mental retardation is not a common clinical symptom. ACTH deficiency in children with panhypopituitarism results in the tendency to hypoglycemia and neuroglycopenic attacks. Besides insufficient production of glucocorticoids, ACTH deficiency also leads to a decreased secretion of sex hormones of adrenal cortex, which together with GTH deficiency participates in the origin of hypogonadism.

Postpubertal panhypopituitarism

The peripheral manifestations of panhypopituitarism in adults are mostly the consequences of deficiency of five tropic hormones: gonadotropins (LH and FSH), TSH, ACTH, and MSH. Characteristically, evidence of target gland deficiencies appears in the above mentioned order, i.e., gonadal, thyroidal, and cortical deficiency.

The early symptoms of developing panhypopituitarism are usually the symptoms of gonadotropin deficiency. **GTH deficiency** in female leads to secondary amenorrhea and diminishing libido. In women with Sheehan's syndrome the failure to lactate and resume menses after delivery are the most common initial clinical symptoms. In men loss of libido and impotence appear.

TSH and **ACTH deficiencies** are manifested by the same clinical symptoms as at primary hypothyroidism and at primary hypoglucocorticoidism. The symptoms of secondary hypothyroidism are, however, less intensive than at primary hypothyroidism. Loss of the thyroid function causes dry skin, cold intolerance, somnolence, bradycardia, and constipation. However, at secondary hypothyroidism typical myxedema usually does not originate. Secondary adrenal insufficiency results from the lack of ACTH stimulation of the adrenal cortex, and, therefore, affects only adrenal steroids under predominant ACTH regulation, namely cortisol and adrenal androgens. Mineralocorticoid secretion, primarily regulated by renin and angiotensin, is preserved, although it may not be optimal. More common symptoms of glucocorticoid deficiency are malaise, anorexia, weight loss, hypoglycemia or hypoglycemia-induced seizure, hypovolemia, postural hypotension, and orthostatic dizziness. ACTH deficiency results also in abnormal response to stress, and a higher mortality rate. A decrease of adrenal androgen production causes in both sexes gradual thinning even loss of axillary and pubic hair (in men there is a coexistent GTH deficiency). In men also facial hair may diminish. **MSH deficiency** (to a certain extent also ACTH deficiency) is manifested by hypopigmentation or depigmentation of the skin, which is expressive mainly in physiologically hyperpigmentated areas of the body (breast areolae, perigenitally, perianally), and by decreased tolerance to sunshine.

If panhypopituitarism is caused by intrasellar or extrasellar expanding tumor, in the clinical picture also local symptoms resulting from compression of surrounding structures are present.

In the past, gradually developing panhypopituitarism was called **Simmond's cachexia**, because in the clinical picture of this disease extreme loss of body weight and atrophy of organs dominated. Those were the patients with severe total insufficiency of adenohypophysis without longterm substitution therapy. Due to present day system of health care, the patients do not reach such progressive phase of the disease, and, therefore, expressive cachexia does not occur in them.

5.4 Pathophysiology of thyroid gland

The thyroid gland is the largest classic endocrine organ. Its disorders are very frequent. If diabetes mellitus, which regularly ranks among metabolic diseases, is not considered, the thyroid gland disorders make about 4/5 of the total number of endocrinopathies. The thyroid gland disorders are much more frequent in women than in men (7:1). They can be classified as follows:

1. Simple goiter
2. Hypothyroidism
3. Hyperthyroidism
4. Inflammations of the thyroid gland (Thyroiditis)
5. Thyroid neoplasms

5.4.1 Goiter (struma)

Goiter is a clinical and morphological term signifying any enlargement of the thyroid gland situated in situ or ectopic. The goiter placed in situ can be diagnosed

by palpation or visually. The size of the goiter can be objectively determined by ultrasonographic volumetric measurement of the thyroid gland. Ectopic struma (struma lingualis, struma mediastinalis, or struma ovarii) is rare and may be diagnosed only by scintigraphy.

From the morphological point of view enlargement of the thyroid gland can be **caused** by:

a) Hypertrophy and hyperplasia of the epithelial cells of follicles;

b) Increased coloid accumulation in the follicles;

c) Inflammation process (inflammatory infiltration and augmentation of connective tissue);

d) Neoplastic process.

From the functional view-point the term goiter (struma) does not explain the actual functional state of the thyroid gland, i.e., what is the production of thyroid hormones in relation to demands of organism tissues.

Goiter may be characterized from several viewpoints. Goiter may be associated with normal, decreased, or increased hormone secretion. Therefore, according to the state of functional activity of its tissue, **eufunctional** goiter, **hypofunctional** goiter, and **hyperfunctional** goiter are distinguished. From the point of view of functional consequences for metabolism of organism, **toxic** goiter (hyperfunctional) and **nontoxic** goiter (eufunctional or hypofunctional) may be distinguished.

According to the histopathological process prevailingly leading to the enlargement of the thyroid gland, **parenchymatous** goiter, **colloidal** goiter, and **fibrous** goiter are known.

The enlargement of the thyroid gland (normally 15 to 20 g in adults) may be generalized or focal. According to that, **diffuse** goiter and **nodular** goiter are distinguished. In the thyroid gland only one (solitary nodule) can be present (**mononodular**, uninodular goiter), or more nodules may occur (**multinodular** goiter). Nodular goiter (struma nodosa) is a clinical term including various morphological changes, e.g., nodular hypertrophy and hyperplasia of the acinar cells, colloido-cystic or fibrous changes, intrathyroidal hematoma, adenoma, carcinoma, sarcoma, fibrosarcoma, and metastases.

Another classification of nodular goiter is due to intensity of radioiodine accumulation at scintigraphy. **Hot nodule** (toxic, hyperfunctional) accumulates a radioactive isotope of iodine in a higher extent. Scintigraphic **cold nodule** (afunctional, inactive) does not uptake radioiodine and is always suspect of malignity. If the nodular goiter is caused by neoplasia, according to the character of neoplastic process, which leads to the origin of the nodular goiter, **benign** goiter and **malignant** goiter can be distinguished.

According to the number of population affected by goiter in a certain geographic region, **sporadic** goiter or **endemic** goiter are known.

Most goiters cause neither functional nor mechanical problems. At the beginning it may be only **a cosmetic defect**. If the thyroid enlargement is considerable, the symptoms resulting from displacement or **compression** of surrounding structures may appear, mainly of the esophagus, the trachea, the recurrent laryngeal nerve, and the superior vena cava. Compression of the esophagus or the trachea leads to dysphagia, a choking sensation, and rarely to inspiratory stridor. Superior mediastinal obstruction may occur with a large retrosternal goiter. Narrowing of the thoracic inlet may compromise the venous return from the head, neck, and upper limbs sufficiently to produce venous engorgement. This obstruction is accentuated when the patient's arms are raised above the head (**Pemberton's sign**). Suffusion of the face, giddiness, and even syncope may result from this manoeuvre. Compression of the recurrent laryngeal nerve leading to hoarseness is rare in simple goiter, and, therefore, its presence suggests malignant neoplasm rather than nontoxic goiter. Sudden hemorrhage into a nodule or cyst may lead to an acute painful enlargement in the neck and may produce the origin or the enhancement of compressive symptoms. The set of introduced symptoms, conditioned by compression of the neck or mediastinal structures neighbouring the goiter, is called **mechanical local syndrome**.

Along with the symptoms of mechanical local syndrome, symptoms resulting from dysfunction of the thyroid gland (hypothyroidism or hyperthyroidism) may also occur.

5.4.1.1 Simple goiter

Simple goiter (nontoxic goiter) may be defined as any thyroid enlargement that is not associated with hyper– or hypothyroidism and that is not the result

of inflammatory or neoplastic process. Hence, it is an eufunctional (euthyroid) goiter, the tissue of which produces sufficient amount of thyroid hormones for maintaining of euthyroid status.

Simple goiter is the most frequent endocrinopathy. It occurs much more in women than in men (7:1). The higher occurrence of simple goiter in women is associated with the increased demands to the thyroid hormone production at puberty, adolescence, pregnancy, and lactation. With increasing number of deliveries, especially in the regions with iodine deficiency in soil and in drinking water, the occurrence of simple goiter or later also of nodular goiter increases. Nowadays, in our country 25 % of middle aged women are affected. It is even more often present at puberty or in adolescent girls (**pubertal** goiter, **adolescent** goiter). In some patients simple goiter may later diminish (regresses), in others it may be present lifelong. But in some young women the simple goiter may henceforth grow, and change morphologically, or sometimes change even functionally, due to gravidity and lactation, but also due to the age if influence of etiological factors recurs.

