases all these symptoms grow. The patients are excited and often aggressive. Consciousness is confused. The muscular tonus is increased and tonic and clonic spasm are frequently observed. The tendon and periostal reflexes are increased. Babinsky's sign is often positive. The pupils are dilated. The tonus of the eyeballs is normal. Body temperature is usually normal. There is no acetone odour in the breath. Respiration is normal or accelerated.

If the necessary therapeutic measures are not applied, or the compensatory mechanisms are insufficient (deficient production of cortisol, catecholamines, hypophyseal somatotrophic hormone), a deep coma develops (areflexia, lowered body temperature, adynamia, cessation of sweating, convulsions, tachycardia and death).

Combined blood glucose monitoring and insulin dosing system

Laboratory diagnosis of diabetes mellitus criteria are:

- Hyperglycaemia,
- Glucosuria,
- Hyperlactacidaemia,
- Increase of NEFA,
- Hypercholesterolaemia,
- Hypertriglyceridaemia,
- Increased alpha, beta, gamma - globulins, glucoproteins and hexoses bound with proteins,
- Hyperketonaemia and
- Ketoniuria (in ketoacidosis),
- Hyperazotaemia and
- Hyperazoturia.

Free insulin in blood is reduced.

Diagnostic tests. To assess the functional state of the insular apparatus there are following tests:

- 1. Glucose content in the blood;
- 2. IRI (immune - reactive insulin);
- 3. Oral glucose tolerance test (with testing the blood for glucose and IRI);
- 4. Test with double glucose load (the Staub - Traugott effect);
- 5. Intravenous glucose tolerance test;
- 6. Glucocorticoid (cortisone) test;
- 7. Intravenous tolbutamide test;
- 8. Tests for sugar in the urine;
- 9. Test for ketone bodies in blood;
- 10. Test for acetone in urine;
- 11. Test with intradermal insulin injections (to prevent allergic reaction);
- 12. HbA1c = Glycated Haemoglobin.

Diagnosis and differential diagnosis of diabetes mellitus. The diagnosis of diabetes mellitus is made on the grounds of the characteristic complaints:

- Polydipsia,
- Polyuria,
- Polyphagia,
- Weakness,
- Loss in body weight,
- Skin itching,
- Hyperglycaemia,
- Glucosuria.

In the doubtful cases it is needed to perform the OGTT (Oral Glucose Tolerance Test).

Diabetes mellitus is differentiated from:

- Renal glucosuria,
- Renal diabetes,
- Alimentary glucosuria,
- Bronzed diabetes and diabetes insipidus.

Renal glucosuria is observed in:

- Pregnancy,
- Nephrosis,
- Pyelonephritis,
- Glomerulonephritis,
- Poisoning with cyanides,
- Organic functional lesions of the CNS,
- Glucocorticoid therapy.

Renal diabetes is consequent upon genetic defects in renal reabsorbtion enzymes - hexokinase and alkali phosphatase.

Renal glucosuria and renal diabetes are caused by decreased renal threshold for sugar. Unlike diabetes mellitus in renal diabetes and renal alimentary glucosuria, the level of glucose in the blood is normal.

In haemochromatosis (bronzed diabetes) diabetes is one of the late symptoms. There is depositing of the iron in the liver, in the skin, and diagnosis is confirmed by biopsy of the skin and biopsy of the liver.

The differential diagnosis with diabetes insipidus is based on the absence of the hyperglycaemia and glucosuria and lower density of urine characteristic for diabetes insipidus.

Prognosis in DM is favourable for life when the treatment (with insulin for type 1) conducted is fulfilled correctly.

Lecture 13.

13.1 Treatment of the Diabetes Mellitus.

The main and obligatory principle in the management of diabetes mellitus is maximum compensation of the disturbed metabolic processes, one of the most easily determinable indices of which is the normalization of the blood sugar content and correction of glucosuria (aglucosuria); normal level of the glycated haemoglobin HbA1c < 6%.

The principal therapeutic methods are:

- diet - therapy;
- insulin - therapy;
- and treatment with oral hypoglycaemic agents (sulphanylamides and biguanides).

Diet. The diet is an obligatory type of treatment in all clinical forms of diabetes mellitus. Foodstuffs with easily assimilated carbohydrates (sugar, honey, jam, pastries, raisins) are excluded from the diet. The diet of a diabetes patient is strictly individual because its compilation must take into account not only the complications of diabetes but the concomitant disease as well.

As an independent therapeutic measure the diet is used in mild diabetes mellitus and in the period when the tolerance to carbohydrates (control period) is determined in patients in whom diabetes mellitus is first revealed even if there are marked hyperglycaemia and glucosuria, but no hyperketonaemia or acetonuria.

The diet may also be the main method of treatment in long-term stable compensation of the disturbed metabolic processes (normoglycaemia, aglucosuria) when small doses of insulin (4-12U daily) or small doses of oral antidiabetic agents are given. Treatment with the diet alone may

be undertaken only if the diabetes patient does not lose weight and is able to work.

The efficacy of diet - therapy as an independent method of treatment may to a certain extent be judged. Only according to tolerance (assimilation of carbohydrates) but also according to the carbohydrate balance.

Tolerance to the carbohydrates is determined by subtracting the amount of sugar discharged by the patient in the daily volume of urine from the sugar value of the diet.

To determine carbohydrate tolerance in patients with just - revealed diabetes mellitus a standard (trial) diet is prescribed under in-patient conditions.

The diet (trial diet) see table N8, 9a, 9

Contains:

300 g of carbohydrates,
100 g of proteins and
70 g of fats
amount to 9366 KJ (1 kilocalorie = 4,2 KJ), about 2200 kcal.

Against the background of the standard diet the content of sugar in the blood on a fasting stomach is normalized and glucosuria is corrected in 5 to 7 days and the glycaemic profile is normalized in 7-14 days. The blood sugar content within 24 hours does not exceed 160 mg% (8,8 mmol/l) and HbA1c = < 6%.

If diabetes mellitus becomes stable compensated with the diet, the diet may be used as an independent method.

Foodstuffs on the test (trial) diet with restricted content of carbohydrates

1 Meat or fish 250 g
2 Cottage cheeses 300 g

3 Milk, yogurt, sour milk 500 ml

4 Butter 30 g

5 Vegetable oil 30 g

6 Cheese 25 g

7 Potatoes (see diet 9) 200-300 g

8 Bread (black, brown) 100 g

9 Vegetables except potatoes 1000 g

10 Carrot and beet 300 g

11 Fruits (except bananas and grapes) 300 g

Kcal - 2300; protein - 100 g; fats - 130 g; carbohydrates - 130 g.

Carbohydrate tolerance is determined as follows

It is known that the patient, for example, had discharged within 24 hours 3,5 litres of urine, the content of sugar in which was 40 g/l.

Multiplying 40 g by 3,5 l. We get 140 g, i.e. the daily glucosuria (the amount of carbohydrates unassimilated with 24 hours). The sugar value of the standard diet is 350 g.

We set the proportion:

350 g - 100%

140 g - X

$$X = \frac{140 \times 100}{350} = 40\%$$

in this instance the percentage of unassimilated carbohydrates in this experimental diet is more than 5% - 40%. It is known that possible glucosuria for the diabetic patient should be higher than sugar value of

sugar foods. It is impossible to use this diet in this instance as an independent method of treatment.

The carbohydrate balance constitutes the difference between the amount of carbohydrates taken with food over a period of 24 hours and 24 hour glucosuria.

If the carbohydrate balance is no less than 250 g, i.e. no less than 250 g are assimilated, that means that working capacity is preserved, while the content of sugar in the blood does not exceed (HbA1c = < 6%) (160 mg% = 8,88 mmol/l), than diet therapy may be used as an independent method of treatment.

After 14 days the content of diet may be enlarged (widened) by adding 25 g of bread (brown) weekly, achieving the caloric value, which is necessary for the patient.

As an independent form of therapy diet is contraindicated in:

- reduced body weight;
- high hyperglycaemia and glucosuria (after control period);
- hyperketonaemia and acetonuria;
- diabetic coma or a precomatose state in the past;
- complications or concomitant diseases:
    - furuncles;
    - carbuncles;
    - pneumonia;
    - retinopathy;
    - gangrene.

The use of diet as an independent method of treatment is restricted in patients:

- employed in physical labor and
- pregnant women.

A diet is prescribed with due consideration given for age, growth, the patient's body weight, type of constitution, sex, and kind of work performed.

The diet ensures a normal proportion of proteins, fats and carbohydrates:

- 60 per cent carbohydrates;
- 24 per cent fats and
- 16 per cent proteins.

When planning the diet one should proceed not from the actual weight of the patient, but from the so-called theoretical mass which, according to Broca's formula is equal to the height of the patient in centimeters with the subtraction of 100 for height 155 to 165 cm. In the height range of 165 - 175 it is subtracted 105; in the height 175 - 185, 110 is subtracted.

To establish the caloric value of a diabetes patient's diet it is essential to know how much energy is expended per 1 kg of body weight. 1 kilocalorie = 4,2 KJ (kilojoules).

- It is known that in a state of complete rest about 25 kcal/kg - 105 KJ/kg is expended per kg of body weight under hospital condition;

- In the hospital condition 30-35 kcal/kg - 126-147 KJ/kg;

- In light mental and physical labour 40 - 45 kcal/kg - 168-189KJ/kg;

- In moderate and heavy physical labour and intense mental work 50-70kcal/kg - 210-294 KJ/kg.

The caloric value (heat energy) of food is calculated by multiplying the amount of energy expending on the character of work by its theoretical mass.

In calculating the ration it should be borne in mind that in the combustion of 1 g of carbohydrates approximately 16,8 KJ (4 kcal) is produced;

1 g of fat - 37,8KJ - 9 kcal and

1 g of proteins - 16,8KJ - 4 kcal.

Having divided the amount of heat energy that is accounted for by:

- Carbohydrates 60%;
- Proteins 16%;
- Fats 24%.

Respectively, the amount of proteins, fats and carbohydrates in the diet in the patient is determined measured in grams. Physiologically it is required per 1 kg of body weight of an adult patient:

Proteins - 1,5 - 2,0 g / per 1 kg

Fats - 0,75 - 1,5 g / per 1 kg

Carbohydrates - 6 -12 g / per 1 kg.

To avoid sharp fluctuations in the blood sugar content a diabetes patient's diet must be divided into portions, the meals taken no less than four times a day.

Six meals a day with the following distribution of the calorie - value is considered the most correct:

Breakfast - 8 a. m - 20%;

Lunch - 12 a.m. - 10%;

Dinner - 2 p.m. - 30%;

Light afternoon meal - 5 p.m. - 10%;

Supper - 7 p.m. - 20%;

Light evening snack - 9 p.m. - 10%.

The frequency of meals also depends on the number of insulin injections. If insulin is injected once, the daily ration consists of 5 meals, if it is injected twice - 6 meals.

In the diet there are included:

The foodstuffs rich in vitamins A, C, B, E:

- brewer and bread yeasts,
- bran,
- hedge rose brew,
- buckwheat,
- beans and peas,
- black bread,
- bakery products and
- cereals.

Proteins must be of full value mainly of animal origin:

- Cottage cheese;
- Cod fish;
- Lean mutton;
- Oatmeal;
- Soya.

Diabetes patients should be given:

- Yogurt,
- Sour milk,
- Unskimmed milk by half with water.

Due to the tendency of diabetes mellitus patients to atherosclerosis, foodstuffs rich in cholesterol are restricted or even completely excluded:

- Egg yolks;
- Caviar;
- Brains;
- Liver.

Vegetables:

- Cabbage,
- Cucumbers,
- Vegetable squash,

- Lettuce,
- Tomatoes,
- Radishes,
- Sorrel,
- Green beans,
- Containing no more than 3% of carbohydrates are allowed in unlimited amounts.

Exception of these are - patties, beets, carrots, the consumption of which is restricted.

The total content of beets and carrots should not exceed 300 g. The diet must provide the organism with minerals and vitamins. Foodstuffs rich in easily assimilated carbohydrates:

- Sugar,
- Honey,
- Jam,
- Pastries,
- Raisins are excluded from diet.

In hyperketonaemia and acetonuria, however, and in concomitant infectious diseases or surgical intervention, easily assimilated carbohydrates are added to the diet, but fats are simultaneously excluded and proteins restricted.

In the diet for diabetic patients sugar is replaced by:

- Sorbitol,
- Xylitol,
- Fructose.

Sorbitol possesses antiketonogenic, cholagogic and mild purgative action. Sorbitol is prescribed for diabetes patients in a daily amount of 20 - 30 g.

Xylitol - 15-20 g to be taken once or twice a day.

Fructose - is twice as sweet as sorbitol. Fructose is prescribed in a daily dose usually no higher than 45 g.

These products have good gustatory qualities, possess the sweet taste flavour and may replace (substitute) the sugar.

Insulin therapy. This is replacement substitution therapy for diabetic patients, on the background of diet. The absolute indications for the prescription of insulin are:

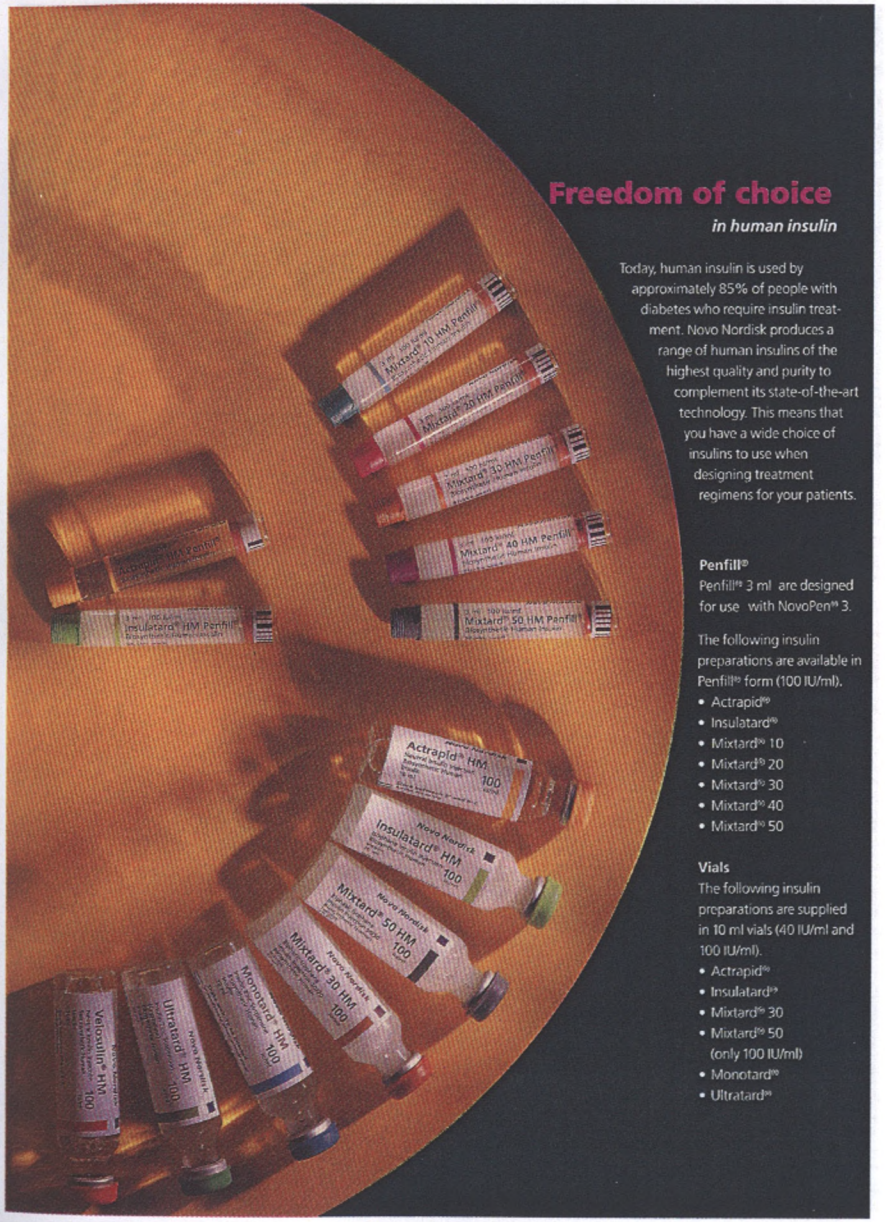
- diabetic coma,
- precoma and ketoacidosis,
- type 1 diabetes in children and adolescence,
- pronounced decompensation of diabetes mellitus with high hyperglycaemia and glucosuria,
- marked undernourishment,
- an insufficient effect of treatment with a diet and oral antidiabetic agents and
- the absence of indications or the presence of contraindications for their prescription.

Temporary prescription of insulin is indicated in concomitant diseases, surgical interventions or injury and in resistance to sulphanylamides. The daily insulin dose depends on the 24 hour glucosuria. The dose of insulin is purely approximate, because the hypoglycaemic effect of insulin depends to a great measure on the reaction of the patient's organism. The reactions may be different in one and the same patients for no obvious reason.

The daily dose of insulin is prescribed on the basis of the premise that one unit of insulin promotes the assimilation of 4 g of sugar, on the average. For example, the sugar value of diet is 340 g. The daily glucosuria is 100 g. The permissible discharge of sugar in the urine in the given example is 17 g (5% of the sugar value of the foodstuffs).

Combined with Penfill® cartridges and NovoFine® needles, NovoPen® 3 PenMate™ forms a perfectly integrated insulin delivery system. Novo Nordisk manufacture and market all parts of the system, ensuring maximum control of the product and safety for the patient.

COURSE OF LECTURES IN CLINICAL ENDOCRINOLOGY
Lecture 13



Freedom of choice

in human insulin

Today, human insulin is used by approximately 85% of people with diabetes who require insulin treatment. Novo Nordisk produces a range of human insulins of the highest quality and purity to complement its state-of-the-art technology. This means that you have a wide choice of insulins to use when designing treatment regimens for your patients.

Penfill®

Penfill® 3 ml are designed for use with NovoPen® 3.

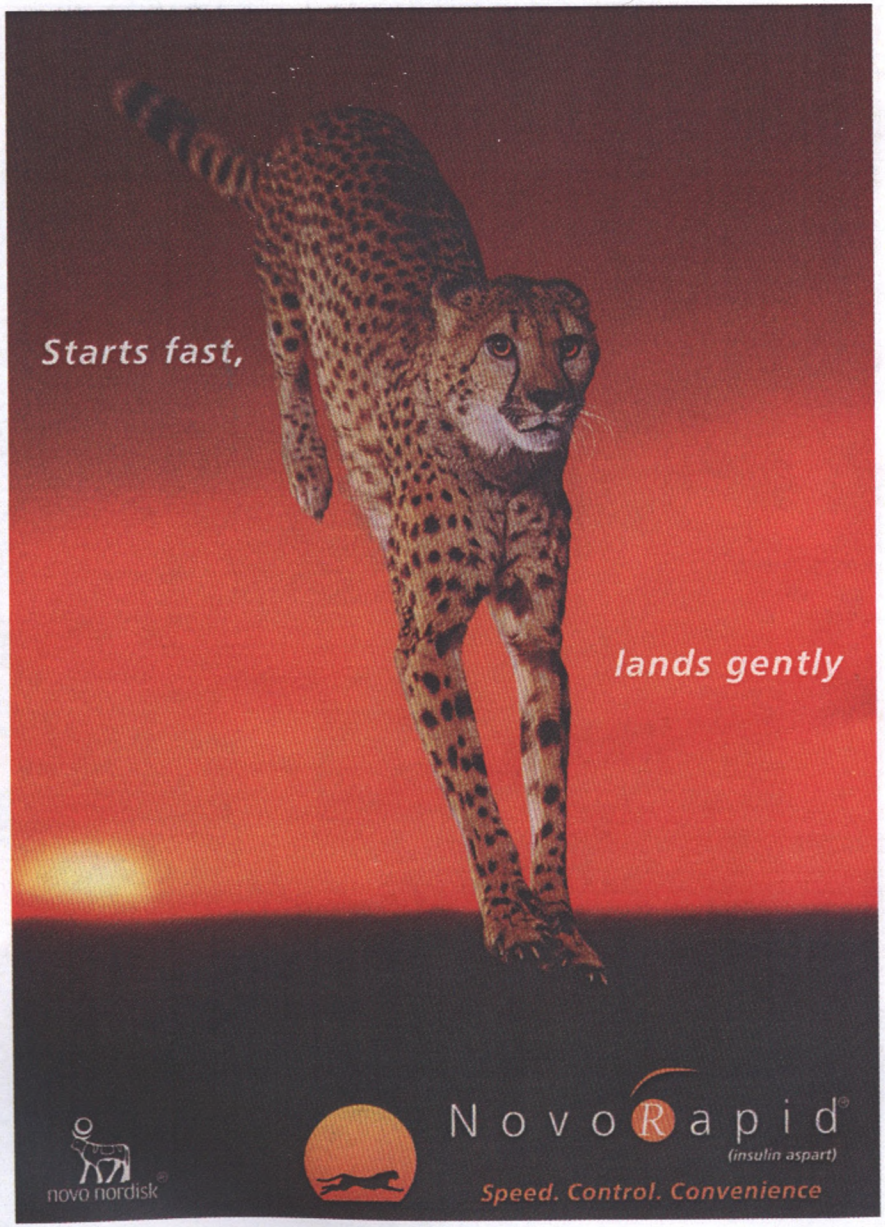
The following insulin preparations are available in Penfill® form (100 IU/ml).