In certain geographic regions simple goiter may occur sporadically or endemically. **Sporadic simple goiter** arises as a result of factors that do not affect the population generally. If in particular geographic localities incidence of simple goiter is more than 10 % of the adult population, or more than 20 % of the children population, it is denoted as **endemic goiter**. Endemic goiter implies an etiologic factor (environmental iodine deficiency is regarded the major etiologic factor), or factors common to a particular geographic region.

Endemic goiter is still a problem of vast public health significance and has been estimated to afflict more than 200 million people throughout the world. Except perhaps in North America, it is present on all continents and occurs mostly in mountainous areas such as Andes, Himalayas, and Alps, where iodine deficiency still exists. But endemic goiter also may occur in nonmountainous regions remote from the sea, such as Central Africa, where iodized salt is not used.

At the beginning of 50s of this century incidence of simple goiter in Slovakia was very high. In some regions, namely Kysuce, Slovenské rudohorie and Žitný ostrov, it was present in 50–80 % of adult women.

Etiology of simple goiter is **multifactorial**. It is often due to a definable cause of impaired thyroid hormone biosynthesis, such as iodine deficiency, and ingestion of goitrogens. Sometimes it is due to an inborn defect in a hormone synthesis pathway, but in some instances its cause is not exactly known.

1. **Iodine deficiency in food and water**. Iodine and tyrosine are the basic substances for the thyroid hormone biosynthesis. At present the optimal daily iodine intake is considered 150–200 microgrammes. However, for eufunctional status of the thyroid gland minimum daily iodine intake of 100 microgrammes is needed. If its daily intake falls under this value, the production of thyroid hormones significantly decreases. Therefore, the **compensatory goiter** begins to develop, however, in some people it is being developed also if daily iodine intake is somewhat more than 100 microgrammes. The compensatory augmentation of thyroid parenchyma is to secure the uptake of such total amount of iodine from circulating blood, which in spite of its insufficient supply to organism, will be sufficient for securing euthyroid status. The uptake and the content of iodine per unit of thyroid tissue weight are, however, significantly lower.

Iodine deficiency may be absolute or relative. **The absolute iodine deficiency** in food and water, and so in the organism as well, in the past was often present in the geographic regions with incidence of endemic goiter. In the noted regions endemic goiter had occurred in several generations. If the iodine deficiency was severe, in considerable number of the patients goitrous enlargement was also associated with varying degree of hypothyroidism. The incidence of endemic goiter has been greatly reduced in many countries by the introduction of iodized salt (in Slovakia since 1951). In our country table salt is enriched with potassium iodide containing 25 mg KI/1 kg.

The relative iodine deficiency may originate mainly during those periods of ontogenesis, which are associated with increased demands to the thyroid hormone production. In girls it is especially during puberty and adolescence, in women during pregnancy and lactation. The origin of simple goiter due to iodine deficiency in boys is rather rare. The increased need of the thyroid hormones is associated with increased demands to iodine intake. However, if the iodine intake remains at the level before the onset of the above mentioned periods of life, it becomes relatively insufficient with respect to the

increased needs of organism. Therefore, it is necessary to increase iodine intake by occasional consumation of sea fish, respectively by use of iodine medical drugs. This is important especially for women during gravidity and lactation because of the demands of the fetus and newborn for iodine.

2. **Increased intake of goitrogens**. A wide variety of chemical agents have the capacity to inhibit the synthesis of thyroid hormones. When the effect of such agents is sufficient to reduce the secretion of thyroid hormones to subnormal levels, secretion of TSH is indirectly increased (via the feedback mechanism), and so they induce goiter formation. Hence such agents are commonly termed goitrogens (strumigens).

From the standpoint of the aspect of iodine metabolism that they inhibit, goitrogens (antithyroid agents) can be grouped into two classes: goitrogens that inhibit iodide transport and thereby reduce substrate for hormone formation, and those that inhibit the initial oxidation (organic binding) of iodide, decrease the proportion of diiodotyrosine (DIT) relative to monoiodotyrosine (MIT), and block coupling of iodotyrosines to form the hormonally active iodothyronines.

Increased intake of goitrogens participates in the origin of the goiter especially if it is associated with mild iodine deficiency in food and water. Increased intake of goitrogens may be applied also in the period of increased needs of the thyroid hormones (puberty, adolescence, pregnancy, and lactation), respectivelly in the persons with mild hereditary deficiencies of enzymes participating in biosynthesis and secretion of thyroid hormones (the persons with heterozygous form of enzymopathy).

Goitrogens are natural or synthetic chemical agents. **Natural goitrogens** are contained in some kinds of vegetables, such as cabbage, cauliflower, kale, kohlrabi, Brussels sprouts, turnips, mustard, cassava, and others belonging to the Brassica and Crucifera plants. They may be also in some animal forage, e.g., clover, rape, and soya. Natural goitrogens contained in forage may be successively found in milk, and probably even in meat of domestic animals, which may so become a source of goitrogens when they are consumed. Well known natural goitrogens are: thiocyanate, 1-5-vinyl-2-thiooxazolidone, and allylisotiocyanate. The role of dietary goitrogens in the induction of disease in humans is uncertain. Their effect may depend on the concomitant iodine intake. Although humans rarely, if ever, eat goitrogenic foods in quantities to lead to goiter (the content of natural goitrogens in the mentioned kinds of vegetables is low), sufficient quantities of goitrogens to cause goiter may be present in milk.

The other group of natural goitrogens are flavonoids (polyhydroxyphenols). They are present in groundnut, beans, and soya. However, their most important source is millet, a significant food in many countries.

Synthetic goitrogens. The most known synthetic goitrogens are: chlorates, perchlorates, iodates, periodates, nitrates, and some medical drugs, e.g., para-aminosalicylic acid, para-aminobenzoic acid, thiobarbiturates, phenylbutazone, resorcine, resorcinol, some antidiabetic drugs (sulfonylureas, tolbutamide, carbutamide), sulfonamids, and lithium drugs. Goiter originated as a sequel of long-term taking larger doses of pharmacological goitrogens is called struma medicamentosa.

In the last decades the higher attention is paid to the contaminants occurring widely in the environment (anthropogenic goitrogens). They include mainly:

a) polychlorinated biphenyls used in the plastic material industry. By their decomposition goitrogenic more effective resorcinols, hydroxypirimidins, and phtalates originate. From these chemical agents goitrogenic dihydroxybenzoic acids originate;

b) polycyclic aromatic hydrocarbons (benzpyrene and methylcholanthrene), which also play an important role in the carcinogenesis;

c) nitrates;

d) insecticides (the most known agent from this group is dichlorophenyl-trichloranthen – DDT, which was used mainly in the past); pesticides (parathione and metathione). From the omnipresent polyvinyl-chloride (PVC) goitrogenic phtalate esters and dihydroxybenzoic acids are being released by moisture, therefore, those chemical agents are present in plastic packet milk, in the vegetables grown in plastic foil greenhouse, and in other foodstuffs.

Simple goiter may be also caused by chronic excessive iodine intake in food (organic form of iodine) or in medical drugs (inorganic form of iodine). The

doses of iodine are supposed to be large (more than 10 mg daily). Large iodine intake inhibits synthesis of thyroid hormones. Chronic administration of large doses of iodine is seen most commonly in patients with chronic respiratory diseases, who are often given potassium iodide as an expectorant. However, **iodine goiter** (iodide goiter) develops in only a small proportion of patients given iodine. In seaside areas, where large quantities of food with excessive content of iodine are consumed (seafish and seaweed), iodide goiter occurs endemically (so called seaside goiter). Increased iodine supply in pregnant women, e.g., long-term therapy by expectorants containing iodine, causes the origin of goiter in newborn infants. In such cases, the mother is usually free of goiter. It is not known whether iodide goiter in newborns results from hypersensitivity of the fetal thyroid to iodine or from the fact that the placenta concentrates iodide several-fold.

3. **Hereditary factors**. Genetically determined defects in thyroid hormone biosynthesis are rare and their share in the origin of simple goiter is not clear enough. In most instances, the defect appears to be transmitted as an autosomal recessive trait. It is supposed, that in some persons with inborn enzyme defect only mild decrease of activity of some of the enzymes in the pathways of thyroid hormone synthesis is present (heterozygous individuals). Unlike severe hereditary enzymopathy (homozygous individuals) resulting in sporadic cretinism, the thyroid gland of heterozygous individuals is, therefore, eufunctional and normal size. This mild enzymopathy may, however, participate in the origin of simple goiter if in the affected person increased needs for production of thyroid hormones (puberty, adolescence, pregnancy, and lactation), mild iodine deficiency, or increased intake of goitrogens occur.

4. **Increased concentration of estrogens in blood**. In the origin of simple goiter in girls at puberty or adolescence (**juvenile goiter**) , and in pregnant women, besides increased need of the thyroid hormones, also estrogen overproduction could participate. Increased plasma estrogen concentration induces the increase of plasma level of the thyroxine-binding globulin (TBG), and thereby also increase of its binding capacity. Increased concentration of TBG may reduce plasma concentration of free thyroid hormones. Because only free thyroid hormones are biologically active, their reduced blood concentration via the feedback mechanism leads to increased secretion of TSH. The increased plasma TSH concentration results in the origin of goiter.

5. **Immunoglobulins**. Recently it has been assumed, that in blood of some patients there may exist a class of thyroid immunoglobulins stimulating only growth of the thyroid gland (thyroid growth immunoglobulins – TGIs). TGIs, like TSH, stimulate growth of the thyroid gland by hypertrophy and hyperplasia of epithelial cells of follicles. However, unlike TSH and thyroid immunoglobulins present in patients with Graves-Basedow disease, they do not increase biosynthesis of thyroid hormones. This might explain why in some persons simple goiter is eufunctional already from the very beginning of its origin. Patients in whom such "autoimmune nontoxic goiter" is thought most likely are those in whom other autoimmune phenomena are present in themselves or in their families.

Pathogenesis of simple goiter. The action of one or several above mentioned etiologic factors (except TGIs) results in reduction of functional efficiency of the thyroid gland. As a sequel of this state, the production of its hormones is not adequate to the needs of the peripheral tissues. The decrease of plasma concentration of thyroid hormone reduces feedback inhibition of TSH secretion. The increased blood level of TSH causes hypertrophy and hyperplasia of epithelial cells of follicles, and also the increase in vascularity of the thyroid gland tissue. The result of these processes is diffuse parenchymatous goiter. This augmentation of parenchyma is a compensational process securing increased uptake of iodide from blood, and thereby normalizing plasma concentration of thyroid hormones, and normalizing TSH secretion as well. The patient becomes again euthyroid and eumetabolic, though goitrous. Therefore, the eufunctional goiter may usually remain only a symptom of a temporary deficiency of thyroid hormones, which appeared sometimes in the past.

If the etiologic factor acts only once and temporarily, the hypertrophy and hyperplasia of the epithelial cells may almost disappear. This process of involution leads to a return of the gland to nearly normal size if the hypertrophy and hyperplasia are of relatively short duration, but probably results in a diffuse colloid goiter if the hyperplastic phase has been present for years. In long-standing goiter, repeated

cycles of hyperplasia and involution eventually lead to formation of nodules, and a multinodular goiter results, and it may reach considerable size. Areas of involution are often interspersed with patchy areas of focal hyperplasia. Fibrosis may demarcate hyperplastic or involuted nodules. Nodules often undergo hemorrhagic or cystic degeneration and may become irregularly calcified.

According to the clinical criteria the simple goiter may be **classified** as follows:

1. Diffuse goiter with homogenous hyperplasia
2. Diffuse goiter with nodular hyperplasia
3. Nodular goiter (mononodular or multinodular)

Clinical features of simple goiter. In patients with simple goiter, the clinical manifestations arise solely from enlargement of the thyroid, since the metabolic state is normal. A small diffuse goiter does not cause any problems, it is only a cosmetic defect. A middle size nodular goiter may induce feeling of a tightening of garments worn about the neck and sometimes feeling of irritation to coughing. A large retrosternal nodular goiter may cause the symptoms of mechanical local sydrome. The symptoms of this syndrome usually occur in the middle age, when evidently enlarged goiter descended behind sternum and became firm in consistency (augmentation of fibrous tissue).

In the patients with simple goiter also functional disorders of the thyroid gland may develop later. In the regions with high incidence of endemic goiter, and with insufficient health education and prevention, goitrous enlargement also may be associated with varying degrees of hypothyroidism. On the other hand, in older patients with long-standing multinodular goiter, the ingestion of excess iodide (mostly by medical drugs) may result in the development of thyrotoxicosis (jodbasedow phenomenon). At the scintigraphy hyperfunctional nodules are manifested as hot nodules. However, in the patients with simple goiter the prognosis is prevailingly good.

5.4.2 Hypothyroidism

Hypothyroidism is the clinical state resulting from thyroid hormone deficiency. This clinical state originates if in the consequence of various morphological or functional abnormalities the production of thyroid hormones is lower than the demands of peripheral tissues for supply of these hormones. Like other diseases of the thyroid, it occurs more frequently in women, mainly in the elderly.

From the etiopathogenetic point of view hypothyroidism is divided into two groups:

1. Peripheral hypothyroidism;
2. Central hypothyroidism.

1. **Peripheral hypothyroidism** (primary hypothyroidism). The cause of the thyroid gland hypofunction is in its parenchyma. Decreased plasma concentrations of thyroid hormones increase TSH production by feedback mechanism followed by the increase of its plasma concentration. According to the size of the thyroid gland two types of peripheral hypothyroidism are known:

A. **Peripheral hypothyroidism without goiter** (thyroprivic hypothyroidism, nongoitrous peripheral hypothyroidism). It is due to subtotal surgical removal of the thyroid gland, or due to lesion of its parenchyma, e.g., extensive strumectomy, overdose of external therapeutic radiation, excessive dosage radioiodine or antithyroid agents (iatrogenic hypothyroidism). For this type of hypothyroidism also developmental defects of the thyroid gland can be responsible. These defects may take the form of hypoplasia or aplasia of the thyroid, or failure of the thyroid to descend properly during embryological development (its ectopic location). The loss or atrophy of thyroid tissue leads to inadequate synthesis of thyroid hormones, despite maximum stimulation of any thyroid remnant by TSH.

B. **Peripheral hypothyroidism with goiter** (goitrous hypothyroidism). It may develop in the patient with Hashimoto thyroiditis or with the tumor massively infiltrating the thyroid gland. This type of hypothyroidism is always present in the patients with heritable defects in thyroid hormone biosynthesis (homozygous individuals). Finally, in areas of environmental iodine deficiency, goitrous hypothyroidism can occur on an endemic basis.

2. **Central hypothyroidism** (trophoprivic hypothyroidism). This type of hypothyroidism is characterized by insufficient stimulation of an intrinsically normal thyroid gland as a result of hypothalamic or

pituitary disease. Production of TSH and its plasma concentration are decreased resulting in atrophy of the thyroid gland. It may originate either due to primary disorder in adenohypophysis (**central adenohypophyseal hypothyroidism**, secondary hypothyroidism, pituitary hypothyroidism), or as a sequel of primary hypothalamic disorder (**central hypothalamic hypothyroidism**, tertiary hypothyroidism, hypothalamic hypothyroidism).

Pituitary hypothyroidism is rare. Its unique origin may be due to isolated TSH hyposecretion. It is, however, more often a part of panhypopituitarism. The cause of TSH deficiency may be a tumor of the pituitary gland or adjacent region, aneurysm in this region, or adenohypophyseal necrosis (most commonly postpartum pituitary necrosis).

Hypothalamic hypothyroidism is less common and results from inadequate secretion of TRH, which is due to the damage of the hypothalamic tissue by inflammatory process, trauma, or tumor.

Peripheral hypothyroidism (nongoitrous and goitrous together) accounts for approximately 95 % of cases of hypothyroidism, only 5 % or less being central (trophoprivic, suprathyroid) hypothyroidism.

The consequences of thyroid hormone deficiency and so the clinical features of hypothyroidism depend on the age at which undersecretion of thyroid hormones occurs. They also depend on the degree and duration (early diagnosis) of thyroid hormone deficiency, as well as on the promptness of adequate replacement therapy. If the thyroid hormone deficiency occurs already during intrauterine life and perinatal period, or at least during the first year of postnatal life, i.e., in the period of the most intensive CNS development, the clinical picture of **infantile hypothyroidism** originates. The origin of the thyroid gland hypofunction after the first year of life, i.e., after the CNS development has almost ceased, but in the period of intensive development of the skeleton, results in the clinical picture of **juvenile hypothyroidism**. The origin of thyroid hormone deficiency after epiphyseal closure causes the development of the clinical picture of **adult hypothyroidism**.

The clinical picture of peripheral hypothyroidism is usually characterized by more severe symptoms of thyroid hormone deficiency than that of central hypothyroidism. At central hypothyroidism myxedema does not occur. The clinical symptoms of central hypothyroidism are milder because in spite of the total TSH absence the atrophied thyroid gland preserves certain autonomous function, and, therefore, some basal production of its hormones persists. As a consequence of that, the thyroid hormone concentration at central hypothyroidism is not so low as that at peripheral hypothyroidism. In the clinical picture of central hypothyroidism the symptoms of ACTH deficiency (mainly tendency to hypoglycemia), and also the symptoms of gonadotropin deficiency (amenorrhea, atrophy of the breast and ovaries) are often simultaneously present.