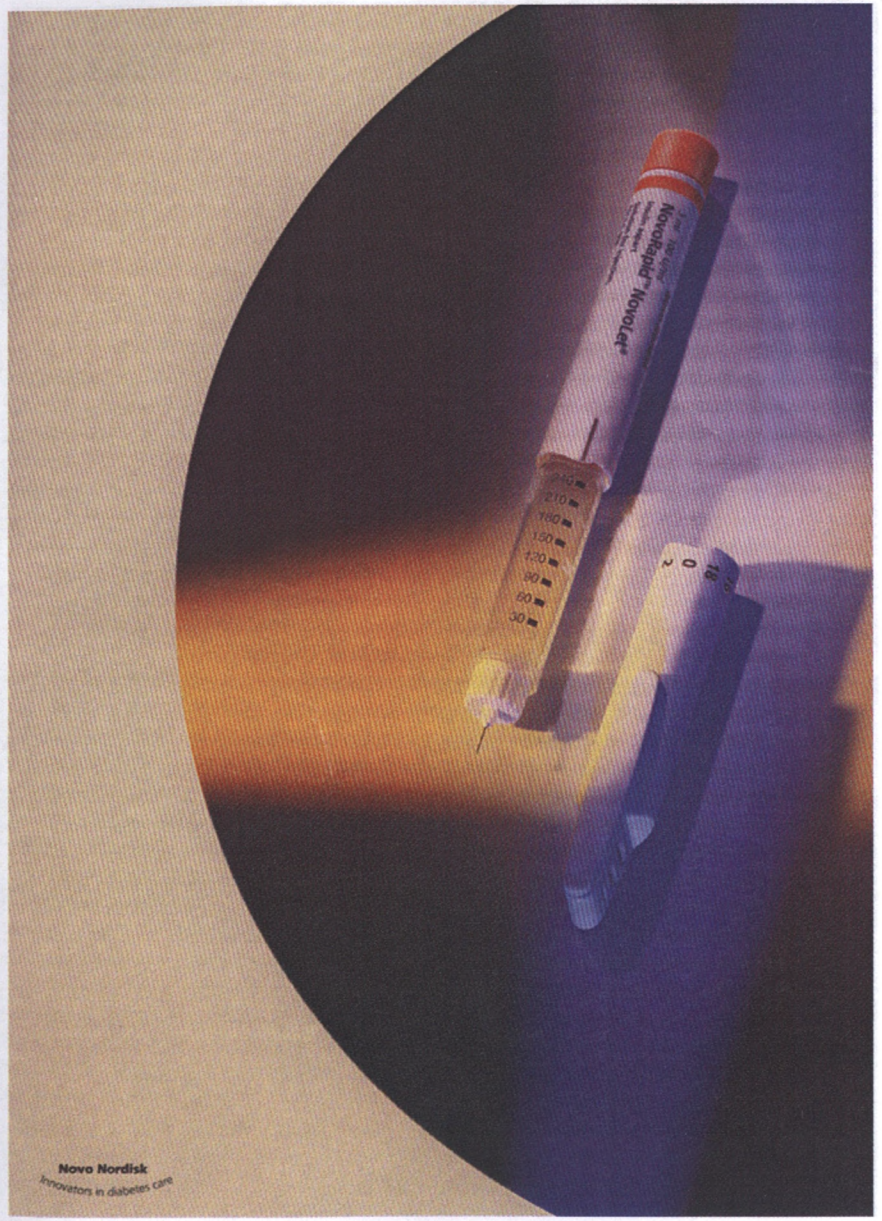
- Actrapid®
- Insulatard®
- Mixtard® 10
- Mixtard® 20
- Mixtard® 30
- Mixtard® 40
- Mixtard® 50

Vials

The following insulin preparations are supplied in 10 ml vials (40 IU/ml and 100 IU/ml).

- Actrapid®
- Insulatard®
- Mixtard® 30
- Mixtard® 50 (only 100 IU/ml)
- Monotard®
- Ultratard®


Starts fast,
lands gently
novo nordisk
NovoRapid®
(insulin aspart)
Speed. Control. Convenience


NovoRapid® NovoLet®
Novo Nordisk
Innovators in diabetes care

Easy for you – easy for your patients

NovoLet®

NovoLet® is a disposable, prefilled insulin injection device, which is easy to use, to learn and to teach. Elderly people in particular are very likely to benefit from its simplicity.

Simple to use

- Just attach the needle and NovoLet® is ready to use.
- Large insulin doses – up to 78 units – can be delivered in 2-unit increments.
- Only one hand is needed to give the injection – the other hand is free to make a skinfold so following correct injection technique becomes easy.

Safe for people

- The only prefilled device that offers dose-setting without resetting.
- High dose-accuracy with a simple turn of the dialling cap.
- Unique colour and tactile coding enables easy identification.
- Designed to minimise mistakes – the label is always visible.
- The large insulin reservoir holds insulin for many days and can be stored for a month at room temperature.

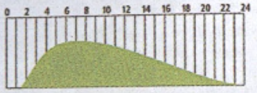
Safe for the environment too!

NovoLet® contains half as much plastic as other prefilled devices and the plastic used is the most environmentally friendly available. With NovoLet®, Novo Nordisk demonstrates its concern for the environment.

Insulin in action

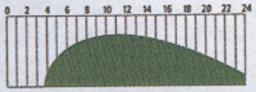
Onset, effect and duration

Actrapid®
Rapid-acting insulin (soluble human insulin)
Onset: within 30 minutes
Maximum effect: 1–3 hours
Duration: 8 hours

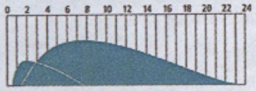


Insulatard®
Intermediate-acting insulin (isophane human insulin, NPH)
Onset: within 1.5 hours
Maximum effect: 4–12 hours
Duration: 24 hours

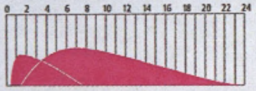
Monotard®
Intermediate-acting insulin (human insulin zinc suspension, 30% amorphous and 70% crystalline)
Onset: within 2.5 hours
Maximum effect: 7–15 hours
Duration: 24 hours



Ultratard®
Long-acting insulin (human insulin zinc suspension, crystalline)
Onset: within 4 hours
Maximum effect: 8–24 hours
Duration: 28 hours

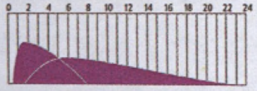


Mixtard® 10
Premixed insulin (biphasic human insulin) Mixtard® 10 consists of 10% soluble and 90% isophane insulin
Onset: within 30 minutes
Maximum effect: 2–8 hours
Duration: 24 hours

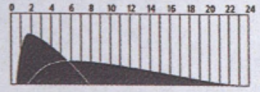


Mixtard® 20
Premixed insulin (biphasic human insulin) Mixtard® 20 consists of 20% soluble and 80% isophane insulin
Onset: within 30 minutes
Maximum effect: 2–8 hours
Duration: 24 hours

Mixtard® 30
Premixed insulin (biphasic human insulin) Mixtard® 30 consists of 30% soluble and 70% isophane insulin
Onset: within 30 minutes
Maximum effect: 2–8 hours
Duration: 24 hours



Mixtard® 40
Premixed insulin (biphasic human insulin) Mixtard® 40 consists of 40% soluble and 60% isophane insulin
Onset: within 30 minutes
Maximum effect: 2–8 hours
Duration: 24 hours



Mixtard® 50
Premixed insulin (biphasic human insulin) Mixtard® 50 consists of 50% soluble and 50% isophane insulin
Onset: within 30 minutes
Maximum effect: 2–8 hours
Duration: 24 hours

Novo Nordisk
Innovators in diabetes care

Safety, comfort and reliability

NovoPen® 3

Novo Nordisk pioneered the development of injection pen systems. The NovoPen® revolutionised the modern treatment of diabetes and improved the quality of life for many people with diabetes.

NovoPen® 3 is the state-of-the-art in durable insulin delivery devices and has a proven record of safety, comfort and reliability. Combined with Penfill® 3 ml cartridges and NovoFine® needles, NovoPen® 3 constitutes a perfectly integrated system, which eliminates the need for syringes and vials.

For your patients, the following special features combine to improve patient compliance, increase self-confidence and allow a more normal social life.

Accurate
Doses are dialled in 1-unit increments, which enables fine-tuning of the insulin regimen to achieve optimal control.

Easy to use
- Dial the dose.
- Push the button to inject.

Convenient
- Simple to learn how to use.
- Portable and discreet.
- Penfill® 3 ml cartridges mean few cartridge changes and minimal insulin wastage.
- NovoPen® 3 can deliver up to 70 units per injection, so people on high-dose regimens can use a pen system.

Durable
NovoPen® 3 has a high-quality metal construction and is virtually unbreakable.

COURSE OF LECTURES IN CLINICAL ENDOCRINOLOGY
Lecture 13

Add a touch of colour to your patient's life
NovoPen® 3 now comes in a choice of colours to suit your patient's personal taste and lifestyle.
- Elegant, stylish, discreet – colour collection offers a choice of tasteful blue or green in addition to the unobtrusive refinement of the classic NovoPen® 3.
- Colourful and fun – just like the children and teenagers who use them, NovoPen® 3 also comes in red and blue.
- Popular with patients – who are delighted to have a choice to suit their personal style.[1]
- Practical too – patients using different types of insulin find the different colours useful to distinguish their insulin types.

When small is beautiful
If your patient needs less than 10 units of insulin per day choose NovoPen® 1.5. This is similar to NovoPen® 3 but designed for use with Penfill® 1.5. There is also a choice of colours with NovoPen® 1.5 – classic, red and blue.

Novo Nordisk
Innovators in diabetes care

References – NovoPen® 3
1. Research carried out by the HCSU Market Research Department, Novo Nordisk A/S.

The daily glucosuria 100 g minus the permissible discharge of sugar in the urine 17 g is equal to 83 g. 83 g : 4 g = about 20 U of insulin.

For rational distribution of insulin doses within 24 hours, the glycaemia (daily rhythm of blood sugar content) and glucosuria profile must be tested.

A single dose of insulin usually does not exceed 30 - 40 U.

The proportion of a single insulin dose in relation to the total daily doses is determined by the level of sugar in the blood and the amount of sugar discharged in the urine in a definite period of time. In the first half of the day the dose of insulin constitutes 2/3; and in the second - 1/3. The evening not later than two or three hours before sleep.

Depending on the glycaemia and glucosuria profile, two or three days after insulin therapy had been started, the dose of insulin may be increased or reduced by 4-20 U.

Treatment with simple insulin is applied only in marked ketoacidosis and continued to its stable disappearance. In all other cases it is expedient to use preparations of insulin of prolonged action, combining them whenever necessary with short - action insulin preparations.

When the patient is changed from simple (with rapid action) insulin to an insulin preparation of prolonged action, or when one type of prolonged - action insulin is replaced by another, the dose of the new insulin preparation must be by 20% smaller than previous one.

Diabetic coma is an absolute contraindication for the prescription of insulin preparation of prolonged action. Ketoacidosis of various degrees is a relative contraindication.

There are insulin preparations of prolonged action - protofan, monotard, lente.

Since the effect of prolonged - action insulin begins slowly, 4 hours after its administration, it is often combined with the injection of simple insulin. Usually the proportion between rapid and prolonged insulin is 1/3 : 2/3.

Insulin with rapidly action is administrated before every meal in small doses 4-6-8 U on the background of 2 injections of prolonged insulin.

The total dose of insulin may be determined by multiplying ideal body weight (mass) by 0,5 U per kg; we get the amount of insulin for 24 hours, which the patient needs to administrate.

If the diabetes has a long time (remoteness, limitation) duration, the count for insulin doses is made as 0,7 U per kg; in ketoacidosis as 1 U (insulin) per kg; in diabetic coma as 1 -1,5 U per kg. Criteria for the compensation are: level of glucose / 24 hour - 8,8 mmol/l + aglucosuria, level of glycated haemoglobin < 6%. Normal levels of lipids.

Treatment with oral hypoglyceamic agents. On the background of diet is conducted in no less than one third of patients with diabetes mellitus.

Two main groups of hypoglycaemic agents are now used:

- sulphanylamides (sulphonylurea compounds) and
- biguanides.

Hypoglycaemic sulphanylamides (HS) and sulphonylurea compounds:

- Hypoglycaemic sulphanylamides: bucarban, carbutamid, oranil.
- Hypoglycaemic sulphonylureas: tolbutamid, orabet.
- Sulphanylamides with chloride (chlorpropamide) tablets 0,5g (are given in doses 0,5 - 2 g/ 24 hours.
  New sulphonylureas have recenly been produced: Hb - 419 - glybenclamid (maninil) tablets 5 mg - 2,5 mg are given in doses of 2,5 - 25 mg / 24 h.

Hypoglycaemic agents have the following mechanism of action:

- stimulate the activity of the insulin producing beta-cells of Langerhans islets;
- increase the sensitivity of the periphery tissues for insulin.

The indications for HS prescription are as follows: diabetes mellitus in patients over 40-45 years of age.

They are contraindicated in diabetic coma, precoma, ketoacidosis, pregnancy, delivery, lactation.

Diet is obligatory when the patients are treated with the hypoglycaemic agents.

Biguanides are now also very widely used. There are:

- phenylethylbiguanides (phenphormin)
- dimethylbiguanides (glucophage)
- butylbiguanides.

Biguanides mostly cause an extrapancreatic effect. Biguanides increase cell - membrane permeability to glucose.

The indications for the prescription of biguanides are as follows: moderately severe diabetes mellitus combined with obesity. Dose: glucophage 500 mg, siofor 850 mg / 24 h.

Contraindication: coma, ketoacidosis, cardiovascular affection with ischemic manifestation, high temperature.

Novonorm (repaglinide) is a new hypoglycaemic agent, ensuring prandial glucose regulation. It is used in type 2 diabetes in dose of 0,5 - 2,0 mg, in pills per os before meals.

IN TYPE 2 DIABETES
NOVONORM®
(repaglinide / Novo Nordisk)
Prandial Glucose Regulation℠ means flexible mealtime dosing.

Abbreviated prescribing information:
NovoNorm® (repaglinide / Novo Nordisk)

Indications: Patients with Type 2 diabetes whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. NovoNorm® is also indicated in combination with metformin in Type 2 diabetes patients who are not satisfactorily controlled on metformin alone.

Dosage: The recommended starting dose is 0.5 mg before each main meal. If patients are transferred from another oral hypoglycaemic agent, the recommended starting dose is 1 mg before each main meal. The recommended maximum single dose is 4 mg before each main meal. The total maximum daily dose should not exceed 16 mg.

Contraindications: Hypersensitivity to repaglinide or any component of NovoNorm®, pregnancy and lactation, Type 1 diabetes, diabetic ketoacidosis. Severe renal and hepatic function disorders.

Precautions: Combination treatment with metformin is associated with an increased risk of hypoglycaemia.

Adverse reactions: In controlled clinical studies, the incidence and severity of adverse events was no different to that observed with other oral insulin secretagogues. Mild hypoglycaemia, transient visual disturbances, gastrointestinal disorders, e.g. diarrhoea or nausea, were the most common adverse events. Isolated cases of a mild and transient elevation in liver enzyme levels were also observed.

Presentations: NovoNorm® 0.5 mg, 1 mg and 2 mg tablets.

NovoNorm® is a registered trademark of Novo Nordisk A/S. Available as Prandin™ from Novo Nordisk in the USA and sold as GlucoNorm® in Canada. Please refer to local prescribing information for further detail.

novo nordisk®

Treatment of ketoacidotic coma

I. Simple rapidly active insulin in small doses 6-8 U / h i/v (i/m) after 2 hours of glucose high 10-12/h i/v or big doses 100 - 200 U 1/2 i/v 1/2 i/m after 2 hour is administered again 1/2 of first doses.

When glucose decreases to 14 mmol/l, insulin will be administered in the common regime.

II. Rehydration in dropper perfusion 2-4 l 0,9% isotonic sodium chloride solution, 5% solution of glucose, Na bicarbonici 4% etc.

Treatment of the Diabetic Coma

The general scheme of treatment of the diabetic coma includes:

- 1. Elimination of the lack of the insulin (insulin insufficiency);
- 2. Fast and optimal rehydration of the organism;
- 3. Restoration of glucose reserve in the organism (glycogen in liver);
- 4. Restoration of the acid-base balance;
- 5. The diagnosis and treatment of concurrent pathologic conditions that have brought the patient to coma;
- 6. The support and restoration of the functions of internal organs (heart, kidneys, lungs).

The scheme of insulin therapy:

In our days there is accepted the regimen of application of "small" or "physiological" doses of insulin for the treatment of the ketoacidotic coma. At first a single dose of 8-10 Units (maximum 20 Units) is injected intravenously as a bolus. 50 Units of insulin in a solution of 500 milliliters of 0,9% sodium chloride - physiological solution, saline, are prepared. After this, a continuous infusion of 6-10 Units per hour is applied drop by drop, during the time calculated, that is 8-10 Units per

hour for 5 hours. If on the background of coma are present infections, then the dose of insulin consists of 12 Units per hour. By the lowering of glycaemia to 11-12 mmol/l the dose is lowered to 2-4 Units/hour and after this, by attaining glycaemia of 8,8 mmol/l, the patient is treated in a normal register of subcutaneous injection of insulin, by 12 Units, every 4 hours.

Rehydration is performed by intravenous infusion, drop by drop, up to 4-6 litres of liquid per 24 hours, as physiological solution (saline), 5% solution glucosae to 11-13 mmol/l, there must be added (included) the 5% solution of glucose, which is necessary to rebuild the supply of glycogen.

Hypoglycaemia is eliminated by the use of 5% glucose solution or saline and 5% solution of potassium chloride, according to the following calculation: 2-3 grams KCl per hour.

Acid-base balance is corrected by the use of a drop-by-drop intravenous infusion of 4% solution of sodium bicarbonate, repeatedly, by 200-300 ml under the control of pH and base reserve.

Collapse is prevented by use of cardiotonics: glycosides (strophantin), cordiamine, caffeine, mesatone. Drugs which enhance microcirculation: polyglycine, rheopolyglycine. In case of infections - antibiotics are used.

Lecture 14.

14.1 Brief Anatomo-Physiological Data of the Adrenals.

The adrenals are a paired vitally important organ of internal secretion. They are situated above the upper poles of the kidneys on a level between the first lumbar and eleventh thoracic vertebrae. The weight of both adrenals ranges from 6 to 12 g. Their length reaches 40-60 mm, breadth 20-35 mm, thickness 6-10 mm.

The adrenals are enclosed in a connective-tissue capsule. Strands arise from the connective-tissue capsule and penetrate adrenal, as a result of which the gland is separated into zones.

The adrenal is composed of two layers:

- a yellow outer and
- an inner medullar layer, which has a reddish-brown tinge.

The adrenal cortex, in turn, consists of three zones:

- 1. The outer glomerular zone (zona glomerulosa) located above the subcapsular layer (it is the narrowest).
- 2. A fascicular zone (zona fasciculata) occupying an intermediate position.
- 3. A reticular zone (zona reticularis) directly adjoining the cortical layer.

The glomerular zone, the narrowest, is composed of cells of multiangular or irregular cubic shape forming glomeruli.

The fascicular zone is the widest; it is composed of large granular cells cubic or multiangular in shape, most frequently prismatic strands of these cells are arranged in bundles stretching from the glomerular to

the reticular zone. The cells of the fascicular zone are rich in cholesterol, ascorbic acid and lipids.

The reticular zone is composed of smaller granular cells arranged as an irregular loose network.

The adrenal medulla has a loose structure; it is about one tenth the size of the cortex.

The medulla is composed of chromaffin (pheochromic) cells, which have a multiangular prismatic or spherical shape, and of sympathetic ganglionic cells.

The chromaffin cells are arranged in strands or groups. On staining with salts of chromic acid, they acquire a brown colour because of which they are also called pheochromic.

Function of the adrenal

Fifty steroid compounds have been isolated from the adrenal cortex to date. A steroid ring of 17 carbon atoms (cyclopentanoperhydro-phenanthrene nucleus) forms the backbone of their chemical structure and they are therefore called corticosteroids.

Three of corticosteroids are true hormones:

- cortisol (hydrocortisone),
- corticosterone and
- aldosterone - 80% of all corticosteroids that are formed.

Aldosterone is formed in the glomerular zone of the adrenal cortex. Cortisol and corticosterone are predominantly formed in the fascicular zone; the sex hormones (testosterone, oestradiol) are produced in the reticular zone.

Corticosterone - a precursor of aldosterone, is also partly synthesized in the glomerular zone.

Depending on the prevalent physiological action, besides the sex hormones:

- glucocorticoids (cortisol, corticosterone) and
- mineralocorticoids (aldosterone) are secreted.

Cortisol is the most active glucocorticoid. Corticosterone possesses marked mineralocorticoid properties, besides the glucocorticoid features.

Cortisol contributes to the regulation of carbohydrate, protein and lipid metabolism.