5.4.2.1 Infantile hypothyroidism

Infantile hypothyroidism is a disease caused by the thyroid hormone deficiency which originates in prenatal period (**congenital hypothyroidism**), in perinatal period (**neonatal hypothyroidism**), or whenever during the first year of life. According to the number of affected children in a geographic region, **endemic** infantile hypothyroidism and **sporadic** infantile hypothyroidism are distinguished. According to the duration of thyroid hormone deficiency, **temporary** neonatal hypothyroidism and **permanent** neonatal hypothyroidism are known. The temporary neonatal hypothyroidism requires substitutive therapy only for certain time, mainly during the crucial phase of CNS development. Later only regular medical checks of the child are needed. The permanent neonatal hypothyroidism requires long-life substitutive treatment.

The temporary neonatal hypothyroidism may develop as a sequel of:

1. Insufficient iodine supply during the last trimester of pregnancy. In a newborn the compensatory goiter is usually present.

2. Large doses of iodine during pregnancy, e.g., iodine medical drugs. In some newborns goiter may be extremely large and may cause death by asphyxiation.

3. Transplacental passage of maternal antithyroid antibodies, which probably block TSH receptors (TSH inhibiting immunoglobulins). This type of temporary neonatal hypothyroidism has a familial occurrence frequently accompanied by irreversible CNS disorders originating already during intrauterine development. It seems to be

analogical, but functionally contrary state like at Graves-Basedow disease in newborns.

4. Transplacental passage of antithyroid drugs or lithium during therapy of pregnant women.

The permanent neonatal hypothyroidism may occur as a sequel of:

1. Anatomical anomaly of the thyroid gland originated due to the disorder of its embryological development (hypoplasia, aplasia, or rudimentary ectopic thyroid).

2. Genetically determined defects in thyroid hormone biosynthesis (disorder of hormonogenesis).

3. Specific disorder of the thyroid that occurs in regions of severe endemic goiter.

Severe degree of nontreated infantile hypothyroidism associated with irreversible CNS disorders, as well as with irreversible disorders of bone ossification, skeletal maturation, and linear body growth is termed **cretinism**. Irreversible CNS disorders are due to deficiency of thyroxine (tetraiodo-L-thyronine, T_4), which is essential for the development of the central nervous system. It is unconditionally needed for maturation of neurons of cerebral cortex, for the growth and myelination of nerve fibres, and for forming of dendritic connections (synapses). Its deficiency in fetal life or at birth results in retardation of the infantile characteristics of the brain, hypoplasia of cortical neurons with poor development of cellular processes, retarded myelination, and reduced vascularity. If the deficiency is not corrected in early postnatal life, irreversible damage results. The both thyroid hormones, i.e., T_4 and T_3 (triiodo-L-thyronine), are necessarily needed also for maturation of bone tissue, respectively for normal ossification and longitudinal bone growth until the period of epiphyseal growth plates fusion. Therefore, the most typical symptoms of the clinical picture of cretinism are **retardation of mental development** and **retardation of somatic development**. In the past it often occurred as endemic cretinism. Possibility of the origin of sporadic cretinism still persists. However, thanks to systematic screening at present the danger of the origin of sporadic cretinism is minimal, and exists only when screening duty is neglected, hence if the diagnosis and therapy of sporadic congenital hypothyroidism are very late.

Severe disorder of intellectual development may result also from nontreated **T_4 deficiency**, which may occur whenever in the course of **the first year of life**. Certain degree of milder, but permanent disorder of mental abilities of the aflicted child may appear also when T_4 deficiency originates from 12th to 18th month of postnatal life. If thyroid hormone deficiency develops between 18th and 24th months of life its clinical picture merges more with that of juvenile hypothyroidism. Nontreated hypothyroidism originated after CNS development finished (**after the second year of life**), causes only typical disorders of bone ossification and linear body growth. Mental disorders associated with hypothyroidism which originates after the second year of life are reversible. These mental disorders result from actual thyroid hormone deficiency.

The clinical features of infantile hypothyroidism reflect the degree of thyroid hormone deficiency. At moderate T_4 deficiency only very mild symptoms of retardation of mental and physical development are present. They may be found out only after more detailed medical examination of a newborn. More expressive T_4 deficiency is manifested by various degrees of cretinous stigmatization. At persisting severe degree of T_4 deficiency, which in the past occurred quite often in regions with endemic goiter, the clinical picture of cretinism fully develops.

Endemic cretinism. It is a severe developmental disorder that in the past occurred in regions where some inhabitants had the severe endemic goiter during several generations. Pathogenesis of its origin is, however, still not exactly known. Aflicted children were usually born to mothers with nodular goiter, iodine deficiency, or hypothyroidism. It is generally accepted that the risk of the origin of foetal hypothyroidism in the mother with hypothyroidism is essentially higher than in the mother without hypothyroidism.

It is supposed, that long-term severe iodine deficiency in mother plays an important role in the origin of foetal endemic hypothyroidism. Production of thyroid hormones in mother is low, therefore, transplacental supply of the foetus by maternal thyroxine is insufficient. Transplacental T_4 supply is, however, unconditionally needed for the supplement of foetal needs also in healthy mother with normal iodine intake. Therefore, as a sequel of thyroxine deficiency during pregnancy irreversible disorder of CNS

development originates already in the foetus. Excessive intake of goitrogens in the food of the mother during pregnancy may to a certain extent participate in the origin of endemic congenital hypothyroidism. Thanks to the introduction of iodized salt in our country endemic cretinism does not occur.

Sporadic cretinism. It occurs in one in every 4 to 5 thousand births. It is due to the morhological anomaly of the thyroid gland in newborn, which originates during embryogenesis, e.g., its aplasia, hypoplasia, or rudimentary ectopic thyroid gland. The most frequent form of the ectopic thyroid is lingual thyroid. It originates if its migration is incomplete, and, therefore, ectopic thyroid tissue lies at the base of the tongue. The form of the congenital hypothyroidism which is due to the morphological anomalies of the thyroid gland is called **nongoitrous sporadic cretinism**.

Genetically determined defects in hormone biosynthesis are a rare cause of sporadic cretinism. It is hereditary enzymopathy transmitted as an autosomal recessive trait. Individuals with sporadic cretinism are homozygous for the abnormal gene. Several members of a family are usually affected, and, therefore, it is denoted as **familial cretinism**. As in patient usually compensatory goiter is present, it is called **goitrous sporadic cretinism**. These hereditary defects in hormone biosynthesis are more common in boys than in girls. The goiter may be present already at birth or shortly thereafter, and since then it is usually associated with severe hypothyroidism. The absence of goiter in a child does not exclude, however, the presence of hypothyroidism.

Five specific defects in the pathways of hormone synthesis have been identified: iodide transport defect, organification defect (peroxidase deficiency), iodotyrosine-coupling defect, iodotyrosine dehalogenase defect (deiodinase defect), and abnormal secretion of iodoproteins (defect of thyroglobulin synthesis).

At endemic cretinism irreversible CNS disorders usually originate already during intrauterine life. On the contrary, CNS disorders conditioned by T_4 prenatal deficiency in sporadic congenital hypothyroidism are mild, and after the prompt diagnosis and adequate substitutional therapy they are reversible. In most newborns with sporadic neonatal hypothyroidism, however, significant thyroid hormone deficiency originates in the postnatal period only.

Clinical features. Presence of the clinical symptoms of congenital hypothyroidism already **at birth** is very rare. The age in which its symptoms appear depends on the degree of prenatal and postnatal T_4 deficiency. The newborns with this disease clinically do not usually significantly differ from healthy newborns. Only in about 4 % of newborns with congenital hypothyroidism (a very severe degree of T_4 deficiency) cosiderable clinical symptoms are present at birth or in perinatal period. Therefore, it is difficult to detect the presence of congenital hypothyroidism during **the first two weeks of life** only on the basis of clinical symptoms. Suggestive symptoms, which could denote the presence of congenital hypothyroidism already in this early period, usually include: higher birth weight and body length, enlargement of the posterior fontanelle, delay in the passage of meconium, hypothermia, dry skin, protuberance of abdomen, slightly protruding tongue, decreased motility, somnolence, and persistence of neonatal jaundice.

More evident and typical symptoms of infantile hypothyroidism will develop not earlier as at the end of the first month of life, but more often during the second or the third month of life. However, the diagnosis of congenital hypothyroidism, detected on the basis of the clinical symptoms appearing in this period, is very late. Peristence of T_4 deficiency during the first 2–3 months of life has, therefore, permanent and severe consequeces for intellectual and motor development of an affected child. Substitutional therapy introduced as late as in this period is able to prevent the origin of disorder of somatic development, but the symptoms of permanent impairment of psychomotor development of an affected child are usually present. By clinical examination it is possible to detect: e.g., decrease of mental capacity, impairment of psychic concentration, impairment of muscular coordination (mainly fine motor activity), impairment of speech development, and the like. Therefore, only the treatment from the first days of life, realized by administration of thyroxine in doses adequate to the weight and age of a child, may prevent the origin of permanent conseqences of neonatal hypothyroidism.

With regard to the need of prompt diagnosis and therapy of neonatal hypothyroidism **screening of congenital hypothyroidism** in all newborns has been done in our country since 1985. The aim is to secure their normal psychomotor and physical development.

Screening examination of newborns is the only possible prevention of permanent consequences of such sporadic congenital hypothyroidism, in which significant T_4 deficiency followed by CNS impairment does not occur prenatally, but as late as in the first days of postnatal life. However, it is generally accepted, that even a short period (lasting only a few days) of significant T_4 deficiency in early postnatal period leads to permanent disorders of psychomotor development, at least to disorders of perception and coordination.

By neonatal screening, concentrations of total and bound T_4 or TSH concentration are measured in samples of capillary blood. The samples are taken after the heel puncture of a newborn on 3rd–5th day of life. The first examination found out only serum T_4 concentration. If its level is low, by another examination of the taken blood sample serum, TSH concentration is assessed as well. By screening examination neonatal hypothyroidism may be diagnosed reliably within the first week of life.

In the past the diagnosis was not frequently made until full-blown signs emerged several weeks or months after birth. Fortunately, this delay has been largely eradicated by the measurement of blood thyroxine level in neonatal screening programs. Such programs are highly successful in preventing the mental retardation and other neurological sequelae that result from prolonged hypothyroidism during early infancy. In the past, when hormonal substitutional therapy did not exist, every severe neonatal hypothyroidism resulted in gradual development of the clinical picture of cretinism. At present, the term cretinism is, however, archaic because in our country thanks to the introduction of iodised salt, endemic cretinism does not exist at all. Alike in instances of sporadic congenital hypothyroidism, thanks to the screening of newborns and following adequate substitutional hormonal therapy, the fully developed clinical picture of sporadic cretinism does not occur as well. In spite of this fact, physicians as well as students of medicine should know the possible consequences of not only delayed diagnosis and delayed therapy of neonatal hypothyroidism, but also the consequences of nontreated neonatal hypothyroidism.

The clinical features of cretinism gradually develop from early childhood to adulthood. **In a child** with congenital hypothyroidism the typical symptoms of infantile hypothyroidism begin to develop from the second or the third month of life. Decreased motility and somnolence of a child become more and more evident. Anorexia causes small increment of body weight. The voice of a child becomes deeper and hoarse, the child cries very little. Larger tonque (macroglossia) is gradually protruding from the permanently open mouth. Constipation is more evident, muscular hypotony and decreased intensity of reflexes appear. Umbilical or inquinal hernia often occurs.

The skin becomes evidently cold, dry, and rough. It is of yellowish colour and feels rough and doughy. Hair becomes dry and grow slowly. Nails are brittle and their growth is pure. The facial appearance of the child gradually acquires myxedematous features. The anterior and posterior fontanelles are not yet closed. Holding up of the head is delayed. Psychomotor development and linear growth of the child are also delayed. Nowadays, when the screening of congenital hypothyroidism is provided for all newborns, such stage of infantile hypothyroidism should not, however, occur.

In the next period the clinical picture of nontreated infantile hypothyriodism is characterized by delayed eruption of the deciduous teeth, by delayed origin of ossification centres and successive **delay in bone age**. X-ray examination reveals decreased number of obviously followed ossification centres of skeletal bones as well as their slow enlargement. The retardation of ossification and longitudinal growth of bones originates because thyroid hormone deficiency is accompanied by both a decrease in secretion and lessened effectiveness of STH as well as with insufficient skeletal maturation. STH efficiency is decreased probably as a sequel of impaired formation of IGF I production, which influences the cartilage of epiphyseal growth plate. Decreased proteosynthesis participates also in retardation of skeletal development.

The deciduous teeth persist for a long time and permanent dentition is rather delayed. The skull shows a poorly developed base. Delayed closure of the fontanelles leads to a head that is large in relation to the body. Neck is usually short and wide. Both, shortening of the skull base and disorder of nasal bones development cause pulling the root of the nose back. Retardation of mental and physical development is manifested by delay in reaching the normal milestones of development, such as holding

up the head, sitting, standing, walking, and talking. Though epiphyseal plates remain open quite long, often even longlife, linear body growth is significantly retarded and finishes prematurely, what is manifested by a short stature.

In the adult, the clinical picture of cretinism is characterized mainly by various degrees of **oligophrenia** (from debility to idiocy), and by **thyroid dwarfism**. The severe disorder of mental development is the result of insufficient differentiation and maturation of cerebral cortex neurons, as well as of their cut in number. The short stature of an adult cretin is characterized by the disproportionately short limbs in relation to the trunk. Impaired bone ossification gives also rise to the origin of various skeletal deformities, which occur especially in the most mechanically loaded spots. Thoracic kyphosis and coxarthrosis originate most frequently. Deformity and restriction of motion of hip joint cause the typical waddling gait (duck gait) of the cretin.

The skin of cretin is dry, coarse, rough, wrinkly, and it often desquamates. It has a yellow tint or even peculiar wax-orange colour. It feels doughy and cool. The secretions of the sweat glands and sebaceous glands are reduced, leading to dryness and coarseness of the skin. Its peculiar colour is induced by hypercarotenemia and successive deposition of caroten into the skin. Hypercarotenemia is due to the disorder of caroten transformation to vitamin A in the liver. Growth of hair is retarded. The hair is dry, brittle, lacks luster, unmanageable sparse, and tends to fall out. Special mucinous (jelly-like) material consisting of protein complexed with mucopolysaccharides (mainly with hyaluronic acid, or also with chondroitin sulphate), electrolytes, and water is accumulated in the dermis. This material is responsible for the peculiar edematous look of the patient skin termed **myxedema** (mucinous edema). Myxedema is a tough edema which on the contrary to normal (true) edema does not leave a pit on the skin surface when an edematous part is pressed on (nonpitting edema).

Special mucinous material infiltrates also other tissues, e.g., tongue muscle, skeletal muscles, myocardium, and mucosa and submucosa of pharynx, larynx, stomach, and intestines. Due to thickening of the mucous membranes of the larynx and vocal chords, caused by myxedematous infiltration, the voice becomes deeper and hoarse.

The facial features of the cretin are considerable (characteristic). The mucinous edema is responsible for the thickened features and puffy apearance of the patient. Dull expressionless face, poor mimic, and permanently open mouth with protruding enlarged tongue are typical. Macroglossia is partially responsible for snuffled speach of the cretin. Lips are thick. Palpebral fissures are narrowed due to periorbital myxedema and ptosis. Lower forehead, wide cheek bones, and flat, broad, saddle-shaped, pulled back nose, along with prognatism and wrinkly skin cause peculiar facial appearance of the cretin, denoted as simian (pithecoid) physiognomy. The teeth are malformed and readily become carious.

Basal metabolic rate (BMR) of the cretin is significantly decreased. Therefore, slightly decreased basal body temperature, cold intolerance, and decreased appetite are present. Serum T_4 and T_3 concentrations are low. Serum TSH concentration is increased. Concentrations of total cholesterol and low-density lipoproteins (LDLs) in serum are increased. Anemia is often present.

Heart rate and respiratory rate are slow (bradycardia and bradypnea). Cardiac output and cardiac index at rest are decreased. Decreased heart rate and cardiac output reflect the loss of the chronotropic and inotropic effects of thyroid hormones. X-ray picture shows enlarged heart shadow as a result of dilatation of flabby myocardium, as well as due to effusion into the pericardial sac of fluid rich in protein and mucopolysaccharides. Mucinous effusions may also occur into any serous cavity.

Cretins are less efficient, they become easily tired. Stiffness, cramping, and aching of muscles are common complaints. Muscles strenght and tonus are slightly decreased. Weakened ligaments cause hyperextensibility of joints and the origin of flat-feet (pedes plani). Muscle hypotonia gives rise to an evident protuberant abdomen, and ptosis of upper eyelid. Peristaltic activity is decreased and, together with the decreased food intake, is responsible for chronic constipation.

The symptoms of hypogonadism are often present. Sexual maturation is retarded, **sexual infantilism** and infertility are usually present. Defective hearing and even **deafness** are very frequent.

Perceptive deafness may occur in association with congenital hypothyroidism caused by genetically determined defect in thyroid hormone biosynthesis,

mainly by a defect in the organic binding of iodine (**Pendred syndrome**). Goiter and hypothyroidism are usually milder. This syndrome has autosomal recessive inheritance.

5.4.2.2 Juvenile hypothyroidism

Juvenile hypothyroidism is a disease caused by the thyroid hormone deficiency which originates whenever in the childhood from the end of the second year of life until epiphyseal fusion. Its most typical clinical symptoms are retardation of somatic and sexual development. Hypothyroidism results also in mental slowness but not in permanent mental retardation.