Cortisol:

- intensifies gluconeogenesis from protein and fat;
- facilitates the deposition of glycogen in the liver;
- takes part in the transport of glucose in the striated muscles and takes part in the adaptation of the organism to the efffect of stress factors (infection, toxicosis, injury) (Hans Selye, 1936, Canadian scientist).

If produced in excess,

Cortisol possesses

- diabetogenic action,
- causes a strong anti-inflammatory and anti-allergic effect, associated with its capacity for reducing capillary permeability and antibody formation, and also contributes to the regulation of arterial pressure.

Aldosterone regulates the water-salt metabolism,

- it promotes the reabsorbtion of sodium ions mainly in the renal tubules;
- reduces the discharge of sodium in the urine;
- intensifies the discharge of potassium ions.

As a result it:

- increases the hydrophilic properties of tissues and the plasma volume and
- increases arterial pressure;
- under the effect of aldosterone a normal balance of sodium and potassium is maintained in the body.

The androgenic corticosteroids take part in the formation of the genitals and the development of secondary sex characters. They also possess an anabolic effect and contribute to libido regulation.

Corticosteroids are formed from cholesterol, and possibly also from acetoacetic acid. Specific enzymes and dehydrogenases are directly involved in corticosteroid biosynthesis.

ACTH regulates the production and incretion of glucocorticoids and androgens. ACTH incretion is stimulated by corticotrophin - releasing factor.

Aldosterone incretion increases under the effect of the:

- juxtaglomerular apparatus of the kidney;
- hyperkalaemia;
- hypovolaemia; and
- to a lesser extent, under the effect of ACTH.

In the circulation (blood) most of the hormones bind with the plasma proteins, first of all with transcortin (alpha-1-glucoprotein related to the plasma alpha-1-globulins).

In the liver most of the cortisol, corticosterone and aldosterone is converted to tetrahydrocompounds which are biologically inactive.

Approximately 10% of cortisol is converted in the liver to 11-oxy-17-ketosteroids. The adrenal androgens are discharged in the urine as 17-ketosteroids (17-CS).

In females 17-CS are composed only of the adrenal androgens; in the males + 1/3 (one third the testicular androgens).

Adrenaline (epinephrine) and noradrenaline (norepinephrine) form in the parenchymal cells of the adrenal medullary substance, but the main site of noradrenaline synthesis are the sympathetic paraganglia.

Adrenaline and noradrenaline originate from the amino acid phenylalanine. As a result of several succesive processes (oxidation, decarboxylation) phenylalanine is converted to dioxyphenylalanine (DOPA), dopamine, and ultimately to noradrenaline (the precursor of adrenaline) and adrenaline.

It should be noted that noradrenaline which is formed in the sympathetic paraganglia does not transform to adrenaline. The incretion of adrenaline and noradrenaline is controlled by:

- the sympathetic nervous system and
- the higher centres located in

1. the cerebral cortex,
2. reticular formation, and
3. hypothalamus.

Glucocorticoids intensify adrenaline formation. The half-life of free adrenaline and noradrenaline does not exceed three minutes.

Adrenaline:

- intensifies cardiac contraction,
- increases the pulse rate,
- causes elevation of arterial pressure (mainly at the expense of systolic pressure),
- contributes to the increase of pulse pressure.
- It also relaxes the smooth muscles of the bronchi and intestine.

- Adrenaline dilates the vessels of the muscles and heart and
- It constricts the vessels of the skin, mucous membranes and abdominal organs,
- It promotes the contraction of the muscles of the uterus and the spleen,
- It takes part in pigment metabolism and
- It increases thyroid sensitivity to the effect of TSH.

Adrenaline plays an important role in the organism's reaction to stress situations. The production of ACTH and consequently that of corticosteroids also increases under the effect of adrenaline.

Unlike adrenaline noradrenaline has hardly any effect on carbohydrate metabolism and the smooth muscles. It increases arterial pressure mainly at the expense of the diastolic pressure, which is mainly caused by its capacity to reduce constriction of the muscular layer of the arterioles' wall.

Besides adrenaline and noradrenaline, dopamine (the precursor of noradrenaline) also possesses biological activity.

Adrenaline, noradrenaline and dopamine are embraced under the common name catecholamines.

14.2 Chronic Adrenocortical Insufficiency (Addison's Disease, Hypocorticism, Bronzed Disease)

Addison's disease is a severe chronic disease caused by partial or total loss of the hormonal function of the cortex of both adrenals as a result of its bilateral affection. Addison's disease is relatively rare and is usually encountered between the ages of 20 and 40 and with equal frequency among males and females.

History. The disease was described for the first time by Thomas Addison in 1855.

Aetiology. The most common cause of Addison's disease is primary and less frequently secondary affection of the adrenal cortex.

The most common cause of primary adrenal insufficiency is tuberculosis of the adrenals (in 50-80% of cases), usually occurring as the result of haematogenic dissemination from other organs (the lungs, urogenital system, bone system, lymph nodes) and rarely as a localized lesion.

Primarily adrenal insufficiency is often a consequence of an auto-immune process in the adrenal cortex. Sometimes, however, it's consequent upon:

- amyloidosis,
- bilateral tumour or
- metastases of carcinoma in the adrenals.

In rare cases Addison's disease may develop as the result of:

- haemorrhages into the adrenals or
- thrombosis of their vessels in infections diseases (influenza, brucellosis) or
- in toxemia of pregnancy or
- as the result of their chronic, purulent inflammation.

The main cause of secondary adrenal insufficiency is believed to be deficient ACTH production resulting from various disorders in the hypothalamo-hypophyseal system and particularly in long-term therapy with large doses of glucocorticoids for various chronic diseases.

Pathogenesis

Glucocorticoid (cortisol and corticosterone) deficiency leads to:

- adynamia,
- cardiovascular and
- gastro-intestinal disorders,
- sharp decrease in the organism resistance to unfavourable

factors (infection, toxicosis),
- a decrease in the blood sugar content,
- neuropenia,
- eosinophilia,
- lymphocytosis.

Mineralocorticoids (aldosterone) deficiency leads to:

- hyponatraemia, hypochloraemia, hyperkalaemia,
- dehydration and
- hypotension.

A decrease in the production of the sex hormones (androgens and oestrogens) by adrenal cortex causes:

- impotence in males and
- disorders of the menstrual cycle in females.

The development of pigmentation is due to increased deposits of the pigment melanin in the papillary layer of the skin and mucous membranes.

Pathology

The morphological changes in the adrenals are determined by the cause of the disease. In Addison's disease of tuberculous aetiology destruction of the cortex and medulla of both adrenals is found on autopsy.

Caseosis, specific tuberculous foci of disintegration and calcification are revealed. The Addison's disease consequent upon primary or secondary atrophy of the adrenals. The adrenal glands are hypoplastic with degenerative changes seen mainly in the fascicular and reticular zones of the cortex.

In primary atrophy of the adrenal cortex the development of fibrous tissue, round-cell infiltrates consisting of accumulations of lymphocytes and plasma cells are seen in the cortex as well as hyperplastic islets of

hypertrophied cortical cells. Lymphoid infiltration of the thyroid gland and the development of fibrous tissue in it are a frequent finding. Atrophic changes are also revealed in all organs (liver, heart, muscles).

Classification

According to the mechanism of its origin, Addison's disease may be separated into a disease caused by:

- primary adrenal insufficiency and
- a disease caused by secondary adrenal insufficiency (Zefirova).

According to the clinical course are distinguished:

- a typical form and
- a typical form such as mineral (of the type of hypoaldosteronism),
- non-pigmental.

Addison's disease may be:

- mild,
- moderate or
- severe.

In the mild form is achieved positive effect by means of diet, with no substitution hormonal therapy such as:

- a favourable clinical effect
- correction of the disturbed metabolic processes, decrease in pigmentation and adynamia, normalization of arterial pressure and body weight, rehabilitation of working capacity.

In moderate Addison's disease, for achieving clinical effect is necessary therapy with glucocorticoids, such as cortison, hydrocortisone, prednisolon.

Patients with the severe form of the disease show a tendency to develop an Addisonian crisis. A clinical effect in such patients may be produced only by means of continuos substitution therapy such as glucocorticoids combined with mineralocorticoids (desoxycorticosterone acetate, fluorohydrocortisone).

Clinical picture

The disease develops gradually.

Patients complain of:

- utter weakness,
- rapid physical fatiguability,
- darkening of the skin,
- loss of appetite,
- nausea, vomiting, diarrhea, loss of body weight and
- muscle pain in the upper and lower limbs and
- muscle pain in the small of the back.

The patients' skin is usually - golden brown (a dusky - bronze). Pigmentation is particularly marked on the open parts of the body (face, the folds of the palms, the dorsal surface of the hands, and feet and areas against which the clothes rub:

- the axilla,
- the groin,
- elbows,
- knees,
- small of the back,
- skin folds.

Pigmentation of the postoperative cicatrices is also noted and intensified pigmentation in areas of natural pigment deposits (nipples of the mammary glands, the genitals).

Pigmentation of the mucous membranes in the form of grayish black spots (on the lips, gums, cheeks, tongue, hard and soft palate), is particularly characteristic.

Hypothermy is quite frequent, changes in the cardiovascular system usually occur in the form of hypotonia (mainly at the cost of reduced systolic pressure) and a decrease in the pulse pressure and the minute blood volume.

The pulse is rapid, small and soft. The dimensions of the heart are diminished and the sounds are muffled. The ECG often demonstrates a low voltage, the S - T interval below the isoelectric line, flattened negative or double - phase T wave, prolonged P - Q interval and prolonged QRS complex. Signs of active or inactive tuberculous process are found in the lungs.

Gastro-intestinal abnormalities are manifested as dyspepsia, attacks of abdominal pain (Addisonian gastro-intestinal crises), reduced acidity of the gastric juice and diminished external secretion of the pancreas.

Chronic gastritis develops in some cases. Addison's disease may be combined with gastric or duodenal ulcer. Multiple superficial ulcerations of the gastro-intestinal mucosa occur in some cases.

The anti-toxic, protein-producing and glycogen - producing functions of the liver are disturbed. Disorders of renal function are displayed in reduced glomerular filtration and diminished reabsorbtion of sodium and chlorides particularly manifest during a crisis.

Changes in the sexual sphere are inconstant. Some males have diminished libido and potency, females suffer from disorders of the menstrual cycle.

The neuropsychic disorders are manifested by increased nervous excitability or depression and insomnia.

Psychosis may sometimes develop. Paraesthesia and convulsions occur in some cases. In severe forms of this disease the EEG after demonstrates the prevalence of slow activity of the type of theta- and delta- range of frequencies and the absence of alpha-rhythm, which is evidence of diminished activity of the cerebral cortex.

Addison's disease of hypothalamo-hypophyseal genesis is characterized by a milder course, the absence of a sharp fall of arterial pressure (with the exception of severe forms of the disease), positive Thorn's test, and maintained potential reserves of the adrenal cortex.

Addison's disease of the hypoaldosteronism type is caused by disturbed function of only the glomerular zone of the adrenal cortex. In this form of the disease all symptoms inherent in Addison's disease are present, but signs of disturbed water-salt metabolism prevail (marked hyperkalaemia, hyponatraemia and hypocholoraemia), drastic decrease in aldosterone excretion in the urine). The excretion of 17-OCS and 17-CS is usually normal.

Addisonian crisis (acute adrenal cortical insufficiency) is a menacing complication of Addison's disease.

Its development is promoted by acute infection, toxicosis, surgical interventions, pregnancy and improper treatment of Addison's disease.

The lack of cortisol and aldosterone in the organism leads to dehydration of the body, collapse, disorders of renal function, severe hypoglycaemia, which are mainly responsible for the clinical manifestations of this severe complication.

An Addisonian crisis usually develops gradually and less frequently abruptly (within a few hours). In its gradual development the symptoms of the disease grow within several days, even weeks.

General weakness intensifies little by little, there are loss of appetite, rapid loss of weight, increased pigmentation, very often pain in the abdomen that resembles symptoms of acute diseases involving organs of the abdominal cavity.

Nausea appears, quite often the smell of acetone is felt in the breath, uncontrollable vomiting occurs and diarrhea, which intensifies dehydration.

Dehydration is manifested by the diminished turgor of the skin and a drop in intraocular pressure, the drastic fall of arterial pressure, thickening of the blood.

Phenomena of acute cardiovascular insufficiency intensify. In the absence of infection body temperature is low. Clonic spasms and the meningeal syndrome often occur at times attended by dimmed consciousness.

Hyperhaemoglobinaemia is registered in the blood, leucocytosis, increased ESR, acute hyponatraemia, hypochloraemia and hyperkalaemia, often hyperketonaemia, quite frequently marked hypoglycaemia, the heightening of residual nitrogen and urea caused by the sharp drop in the glomerular filtration due to dehydration and collapse are encountered.

Acetone often appears in the urine and there are proteinuria, leucocyturia, microhaematuria, cylindruria (hyaline and granular casts). There is a sharp decrease of 17-CS and 17-OCS excretion in the urine. Unless timely treatment is applied, the patient loses consciousness; this is followed by coma (hypochloraemia) and death.

Laboratory findings

Lymphocytosis and eosinophilia are registered in the blood. In a number of cases there is secondary normocytic anemia. The ESR is decreased but becomes heightened with the development of an active tuberculous

process. Quite often (in the severe form of the disease) there are hyponatraemia, hypochloraemia, hyperkalaemia. The content of cortisol and sugar in the blood on a fasting stomach is decreased.

After glucose loading the sugar curve is flat with a marked hypoglycaemia phase by the third hour after the load and frequently there are hypoalbuminaemia, hyperglobulinaemia and a tendency to hypocholesterolaemia.

The excretion of potassium in the urine is reduced while that of sodium and chloride is increased. The content of aldosterone, 17-CS and 17-OCS in the urine is reduced. A diminished basal metabolism is noted in the severe form of the disease.

Diagnostic tests

Thorn's eosinophilia test is conducted in the diagnosis of subclinical forms of Addison's disease.

In healthy persons it is positive, i.e. after injection of ACTH the eosinophil count decreases by 50 per cent and more. A decrease in the absolute number of eosinophils four hours after intramuscular injection of 25U of ACTH by less than 50% is evidence of diminished adrenocortical function and interpreted as negative Thorn's test.

The Robinson-Power-Kepler water test is also used in the diagnosis of Addison's disease (in the absence of the oedema syndrome). It is based on the retention of water in patients suffering from Addison's disease, increased discharge of chlorides and relative retention of urea. The test is begun at 6 p.m. when the patient is not allowed to eat or drink. At 10 p.m. the urinary bladder is evacuated and the urine is collected till 8 a.m. the next morning.

The volume of collected urine is measured, after which the patient is given 20 ml/kg of water to drink over a period of 45 minutes.

The volume of excreted urine is then measured every hour for four hours. In healthy persons the largest volume of a 1-hour portion of urine is larger than the volume of the nocturnal urine. In patients with Addison's disease the proportions are reversed. The index of the sodium: potassium ratio in blood serum is another diagnostic test. It is 30 in the healthy persons but falls to 22 in hypocorticism.

In patients with Addison's disease the water test index is below 25, in healthy individuals it is more than 30.

The existing and potential reserves of the adrenal cortex (Labhart's test) and the blood ACTH level are determined in the differential diagnosis of primary and secondary adrenocortical insufficiency.

The blood plasma ACTH content is increased in primary and decreased in secondary adrenocortical insufficiency. After daily intramuscular injection of 40U of ACTH with prolonged 24-hour action for three days in succession the excretion of 17-OCS in the urine in the first 24 hours increases by 100% as compared to the initial level (the existing reserves of the adrenal cortex) and reaches 300% on the following second and third days (potential reserves of the adrenal cortex).

In primary adrenocortical insufficiency, the existing and potential cortical reserves are diminished or absent whereas in secondary (hypothalamo - hypophyseal) insufficiency the existing reserves are preserved, while the potential may be reduced.

Diagnosis and differential diagnosis

The diagnosis of Addison's disease is based on the characteristic symptoms of the sickness:

- adynamia,
- arterial hypotension,
- pigmentation,
- on the laboratory findings and

- diagnostic tests.

Melanoderma in Addison's disease is differentited from:

- bronzed diabetes (haemochromatosis),
- pellagra,
- systemic scleroderma,
- the pigment form of the toxic goitre and
- acanthosis nigricans.

In some cases a differential diagnosis has to be made with pigmentation in chronic malaria, pruritus dermatitis, repeated irradiation of the skin with X-rays, chronic poisoning with lead, mercury, silver hydrate and arsenic, sunburn combined with the hypotonic syndrome and with racial pigmentation.

The characteristic symptoms providing evidence in favour of bronzed diabetes but against Addison's disease are hepatomegaly, splenomegaly, cirrhosis of the liver, pancreas and other internal organs combined with diabetes mellitus and deposition in the skin of an iron-containing pigment (haemosiderin) and a pigment which does not contain iron (haemofuscin), which lends the skin a slate gray colour.

As distinct from Addison's disease, pellagra is characterized by a triad:

- dermatitis preceding the pigmentation,
- acquired dementia and
- diarrhea.

In pellagra the pigmentation is found only on the open parts of the body (hands, face, neck).

The features distinguishing systemic scleroderma from Addison's disease are diffuse firm oedema of the skin or its thickening and atrophy and trophic disorders of the skin (abscesses, ulcerations).

The skin pigmentation is usually combined with areas of depigmentation which makes the skin motley.

In differential diagnosis of Addison's disease and pigmented form of toxic goitre, the evidence against the former are the characteristic clinical (goitre, ocular symptoms, increased systolic and pulse pressure) and laboratory findings (increased content of PBI in blood, increased basal metabolic rate and I131 uptake in the thyroid).

In acanthosis nigricans there are no clinical laboratory signs of adrenocortical insufficiency. In the last stages of disease, as distinct from Addison's disease, there are hyperkeratosis and papillomatous growths of the skin.

The medical history and clinical and laboratory findings are of decisive importance in differential diagnosis of skin pigmentation caused by chronic adrenocortical insufficiency from other types of skin pigmentation.

Prognosis

The prognosis of the disease is determined by the character and severity of the pathological process, timely diagnosis and efficacy of treatment.

If the treatment is organized properly, patients survive 15-20 years and longer. If no treatment is applied the prognosis with regard to survival is unfavourable. The prognosis is less favourable in tuberculosis of the adrenals and more favourable in their simple atrophy.

Addisonian crisis, coma and severe hypoglycaemia constitute the greatest hazard for the patient's life.

In the mild form of Addison's disease individuals engaged in mental work often retain their working capacity, although an occupation linked with considerable neuropsychic tension is contraindicated. Persons suffering from this form and employed in physical labour are often rated group III invalids.

A moderately severe form of the disease usually leads to group III invalidity, the severe form to group II and even group I invalidity.

Treatment

A diet with a sufficient content of proteins, fats, carbohydrates, sodium salts, vitamin C and vitamins of the B complex and poor in potassium salts is prescribed in the mild form of the disease.

Meat is sharply restricted in the diet, while peas, beans, nuts, bananas, baked potatoes, cocoa and other potassium - rich foodstuffs are excluded.

Sodium chloride (up to 10 g) and ascorbic acid (0,5-1,0 g) are prescribed in addition daily.

Substitution hormonal therapy with gluco- and mineralocorticoids is prescribed in the moderate and severe forms of Addison's disease.

Cortisone and hydrocortisone is given intramuscularly in daily doses of 12,5-50 mg.

Oral medication is prescribed with:

- prednisolone or prednisone (5-20 mg daily),
- dexamethasone (1-2 mg daily).

If the clinical effect is insufficient (no normalization of arterial pressure, gain in body weight), agents possessing a mineralocorticoid action are prescribed in addition (deoxycorticosterone acetate, DOCA; deoxycorticosterone trimethylacetate; fluohydrocortisone).

DOCA is prescribed in the form of a 0,5 per cent oil solution in a dose of 5 mg given intramuscularly every day, every other day or twice a week, or in the form of 5-mg tablets taken under the tongue two to four times a day.

DOCA tablets of 100-200 mg are implanted under the skin. The therapeutic effect of the implantation lasts three to twelve months.

Deoxycorticosterone trimethylacetate is prescribed as an aqueous 2,5 per cent suspension for intramuscular injection of 1 ml given once in two or three weeks.

Fluohydrocortisone is sometimes prescribed in a daily dose of 0,1-0,2 mg taken by month (per orally).

Treatment of patients with Addison's disease is conducted under control of body weight, arterial pressure, dynamometery, examination of general condition and the excretion of 17-CS and 17-OCS in the urine.

In Addison's disease of tuberculous aetiology streptomycin is prescribed in a dose of 0,5-1,0 g daily (total dose 50 g) in combination with phthivazid, isoniazid, PASA or other agents causing an antituberculous effect.

To control dehydration and collapse in Addisonian crisis, intravenous (or intramuscular) drip of two-three liters of 5 per cent glucose in isotonic sodium chloride solution with 100-300 mg of hydrocortisone (special preparation for intravenous administration) or 50-150 mg of prednisolone, 50 ml of a 5 per cent ascorbic acid solution and 4-6 ml of cordiamine are prescribed.

If there is a sharp fall in arterial pressure, 1-3 ml of adrenaline, noradrenaline or 2-3 ml of mesaton, are added into the dropper. A simultaneous intramuscular injection of 100 mg of hydrocortisone, cortisone or 30-40 mg of prednisolone is given with subsequent repeated injections of 50 mg hydrocortisone or cortisone every 4-6 hours.