The most common cause of **peripheral** (primary) juvenile hypothyroidism is autoimmune thyroiditis (Hashimoto disease). Sometimes, it may be the result of decompensation either of an ectopic (dysgenetic) thyroid gland, or of heterozygous type of genetically determined defect in thyroid hormone biosynthesis. Its rare cause is subacute or acute thyroiditis. In exceptional cases it may originate due to infiltration of thyroid gland tissue in patients with histiocytosis and cystinosis. **Central** juvenile hypothyroidism is very rare. It may usually occur due to a tumor in the area of pituitary or hypothalamus, most often due to craniopharyngioma.

Clinical features. In a child whose mental development and physical growth were normal before the onset of hypothyroidism, the clinical symptoms of thyroid hormone deficiency start gradually appaer. Skeletal maturation is markedly delayed. **Growth failure** precedes the appearance of other symptoms. The rate of linear growth is characteristically less than that of weight gain, which is due to development of myxedema. Permanent dentition is delayed, too. Perception of the child gradually decreases, the child becomes less bright, and a poor performance at school is evident. **Poorer psychic activity** and intellectual performance of the child result from the actual thyroid hormone deficiency, and, therefore, are reversible.

Sexual maturation is retarded and the onset of puberty is delayed. The result of growth and sexual development retardation is a patient who appears much younger than his or her chronological age (youthful appearance, infantile appearance). In spite of the delay of epiphyseal union **the stature** of the patient in the adulthood is short and disproportional. Legs are relatively shorter compared with the trunk, therefore, the ratio between the upper body segment (head, neck, and trunk) and lower body segment (legs) is increased.

In the clinical picture of juvenile hypothyroidism **the other symptoms** of thyroid hormone deficiency are also present. They are similar to those of adult hypothyroidism, however, they are present to a varying, but usually milder degree.

Early diagnosis of juvenile hypothyroidism guarantees its very good prognosis, because hormone substitutional therapy prevents the origin of disorders of growth and sexual development, and settles psychic activity and intellectual performance of the child. Permanent mental disorders do not occur, as CNS development was taking place already in the period when thyroid hormone deficiency was not present.

5.4.2.3 Adult hypothyroidism

Clinical syndrom of adult hypothyroidism (Gull's disease) is developed if the thyroid hormone deficiency originates as late as the epiphyseal growth plates are closed. It occurs in about 1 % of adult population. It is more common in women than in men (7:1) and appears most often between the ages of 40 and 60. Its characteristic manifestations are decrease of BMR, fall of all activities of organism, and myxedema. At present, with regard to the sufficient health care and therapeutical possibilities, fully developed clinical picture of adult hypothyroidism practically does not occur.

In most instances it is a peripheral (primary) hypothyroidism, which accounts for 95 % of all cases of hypothyroidism, the remaining 5 % being central (secondary and tertiary) hypothyroidism.

Peripheral hypothyroidism may be either **spontaneous** (about 65 %) or **iatrogenic** (about 35 %). The most common cause of spontaneous primary hypothyroidism is Hashimoto thyroiditis, mainly its final stage in which goiter is either absent or has gone unnoticed. The presence of circulating thyroid autoantibodies in up to 80 % of the patients may be revealed. Rarely it may occur in later life of the patients with multinodular goiter. Iatrogenic primary hypothyroidism may be **postablative** (surgery or radioiodine) or **postradiation** (e.g., for lymphoma).

Central hypothyroidism is most commonly the result of postpartum pituitary necrosis and less commonly the result of a tumor of the adenohypophysis or adjacent regions (**pituitary hypothyroidism**). Less

common is **hypothalamic hypothyroidism** which results from inadequate secretion of TRH due to impairment of hypothalamic cells by various destructive processes.

The first symptom of developing primary hypothyroidism in adults is an increase of serum TSH concentration. The state of increased serum TSH concentration, however, still without presence of classic clinical symptoms of hypothyroidism (serum thyroid hormone concentration is still normal) has been recently demonstrated as **subclinical hypothyroidism**. Other synonyms for this phase of primary adult hypothyroidism are: preclinical hypothyroidism, biochemical hypothyroidism, or decreased thyroid reserve. Some specialists acquire also the presence of circulating thyroid autoantibodies for diagnosis of this functional state. In some patients with subclinical hypothyroidism also the presence of the disorder of lipid metabolism (increased plasma LDL, total cholesterol, apoprotein B, and triacylglycerols concentrations) was proved. From the total number of the patients with diagnosed subclinical hypothyroidism in about 5 % of cases clinically manifested hypothyroidism develops yearly.

The clinical picture of primary hypothyroidism in adults usually develops very slowly. Its first symptoms start develop only after destruction of significant part of thyroid parenchyma. The onset of hypothyroidism is usually so insidious that the classic clinical manifestations may take months or even years to appear and frequently go unnoticed by persons well acquainted with the patient. Therefore, the symptoms are often attributed incorrectly by the patients and relatives to increasing age. The gradual development of the hypothyroid state is due to a slow progression of both thyroid hypofunction and the clinical manifestations after thyroid failure is complete.

The early symptoms of adult hypothyroidism are variable and nonspecific. Cold intolerance, drowsiness and slowing of intellectual and motor activities may be early manifestations. Increasing tiredness, weakness, slowness, and lethargy are common and lead to difficulty in performing a full day's work. The patients complain of poor memory and evident somnolence. They become apathetic and listless, and lose interest in work and environment. Their trains of thoughts are slow, they are bradypsychic. Despite a reduction in appetite, modest weight gain often occurs. Constipation may develop or, if present, become worse. The patients almost do not sweat. Their skin becomes drier and cooler. Women may complain of menstrual disturbances. Poor libido occasionally occurs in both sexes. At this stage of the disease the BMR is moderately decreased.

The fully developed clinical picture of adult hypothyroidism is characterized by typical facial appearance. Periorbital puffiness, broader and flat nose, thickened lips, sparce eye-brows, and poor mimic are evident (**facies myxoedematica**).

Skin ot the patient is dry, coarse, rough, and scurfy. It feels cool and dougher. Skin is pallor with orange tint. **Hair** is sparce, dry, and lacks luster. **Nails** are thin, fragile, brittle, and grow slowly.

Myxedema is most apparent on the face, the dorsa of the hands and feet, forearms, and in supraclavicular fossae. Mucinous material infiltrates also other tissues. Therefore, tongue is thick and enlarged (**macroglossia**) causing articulatory (pronunciational) problems (**dysarthria**). Dysarthria together with slow train of thoughts (**bradypsychism**) results in slow speech (**bradylalia**). **Voice** becomes deeper and husky. Myxedemotous infiltration of mucous membranes of Eustachian tube and middle ear, as well as myxedematous changes of cochlear fluid cause **defective hearing**.

With progression of the diesease **the BMR** falls to its minimal value, usually between –35 and –45 %. The decrease in energy metabolism and heat production is reflected in the low BMR , decreased appetite, cold intolerance, and slightly lower basal body temperature (moderate hypothermia). The rate of absorption of glucose from the gut is decreased, therefore, the oral glucose tolerance curve is characteristically flat. The decrease in lipid degradation results in the increase of serum cholesterol, triacylglycerols, and LDL concentrations. Serum concentration of high-density lipoprotein (HDL) is decreased. These changes of serum lipid concentrations usually accelerate the development of atherosclerosis and its complications, however, only in the hypothyroid patients with the presence of arterial hypertension.

Decreased adrenergic activity, respectivelly **depressed response of tissues to catecholamines** accompanies thyroid hormone deficiency. The mechanism underlying the decreased adrenergic responsiveness is uncertain. It is assumed that one of the causes could be the decrease of the number of adrenergic

receptors. **The cardiac output** and cardiac index at rest are decreased because of the reduction in both stroke volume and heart rate, reflecting loss of the inotropic and chronotropic affects of thyroid hormones. **Peripheral vascular resistance** at rest is increased, and blood volume is reduced. These hemodynamic alterations result in narrowing of pulse pressure, prolongation of circulation time, and decrease in blood flow to the tissues. The decrease in cutaneous circulation is responsible for the coolness and pallor of the skin and the increased sensitivity of the patient to cold.

Myocardial contractility is decreased. Dilatation of myocardium is evident, but signs of myocardial hypertrophy are not present. The heart is enlarged owing to the both dilatation and pericardial effusion. Electrocardiographic changes include sinus bradycardia, prolongation of the PR interval, low amplitude of QRS complex, and flattened or inverted T waves. Histopathological examination of the myocardium reveals presence of interstitial deposits of mucinous material (interstitial myxedema) and swelling of cardiomyocytes, with loss of striation. The set of introduced signs, concerning myocardium, respectively heart, has been termed **hypothyroid cardiomyopathy** (myxedema heart).

Skeletal muscles are usually stiff and aching. Delayed muscle contraction and relaxation are responsible for the slowness of movement. Tendon jerks are also delayed, evidently Achilles tendon reflex. On histopathological examination, the muscle fibers may show swelling, loss of normal striations, and separation by mucinous deposits.

Thyroid hormone deficiency and successive myxedematous infiltration of mucous membranes of GIT cause **decrease of peristaltic activity**, as well as of intestinal wall tonus. Decreased peristaltic activity, together with the decreased food intake, is responsible for the frequent complaint of constipation. These intestinal disorders may be extreme, leading to fecal impaction and great distention of colon (myxedema megacolon). Gaseous distention of the abdomen may also occur (myxedema ileus, adynamic ileus). The effects of hypothyroidism on intestinal absorption are complex. Although the rates of absorption of many substances are decreased, the total amount eventually absorbed may be normal because the decreased motility of the bowel may allow more time for absorption to take place.

Psychic and motor activities of the hypothyroid patients are slow. The patients are not able to concentrate to their work. There is loss of initiative. One of the characteristic features is a general slowing of all intellectual functions, including speech. Slow-wittedness, slowness in answering questions, and memory defects are common. Lethargy and somnolence are prominent. Dementia may occur and in the elderly patient may be mistaken for senile dementia. Psychiatric reactions are not uncommon and are usually of the paranoid or depressive type. The mentioned changes of CNS function originate due to actual thyroid hormone deficiency, and, therefore, they are reversible after adequate hormone therapy.

In the both sexes, **sexual activity** and **reproductive function** are significantly decreased. In men, hypothyroidism is usually accompanied by diminished libido, impotence, and oligospermia. In women, it is commonly associated with diminished libido, disorders even failure of ovulation, and irregular menstrual bleeding (rarely menorrhagia, but more frequently oligomenorrhea even amenorrhea).

The mild normocytic, normochromic **anemia** often occurs in the patients with hypothyroidism. It is the result of hypofunction and hypocellularity of the bone marrow. It is the response to the diminished oxygen requirements of tissues and to decreased production of erythropoietin. In about 12 % of patients with primary hypothyroidism pernicious anemia associated with the presence of an atrophic gastric mucosa occurs. In these patients also achlorhydria after maximal histamine stimulation, and achylia gastrica are usually present. The coexistence of pernicious anemia with primary hypothyroidism occurs in those instances in which autoimmune mechanism plays a primary role in the pathogenesis of primary hypothyroidism. In circulating blood of these patients besides antithyroid immunoglobulins G (IgG) also autoantibodies against gastric parietal cells have been found. Immediate cause of pernicious anemia is the deficiency of vitamin B12 induced by its impaired absorption. Insufficient vitamin B12 absorption is caused by deficiency of intrinsic factor due to atrophy of parietal cells. Folate deficiency resulting from malabsorption may also be responsible for a megaloblastic anemia. The both, menorrhagia and ineffective absorption of iron resulting from achlorhydria may lead to a microcytic, hypochromic anemia.

In the blood of a patient with primary hypothyroidism low T4 and proteine-bound iodine concentrations, and a high TSH concentration are present. In patients with central hypothyroidism blood TSH concentration is low.

At present the late stage of fully developed clinical picture of adult hypothyroidism does not occur. In the past, when the patients with severe long-standing hypothyroidism were untreated, they usually died of the consequences of accelerated atherosclerosis (most frequently coronary or cerebral), less frequently due to myxedema coma.

Myxedema coma. It is a rare acute complication of hypothyroidism, which may be fatal. The factors predisposing to myxedema coma include cold exposure, trauma, infection, and administration of CNS depressants. It is manifested by significant decrease of all metabolic processes, by evident hypothermia (decrease of rectal temperature to 35–32°C), extreme bradycardia, systemic arterial hypotension, thready pulse, and respiratory insufficiency. Extremely somnolent patient gradually becomes soporous, and finally develops coma. Mortality of the patients with myxedema coma is high, usually 50–70 per cent.

5.4.3 Hyperthyroidism

The complex of clinical, biochemical, and functional findings that originate when the tissues are exposed to, and respond to, excessive quantities of the thyroid hormones is termed **thyrotoxicosis**. The term **hyperthyroidism** is best reserved for denoting only those disorders in which *sustained hyperfunction* of the thyroid gland (overproduction of thyroid hormones) leads to thyrotoxicosis. Thus thyrotoxic states can be **classified** according to whether or not they are associated with hyperthyroidism:

I. **Thyrotoxicosis associated with hyperthyroidism**

A. Hyperthyroidism due to immunogenic thyroid autonomy

B. Hyperthyroidism due to nonimmunogenic thyroid autonomy

   a) Toxic multinodular goiter

   b) Toxic adenoma

C. Hyperthyroidism due to nonimmunogenic abnormal thyroid stimulator

D. Hyperthyroidism due to increased TSH production

E. Iodine-induced hyperthyroidism

II. **Thyrotoxicosis without hyperthyroidism**

A. Thyrotoxicosis factitia

B. Transient thyrotoxicosis associated with thyroiditis

C. Thyrotoxicosis due to ectopic production of thyroid hormones

In the patients with thyrotoxicosis total serum T_3 and T_4 concentrations, as well as free T_3 and T_4 concentrations are increased. In some patients with hyperthyroidism only serum T_3 concentration may be extremely increased. Whether this phenomenon results solely from the preferential increase in thyroid secretion of T_3 or whether there is in addition a disproportionate increase in peripheral conversion of T_4 to T_3 is uncertain, but the former factor is likely responsible in the majority. The thyrotoxic state resulting from extremely increased serum T_3 concentration has been designated **T_3 toxicosis**. The serum total T_4 concentration and free T_4 concentration are normal or decreased in the absence of a deficiency of TBG. In some patients, T_3 toxicosis may be the forerunner of the usual form of thyrotoxicosis in which production of both T_3 and T_4 is increased, whereas in other patients it may persist as such. T_3 toxicosis tends to be more frequent in the elderly population. It may occur in association with Graves-Basedow disease, toxic adenoma, or toxic multinodular goiter. Preliminary experience suggests that patients with T_3 toxicosis are more likely to enjoy a long-term remission after withdrawal of antithyroid drug therapy than patients with the usual form of thyrotoxicosis, in which production of both T_4 and T_3 is increased.

Thyrotoxicosis may sometimes be associated with a clear elevation of serum T_4 concentration, but with a normal or decreased serum T_3 concentration. This syndrome is termed **T_4 toxicosis**. It occurs most commonly in the setting of prior excess iodine exposure (iodine-induced thyrotoxicosis) in patients who are elderly, ill, or both. Increased iodine intake favors T_4 biosynthesis. In the absence of a history of excess iodine, the combination of high serum T_4 concentration and normal serum T_3 concentration presumably

reflects inhibition of peripheral T_3 generation from T_4 .

The clinical syndrom of thyrotoxicosis is characterized by manifestation of symptoms resulting from affection of several organs or organ systems. The major of these symptoms are induced by hypermetabolic state of organism. Hyperthyroidism and thyrotoxicosis belong to the most frequent endocrine diseases. They occur in 2–5 % of adult population, much more often in women than in men (5–7:1).

5.4.3.1 Thyrotoxicosis associated with hyperthyroidism

Thyrotoxicosis associated with hyperthyroidism encompasses those diseases that lead to **sustained overproduction** of hormones by the thyroid gland itself. The most frequently, hyperfunction of the thyroid results from the action of an abnormal (immunogenic or nonimmunogenic), homeostatically unregulated thyroid stimulator of extrapituitary origin, as in Graves-Basedow disease (being the most common), or in hyperthyroidism associated with trophoblastic tumor (being rare). Hyperthyroidism may be also relatively frequent due to the development of one or more areas of autonomous hyperfunction within the gland itself. The hyperfunction of the thyroid gland rarely results from excessive TSH secretion.

A. Hyperthyroidism due to immunogenic thyroid autonomy (Graves-Basedow disease)
Graves-Basedow disease is the most frequent form of hyperthyroidism. It is an autoimmune disease in which the thyroid gland escapes feedback regulatory influence, and becomes autonomous, i.e., independent from TSH. It is more common in women than in men and appears most often between the ages of 20 and 40. It is very rare before 10 and after 70 years of age. In the English-speaking world this disorder is known as Graves disease and on the continent of Europe as Basedow disease.