A daily dose of 10-15 mg of a 0,5% oil solution of DOCA is injected intramuscularly every 6-8 hours in addition to this treatment.

In uncontrollable vomiting 5-10 ml of a 10 per cent sodium chloride solution is injected intravenously.

With the improvement of the patient's condition the dosage of the preparations is gradually reduced.

Antibacterial therapy is carried out when there are indications.

Lecture 15.

15.1 Congenital Virilizing Adrenocortical Hyperplasia (Adrenogenital Syndrome, Congenital Adrenocortical Dysfunction).

Congenital virilizing adrenocortical hyperplasia is caused by congenital disorders of hormone biosynthesis in the adrenal cortex, as a result of which excessive amounts of androgens are produced. It is a rare disease and its incidence among females is approximately four to five times that among males.

History. The disease was first described in 1856 by Krechio. In 1950 Wilkins and others suggested treating congenital virilizing adrenocortical hyperplasia with cortisone.

Aetiology. The disease is caused by congenitally determined deficiency of the enzymatic systems participating in normal steroidogenesis in the adrenal cortex. This deficiency results from hereditary transmission of a mutant (autosome recessive) gene.

Pathogenesis

The lack of enzymes (probably 21-hydroxylase, in the first place), contributing to the biosynthesis of corticosteroids, leads to diminished cortisol production as a consequence of which there is a compensatory intensification of ACTH production by the hypophysis. The reduced formation of cortisol is attended by accumulation in the blood of the precursors of its metabolism (17-oxyprogesterone, progesterone and pregnenolone) with increased excretion of their metabolites (pregnanediol, pregnanetriol, pregnanetriolone, dehydroepiandrosterone and etiocholanolone) in the urine.

As the result of the continuously increased stimulation of the adrenal cortex by ACTH, hyperplasia of its reticular zone occurs, on the one hand, and excessive production of androgens, of the other. This, in turn, leads to virilization (masculinization) of the child's organism.

In children with a female genotype, the excess of androgens leads to the development of female pseudohermaphroditism (hypertrophy of the clitoris, the formation of a urogenital sinus with the vagina and urethra having a common opening, underdevelopment of the vagina, uterus and mammary glands, abnormally developed muscles, hypertrichosis, a hoarse voice, absence of menstruation).

In children with the male genotype, the excess of androgens leads to premature acceleration of growth (height), enlargement of the penis and the appearance of secondary sex characters, libido and erection. In profound deficiency of the enzyme 21-hydroxylase, besides a low production of cortisone there is also a sharp reduction in aldosterone biosynthesis as a result of which the salt-losing syndrome develops.

The occurrence of this syndrome is also attributed to the increase in the amount of cortisol precursors possessing anti-aldosterone activity. The increased excretion of sodium and chlorides in the urine leads to dehydration and hypotension. It is believed that in lack of the enzyme 11-hydroxylase, along with disorders of cortisol and aldosterone synthesis, there is excessive production of the cortisol precursor 11-deoxycorticosterone possessing marked mineralocorticoid activity.

The excess of 11-deoxycorticosterone induces arterial hypertension but without disturbing the body electrolyte balance. It is claimed that in 3-beta-dehydrogenase deficiency the synthesis of all steroid hormones is disturbed or markedly weakened against the background of maintained production of androgens. As a result, in addition to virilization, pronounced signs of adrenocortical insufficincy (the salt-losing syndrome, collapse), develops with rapid death.

Pathology

Pathological examination reveals considerable hyperplasia of the adrenal which is most marked in the reticular zone. The glomerular zone may be intact, hyperplastic or hyperplastic. The fascicular zone is intact or hypoplastic. The external genitals in children with the female genotype imitate the male genitals (urogenital sinus, hypertrophy of the clitoris).

Sharp atrophy of the uterus occurs. The ovaries are either hypotrophied or sclerosed and have numerous small cysts and a thickened tunica albuginea. In children with the male genotype, the penis is enlarged.

The testes are usually atrophied and there is no spermatogenesis, in rare cases they are normally developed. Tumours, leydigomas are often encountered.

Classification

According to form, congenital virilizing adrenocortical hyperplasia may be prenatal (intrauterine) or postnatal. According to the clinical course:

- the virile,
- salt-losing and
- hypertonic forms are distinguished.

Clinical picture

The symptoms of the disease depend on the age and the character of disturbances in the enzymatic systems contributing to corticosteroidogenesis. The prenatal form is the most common, the postnatal form is encountered less frequently. The virile form caused by hyperproduction of androgens is the most commonly encountered among the clinical forms (in 60% of cases).

The overproduction of androgens before the gonads are finally formed leads to the development of female pseudohermaphroditism. This is manifested in drastic hypertrophy of clitoris which resembles the penis,

enlargement of the large and underdevelopment of the small prudential lips, vagina and uterus, and the formation of urogenital sinus.

In hyperproduction of androgens after differentiation of the gonads and genital ducts in girls there is only moderate hypertrophy of the clitoris.

In overproduction of androgens after birth, the genitals of newborns are normally developed; they alter later with the gradual increase in adrenocortical dysfunction. Disorders of sexual development in girls are manifested by early sexual hirsutism by the masculine type, hypertrophy of the clitoris, underdevelopment or absence of the mammary glands, underdevelopment of the uterus, disturbed menstrual cycle or amenorrhoea. After the birth of a boy disorders in his sexual development are manifested in early sexual hirsutism, enlargement of the penis and prostate, retarded development of the testes and absence or spermatogenesis.

Early libido and erections are noted. Hypertension often develops if the disease occurs during sexual maturation. As a result of the anabolic effect of androgens, both in girls and in boys, growth is accelerated, the muscles are abnormally developed and they become very strong; the skeleton matures early.

Because of the early closure of the epiphyseal growth zones, however, such children remain of short stature with a long trunk and short lower limbs. The trunk of a girl resembles that of a male. As a consequence of androgen hyperproduction, the voice grows hoarse and acne develop.

The salt-losing form of the disease is encountered less frequently (in 30-33 per cent of cases) and is usually diagnosed in the newborns and in children of the first year of life. It is mostly encountered among boys.

The characteristic symptoms are dyspepsia (regurgitation, vomiting, diarrhea), loss in body weight, hypotension, sharp disorder of water-salt metabolism. Crises develop often with attendant convulsions,

cyanosis, collapse, dehydration of the organism and hyperkaliaemia. They are often fatal.

In the comparatively rare hypertonic form of the disease (7 per cent of cases), in addition to marked virilization in girls and macrogenitosomia in boys, there are stable arterial hypertension attained by early changes in the vessels of the kidneys and of the funds oculi, and hypertrophy of the left ventricle. The disease may also develop in adult females.

Symptoms of virilization appear: hypertrophy of the clitoris, general hypertrichosis, hirsutism, growth of pubis hairs by the masculine type, atrophy of the mammary glands, and disorders of the menstrual cycle and even amenorrhoea. Sterility is often encountered.

Laboratory findings. The blood plasma ACTH content is elevated, as a rule.

In the salt-losing type of the disease the bood aldosterone content is low and there are hyponatraemia, hypochloraemia, hyperkalaemia and sometimes hypoglycaemia.

The excretion of 17-CS in the urine is considerably increased, mainly at the cost of hydroepiandrosterone and sometimes androsterone and etiocholanolone.

The daily excretion of 17-OCS in the urine is normal or reduced, but the ratio of the excreted cortisol metabolites is disturbed: more tetrahydrocortisone is excreted in the urine than tetrahydrocortisol and more 11-ketoetiocholanolone than 11-hydrooxyetiocholanolone. The excretion in the urine of large amounts of pregnanediol, pregnanetriol and especially etiocholanolone is typical of the disease. No gonadotropins are found in the urine.

Diagnosis tests. The dexamethasone or prednisolone test is used in the diagnosis of congenital adrenocortical dysfunction. It is based on the

ability of corticosteroid agents to suppress ACTH production as a consequence of which the excretion of 17-CS in the urine decreases.

The patient is given 0,5 mg of dexamethasone or 5 mg of prednisolone per os every six hours for two days. The daily excretion of 17-CS following the administration of corticosteroid agents is decreased by 50% and more, as compared to the elevated initial level, which testifies in favour of congenital dysfunction of the adrenal cortex.

The genetic sex is determined by examining the sex chromatin. In female pseudohermaphroditism genetic females are always chromatin positive. In male pseudohermaphrodtism genetic males are chromatin negative.

X-ray diagnosis

Tomogram made by means of pneumosuprarenography demonstrates hyperplasia of both adrenals which have a homogenous structure.

In hermaphroditism the internal genitals are examined by pneumogynaecography (pneumopelvigraphy). Hypoplasia of the sex apparatus is found on the pneumogynograms.

Diagnosis and differential diagnosis

The diagnosis of congenital adrenocortical dysfunction is made on the grounds of the medical history (gradual virilization), the characteristic clinical picture (improper formation of the genitals, hirsutism, accelerated physical development) and the findings of laboratory tests (increased blood plasma ACTH content, increased excretion in the urine of 17-CS, pregnanediol, pregnanetriol, etiocholanolone), X-ray examination and diagnostic tests.

Congenital adrenogenital dysfunction is differentiated from androsteroma (tumour of the adrenal cortex), premature puberty consequent upon hypothalamo-hypophyseal disorders and tumour of the pineal gland.

A differential diagnosis is also made with tumour of the testis, virilizing tumours of the ovaries (arrhenoblastoma) and the Stein-Leventhal syndrome.

The rapid virilization, the absence of a decrease in 17-CS excretion in the urine after intake of corticosteroid agents (cortisone, dexamethasone or prednisolone), the discovery of a unilateral adrenal tumour on the radiograph, are evidence of androsteroma.

As distinct from congenital adrenocortical dysfunction, in diseases of hypotalamo-hypophyseal genesis premature puberty is always of true character and isosexual in type.

The testes develop normally to the size characteristic of the adult male. During biopsy of the testes, histological examination reveals a large number of Leydig cells and spermatogenesis. In premature puberty, due to abnormality of the pineal gland as distinct from congenital adrenocortical dysfunction, there are marked neurological symptoms (increased intracranial pressure, headache, papilloedema, nystagmus) and maturity is always true, of the isosexual type; the amount of metabolites of androgens of adrenal origin (dehydroepiandrosterone, androsterone, etiocholanolone) in the urine is not increased.

Unilateral enlargement, hardness and irregular surface of the testis revealed by palpation and findings of biopsy are evidence of a hormonally active testicular tumour.

Unlike congenital adrenocortical dysfuncion in virilizing tumours of ovaries the content in the urine of the adrenal androgen fractions is not increased.

In the Stein-Leventhal syndrome, in contrast to congenital adrenocortical dysfunction, the constitution is of the feminine type and the mammary

glands are intact. The excretion of 17-CS in the urine increases after the administration of chorionic gonadotrophin. The pneumogram shows polycystic disease of the ovaries.

Prognosis

In early recognition and treatment of the disease the prognosis is favourable. The physical and sexual development of children is usually normalized. If treatment is late, sexual development is normalized, but hypertrichosis, small stature and complications caused by arterial hypertension usually remain.

Without regular substitution therapy acute adrenocortical insufficiency may develop, particularly in concomitant infection, toxicosis, injury, and lead to sudden death from severe collapse, dehydration and possibly hyperkaliaemia, it is advisable to determine the genetic sex no later than at the age of three years.

Treatment

Life - long medication with glucocorticoids (cortisone, hydrocortisone, prednisolone, dexamethasone and so on), is the only method of treatment of congenital adrenocortical dysfunction. These drugs, on the one hand, reduce ACTH incretion as a result of which the production of androgens by the adrenal cortex decreases and, on the other, compensate for the lack of glucocorticoids in the body. To normalize sexual and physical development, glucocorticoid therapy should be begun between the ages of 2 and 10 years. Predisolone is usually prescribed first in a daily dose of 10-20 mg given for 5-10-15 days or dexamethasone in a daily dose of 2 mg given for 5-7 days.

In marked decrease in the daily 17-CS excretion in the urine, strictly individualized maintenance doses are prescribed. The daily 17-CS excretion in the urine should remain within normal level of the "bone" age.

Glucocorticoid therapy is also conduced under control of growth (height), body weight, "bone" age, arterial pressure, daily excretion in the urine of oestrogens (oestrogene, oestriol, oestradiol) and pregnanediol, pregnanetriol and etiocholanolone.

The developmental defects of the genitals in females are corrected by a plastic operation which is usually undertaken no earlier than 12 months after glucocorticoid therapy.

In the salt-losing type of the disease, in addition to glucocorticoids, sodium chloride and mineralocorticoids (DOCA, fluohydrocortisone) are prescribed. In the hypertensive form of the disease the treatment is the same as in the virile form. If acute adrenocortical insufficiency develops, the same treatment as in Addisonian crisis is prescribed.

15.2 Acute Adrenocortical Insufficiency (Syndrome of Waterhouse-Friderichsen).

Acute adrenocortical insufficiency is a catastrophic state threatening the life of the patient and developing as a result of the rapid or sudden decrease in the functional reserves of the adrenal cortex against the background of stress.

The disease may develop at any age with equal frequency both among males and females.

The Waterhouse-Friderichsen syndrome develops mainly in newborn infants and women in childbirth.

History. The disease caused by bilateral haemorrhage into the adrenal cortex was described in detail by Waterhouse in 1911 and by Friderichsen in 1918.

Aetiology. Acute insufficiency of the adrenal cortex may be caused by birth, injury, meningococcal sepsis inducing extensive haemorrhages in the adrenal cortex, bilateral adrenalectomy, removal of glucosteroma

in the presence of atrophy of the contralateral adrenal, stress conditions (infections, surgical interventions), occurring against the background of a status thymico-lymphaticus or long-term glucocorticoid therapy, and primary and secondary insufficiency.

Pathogenesis. Sharp deficiency in corticosteroid hormones (glucocorticoids and mineralocorticoids) forms the basis of the pathogenesis.

Pathology. Autopsy in the Waterhouse-Friderichsen syndrome reveals extensive haemorrhages and haemorrhagic necrosis in the cortex of both adrenals.

In acute adrenocortical insufficiency, caused by other factors, the findings include hypoplasia, atrophy, caseous tuberculosis, thrombosis of the adrenal veins and sometimes syphilitic gummata or carcinoma metastases.

Histological examination discloses the main pathological changes in the fascicular and reticular zones of the adrenal cortex.

Classification. Acute adrenocortical insufficiency may be primary, caused by primary affection of the adrenals, or secondary of hypothalamo-hypophyseal genesis.

Clinical picture. The symptoms of acute adrenocortical insufficiency are the same as those of Addisonian crisis, but unlike the latter they usually develop in a few hours, or, less frequently, in one or two days.

The Waterhouse-Friderichsen syndrome has some specific features. It occurs abruptly and follows a fulminating course. Death often occurs within the first 24 hours. The patients have headache, dyspnoea, severe abdominal pain, vomiting, diarrhea, sharp nervous excitation, convulsions, chills, high fever, cyanosis and extensive confluent petechial skin haemorrhages, severe collapse with a sharp fall of arterial pressure develops.

Death occurs from collapse, pulmonary oedema and dehydration.

Diagnosis and differential diagnosis

The diagnosis of acute adrenocortical insufficiency is made on the grounds of the medical history, characteristic clinical symptoms (dehydration, acute cardiovascular insufficiency, abdominal disorders) and the results of laboratory studies (drastic hyponatraemia, hypochloraemia and hyperkalaemia, marked hypoglycaemia, a sharp decrease in the excretions of 17-CS and 17-OCS in the urine).

The diagnosis of the Waterhouse-Friderichsen syndrome is based on abrupt onset, septic condition (meningococcal sepsis), dyspnoea, cyanosis, high body temperature, severe collapse and hypotension, petechial skin haemorrhages combined with other signs characteristic of acute adrenocortical insufficiency. Acute adrenal insufficiency has to be sometimes differentiated from food poisoning, acute gastrointestinal diseases, myocardial infarction and cerebral stroke.

As distinct from acute diseases of the abdominal organs, the pseudoperitoneal form of acute adrenocortical insufficiency usually produces no symptoms of peritoneal irritation, but there are severe collapse, eosinophilia without neurotrophilic leucocytosis, and marked hypoglycaemia.

Besides the characteristic clinical and laboratory findings the absence of a history of diseases of the circulatory organs and the like speak in favour of acute adrenocortical insufficiency but against myocardial infarction or cerebral stroke.

Prognosis

If the diagnosis had been made early and timely treatment had been applied, the prognosis is usually favourable. If no treatment is given, death occurs in one or two days.

Prevention

The prevention of acute adrenocortical insufficiency consists in early recognition of this condition and active detection and constant medical observation of patients suffering from Addison's disease and treated for a long time with corticosteroids for various chronic diseases.

It is necessary to apply corticosteroids in good time in the period of stress situations (operations, infection) in individuals with suspected hypofunction of the adrenal cortex, and to increase the dose of corticosteroids during stress in patients with Addison's disease.

Treatment

Acute adrenocortical insufficiency is managed just as Addisonian crisis. Large doses of antibiotics in combination with sulphanylamides are prescribed to control infection.

Lecture 16. Primary Hypercorticism

16.1. General Information. Classification

Primary hypercorticism is a group of diseases caused by increased incretion of glucocorticoids, mineralocorticoids, androgens and oestrogens by the adrenal cortex.

Classification:

1. Aldosteroma, an aldosterone - producing tumour of the adrenal cortex. Causes primary aldosteronism (Conn's syndrome).

2. Glucosteroma, a tumour of the adrenal cortex producing mainly glucocorticoids. It is manifested clinically for the most part by metabolic disorders (Cushing's syndrome).

3. Androsteroma, a tumour of the adrenal cortex predominantly producing androgens. Leads to the development of the virilization syndrome.

4. Corticoestroma, a tumour of the adrenal cortex producing estrogens (female sex hormones). It induces gynecomastia and feminization in males.

5. Mixed tumours (glucoandrosteroma, glucoaldosteroma and others).

These types of tumours produce several steroid hormones differing in their effect on the organism. The name of a mixed tumour is associated with the clinical manifestations.

Glucoandrosteroma, for instance, produces glucocorticoids and androgens. It is characterized clinically both by the virilization syndrome and the Cushing's syndrome.

Note: each of the forms of tumours listed in the classification may be benign or malignant. The classification fully retains its significance in

ectopic tumours developing from the aberrant tissue of the adrenal cortex.

16. 2. Glucosteroma

Glucosteroma is a hormonally active tumour of the adrenal cortex which arises mainly from its fascicular zone and produces excess amounts of corticosteroids, prevalently glucocorticoids. It is characterized by a clinical picture resembling that of the Itsenko-Cushing disease.

Glucosteroma usually occurs in females, particularly between the ages of 18 and 42.

History. The syndrome of glucocorticoid hypercorticism was described for the first time by Cushing in 1912.

Aetiology. The cause of the disease is unknown.

Pathogenesis

The pathogenesis of glucosteroma is similar to that of Itsenko-Cushing's disease and is caused by the increased production mainly of glucocorticoids.

Pathology

Pathological examination reveals a tumour of the adrenal cortex, usually malignant, less frequently benign. The weight of the tumour varies from 5 g to 5 kg. Areas of hemorrhages and necroses are usually found in the tumours.

Histological examination shows the predominance of cells of the fascicular zone (compact cells with oval nuclei, which are arranged in strands).

In cases with malignant tumour there is rapid metastatic spread to the contralateral adrenal, the liver, lungs, brain and bones. The contralateral

adrenal is hypotrophied, as a rule. The morphological changes in the other organs and systems are mostly the same as those in Itsenko-Cushing's disease.

Clinical picture

Glucosteroma resembles Itsenko-Cushing disease in the clinical picture in many respects. Unlike the latter, the course of glucosteroma, particularly in the malignant form, is more rapid with more pronounced virilism (hirsutism, hypertrichosis, etc.).

X-ray, CT, MRI diagnosis

Demonstrates unilateral adrenal tumour and hypoplasia of the contralateral adrenal.

Diagnosis and differential diagnosis

The diagnosis of the disease is made on the grounds of the characteristic clinical picture, the results of diagnostic tests and mainly on the findings of X-ray diagnosis (pneumosuprarenography, angiography of the adrenals), CT and MRI diagnosis.

Prognosis

With early diagnosis and timely surgical management of a benign adrenal adenoma the prognosis is favourable, but in adenocarcinoma with metastatic spread it is unfavourable. If an operation is not undertaken, the patients die from haemorrhages into the brain, cardiac decompensation, sepsis, pneumonia, renal insufficiency, metastatic spread of the tumour to vitally important organs (liver, lungs).

Treatment

An operation for the removal of the tumour is the only method of treatment. Because of hypotrophy of the contralateral adrenal,

substitution corticosteroid therapy is prescribed in the postoperative period. In cases with inoperable form of carcinoma of the adrenal cortex, agents blocking the synthesis of corticosteriods (chloditan, elipten) may be used.

16.3. Primary Aldosteronism (Conn's Syndrome)

Primary aldosteronism or Conn's syndrome is caused by excessive production of aldosterone by a tumour if the adrenal cortex. It is comparatively rare and occurs more frequently in females between 20 and 50 years of age.

History

The syndrome was described in 1955 by Conn.

Aetiology. The most common cause of Conn's syndrome is a hormonally active tumour in the glomerular zone of the adrenal cortex (aldosteronoma) and very rarely its bilateral hyperplasia.

Pathogenesis. Because of increased production of aldosterone, sodium reabsorbtion in the renal tubules is intensified and, as a result, excretion of potassium in the urine increases. Lack of potassium in the organism leads to the development of muscular weakness, paraesthesia, transient muscular paralyses, and renal symptoms (polyuria, polydipsia, nicturia, etc). Polyuria is caused by dystrophic changes in the renal tubules as a result of which they lose the ability to react to the antidiuretic hormone. As the result of hypokalaemia, the intracellular potasium is replaced by sodium and hydrogen ions which is the cause of intracellular alkalosis. This, in turn, causes tetany. The predominant accumulation of sodium in the walls of the arterioles facilitates their swelling, the narrowing of their lumen, which leads to arterial hypertension and associated symptoms (headache, changes in the fundus oculi, left-ventricular hypertrophy).

Pathology

Pathological examination usually discloses a solitary or multiple tumours of the cortex of one and rarely of both adrenals. The tumour is usually benign, although in 5 per cent of cases it may be malignant. In many instances the adenoma is small and on section orange and yellow in colour with a grayish hue in places. Histological examination most frequently reveals cells of both the glomerular and fascicular zones of the adrenal cortex in the tumour.

In 9 percent of cases only bilateral diffuse hyperplasia of the adrenal cortex is found on autopsy. Histological study reveals thickening of the glomerular zone. In rare cases there are no pathological changes in the adrenal cortex. Hydropic and fatty degeneration on the tubular cells and thickening of the basal membranes are frequent findings in the kidney. The dystrophic processes are found mainly in the proximal and less frequently in the distal tubules.

Hyalinization of the glomeruli, sclerosis of the renal arterioles and pyelonephritis are sometimes encountered. Some patients have localized necroses of the heart muscle and skeletal musculature.

Clinical picture

Patients complain of severe headache, episodes of sharp muscular weakness and convulsions, thirst, copious and frequent urination, paraesthesia and sharp pain in the muscles; aching non-referred pain in the region of the heart, dyspnoea, palpitation and intermission of the heartbeat are often noted.

The cardiovascular signs include shifting of the left boundary of the heart, diminished cardiac sounds, accentuated second aortic sounds and systolic murmur at the apex. There is a stable elevation of arterial pressure at the cost of the systolic and especially the diastolic pressure, with a decrease in the pulse pressure. The ECG usually demonstrates

elongation of the Q-T interval, a flattened or negative T wave, and S - T below the isoelectric line which is due to hypokalaemia.

There is usually no oedema, although it may occur if cardiac insufficiency develops (in less than 10 per cent of patients).

Episodes of sharp muscular weakness are a characteristic symptom. Flaccid paralyses of the muscles, mainly of the lower limbs, develop frequently.

They occur rapidly or even abruptly and regress in a few hours or, less frequently, in a few days or weeks. Attacks of tetany occur often in the form of convulsions of the upper and less frequently of the lower limbs attended by increased tendon reflexes and positive Chvostek's and Trousseau's signs. Disorders of renal function are manifested in diminished reabsorption of water in the renal tubules and reduced glomerular filtration and renal blood flow.

Laboratory findings

The aldosterone content in blood is increased and there are hypokalaemia and often hypernatriaemia and hypochloraemic alkalosis. Carbohydrate tolerance is reduced in some cases.

Plasma renin activity is diminished (often to zero). The urinary reaction is alkaline. Hypoisosthenuria, proteinuria, hyperkaliuria and hyponatriuria are found. Increased excretion of aldosterone in the urine is characteristic finding. The daily excretion of 17-OCS and 17-CS in the urine is usually normal.

Diagnostic tests

In hypokalaemia the aldactone (spironolactone) test is used. It is based on the ability of aldactone to block the effect of the aldosterone on the renal tubules. An increase in the blood potassium level after oral administration of spironolactone (aldactone) in a dose of 100 mg four times a day for three days on the morning of the fourth day by more

than 1 mmol/l indicates the dependence of hypokalaemia on the excess of aldosterone. The test with hypothiazide load is sometimes used. After a single intake of 100 mg of hypothiazide, the blood potassium level may decrease in patients with primary aldosteronism. With a chloride ammonium load or of anhydrous hydrochloric acid the urine reaction does not change (remains alkaline) in patients with Conn's syndrome.

X-ray diagnosis. A radiograph (taken by means of pneumosuprarenography), CT and MRI of the adrenals demonstrate, in some cases, tumour of one adrenal and atrophy of the contralateral gland or bilateral hyperplasia of both adrenals.

Diagnosis and differential diagnosis

The diagnosis of primary aldosteronism is made from the characteristic symptoms of the disease (episodes of drastic muscular weakness and tetany, transient flaccid paralyses, arterial hypertension, moderate polyuria, polydipsia), the findings of laboratory studies (hypokalaemia, reduced plasma renin activity, increased excretion of aldosterone in the urine, hypoisosthenuria), X-ray, CT and MRI diagnosis and diagnostic tests.

Primary aldosteronism is differentiated from hypertensive disease, tetany, diabetes insipidus, nephritis with loss of potassium, congenital form of hyperaldosteromism, renal hypertension caused by ischemia of the kidneys, hyperparathyroidism and secondary aldosteronism (in heart diseases, nephrosis and cirrhosis of the liver).

Prognosis

The prognosis is usually favourable if the diagnosis is made early and operative treatment is applied in good time (before irreparable changes

develop in the kidneys and the vascular system) and the patient recovers completely. Without treatment the patients die in a late period of the disease from progressive arterial hypertension and/or cardiac insufficiency.

Treatment

The radical method of treatment of primary aldosteronism is surgical removal of the aldosteronoma or subtotal or total resection of hyperplastic adrenals.

A diet with restriction of sodium and an increased content of potassium is prescribed in the preoperative period. To normalize the potassium level in the blood, 0,5 g of potassium chloride is given orally two or tree times a day and spironolactone (aldactone or verospiron) is given in doses of 0,025 - 0,05 g four times a day before the operation. Intramuscular injections of glucocorticoids (cortisone, hydrocortisone) are given before and during the operation to avoid acute insufficiency of the adrenal cortex. Substitution therapy is prescribed in the postoperative period.

16.4. Corticosteroma

Corticosteroma is a hormonally active tumour of the adrenal cortex which arises from the reticular and facicular zones. It produces excessive amounts of oesterogens and, in some cases, glucocorticoids, and is characterized by the feminization syndrome and sometimes also by symptoms typical of the Itsenko-Cushing's disease. The tumour is very rare and encountered in males.

Aetiology. The cause of the disease is unknown.

Pathogenesis. The pathogenesis of corticosteroma is caused mainly by excessive production of oestrogens and, in some cases, of glucocorticoids.

Pathology. Autopsy reveals a tumour arising from the cells of the adrenocortical reticular and fascicular zones.

Clinical picture. The mammary glands of males become enlarged (gynecomastia), the subcutaneous fat is redistributed after the feminine type, growth of hair on the face ceases, the voice takes on a higher timbre and potency reduces or is even completely lost.

In some cases, in addition to gynecomastia, symptoms characteristic of Itsenko-Cushing's disease develop due to hyperproduction of glucocorticoids by the tumour.

Laboratory findings

Increased excretion of oesterogens in the urine and in some cases of 17-CS and glucocorticoid metabolites (17-OCS), is noted.

X-ray, CT and MRI diagnosis reveal an unilateral adrenal tumour.

Treatment

Operation for removal of the adrenal tumour is the only method of treatment. In the development of acute adrenocortical insufficiency, the same therapy is applied, as in Addisonian crisis.

16.5. Androsteroma

Androsteroma is a hormonally active tumour of the adrenal cortex arising mainly from its reticular zone. It secretes corticosteroids and mainly androgens in excess amounts and is characterized by a clinical picture resembling of congenital adrenocortical dysfunction. The disease may be encountered at any age both among females and males.

Aetiology

The cause of the disease remains unknown.

Pathogenesis

The pathogenesis of androsteroma is caused by increased production of hormones, mainly androgens by the tumour tissue.

Pathology. Pathological examination reveals a tumour of the adrenal cortex. It is usually soft and incapsulated. Histologically, the tumour consists mainly of dark cells which are characterized by marked polymorphism. In some cases the histological picture of the tumour resembles the structure of the reticular zone of the adrenal cortex.

In malignant androsteroma there are pronounced polymorphism, cell atypia, infiltrative growth of tumour cells and numerous foci of necrosis. Metastatic spread of the malignant androsteroma may occur into the retroperitoneal space, liver and lungs.

Clinical picture

The clinical picture of androsteroma is similar in many respects to congenital adrenocortical dysfunction but is distinguished by the rapid development of virilization which is particularly sharp in cases with malignant androsteroma. Separate symptoms inherent in the Itsenko-Cushing's disease sometimes appear as the result of glucocorticoid hyperproduction.

X-ray, CT, MRI diagnosis reveal unilateral tumour of the adrenal.

Diagnostic tests

After medication with corticosteroid agents (oral dexamethasone given in a dose of 2 mg at intervals of six hours for two days, or other agents) 17-CS excretion in the urine does not change if there is an androsteroma.

Treatment

Operative removal of the adrenal involved in the tumour is the only method of treatment.

Lecture 17. Pheochromocytoma

17.1. Brief Anatomo-Physiological Data of the Adrenal Medulla.

The adrenal medulla has a loose structure; it is about one tenth the size of the cortex. The medulla is composed of chromaffin (pheochromic) cells, which have a multiangular prismatic or spherical shape, and of sympathetic ganglionic cells.

The chromaffin cells are arranged in stands or groups. On staining with the salts of chromic acid, they acquire a brown colour because of which they are also called pheochromic.

Adrenaline and noradrenaline form in the parenchymal cells of the adrenal medullary substance, but the main site of noradrenaline synthesis are the sympathetic paraganglia. The incretion of adrenaline and noradrenaline is controlled by the sympathetic nervous systems and higher centres located in the cerebral cortex, reticular formation and hypothalamus.

Adrenaline intensifies cardiac contraction, increases the pulse rate, causes elevation of arterial pressure (mainly at the expense of systolic pressure) and contributes to the increase of pulse pressure. Adrenaline plays an important role in the organism's reaction to stress situations.

Unlike adrenaline, noradrenaline has hardly any effect on carbohydrate metabolism and the smooth muscles. It increases arterial pressure mainly at the expense of the diastolic pressure, which is mainly caused by its capacity to reduce constriction of the muscular arterioles. Adrenalin, noradrenaline and dopamine (the precursor of noradrenaline) are embraced under the common name "catecholamines".

17.2. Pheochromocytoma.

Pheochromocytoma is a hormonally active tumour arising from the chromaffin tissue of the adrenal medulla, paraganglia or sympathetic ganglia. It is comparatively rare. The tumour usually occurs at the age of 20-40 years and is encountered with equal frequency among males and females.

History

The first description of the disease was given in 1886 by Frenkel. The name pheochromocytoma was suggested in 1912 by Pick after the predominant cells staining brown with salts of chromic acid.

Aetiology

The cause of the disease is unknown, a genetic predisposition to the development of pheochromocytoma is noted, especially among children.

Pathogenesis

The pathogenesis of pheochromocytoma is caused by excessive production of catecholamines (adrenaline and noradrenaline) by the chromaffin cells of the tumour.

The symptoms of the disease may vary depending of the amount and the ratio of adrenaline and noradrenaline. In the predominance of adrenaline collapse may develop and excitation, trembling, dilatation of the pupils, tachycardia, hyperglycaemia and glucosuria occur; if noradrenaline prevails, there are increased sweating, bradycardia, increase of systolic and diastolic arterial pressure, basal metabolic rate. A definite role in the pathogenesis of the of the disease is attributed to increased excitability of the vegetative centres of the hypothalamus and cerebral cortex.

Pathology

The medulla of one of the adrenals is the most common site of pheochromocytoma.

Much more rarely, in 10-15 per cent of cases the localization of the tumour is extra - adrenal. An extra-adrenal pheochromocytoma is most frequently found in the sympathetic paraganglia along the length of the abdominal aorta and at is bifurcation, less frequently in the mediastinum and sometimes in the cranial cavity and wall of the urinary bladder. In approximately 10 per cent of cases the tumours are bilateral or multiple. Most frequently a pheochromocytoma localized in one adrenal has a benign structure whereas in bilateral or extra-adrenal localization the tumours are malignant. A malignant tumour (pheochromocytoma) usually produces metastasis to the retroperitoneal lymph nodes, liver, bones and lungs. The tumour usually weighs no more than 75 g, but sometimes its weight may reach 3600 g. The tumour is greenish - brown, on section it is grayish-red or brown and soft in consistency. There are numerous foci of haemorrhages and necrosis. Histologically large polygonal cells or irregularly shaped cells with a fine granular protoplasm are most frequently found.

Classification

According to the clinical course, there forms of the disease are distinguished:

- 1. adrenalo-sympathetic (paroxysmal);
- 2. stable form (stable increased arterial pressure without crises) and
- 3. asymptomatic form.

Clinical picture

The **adrenalo-sympathetic form** with characteristic episodes of hypertensive crises is encountered most commonly. The crises develop against the background of initial normal or elevated arterial pressure.

Their occurrence is promoted by emotional stress, abundant diet, awkward position of the trunk and palpation of the tumour which causes increased liberation of catecholamines from the tumour into the blood.

The episode usually occurs suddenly. The patient is frequently excited during it and complains of a chill, a sensation of ungrounded fears and formication (a sensation of insects creeping over the skin). Diplopia develops in some cases. Severe headache and dizziness occur at the peak of the episode. Epileptiform convulsions may also occur.

The pupils are often dilated during the episode. The skin and mucous membranes are pale and the limbs cold. Body temperature is elevated, as a rule, sometimes (in adrenaline - producing tumours) up to 40 grades Celsius and even higher.

The cardiovascular disorders are manifested by dyspnoea, pain in the region of the heart, cyanosis, tachycardia, rarely bradycardia. There may be disorders of the cardiac rhythm (extrasystole, paroxysmal form of fibrillation tachyarrhythmia). Arterial pressure is usually sharply elevated at the expense of both the systolic and diastolic pressure. The duration of the hypertensive crisis varies from a few minutes to several hours. At the onset of the disease the hypertensive crises occur relatively rarely at intervals of months and even years. With the advancement of the disease the crises become frequent and may recur several times a day.

The **form of pheochromocytoma with stable hypertension** without crises is less frequent. It resembles malignant hypertension in its course with the typical complications (nephrosclerosis, sclerosis of the coronary vessels and cerebral vessels, myocardial infarction). Diabetes mellitus develops in 10 per cent of patients with this form.

The **asymptomatic form** of the disease is rare. The tumour in such cases possesses no marked hormonal activity. In some patients in a stress situation (operation, childbirth, injury), however, shock or acute

adrenal insufficiency develops. This is linked with hypersensitivity of these patients to overstress.

Laboratory findings

Leucocytosis, transient lymphocytosis and eosinophilia are usually found in the blood during an attack, which is attributed to contraction of the splenic muscles under the effect of catecholamines. There may also be erythrocytosis and increased ESR, hyperglycaemia, hyperkalaemia, increased concentration of NEFA and increased fibrinolytic activity and coagulation of blood. Transient proteinuria, often glucosuria, cylindruria and a high content of adrenaline, noradrenaline and their metabolites are found in the urine. There are no abnormalities in the blood and urine between attacks. In the stable form of the disease, proteinuria and cylindruria are revealed in some cases. The basal metabolic rate is increased.

Diagnosis tests

In marking the diagnosis of pheochromocytoma, the blood and urine are tested for the content of catecholamines and their metabolites in the urine, vanillylmandelic acid.

Pharmacological tests are also performed, which are based either on stimulation of the chromaffin substance (histamine test) or on the blocking effect of catecholamines (thropaphen or regitine test). Under normal conditions the 24-hour adrenaline excretion in the urine is 10±5 microg, that or noradrenaline 40±20 microg and that of vanillylmandelic acid 1,5-6,5 mg. In pheochromocytoma the excretion of adrenaline in the urine usually exceeds 50 microg, while the excretion of noradrenaline exceeds 150 microg. In some patients the excretion of catecholamines in the urine exceeds the normal level tens and even hundreds of times. The use of the histamine test is indicated in the paroxysmal form of

hypertension marked by normal arterial pressure between crises and normal or moderately increased content of catecholamines in the 24-hour urine.

The histamine test may be undertaken when the initial arterial pressure is no higher than 150/100 mm Hg. In patients with pheochromocytoma two or three minutes following rapid intravenous injection of 0,025-0,05 mg histamine in 1-2 ml of an isotonic sodium chloride solution the arterial pressure increases considerably by more than 50/40 mm Hg of the initial level even with the development of hypertensive crisis.

The excretion in the urine of catecholamines and vanillylmandelic acid also grows sharply after histamine injection. In healthy individuals and in patients with hypertension of another genesis, there is only a mild rise in arterial pressure.

The test with thropaphen or regitine is performed when the initial arterial pressure is more than 160/100 mm Hg. After intravenous injection of 1 ml of a 1 per cent thropaphen solution (10 mg for adults and 5 mg for children) within 5-10 seconds the arterial pressure decreases by no less than 50/30 mm Hg in patients with pheochromocytoma. In hypertension of other genesis there is either a slight decrease in arterial pressure or none at all.

X-ray, CT, MRI diagnosis

Pneumosuprarenoradiography with tomography and CT, MRI are used to establish the localization of the pheochromocytoma. In some cases retrograde pyelography and the angiography of adrenals are used in the topical diagnosis of the pheochromocytoma. The content of catecholamines in the blood at different levels of the system of the inferior and superior venae cavae is sometimes studied by the method of catheterization for the same purpose.

Diagnosis and differential diagnosis

The diagnosis of pheochromocytoma is made on the basis of characteristic adrenalosympathetic crises, laboratory findings (repeated excretion in the urine within 24 hours of more than 50 microg adrenaline, 100 to 150 mcg noradrenaline and 6 mg of vanillylmandelic acid), pharmacological tests and the data of X-ray, CT and MRI diagnosis.

Differential diagnosis of pheochromocytoma is made to distinguish it from the hypertensive disease, hypothalamic vegetative-vascular crises, toxic goiter in combination with hypertension, and from diabetes mellitus in combination with the hypertensive disease.

Evidence of the hypertensive disease is seen in psychic traumas or long-term nervous overstress recorded in the case history, less pronounced vegetative shifts during crisis, the efficacy of ordinary hypotensive therapy, normal or slightly increased content of catecholamines and vanillylmandelic acid in 24-hour urine or in a 3-hour portion of urine after a provocative pharmacological test. As distinct from pheochromocytoma, in symptomatic hypertension of renal genesis crises occur rarely, there are typical pathological changes in the urine, signs of disturbance in renal function and negative pharmacological tests.

In contrast to pheochromocytoma, in hypothalamic vegetative vascular crises there are indications in the case history of cerebro-cranial traumas, infections (influenza, rheumatism, tonsillitis), intoxications.

Hypothalamic vegetative vascular crises occur more often in women. The excretion of catecholamines in the urine within 24 hours is not as great as in pheochromocytoma.

Evidence of toxic goitre can be found in the characteristic case history (physic trauma, infection), the peculiarities of hypertension (the heightening of systolic pressure alone while diastolic pressure is normal or reduced), the absence of crises with elevated arterial pressure, a rise in T3 and T4 in the blood and the I131 uptake by the thyroid, a lesser

24-hour excretion of catecholamines in the urine as compared with pheochromocytoma.

In the differential diagnosis of pheochromocytoma and diabetes mellitus combined with hypertension much assistance is provided by the results of pharmacological tests and study of the excretion in the urine of catecholamines and their metabolites (vanillylmandelic acid, metanephrine and normetanephrine).

Prognosis

In early diagnosis and timely operative treatment the prognosis is favourable, if no treatment is applied, the prognosis is unfavourable. Death may result from a cerebral stroke, myocardial infarction, pulmonary oedema, collapse, extensive haemorrhages into the tumour with subsequent bleeding or peritonitis, gastro-intestinal bleeding, malignant degeneration of the tumour. Without treatment patients live three to four years, on the average, although sometimes patients live up to twenty years.

Treatment

The patient can recover only after the operative removal of the tumour. In the period of preparation for the operation the patient must be provided with complete rest (to exclude physical and emotional stress, over-cooling and over-heating of the body).

To prevent hypertensive crises during examination and operation, tablets of phentolamine hydrochloride are given per os in doses of 25 mg (6-8 tablets) or thropaphen in a dose of 1 ml of a 2 per cent solution injected intramuscularly or intravenously. If collapse develops noradrenaline and cardiac agents are injected intravenously.

Lecture 18. Diseases of the Gonads

18.1 Diseases of the Female Gonads. Brief anatomo-physiological data.

The ovary is one of the paired organs situated in the small pelvis on the posterior surface of the ligamentum ovarii proprium.

The surface of the ovary is formed by the layer of cells of the germinal epithelium, under which there is a dense connective-tissue capsule (tunica albuginea).

The ovary consists of two layers:

- The external (cortical) and
- The (medullary) internal.

The internal (medullary) layer has a loose connective tissue framework, embryonal remnants of the Wolffian duct, and a rich network of blood vessels. The place where vessels enter the ovary is called the hilium. Aggregation of cells resembling the Leydig cells of the testis are found in the hilium. These cells may secrete androgens. The cortical layer contains the sexual cells, ovicells, surrounded by:

- 1. rows of cells of the membrana granulosa and
- 2. the inner theca (follicles), which are in various stages of development.

The stroma around a maturing follicle is composed of cells of the outer theca (cells of the tunica externa, connective-tissue layer) and cells of the inner theca of the follicle (cells of the tunica interna, the epithelial layer).

A thickened layer of follicular epithelium lining the inner wall of the follicle is called the granular layer (zona granuloza).

The primordial follicles develop from the germinal epithelium in the ovary. By the time of sexual maturation there are about 40.000 primordial follicles.

With the onset of sexual maturity only a negligible part of these follicles approximately one hundredth develop in succession into a mature follicle, the Grafian vesicle.

The rest of the primordial follicles undergo retrogression without attaining the stage of the Graffian follicle.

The maturation of a follicle takes 12-14 days (till Grafian follicle).

A Grafian vesicle (follicle) containing an enlarged oocyte moves to the surface of the ovary and ruptures (ovulation); this occurs (the place of ovulation) between the 14th and 16th days of the menstrual cycle.

The oocyte is released into the abdominal cavity and then enters the uterine (Fallopian) tubes where it transforms into mature ovum and is fertilized.

At the site of the Grafian vesicle the cells of the granules and inner theca form the yellow body (corpus luteum).

Two sex hormones - progesterone and oestradiol - are produced in the ovary.

The corpus luteum produces progesterone. A small amount of progesterone is also produced by a maturing follicle (cells of the granulosa). In pregnancy progesterone is also formed in the placenta.

In the uterus progesterone creates conditions for receiving the fertilized ovum and maturation of the foetus, inhibits the contractile muscular excitability of the uterus, stimulates the growth of alveoli in the mammary glands, suppresses the effect of oestrogens on the uterine mucous during the menstrual cycle, and possesses a diuretic effect.

In the liver progesterone is converted to pregnanediol which combines with glucuronic acid and is excreted in the urine.

If the ovum is not fertilized, the corpus luteum functions for 10-12 days and then undergoes progressive retrogression and menstruation occurs (appears), which usually lasts three - five days. The duration of the menstrual cycle is individual and is 24-21-28-30 days.

In fertilization of the ovum, the corpus luteum functions for three and a half to four months and is called corpus luteum verum. At the end of pregnancy it also undergoes retrogression.

Oestradiol is mainly produced in the cells of the granules and inner theca. The small amounts of oestrogens are produced in the corpus luteum and reticular zone of the adrenal cortex.

Oestradiol is the most active oestrogen.

The products of oestradiol metabolism, oestrone and oestriol (less active), also possess hormonal properties.

Oestradiol promotes enlargement of the uterus and vagina, and proliferation of the endo- and myometrium, provides the development of female secondary sex characters:

- the development of the mammary glands,
- shaping of the feminine figure and the corresponding
- features of the skeleton; and
- accelerates the differentiation and ossification of the skeleton protein since they possess a protein anabolic effect.

The cells of the inner theca and hilum of the ovary produce a small amount of androgens. Having entered the blood, the greater part of the oestrogens circulate in it bound with proteins, glucuronic and sulphuric acids.

Only a small part remains in a free state.

Oestrogens are mainly inactivated in the liver and partly in the lungs, uterus, kidneys. From the liver they enter the intestine in the bile and are partly absorbed in the blood.

Excretion of oestrogens from the body occurs mainly in the urine (about 65%) and in a small amount in the faeces (about 10%). In the urine oestradiol is excreted in the form of oestradiol, oestriol and oestrone.

The ovarian function is controlled by the hypothalamo-hypophyseal system. As a result of the joint action of the follicle-stimulating hormone (FSH) and small amounts of the luteinizing hormone (LH) the follicles grow and develop, produce and increte oestrogens.

Ovulation occurs when the LH reach the ovulatory peak induced by the preovulatory peak of oestrogens.

The ovarian hormones, in turn, cause an effect on the hypothalamic centres, which produce the realizing factor, thus regulating the incretion of gonadotrophic hormones by the hypophysis.

Small amounts of oestrogens stimulate FSH incretion while large (physiological) amounts inhibit.

LH incretion from the hypophysis is intensified under the effect of small amounts of progesterone, but is inhibited under the effects of large amounts.

Primary hypogonadism of the female

Primary hypogonadism is a syndrome caused by the direct effect of a pathological process on the activity of the ovaries as a result of which the incretion of oestrogens is sharply reduced.

Aetiology

Primary insufficiency of the ovaries may be consequent upon congenital disorders of sexual differentiation (gonadal dysgenesis), damage to the ovaries by an infectious process (mumps, syphilis, tuberculosis and other infections), surgical removal of the ovaries.

Pathogenesis

The underlying factor of the pathogenesis of primary hypogonadism is diminished production of oestrogens as the result of which the sexual organs and mammary glands are atrophied, and there are primary amenorrhoea and other changes. If the ovaries do not function till puberty, the secondary sex characters do not develop.

Pathology

Histological examination of bioptic ovarian specimens reveals growth of connective tissue, desolation of the follicles.

Clinical picture

If damage to the ovaries occurs in childhood, the secondary sex characters either fail to develop or are weakly pronounced (partial or total underdevelopment of the mammary glands, sparse growth of hair on the pubis and axillae). The uterus, vagina and ovaries remain underdeveloped and primary amenorrhoea is encountered. The body is marked by eunuch-like proportions, the pelvis is narrow and the buttocks are flat. There is no disproportion in the skeleton if the disease develops in adults. The underdevelopment of the glands is less noticeable. Secondary amenorrhoea and often various manifestations of vegetoneurosis occur.

Laboratory findings

The level of gonadotrophic hormones in the blood is elevated, while that of oestrogens is considerably reduced. The excretion of gonadotrophic hormones in the urine is increased, while the excretion of oestrogens is sharply diminished.

X-ray diagnosis

Pneumopelvograms demonstrate drastic hypoplasia of the uterus and ovaries. X-ray examination of the osteoarticular system reveals delayed

maturation of the skeleton and osteoporosis (usually in the bones of the wrist joint and vertebral column).

Craniography often demonstrates hyperpneumatization of the basilary sinuses and small sella turcica with "juvenile" (straightened-out) dorsum.

Diagnosis and differential diagnosis

The diagnosis is based on the medical history and the clinical and laboratory findings.

Primary hypogonadism is differentiated from secondary hypogonadism. As distinct from the primary hypogonadism, secondary hypogonadism occurs as a consequence of lesion of the hypothalamo-hypophyseal system and is characterized by diminished level of gonadotrophic hormones in the blood and their diminished excretion in the urine.

Prognosis

Life prognosis is favourable but with regard to complete recovery it is unfavorable. The patients remain sterile.

Treatment

Physical development in the prepubertal period is stimulated by anabolic steroids; oral methandrostenolone (nerobol) in a dose of 0,1 - 0,15 mg/kg or intramuscular retabolil in a dose of 1 mg/kg is given once a month.

Anabolic therapy is applied for long periods in interrupted courses (2-3 months at intervals of 1 month) for many years.

It should be borne in mind that medication with anabolic steroids may cause virilization (enlargement of the clitoris).

Oestrogens are prescribed from the age of 15 years. To preserve the epiphyseal growth zones, these agents are given in small doses (no more than 5000U daily as recalculated for folliculin) at the beginning of treatment.

The oestrogens (sinestrol, diethylstilbestrol, oestradiol dipropionate) are at first given continuously until menstrual-like bleeding appears, after which they are given intermittently, imitating the normal menstrual cycle. When a proliferate type of the vaginal smear is attained, the estrogen agents are combined with pregnenolone or progesterone (estrogens are given 15 to 16 days of each month and in the following week pregnenolone is given in a dose of 10 mg three times daily sublingually or 1 ml of 0,5% progesterone solution is injected intramuscularly or subcutaneously).

After closure of the growth zones, preparations of female sex hormones in the commonly used therapeutic doses are applied. Synthetic progestins (infecundin, bisecurin) have good effects.

Among the new agents there is "Diane-35"; it is prescribed during 21 days beginning on the first day of menstrual cycle.

Secondary hypogonadism in the female

Secondary hypogonadism is a syndrome caused by diminished production of gonadotrophic hormones by the anterior pituitary as a result of which the incretion of oestrogens by the ovaries is drastically reduced. The syndrome is characterized by amenorrehoea, retrogression of secondary sex characters, hypoplasia of the external genitals and uterus.

Etiology and pathogenesis

Secondary hypogonadism may be caused by diseases of the hypothalamo-hypophyseal system marked by disturbed relationship between the hypothalamus and the anterior pituitary (Simmonds' syndrome, Sheehan's syndrome, craniopharyngioma, Chiari-Frommel's syndrome).

It occurs in some endocrine diseases due to hormonal disbalance (hypothyroidism, congenital adrenocortical dysfunction, Itsenko-

Cushing's disease). Secondary hypogonadism may occur after a psychic trauma which in some cases causes inhibition of the activity of the hypothalamic centres which, in turn, leads to diminished production of the releasing factors and gonadotrophic hormones. Secondary hypogonadism may be consequent upon severe infection, alimentary dystrophy, and obesity suffered by a young girl during puberty.

Clinical picture

The clinical picture is determined as a whole by the principal disease. Amenorrhoea and involution of secondary sex characters are encountered. The uterus and external genitals become hypoplastic.

Laboratory findings

The level of gonadotrophic hormones and oestrogens in blood and excretion of gonadotrophic hormones and oestrogens in the urine are reduced.

X-ray diagnosis

Craniography (in central genesis of hypogonadism) often demonstrated tumours of the intermediate-hypophyseal area (craniopharyngioma and others). In prepubertal secondary hypogonadism the X-ray findings are the same as in primary hypogonadism.

Diagnosis

The diagnosis is made on the basis of the medical history and clinical and laboratory findings. The differential diagnosis is discussed in the section of "Primary Hypogonadism".

Prognosis

The prognosis in secondary hypogonadism is determined by the principal disease.

Treatment

The principal disease must be treated first of all as a result of which secondary hypogonadism is also relieved. Preparations of chorionic gonadotrophin are sometimes prescribed after stimulating the ovaries. Treatment with ovarian hormonal preparations (oestrogens, progesterone) should be applied with caution so as not to suppress hypophyseal gonadotrophic activity much, as it has already suffered. Clomiphene; Diane-35 are sometimes prescribed.

Climacteric and pathological climacteric

Climacteric is a normal physiological condition of the organism, the transition from the reproductive period to the menopause.

Climacteric neurosis is a condition of the organism caused by pathological age, changes in the function of the central nervous system, of hypothalamic centers in the first place; it is characterized by vegeto-nervous and neuropsychic disorders.

In females climacteric occurs between 45-55 years of age. A climacteric which appears before the age of 40 is called premature.

Laboratory findings

There is relative hyperoestrogenaemia in the first period of the climacteric.

When the menopause begins there is a high content of gonadotrophic hormones in the blood and gradual transition to hypoestrogenism. There are low levels of oestrogens in the blood, the level of the gonadotrophins in high.

In climacteric neurosis the blood noradrenaline level is often elevated.

Treatment

From 10 to 50% of patients with abnormal climacteric require treatment. The principal therapeutic method is medication with neuroleptics of the phenothiazine series:

- 1. Phrenolon, etaperazine,
- 2. Reserpine,
- 3. Small doses of barbiturates, progesterone or its synthetic analoques (oxyprogesterone capronate) are prescribed if menstruation continues.

There are the new group of agents: climen, climadenon. Sometimes oestrogen preparations are prescribed under the control of the colpocytogram.

There is usually applied combined treatment with oestrogens and androgens (1: 50).

Parlodel (Bromergone, Bromcriptine) 2,5 mg tablet is prescribed under control of prolactin level.

Stein-Leventhal's Syndrome (sclerotic disease of the ovaries, hyperandrogenic dysfunction of the ovaries)

Treatment

Till recently, ovarian wedge resection was considered to be the radical method of treatment, now there are agents which suppress the cystic degeneration of the ovaries.

- 1. Parlodel with modulatory action to gonadotrophic hormones;
- 2. Diane-35 - combination of oestrogens and progestines.

Hormonally active tumours of the ovaries:

- Granulosa-cell tumour of the ovaries (from the granuloza of the follicles).

COURSE OF LECTURES IN CLINICAL ENDOCRINOLOGY
Lecture 18

- Thecoma - theca cell tumour from the cortical stroma theca of the ovaries.

They may have production of the oestrogen (feminizing effect) or androgen (virilizing effect).

Arrhenoblastoma - is a tumour arising from male elements of a female gonad.

Provokes defeminization and then virilization of the female organism.

Treatment. Surgical removal of the tumour followed by radiation therapy is the only method of treatment in malignant growth.

18.2 Diseases of the Male Gonads.

Brief anatomo-physiological data

The testes are a paired glandular organ situated in the scrotum. A testis is 3-5 cm long and 2-3 cm wide and weighs 15-30 g.

The testes are covered by three coats:

- the outer serous coat;
- the tunica albuginea and
- the vascular coat directly covering the testicular parenchyma.

Connective - tissue septa arising radially from the tunica albuginea separate the testicular parenchyma into numerous lobuli. Each lobulus contains convoluted and straight seminiferous tubules.

They are continous with larger efferent tubules which merge developing into a vas deferens draining into the urethra.

The convoluted seminiferous tubules consist of semenproducing epithelium and Sertoli's cells rich in RNA and enzymes. They provide the spermatogenic cells with nutrition.

The spermatogenic cells undergo a series of changes and transform into spermatozoa. Interstitial Leydig cells are found in the interstitial tissue between the tubules. The testes are supplied with blood by the internal spermatic arteries which are branches of the abdominal aorta.

The testes are innervated by fibers of the sympathetic nerves. Androgens are produced in the Leydig cells (testosterone, androstanedione and dehydroepiandrosterone).

Testosterone is a male sex hormone, all the other androgens are the products of its metabolism (androstanedione, dehydroepiandrosterone, androsterone, etiocholanolone). Under the effect of testosterone

- the external genitals form and grow;
- the secondary sex characters develop;
- the prostate and the seminal vesicles grow and develop;
- the skeletal and muscular systems form;
- protein anabolism increases;
- the growth zones in the bones close;
- testosterone determines libido.

Testosterone is mainly inactivated in the liver where it is converted into metabolites, which are excreted in the urine as 17-CS. The function of the testis is controlled by the hypothalamo-hypophyseal system. Maturation of the spermatozoa occurs under the effect of the follicle-stimulating hormone (FSH), while the incretion of androgens takes place under the effect of the hormone which stimulates the interstitial cells (ICSH), which in females is called the luteinizing hormone.

Regulation of the gonadal function by the gonadotrophic hormones is accomplished according to the feedback principle.

Hypofunction of the male sexual glands primary hypogonadism

Primary hypogonadism is a syndrome caused by the direct effect of the pathological process on the testicular parenchyma.

Aetiology

Primary hypogonadism may be congenital or acquired. The congenital causes of disturbed testicular function are seminiferous tubule dysgenesis (Klinefelter's syndrome), dysgenesis or aplasia of the testes and aplasia of the embryonal tissue.

Acquired disorders of the function of the testes occur as consequences of their injury, surgical castration, tuberculosis, complications after orchitis due to acute infections (mumps), syphilis, gonorrhea, the effect of ionizing radiation.

Pathogenesis

Deficient production of androgens by the testes underlies the pathogenesis of primary hypogonadism. This results in deficient development of the sexual organs, weak development of sex characters, retarded growth of the skeleton (insufficient anabolic effects of androgens on the bone matrix).

Pathology

Histological examination of bioptate testicular tissue reveals hyaline degeneration of the seminiferous tubules, growth of connective tissue between them and the absence of spermatogenesis. The prostate is atrophied.

Clinical picture

The clinical picture of the disease depends on the age at which the injury to the testes occurred. In congenital deficient development of the testes, or their injury before puberty, eunuchoidism develops. It is manifested clinically by tall growth with disproportional long limbs, obesity with deposition of fat according to the feminine type and gynaecomastia are frequent occurrences.

The muscles are weakly developed. The testes are flabby to the touch. The secondary sex characters are weakly pronounced (poor growth of hair on the pubis, frequent absence of hair on face and body). Libido is diminished or absent. The patients are sterile.

There is no skeletal disproportion in diseases developing in postpubertal period, because of timely closure of epiphyseal zones of growth. Underdevelopment of the genitals is less sharp.

Libido is often preserved.

Demasculinization is noted: lesser growth of hair, diminished muscular strength, progressive adiposity of the feminine type, weakened potency and even impotence. Patients are sterile because of azoospermia.

Laboratory data

The blood testosterone level is reduced whereas the level of the gonadotrophic hormones in the urine is considerably increased while that of testosterone and 17-CS is reduced.

X-ray diagnosis

In congenital underdevelopment of or injury to the testes before puberty, radiographs of the hand and wrist show delayed bone development, which testifies to delayed maturation of the skeleton.

Osteoporosis is often seen in the bones of the wrist joint and the spine. Craniography often demonstrates hyperpneumatization of the sphenoidal sinus, a small sella turcica with a straightened dorsum ("juvenilization").

Prostatography reveals drastically reduced prostate and a change of its shape.

Diagnosis and differential diagnosis

The diagnosis of primary hypogonadism is made on the bases of the medical history, characteristic clinical picture (eunuchoidism,

underdevelopment of the testes, penis and secondary sex characters) and the findings of laboratory tests.

Primary hypogonadism is differentiated from secondary hypogonadism. Secondary hypogonadism is confirmed by the medical history (the development of hypogonadism following diseases of the hypothalamo-hypophyseal system, tumour of the hypophysis, diabetes mellitus, hypothyroidism), demonstration of abnormality of the sella turcica on radiographs of the skull (its enlargement in cases of a tumour or a small size in hypophyseal nanism), reduced excretion of gonadotrophic hormones in the urine, and other signs.

Prognosis

The life prognosis is favourable. The prognosis with regard to full recovery is poor.

Treatment

Substitution therapy with preparations of male sex hormones is conducted.

Intramuscular injection of 1 ml of 5% testosterone propionate oil solution once a week or 1 ml of a 10% testoenatum oil solution once in 15 days or 1 ml of sustanon-250 once a month is prescribed. The last named preparation consists of 30 mg of testosterone propionate, 60 mg of testosterone-phenyl-propionate, 60 mg of testosterone isocapronate and 100 mg of testosterone decanoate. Methyltestosterone is given sublingually in a daily dose of 30-10 mg.

Secondary hypogonadism

Secondary hypogonadism is a syndrome which usually develops as a result of hypothalamo-hypophyseal insufficiency which leads do diminished production of gonadotrophic hormones and subsequent decreased incretion of androgens.

Aetiology

Among the causes of secondary hypogonadism are traumatic injury to the hypophysis or its tumour, genetic nanism, diseases causing hormonal dysbalance (hypothyroidism, diabetes mellitus and others), severe somatic disease.

Pathogenesis

Insuficient production of gonadotrophic hormones and subsequent reduced androgen incretion underlie the pathogenesis of secondary hypogonadism.

Pathology

In the typical form of hypogonadism the size, histological structure and consistency of the testes are the same as before puberty.

Non-differentiated germinal epithelium with early spermatogonia is revealed histologically in the seminiferous tubules.

Sertoli's and Leydig cells do not develop.

In partial (incomplete) hypogonadism the germinal epithelium of the seminiferous tubules differentiates early, but the interstitial tissue is weakly developed.

Clinical picture

The clinical picture is discussed in the section "Primary Hypogonadism".

Laboratory findings

The level of gonadotrophic hormones and testosterone in blood is reduced. The excretion of gonadotrophic hormones, testosterone and 17-CS in the urine is diminished.

Diagnostic tests

The chorionic gonadotrophin test is made to appraise the functional condition of the testes. It is based on stimulating androgen-producing Leydig cells of the seminiferous tubules by chorionic gonadotrophin.

Chorionic gonadotrophin is injected intramuscularly in a daily dose of 1500U for five days after which 17-CS excretion in the urine is determined. As distinct from primary hypogonadism, in secondary hypogonadism the excretion of 17-CS in the urine increases.

X-ray diagnosis

In hypogonadism of central genesis, craniography often demonstrates tumours of the hypothalamo-hypophyseal area. The X-ray signs of secondary hypogonadism which develops in the prepubertal period are the same as in primary hypogonadism.

Diagnosis and differential diagnosis

The diagnosis of secondary hypogonadism is based on the characteristic clinical picture and laboratory findings. The differential diagnosis is discussed in the section "Primary Hypogonadism".

Prognosis

The life prognosis is determined by the principal disease.

Treatment

Chorionic gonadotrophin (resembling Interstitial Cells Stimulating Hormone, ICSH, in action), is prescribed intramuscularly in doses of 1500U given two or three times a week for six to eight weeks.

The treatment is repeated at intervals of one-two months. If no effect is produced after six or eight therapeutic courses, substitution therapy is produced after six or eight therapeutic courses, substitution therapy with preparations of male sex hormones is prescribed.

Serum gonadotrophin (resembling FSH in action) in combination with preparations of male sex hormones may be prescribed.

Lecture 19. Congenital Disorders of Sex Differentiation

19.1 General Information About Gonadal Dysgenesis.

The formation of the sex is determined by the set of sex chromosomes in the fertilized ovum (zygote). Each gamete (ovum and spermatozoid) contains 22 somatic chromosomes (autosomes) and one sex chromosome.

The X-chromosome is present in the ovum whereas the Y-chromosome is found in the spermatozoid. A zygote contains 46 chromosomes (22 pairs of autosomes and two sex chromosomes). The presence of XX-chromosomes in the zygote determines the development of a female organism, whereas the presence of XY-chromosomes determines the development of a male organism. With further division of cells containing XX-chromosomes, one of these chromosomes is inactivated. The inactivated X-chromosome is situated on the periphery of the cell nucleus and is called sex chromatin (Barr body). The sex chromatin is demonstrated (is positive) only if no less than two X-chromosomes are present in the karyotype. The sex chromatin may therefore be positive only in females. Examination of 100 cell nuclei in healthy females reveals 20 to 80 per cent of cells containing the sex chromatin; in healthy males there are either none or only up to five per cent of such cells.

The sex chromatin makes it possible to reveal a discrepancy between the genetic sex (genotype) of the individual and its external appearance (phenotype) which occurs in anomalies of sex development.

Various anomalies of sex development may occur either as a consequence of disturbed division of chromosomes during the process of meiosis (the formation of sex cells) or in the early stages of mitotic division of the zygote. The chromosome anomalies are manifested in

the altered shape of the chromosomes and a decrease or increase in their number. For instance, the Shereshevsky - Turner syndrome develops in karyotype 45,X; in karyotype 47, XXY - the Klinefelter syndrome.

In some cases disturbed sex differentiation results from injury to the gene composition of the sex chromosomes. The shape and number of sex chromosomes in the karyotype may be normal in such cases.

Mosaicism may sometimes be the cause of various sex anomalies. It occurs as the results of unequal division (or loss) of sex chromosomes during the first and subsequent divisions of the zygote. As a result, one part of the cells have one set of sex chromosomes, while the other has a different set (mosaicism). Mosaicism in females may be represented as 45, X / 47, XXX whereas in males - as 45,X /47, XXY. With the loss of the X chromosome, mosaicism in females will be 45,X/46 XX whereas that in males 45, X/46 XY.

19.2. Shereshevsky - Turner syndrome.

The Shereshevsky-Turner syndrome (gonadal dysgenesis) is caused by anomaly of the sex chromosomes as consequence of which gonadal development in the early embryonal period is sharply disturbed.

The syndrome is relatively rare (one case per 3000 girls that are born).

History. The syndrome was first described by Shereshevsky in 1925 and much later by Turner (1938).

Aetiology. The non-separation of the sex chromosomes during meiosis in the parents.

Pathogenesis

Anomaly of the sex chromosomes underlies the disease, which, in turn, leads to congenital anomaly of sex differentiation and often to various somatic anomalies. Instead of the XX sex chromosomes inherent in a

female organism, there is usually only one X-chromosome. This occurs due to the loss of the second sex chromosome in the process of meiosis. As a result, an incomplete set of chromosomes (karyotype 45,X) occurs.

In this disease, however, various mosaic variants may be encountered: 45,X/46,XX; 45,X/46XY; 45,X/47,XX and others. Congenital absence of the gonads in the pubertal period causes hypogonadism. The concomitant characteristic symptoms (retarded growth, congenital heart diseases, development anomalies of the kidneys), depend on the gene pathology of the autosomes.

Pathology

The gonads are absent and are replaced by connective tissue strands. The uterus is hypoplastic. Various congenital defects of the viscera are found (double ureters, occulusion of the renal arteries, coarctation of the aorta).

Clinical picture

The patients are of short stature, their height usually not exceeding 150 cm; retarded growth is proportional. Retardation of growth usually begins in the first years of childhood, but becomes more marked during puberty. The lower jaw is often shortened. The ears are situated lower than usual. The hairline at the nape of the neck is low. The neck is usually short. Skin folds often pass from the head to the shoulders giving the patient a sphynx - like appearance (webbed neck). The chest is broad. Anomalies of the skeleton are a common occurence: a depression in the region of the sternum, a shortening of the fourth and fifth metacarpal bones, a moderate redardation of bone age from the actual age (usually of no more than three years), a high hard palate, moderate osteoporosis.

There are frequent development anomalies of the viscera (ventricular septal defect, patent ductus arterious, stenosis of the pulmonary artery or of the isthmus of the aorta).

Arterial hypertension often develops as a consequence of occlusion of the renal arteries.

Developmental anomalies of the kidneys (double pelvis, hypoplastic or horse - shoe kidney), occur in some cases. Congenital defects of the organ of vision (ptosis, daltonism, strabismus) are frequently encountered. The secondary sex characters are either absent or weakly pronounced (sparse growth of hair on the pubis and in the axillae), absence of the mammary glands, amenorrhoea. Hypoplasia of the large and small pudendal lips and uterus and a narrow vagina are encountered. The ovaries cannot be defined.

In patients with germs of the testicular tissue (chromosome complex 45,X/46, XY) features of virilization develop (hypertrophy of the clitoris, hirsutism, hypertrichosis.). The intellect in sometimes impaired.

Laboratory findings

The level of the gonadotrophic hormones in the blood is increased while the level of oestrogens is drastically reduced, sometimes the level of the growth hormone is slightly elevated. The content of thyroid hormones (T3, T4) is within normal levels. There is a high excretion of gonadotrophins and low excretion of oestrogens in the urine. The excretion of 17-CS and 17-OCS in the urine is at minimum normal level.

Diagnostic tests

The chromosome complex and sex chromatin are investigated to determine the genetic sex. Study of the chromosome complex usually reveals the 45,X; karyotype. Mosaicism may be expressed as 45,X/46, XX; 45,X/46, XY; 45,X/47,XXX.

The sex chromatin is negative in a chromosomal set of 45,X or 45,X/46, XY; in a 45,X/46,XX clone it is found in a small amount. The sex

chromatin is usually studied in the epithelial cells of the oral or vaginal mucosa.

X-ray diagnosis

Craniography usually demonstrates a sella turcica of a normal size, less frequently it is smaller; hyperpneumatization of the sphenoid sinus is a frequent finding. X-ray study of other bones reveals hypertrophic osteoporosis with clearly outlined cyst-like defects in the bone substance. Pathological synostosis is encountered in the metaepiphyseal zones of the skeleton. Solitary or multiple developmental anomalies of the bones, most frequently in the wrist joints, the bones of the hands and the knee joints, and in the spine (relative shortening of the finger phalanges, Madelung-type deformity of the wrist joint), are also found. Radiographs of the hands and wrist joints reveal that the bone age does not coincide with the patient's actual age (maturation of the skeleton is usually delayed by three to three and a half years). The pneumopelvigram and US shows drastic atrophy of the uterus and ovaries.

Diagnosis and differential diagnosis

The diagnosis of the Shereshevsky-Turner syndrome is based on the characteristic clinical picture and the findings of diagnostic tests. The differential diagnosis of the disease is discussed in the lecture on hypophyseal nanism.

Prognosis

Early detection and timely and regular substitution therapy with anabolic steroids and preparations of female sex hormones, makes it possible to achieve an increase in height and sufficient feminization. The prognosis with regard to full recovery is unfavourable.

Treatment

The treatment of this syndrome is discussed in the lecture "Diseases of the Female Gonads".

19.3. Klinefelter's syndrome.

Klinefelter's syndrome (dysgenesis of the seminiferous tubules) is a disease caused by anomaly of the sex chromosomes, the characteristic symptom of which is disturbed spermatogenesis. The incidence of the disease among individuals with the male phenotype is 1:1100, among sterile males 1:9.

History. The syndrome was first described by Klinefelter in 1942.

Aetiology. The cause of the disease is unknown.

Pathogenesis. The disease is due to chromosomes anomaly. Patients usually have one extra X-chromosome, less frequently several X-chromosomes (karyotype 47,XXY; 48, XXXY; 49, XXXXY). In some cases Y-chromosome polysomia with X-chromosome monosomia is revealed as well as X-chromosome and Y-chromosome polysomia.

Patients with mosaicism may have different sex chromosomes in different tissues. As a result, the disease may be revealed in negative sex chromatin. Mosaicism is most frequently represented by 46,XY/47, XXY. The formation of the testicles and the male genitals in the embryonal period is normal because of the presence of the Y-chromosome in the karyotype.

In the pubertal period, however, degenerative changes occur in the testis with impairment of its normal development and function. Insufficient incretion of testosterone by the testes leads to a sharp increase in gonadotrophic hormones, the formation of eunuchoid proportions of the body, weak development of the secondary sex characters.

Pathology. Histological examination of bioptate testicular material in the postpubertal period shows the absence of spermatogenesis and sclerosis hyalinization in the tunica propria of the seminiferous tubules. There is drastic deneration of Sertoli's cells and hyperplasia of Leydig sells. Until puberty, the histological structure of the testes is normal.

Clinical picture

Patients complain of underdeveloped genitals, enlarged mammary glands, absence of hair growth on the face, sterility.

The disease is manifested during puberty. Patients with the classical form of Klinefelter's syndrome are tall, with eunuchoid body proportions: the limbs are disproportionately long in relation to the trunk, there is female - type deposition of fat, a wide pelvis, narrow shoulders, and a typical true gynaecomastia.

The secondary sex characters are weakly pronounced: sparse growth of hair on the face and in the axillae; the hair on the pubis grows by the feminine type.

The penis is usually normal in size. The testes are small, flabby, sometimes firm. Libido is often preserved, but patients are sterile because of azoospermia. The intellect is usually impaired. It has been established that mental retardation grows with the increase in the number of X-chromosomes.

In karyotype 49,XXXXY there is usually severe mental retardation and, in many cases, cryptorchism.

Abnormalities in the organ of vision, are sometimes encountered: bilateral epicanthus, punctate opacification of the lens capsule, coloboma of the iris and the choroid.

Laboratory findings

There is azoospermia. The level of gonadotrophic hormones and the growth hormone in the blood is increased, while the level of testosterone is reduced. Glucose tolerance is often reduced and diabetes mellitus may even develop.

The excretion of testosterone in the urine is reduced, while that of oestrogens may be increased.

The excretion of total 17-CS and their separate fractions (androsterone, etiocholanolone) in the urine is mildly diminished.

Diagnostic tests

The sex chromatin and chromosome complex are studied to determine the genetic sex. The sex chromatin is usually positive in this syndrome. Study of the chromosome complex usually reveals karyotype 47,XXY. In a disease caused by Y-chromosome polysomia there may be karyotype 47,XYY; 48,XYYY with negative sex chromatin. In mosaicism sex chromatin may be negative or positive.

X-ray diagnosis

Craniography demonstrates the sella turcica of usual shape and size. Hyperpneumatization of the sphenoid sinus and retarted maturation of the skeleton without disorders in bone structure are frequent findings.

Diagnosis and differential diagnosis

It is difficult to make the diagnosis of Klinefelter's syndrome before puberty. During puberty attention is drawn to gynaecomastia, delayed development of the male secondary sex characters and azoospermia. The results of studying the sex chromatin and the chromosome complex are decisive in making the diagnosis.

Klinefelter's syndrome is differentiated from other forms of hypogonadism. As distinct from Klinefelter's syndrome, acquired hypogonadism is marked by karyotype 46,XY and absence of the sex chromatin. In some cases gynaecomastia in Klinefelter's syndrome has to be differentiated from pubertal gynaecomastia in which physical and sexual development is normal, there is karyotype 46,XY and no sex chromatin.

Prognosis

With regular long - term substitution therapy muscular strength increases and the patient's general condition improves. With regard to full recovery, however, the prognosis is unfavourable. The patients remain sterile. The growth of hair on the face does not ordinarily increase. The working capacity depends on the degree of mental retardation.

Treatment

Substitution therapy with preparations of the male sex hormone or their synthetic analogs is applied (see the lecture on hypogonadism in the males). It is usually poorly effective because of diminished body sensitivity to androgens.

Lecture 20. Obesity

Obesity is a disease of the organism characterized by excessive accumulation of subcutaneous fat and other tissues as the result of disturbed metabolism.

It may occur as an independent disease (ordinary or true alimentary obesity, constitutionally hereditary obesity) or as a symptom of diseases mostly caused by disorders of endocrine function or affection of the central nervous system. Alimentary obesity is very common. Obesity incidence reaches 50 per cent among females, 30 per cent among males and 10 per cent among children. The average body weight usually decreases after the age of 70.

History. The problems of diet therapy are first discussed by Hippocrates in a special book on dietetics. The works of Diocles (4th century B.C.), Ibn Sina (Avicenna) (more than one thousand years ago), Galen, Falt, Noorden and others deal with obesity and the methods of its treatment.

Aetiology

There is the conception that the deficiency of the hypothalamic centres regulating appetite are of primary and principal importance in the development of alimentary obesity. Among the factors contributing to the development of alimentary obesity are excessive intake of food, particulary that which is rich in carbohydrates and fats, abuse of alcoholic beverages, insufficient physical activity, age above 40 and hereditary predisposition to obesity.

Symptomatic obesity is usually a consequence of endocrine diseases (adipose genital dystrophy, Cushing's symptome, hypothyroidism, hyperinsulinism, hypogonadism), or pathological processes in the central nervous system (brain injury, encephalitis, tumours of the floor of the third cerebral ventricle).

Pathogenesis

The principal pathogenetic role in the development of alimentary obesity belongs to functional disorders of the cerebral cortex and the hypothalamus and first of all of the nerve structures in the posterior part of the hypothalamus, the ventromedial and ventrolateral nuclei comprising the feeding centre.

Affection of the ventromedial nuclei (satiety centres) leads to stimulation of the ventrolateral nuclei (appetite centres). The increased supply of food (carbohydrates, fats) due to stimulation of the feeding centre in insufficient physical activity leads to the accumulation of fat in the fat depots.

Diminished lipolysis (the splitting of fat) because of the predominance of the tonus of the parasympathetic part of the vegetative nervous system over that of the sympathetic part may be very significant in the development of obesity. It leads to stimulation of insulin production by the cells of the Langerhans' islets and subsequent obesity.

Endocrine factors play a mild role in the development of alimentary obesity, but much significance is attached to them in the development of symptomatic obesity. As the result of insufficient production of the fat mobilizing hormone (ACTH, TSH, STH, thyroxine, triiodthyronine, adrenaline, noradrenaline and glucagon) lipolysis diminishes. This is the cause of the insufficient use of the fat depot as an energy source.

Diminished production of sex hormones is conductive to the development of obesity, the symptomatic type first of all, which leads to shifts in pentose cycle of glucose metabolism and an increase in the production of glucocorticoids which intensify glycogen deposition in the liver and thus inhibit lipolysis. Excessive accumulation of fat often leads to affection of the cardiovascular system and respiratory organs with the possible development of cardiac or cardiopulmonary insufficiency, disturbed function of the gastro-intestinal tract, liver etc.

Pathology

In alimentary obesity, fat is accumulated in the skin, subcutaneous fat, mesentery, omentum, pararenal and mediastinal tissue, epicardium, myocardium, liver and pancreas. The liver is enlarged because of fatty infiltration and congestion. The morphological changes in symptomatic obesity depend on the principal disease.

Classification. There are distinguished the following forms of obesity.

General obesity:

1. Alimentary forms:

a/. habitual hyperalimentary;

b/. dysregulated:

c/. constitutionally hereditary;

d/. mixed.

2. Endocrine forms:

a/. hypothyroid;

b/. hypogenital;

c/. adrenal (adrenocortical);

d/. pituitary;

e/. mixed (polyendocrine).

3. Cerebral (nervous) forms:

A. Following to the type of local disorders:

a/. cortical (psychosomatic);

b/. hypothalamic (diffuse);

c/. hypothalamic-hypophyseal (Pekhkranz - Babinsky - Froehlich syndrome);

B. According to the aetiological factors:

a/. post-traumatic;

b/. post-infection.

The following grades of ordinary adiposity are distinguished:

Grade 1 (mild), body weight exceeds the ' ideal' weight for the given person by 10-29 per cent;

Grade 2 (moderate), by 30-49 per cent;

Grade 3 (severe), by 50-99 per cent;

Grade 4, body weight exceeds the 'ideal' weight by 100 per cent and more.

Depending on the stage:

ordinary adiposity may be stable or progressive.

Complicated and non-complicated cases of ordinary obesity are recognized.

There is the classification of the obesity depending on the Body Mass Index (BMI).

Classification of obesity

BMI (Body Mass Index)	Obesity class	Type
<18,5		Underweight
18,5 - 24,9		Normal
25,0 - 29,9*		Overweight
30,0 - 34,9*	I	Obese
35,0 - 39,9	II	Obese
≥40*	III	Extreme obesity

*≥ 40 inches waist adds risk for cardiovascular disease.

Clinical picture

Patients with ordinary (true) obesity complain of marked gain body weight, dyspnoea, pain in the region of the heart, excessive sweating, lassitude, apathy, somnolence, fatigability, dizziness, headache, increased appetite, tendency to constipation, etc.

The fat in these patients is usually deposited uniformly but with the advancement of the disease fat is mainly accumulated on the abdomen, chest, neck, back and the pelvic circle.

The skin is moist (hyperhydrosis), often pruffy and with hyperfunctioning sebaceous glands. Eczema, pyoderma and furunculosis are frequent occurrences.

Umbilical and inguinal hernias form.

The cardiovascular system is marked by a tendency towards bradycardia. The apex beat is sometimes weak or absent. The heart boundaries are distended (transverse position), the cardiac sounds are muffled and arterial hypertension is often found. Systemic atherosclerosis consequent upon disturbances in lipid metabolism frequently develops. As the result of atherosclerosis of the cardiac coronary arteries, myocardial circulation is impaired, which leads to the development of ischemic heart disease (angina pectoris, cardiosclerosis, myocardial infaction). Circulatory insufficiency (dyspnoea, cyanosis, oedema, etc) is encountered in many patients. The incidence of cardiovascular disorders in obese patients is about twice more than in persons with normal body weight.

Respiratory disorders are manifested by respiratorry insufficiency, which is caused by the high position of the diaphragm because of fat accumulation in the omentum.

The vital, respiratory and reserve lung capacity are diminished, which leads to oxygen lack in the organism.

Dyspnoea develops during small physical exertion and later also at rest; cardiac and pulmonary insufficiency often develops.

There is a tendency towards bronchitis and pneumonia, the development of which is promoted by stasis in the pulmonary circulation and shallow breathing. The alimentary organs are also involved in the pathological process. The stomach is dilated and displaced downward (gastroptosis), gastritis occurs sometimes. The liver is usually enlarged because of its fatty infiltration on the one hand, and stasis on the other.

Cholecystitis and cholangitis, cholelithiasis and acute and chronic pancreatitis are frequent occurrences.

Impaired function of the urinary system is manifested by pyelitis, urethritis, cystitis and urolithiasis. The genital system also suffers; the menstrual cycle in females is often disturbed, infertility develops and spontaneus abortion occurs. In males libido and potency are diminished.

The changes in the nervous system are displayed by somnolence, insomnia, headache and poor memory. Persistent myalgia, neuralgia and neuritis may occur. Some of these patients develop the Pickwick Syndrome due to disorders of lung ventilation. The syndrome is characterized by drastic obesity combined with hypersomnia, difficult breathing, particularly during sleep (loud snoring) and often cyanosis of the mucous membranes and skin.

Laboratory findings

The blood is often marked by an increased content of cholesterol, beta-lipoproteins and free fatty acids.

Carbohydrate metabolism is often impaired and diabetes mellitus may even develop.

An elevated level of uric acid in the blood is often found as a manifestation of disturbed purine metabolism with the development of gout.

Urine analysis often shows proteinuria and in some cases microhaematuria as a consequence of stasis in the kidneys. The basal metabolism and the iodine cumulative capacity of the thyroid are often diminished.

Diagnosis and differential diagnosis

The diagnosis of ordinary obesity (independent disease) is based on the medical history (regular overeating, particularly abuse of foodstuffs rich in carbohydrates and fats, a sedentary way of life, hereditary predisposition to adiposity) and the findings of objective examination (uniform distribution of fat over the entire body, absence of symptoms of primary endocrine insufficiency).

Alimentary obesity is differentiated from obesity in Itsenko-Cushing's disease and glucosteroma, adiposogenital dystrophy, hypothyroidism, hyperinsulinism, primary hypogonadism and disease of the central nervous system.

As distinct from ordinary obesity, Itsenko-Cushing's disease and glucosteroma are marked by selective accumulation of fat on the face, neck, chest, abdomen combined with relatively thin limbs. Obesity of adrenal origin is also characterized by a crimson-marble skin pattern, dystrophic processes in the skin and muscles, hirsutism, the corresponding laboratory data (high values of the hormonal background) and the findings of X-ray, CT, MRI examination (hyperplasia of both adrenals or tumour of one of them).

Feminine - type accumulation of fat (on the chest, abdomen, pubis, hips and pelvis), combined with drastic hypoplasia of the genitals, is evidence in favour of adiposogenital dystrophy. In obesity due to hypothyroidism, the uniform accumulation of fat is combined with symptoms of hypothyroidism (somnolence, increased sensitivity to cold, dry and puffy skin, bradycardia, low values of blood level of thyroid hormones and higher level of TSH). Obesity in hyperinsulinism is

characterized by uniform accumulation of fat and by attacks of hypoglycaemia (lassitude, excessive sweating, feeling of hunger, trembling, the low blood sugar content).

Hypogenital obesity is characterized by feminine - type accumulation of fat, eunuchoid proportions of the skeleton (tall height and long limbs with a relatively short trunk) in combination with underdeveloped genitals and secondary sex characters.

In hypothalamic obesity there is a rapid gain of body weight within a few months and the fat is accumulated according to the feminine - type. This form of obesity is characterized by bulimia and polydipsia and a combination of obesity with symptoms of an organic lesion of the central nervous system. The organic neurological symptoms occur soon after a cranio-cerebral trauma or infection, mostly neuroinfection (influenza, meningitis, encephalitis).

Prognosis

With early and regularly applied treatment the prognosis is favourable.

Cardiovascular disease (myocardial infarction, cerebral stroke) and pneumonia are the main causes of death. In grades I and II obesity the patients are usually capable of working. Patients with drastic obesity (excess of bogy weight above 50 per cent) are often qualified as group III invalids, and when cardiovascular complications develop sometimes as group II invalids.

Prevention

Rational diet with restriction of foodstuffs rich in carbohydrates and fats, and a simultaneous increase of protein-rich foods is essential for preventing obesity. Regular physical exercises (morning exercises, sports, long walks) are effective. They are chosen with due account for the patient's age and condition of the cardiovascular and other body systems.

Preventive measures are primarily essential for individuals with hereditary predisposition to obesity and those over 40 years of age, particularly if they lead a sedentary life.

Treatment

The principal method of obesity management is diet which must be observed throughout life.

Diet therapy is conducted under the control of body weight measured no less than once in one or two weeks. The diet must be protein - vegetable. It is calculated with due account for the patient's height, body weight, constitution, character of work, age and sex.

The caloric value is calculated per 1 kg of the theoretical (ideal) body weight of the patient.

The caloric content of food is restricted by one fifth (8.400 KJ) in grade I obesity and by two fifths (5880 - 6300 KJ) in grade II obesity.

Under inpatient conditions the food caloric content may be limited to three fifths of the normal value (4200 - 5040 KJ).

In conformity with the recommendation given by the Dietary Institution (Russian AMS) persons with obesity employed in mental or light physical work are prescribed diet N1 (138,6KJ) per 1 kg of the theoretical body weight: 1,5 g of proteins; 0,9 g of fats; and 4,5 g of carbohydrates per 1 kg of the theoretical body weight).

Under inpatient conditions they are given diet N2 (88,2KJ per 1 kg of the theoretical body weight: 1,5 g of proteins, 0,9 g of fats and 1,5 g of carbohydrates). The daily amount of fluid is restricted to 1 L and daily amount of sodium chloride to 3-5 g.

To reduce the feeling of hunger food is given in small portions but often (at least four times a day).

Days of a restricted diet are prescribed (one or three times a week), when the patient is a given a very low - caloric diet.

Heavy physical work and long walks (longer than 2-3 km) are contraindicated on such days. The restricted diet may consist only of carbohydrates (apples, 1,5 kg daily; or 1 kg of barries daily; or 2 kg of cucumbers daily); proteins (400-600g of cottage cheese poor in fats; 60 g of sour-cream, 100 g of milk; 400-600 of lean boiled meat with 120 g of green peas and 200 g of cabbage).

A hunger diet may be prescribed instead (1,5-2,0 L of alkaline mineral water such as Borjomi, N4 or 20 Essentuki, Smirnovskaya or Slavyanskaya mineral water). If there are no contraindications it is recomendended dosaged starving diet under in-patient conditions for 25-30 days (sometimes for 35-40 days). To avoid avitaminosis, two drops or two pills of vitamins A and D are given daily.

Anorexigenic agents (teronac, phepranon, desopimon, mirapront and other) are prescribed together with the diet in the absence of pregnancy, ischaemic heart disease, diffuse toxic goiter or hypertensive crises.

These agents possess a sympathomimetic effect but do not stimulate the central nervous system considerably.

They reduce an excessive appetite by inhibiting the activity of the hypothalamic feeding center, intensify the mobilisation of fat from the fat depots and reduce the blood lipid and cholesterol level.

Anorexigenic agents are given twice a day in a dose of 0,025 g 30 minutes before breakfast and dinner under control of the pulse and arterial pressure; mirapront is prescribed in a dose of 0,015 g taken once a day after breakfast.

Whenever necessary, the dosage of the drugs may be increased by 50 to 100 per cent. They are given in courses of 4-6 weeks, on the average, at intervals of the same duration.

In some cases obesity is treated with adiposine, which is a protein preparation possessing a fat-mobilizing effect and is produced from the anterior pituitary of slaughtered cattle.

Adiposine is injected intramuscularly in a dose of 50 mg twice a day for 20 days.

It is contraindicated in grade II-III circulatory insufficiency, cardiac fibrillation, atrioventricular block, marked arterial hypertension, allergic reactions and severe diabetes mellitus.

Methionine and vitamins of the B complex are prescribed to improve lipid metabolism.

Thyroidine, L-thyroxine and triiodthyronine hydrochloride are sometimes prescribed under control of the pulse and arterial pressure to intensify metabolic processes in the body (especially in thyroid hypofunction).

Thyroidine is prescribed in a dose of 0,03-0,05 g two or three times a day for 4-6 weeks with the course repeated no earlier than 6 to 8 weeks, or in a dose of 0,1-0,2 g two or three times a day in courses of 10-15 days.

Triiodothyronine hydrochloride is given in a dose of 5-20 microg once or twice a day. L-thyroxine is given in a dose of 25-100 microg once or twice a day.

In obesity with diminished gonadal activity, males are prescribed preparations of male sex hormones (methyltestosterone, testosterone propionate, sustanon-250, omnadren and others), whereas for females there are recomended oestrogens (folliculin, synestrol) and progesteron; or Diane-35 and other.

Diuretics are used under control of the blood sugar level: dichlothazide (hypothiazide) in a dose of 0,025 g once or twice a day for two or three days a week; diacarb in a dose of 0,25 g once or twice a day 1 or 2 times

a week; furosemid (lasix) in a dose of 0,04 g once in 5-7 days; preparations of potassium such as a 10 per cent potassium acetate solution, one tablespoonful taken four times daily.

Elderly patients with obesity are given antisclerotic agents: diosponin in a dose of 100 microg given twice a day after a meal for 10 days followed by intervals of 4-5 days, the treatment lasting no less than 3-4 months; clofibrate (miscleron) taken in a dose of 50-100 mg three to four times a day; atheroid given by mouth (20 to 50 mg daily) or in injections (50-100 mg daily), and others.

Patients with constipation are recommended purgatives (rhubard, buckthorn, magnesium sulphate, mineral waters such as Batalinskaya).

Therapeutical physical exercises, swimming, long walks, baths and various types of douches (rain, circular, Scotch, Charcot's, etc), carbon dioxide and mineral water baths, rubdowns, local and general massage are indicated.

Treatment usually consists of 15-30 sessions taken daily or every other day. In the absence of contraindications treatment at spa and health resorts (Kislovodsk, Zheleznovodsk, Borjomi, Essentuki, Pyatigorsk and other) is recommended.

In symptomatic obesity the principal disease is treated first of all.

Appendix I

Table 1 Values, names and symbols of the prefixes recommended for use according to **SI**

Coefficient	Prefix	Symbol
10^{-3}	milli	m
10^{-6}	micro	μ
10^{-9}	nano	n
10^{-12}	pico	p
10^{-15}	femto	f
10^{-18}	atto	a
10^{3}	kilo	k
10^{6}	mega	M
10^{9}	giga	G
10^{12}	tera	T
10^{15}	peta	P
10^{18}	exa	E

Table 2 Conversion table for concentrations of main biochemical parameters (from "mg/dl" to "mmol/l")

PARAMETER	UNITS	MULTIPLY-BY	NEW(SI) UNITS
GLUCOSE	mg/dl	0.05549	mmol/l
CREATININE	mg/dl	88.4	μmol/l
CHOLESTEROL	mg/dl	0.0258	mmol/l
TRIGLYCERIDE	mg/dl	0.0113	mmol/l
BILIRUBIN	mg/dl	17.1	μmol/l

Table 3 Conversion table for concentrations of main hormonal parameters

Hormone	Old units	Multiply-by	New(SI) units
Insulin (IRI)	mU/l	7.184	pmol/l
C-peptide	μg/l	330.0	pmol/l
Glucagon	ng/l	0.2869	pmol/l
Somatostatin	ng/l	0.625	pmol/l
STH	μg/l	47.0	pmol/l
ACTH	ng/l	0.222	pmol/l
β-endorphin	ng/l	0.2899	pmol/l
Cortisol	μg/l	2.759	nmol/l
Aldosterone	ng/l	2.774	pmol/l
Prostaglandins (A1+E1)	μg/l	2.969	nmol/l
Prostaglandin F2α	μg/l	2.835	nmol/l

Note: **Mol** = the number of grams of the substance, quantitatively equal to its molecular weight.

Table 4 Conversion table for main nuclear medicine parameters

Parameter	SI name(symbol)	Old name(symbol)	Formula
Energy dose	Gray(Gy)	Rad(rd)	$1rd=10^{-2}$ Gy
Activity of a radioactive substance	Becquerel(Bq)	Curie(Ci)	1Ci=37GBq

Appendix II

Normal values of the basal level of Hormones and in the dynamic of the tests for exploration of the Endocrine function

Hypothalamus

Vasopressin – 2,5 – 8 ng/L/ 1 – 4,5 pmol/L
Dehydration test with loss of 3-5% of the body weight: in the normal test urine density >1010 – 1015; osmolarity of the urine - 400 – 800 mOsm/kg.

Hypophysis

STH (GH) basal – 5-10ng/mL (10-20mIU/L);
- test of the suppression by provocated hyperglycaemia: GH < 1 ng/mL (2mIU/L);
- test of the stimulation with insulin 0,1 U/ kgBM: GH increases to >10 ng/mL (20 mIU/L).

Prolactine < 20 ng/ mL (M- 3,5-10 ng/mL; F- 9-18ng/mL)
TSH basal - 0,5-5,7mU/L
TSH after stimulation by TRH increases with > 5mU/L;
ACTH basal – 3-15 pmol/L; circadian rhythm.
FSH in females depending upon phase of cycle
proliferation – 1-9 U/L;
ovulation – 12-30 U/L;
secretion- 1-9 U/L.
FSH in males - 5-20 IU/L;
LH in females depending upon phase of cycle
proliferation – 1-12 U/L;
ovulation – 12-100 U/L;
secretion- 1-12 U/L.

LH in males - 5-20 IU/L;

Thyroid gland

Ioduria (the inorganic iodine in the urine) >50 µg/1g creatinine/24h;
PBI (Protein Bound Iodine) – 4-8 µg/dL;
Thyroxine (T_4) – 4-11 µg/dL (70-140 nmol/L);
Triiodothyronine (T_3) – 80-220 ng/dL (1,2 – 3 nmol/L);
Free T_4 – 9-22 pmol/L;
Thyroxin binding globulin (TBG) – 7-17 mg/L;
Radioactive Iodine Uptake
by thyroid in percents – 5-10%/ 2 h;
- 10-20%/ 24 h;
Antibody to antithyreoglobulin: (in normals) > 1/20;

Parathyroid glands

Calcitonine < 50 pg/mL / < 27pmol/L;
Parathormone (PTH) < 10-65 pg/mL;
Calcium ionized 4-4,6 mg/dL (1-1,5 mmol/L)
total – 9-10,5 mg/dL (2,2-2,6 mmol/L)
Phosphorus – 2,5-4,5 mg/dL;

Pancreas

Insulin – 5-20 мU/mL;
C - Peptide – 0,5-2 ng/mL
Glucagon – 50-100 pg/mL;
Glycaemia (basal) – 60-100 mg/dL
Oral glucose tolerance test 2 h post load:
normal < 140 mg/dL;
IGT (Impaired Glucose Tolerance): 140-200 mg/dL;
Diabetes mellitus > 200 mg/dL
Glycosylated Haemoglobin (HbA1c) <8%

Adrenals

Cortisol 8 a.m. – 8-24μg/dL;
4 p.m. – 2-15μg/dL;
Dexamethasone suppression test: cortisol < 5 μg/dL;
DHEA – 0,2-20 μg/L;
DHEAS – 0,8-3,4 μg/dL;
Aldosterone < 8 ng/dL;
Adrenaline – 30-95 pg/mL (170-520 pmol/L);
Noradrenaline – 15-475 pg/mL (0,3-2,8 nmol/L);

Gonads

- Oestrogens:
  F – basal 20-60 pg/mL (70-220 pmol/L);
  ovulation (peak) > 200 pg/mL (> 740 pmol/L);
  M - < 50 pg/mL (< 180 pmol/L);
- Progesterone:
  F – secretion phase 10-20 ng/mL (30-64 nmol/L);
  - follicular phase < 2 ng/mL (< 6 nmol/L);
  M - < 2 ng/mL (< 6 nmol/L);

Testosterone

F - < 1 ng/mL (< 3,5 nmol/L);
M - 3-10 ng/mL (10-35 nmol/L).

References

1. Alberti KGMM, Zimmet P, DeFronzo RA. Textbook of Diabetes Mellitus. 2nd ed. Chichester (UK): John Wiley & Sons Ltd; 1997, 1930 P. (ISBN 0-471-93930-7)

2. Balabolkin MI. Endocrinology. 2nd ed. Moscow: Universum Publishing; 1998, 582 P. (ISBN 5-7736-0018-8) (In Russian)

3. Balabolkin MI. Diabetology. Moscow: Meditsina; 2000, 672 P. (ISBN 5-225-04591-X) (In Russian)

4. Baranov VG. Textbook of clinical endocrinology. Sankt Petersburg: Meditsina; 1977, 664 P. (In Russian)

5. Braunwald E, Fauci AS, Kasper DL, Hauser K, Longo DL, Jameson JL. Harrison's manual of medicine. 15th PDA/Book ed. New York (NY): McGraw-Hill; 2003. (ISBN 007143125X)

6. Burch WM. Endocrinology. 3rd ed. Baltimore (MD): Williams & Wilkins; 1994, 216 P. (ISBN 0-683-01131-6)

7. Coculescu M. Endocrinologie clinică. Ed. a III-a. Bucureşti: Ed. Medicală; 1998, 160 P. (ISBN 973-39-0347-7) (In Romanian)

8. Drury PL, Howlett TA. Endocrinology. In: **Kumar P, Clark M (eds). Clinical medicine.** 4th ed. Edinburgh (UK): W.B.Saunders; 1999. 1326 P., p.895-958. (ISBN 0-7020-2458-9)

9. Dumitrache C. Endocrinologie mică enciclopedie. Bucureşti: Editura Naţional; 1998, 480 P. (ISBN 973-9308-84-8) (In Romanian)

10. Dumitru EM. Endocrinologie. Cluj Napoca: Tipografia UMF; 1996, 194 P. (In Romanian)

11. Efimov AS. Diabetic angiopathies. Moscow: Meditsina; 1989, 288 P. (ISBN 5-225-01218-3) (In Russian)

12. Efimov AS, Bodnar PN, Zelinsky BA. Endocrinology. Kiev: Vyshcha Shkola; 1983, 328 P. (In Russian)

13. Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL. Harrison's principles of internal medicine. 14th ed. New York (NY): McGraw-Hill; 1998. (Section Endocrinology and metabolism. In: Romanian Edition. Bucureşti: Teora; 2001, 2842 P., p. 2159-2506, ISBN 973-20-0265-4) (In Romanian)

14. Felig P, Baxter JD, Frohman LA. Endocrinology and metabolism. 3rd ed. New York (NY): McGraw-Hill; 1995, 1940 P. (ISBN 0-07-020448-9)

15. Felig P, Frohman L. Endocrinology and metabolism. 4th ed. New York (NY): McGraw-Hill; 2001, 1562 P. (ISBN 0070220018)

16. Gale EAM, Anderson JV. Diabetes mellitus and other disorders of metabolism. In: **Kumar P, Clark M (eds). Clinical medicine.** 4th ed. Edinburgh (UK): W.B.Saunders; 1999, 1326 P., p.959-1005. (ISBN 0-7020-2458-9)

17. Grossman A. Clinical endocrinology. 2nd ed. London (UK): Blackwell Science; 1997, 1184 P. (ISBN 0-86542-629-5)

18. Hîncu N. Obezitatea şi dislipidemiile în practica medicală. Bucureşti: Editura INFO-Medica; 1998, 244 P. (ISBN 973-98331-9-5) (In Romanian)

19. Hîncu N, Vereşiu IA. Diabetul zaharat. Nutriția. Bolile metabolice. Bucureşti: Editura Național; 1999, 630 P. (ISBN 973-9459-20-X) (In Romanian)

20. Ionescu-Tîrgovişte C. Diabetologie modernă. Bucureşti: Editura Tehnică; 1997, 560 P. (ISBN 973-31-1056-6) (In Romanian)

21. Jubiz W. Endocrinology. A logical approach for clinicians. New York (NY): McGraw-Hill Book Company; 1979, 418 P. (ISBN 0-07-033065-4)

22. Kahn CR. New concepts in the pathogenesis of diabetes mellitus. In: **Schrier RW, Baxter JD, Abboud F, Fauci AS (eds). Advances in internal medicine.** Vol 41. Chicago (IL): Mosby-Year Book, Inc.; 1996, 745 P., p.285-314. (ISBN 0-8151-8314-3)

23. Larsen PR, Kronenberg HM, Melmed S, Polonsky KS. Williams textbook of endocrinology. 10th ed. New York (NY): Wilson Churchill LivingStone; 2002, 1500 P. (ISBN 0721691846)

24. Lavin N. Manual of endocrinology and metabolism. 2nd ed. Boston/ New York (NY): Little, Brown and Company; 1994. (ISBN 0721691846) (Lavin N. Endocrinology. Translated by V.Kandror. Moscow: Praktika; 1999, 1128 P., ISBN 5-89816-018-3) (In Russian) 255

25. Mazzaferri EL. Textbook of endocrinology. 3rd ed. New York (NY): Medical Examination Publishing Company; 1985, 840 P. (ISBN 0-87488-514-0)

26. Potemkin VV. Endocrinology (Translated from Russian by Arthur Aksenov). Moscow: Mir Publishers; 1981, 332 P.

27. Potemkin VV. Endocrinology. 2nd ed. Moscow: Meditsina; 1986, 430 P. (In Russian)

28. Starkova NT. Textbook of clinical endocrinology. Sankt Petersburg: Piter-Press; 1996, 540 P. (ISBN 5-88782-154-X) (In Russian)

29. Williams RH. Textbook of endocrinology. 4th ed. Philadelphia (PA): W.B.Saunders Company; 1968. (Williams RH. Traité d'endocrinologie. Translated by Jean Gontier. Paris: Flammarion Médecine-Sciences; 1972, 1348 P., Editor's No. 9091) (In French)

30. Zbranca E, Mogoş V, Galeşanu C, Vulpoi C. Endocrinologie clinică. Vaslui: Editura Cutia Pandorei; 1997, 240 P. (ISBN 973-98152-4-3) (In Romanian)

Note: References were given according mainly to the "Vancouver style", recommended by the International Committee of Medical Journal Editors (http://www.icmje.org/).

Internet WWW Links

1. American Association of Clinical Endocrinologists
   http://www.aace.com/
2. Bart's Department of Endocrinology - Links
   http://www.mds.qmw.ac.uk/endocrinology/links.htm
3. Doctor's Guide- Global Edition
   http://www.docguide.com/
4. DR. ROSE'S PERIPHERAL BRAIN
   http://faculty.washington.edu/momus/PB/tableofc.htm
5. Editura Teora
   http://www.teora.ro/
6. ENDOCRINE SYSTEM
   http://www.univ-st-etienne.fr/lbti/Mednucl/AtlasEnd/aindex.htm
7. ENDOCRINOLOGY LINKS
   http://www.il-st-acad-sci.org/health/endolink.html
8. Endocrinology Links
   http://www.fpnotebook.com/END79.htm
9. Google
   http://www.google.com/
10. Hardin MD : Endocrine System, Endocrinology & Hormones
    http://www.lib.uiowa.edu/hardin/md/endocrin.html
11. Harrison's Online: Home
    http://harrisons.accessmedicine.com/

12. IDF - International Diabetes Federation
http://www.idf.org/home/
13. Links to Endocrinology Resources.
http://www.geocities.com/medcin/endocrn.html
14. New Logic Marketing - Endocrinology Links
http://www.newlogicmarketing.com/endocrinology.htm
15. Penn State Endocrinology Links
http://www.hmc.psu.edu/endocrinology/links/
16. Sicklehut Endocrinology Links
http://www.sicklehut.com/endocrinology/index.asp
17. The Society for Endocrinology
http://www.endocrinology.org/
18. The Society for Endocrinology - Links to other sites
http://www.endocrinology.org/SFE/gateway.htm
19. Web site for Endocrinology.
http://endo.endojournals.org/
20. Yahoo
http://www.yahoo.com/