Etiology and pathogenesis. There is almost universal agreement that the cause of this disease is the origin of immunoglobulins of IgG class. These immunoglobulins act as antibodies against the thyroid TSH reseptors on the plasma membrane of epithelial cells of follicles. They are elaborated by B lymphocytes found directly in the thyroid gland. However, in circulating blood of the patient several types of antithyroid antibodies can be present (it is a heterogeneous group of polyclonal antibodies). Until lately they were called thyroid-stimulating immunoglobulins (TSIs), however, recently a preferable nomenclature is to refer to these immunoglobulins as **TSH receptor antibodies** (TRAbs). This term is preferable because only some of these immunoglobulins after binding to TSH receptors have a stimulating effects on epithelial cells (in ways analogous to the normal action of TSH). Others, however, inhibit the binding of TSH to its receptors in thyroid tissue (TSH-binding inhibitory imunoglobulins – TBIIs). TSH receptor antibodies are present in more than 90 % of patients with active Graves-Basedow disease.

The thyroid-stimulating immunoglobulins (TSIs) after binding to TSH receptors activate adenylate cyclase – cyclic adenosine monophosphate system which stimulates the cascade of intracellular reactions. These reactions lead to the growth of the thyroid gland (via hypertrophy and hyperplasia of epithelial cells), to the increased vascularity of its parenchyma, and to the increased biosynthesis and secretion of thyroid hormones. TSIs are an immunogenic abnormal thyroid stimulator. TSIs have essentially prolonged duration of action relative to that of TSH. Their high concentration in circulating blood effects the epithelial cells of the thyroid parenchyma permanently, while TSH has circadian rythm and a rather short half-life. Effects of TSIs are, for the present, the only example for such situation when autoantibodies do not act destructively.

The basic problem of etiopathogenesis of Graves-Basedow disease is the answer to the question what is **antigenic stimulus** for the production of antithyroid autoantibodies, respectively what causes the origin of clones of **thyroid-sensitized T lymphocytes**. There is a hypothesis about **random mutations** having no proofs for the present. But there is a variety of evidence which links autoimmune thyroid disease to infection with **the gram-negative enteric bacteria**. It has been found out that some bacteria of this type contain a TSH binding site that also binds Graves-Basedow-related IgG. Therefore, the initiating event may be the infection with gram-negative bacteria, mainly by Yersinia enterocolitica and E. coli, that gives rise to antibodies that cross-react with components of the human thyroid cell membranes. In an individual with the predetermined abnormality in immune surveillance, these antibodies

would persist and give rise to the clinical thyroid disease. Immediate impulse of the clinical manifestation of this disease may be various external factors, as e.g., infectious disease accompanied by fever, severe emotinal stress, some medical drugs, or high iodine intake. This hypothesis on **cross-reaction** of antibodies, originally elaborated against antigen of exogenous pathogenic factor, with self-antigen of organism, does not, meanwhile, gives the answer to the question, why antibodies against several antigens of thyroid gland simultaneously originate.

The hypothesis on the origin of **clones of thyroid-sensitized T lymphocytes** would require that sensitized T lymphocytes infiltrate the thyroid and elaborate stimulatory lymphokines, but an evidence that this occurs is lacking. This hypothesis presumes that in patients with chronic autoimmune thyroid disease, a sustained, genetically determined disorder of immune surveillance permits the persistence of clones of thyroid-sensitized immunocytes. This is likely the result of **abnormalities in suppressor T lymphocytes** (disturbance of their function or decrease of their number). Therefore, sensitized helper T lymphocytes start to produce lymphokines which stimulate the specific B lymphocytes. These activated B lymphocytes begin to produce the specific antithyroid IgG.

At present **the pathogenesis of infiltrative ophthalmopathy** (orbitopathy), which is the characteristic part of the clinical picture of Graves-Basedow disease, is not yet clear. The hypothesis on production of abnormal immunoglobulin is the best accepted for the present. This hypothesis assumes that an abnormal IgG acts in concert with an exophthalmos-producing factor composed in part of the beta subunit of TSH. The result of their effect is the induction of mucopolysaccharide synthesis, edema formation, and successive infiltrative changes in retroorbital tissues. There has been no evident progress toward elucidation of **the pathogenesis of the infiltrative dermopathy**. In its origin an abnormal immunoglobulin may also probably take part.

In etiopathogenesis of Graves-Basedow disease **genetic factors** play an important role. Population studies reveal an increased frequency of haplotypes HLA-B8 and HLA-DRw3 in whites. Of particular importance is the HLA-DRw3, which significantly increase the risk of Graves-Basedow disease and may affect its response to treatment. Not surprisingly, there is a distinct familial predisposition to this disease. The hereditary factor in Graves-Basedow disease also appears to involve its autoimmune aspects. This is suggested by the increased incidence in patients with Graves-Basedow disease or in members of their families of other autoimmune disorders, such as Hashimoto disease, primary thyroprive hypothyroidism or pernicious anemia, and probably other diseases with prominent autoimmune features.

Clinical features. Graves-Basedow disease is characterized by four major manifestations:

1. Diffuse goiter;
2. Thyrotoxicosis;
3. Infiltrative ophthalmopathy;
4. Infiltrative dermopathy.

In the individual patients these four major manifestations need not appear together. Infiltrative ophthalmopathy and infiltrative dermopathy may occur independently of the presence of goiter and symptoms of thyrotoxicosis. Ophthalmopathy and dermopathy are specifically related to Graves-Basedow disease. Thyrotoxicosis is manifested by hypermetabolism and by the symptoms resulting from disorders of various organ systems. The first two manifestations, i.e., diffuse goiter and thyrotoxicosis, are termed **diffuse toxic goiter**. This term connotes the presence of thyrotoxicosis resulting specifically from Graves-Basedow disease.

1. Goiter

Almost in all the patients with Graves-Basedow disease the thyroid gland is enlarged. But only in about 3 % of the patients with this disease the thyroid gland is of normal size, however, the symptoms of thyrotoxicosis are usually present. Hyperfunctioning goiter is mostly small or middle size, in some cases it may be rather large. Enlargement of the thyroid is diffuse and usually symmetrical. Goiter is soft and vascular, its surface is usually smooth. Enlargement of the thyroid may be noted as a fullness in the neck. The rich vascularization of goiter may be sometimes manifested by evident pulsation of the thyroid with a possible thrill and bruit (murmour) over it (struma pulsans, vibrans et fremens).

2. Thyrotoxicosis

The symptoms of thyrotoxicosis are common for all

forms of thyrotoxicosis irrespectively of the cause of their origin. However, in the clinical picture of thyrotoxicosis not always all its symptoms must be present. Unlike hypothyroidism the clinical symptoms of thyrotoxicosis are usually developing during shorter period, in the course of several days or weeks. Only seldom they may develop during several months. In the patients, emotional stress may be a forerunner, e.g., a car accident, the death of a member of the family, and the like.

At the onset of the disease mainly subjective symptoms dominate, e.g., nervousness, irritability, emotional tension, emotional lability (inappropriate spells of crying or euphoria), and insomnia. **The initial manifestations** also include excessive sweating and heat intolerance. Weight loss is usual despite well-maintained or increased appetite. The patient gets tired and out of breath at work very soon. Dyspnea and palpitations may occur. Other symptoms of thyrotoxicosis are developing gradually.

Fully developed clinical picture of thyrotoxicosis due to Graves-Basedow disease is rather variable because its individual symptoms are not always present and may occur in various combinations. The most common is **polysymptomatic thyrotoxicosis**, which is manifested by the symptoms resulting from disorders of various organ systems. It is due to the fact that thyroid hormones affect practically all tissues of organism. **Oligosymptomatic thyrotoxicosis** may also appear. The presence of the disease is only in some organs. Various combinations resulting from disorders of individual organ systems may be present. **Monosymptomatic thyrotoxicosis** is very rare. It occurs mainly in older patients. In its clinical picture disorders of only one organ system dominate. The symptoms of alteration of cardiovascular system (**cardial form** of thyrotoxicosis), or of skeletal muscles (**myopathic form** of thyrotoxicosis) are present most frequently. The origin of these monosymptomatic forms of thyrotoxicosis is likely due to the increased sensitivity of tissue of alterated organ system to thyroid hormones.

Metabolic symptoms of thyrotoxicosis. Overproduction of thyroid hormones stimulates metabolic activity of tissues and gives rise to the state of hypermetabolism. Excessive activation of oxidative processes in cells causes the increased consumption of oxygen per weight unit of tissue mass, what is manifested by **the increase of BMR** (in some instances even +100 %). The both, synthesis and degradation of protein are increased, the latter to a greater extent than the former, with the result that there is net degradation of tissue protein. This is evident in negative nitrogen balance, loss of weight, muscle wasting, weakness, and mild hypoalbuminemia. The stimulation of energy metabolism and heat production is reflected in the increased appetite and heat intolerance and in the slightly elevated basal body temperature. Cutaneous vasodilatation and excessive sweating (hyperhidrosis) are the protective mechanism against possible origin of hyperthermia. The increased lipid degradation is reflected in a decrease of plasma cholesterol, LDL, and triacylglycerols concentrations. The oral glucose tolerance curve is usually abnormal, often with high amplitude and steep incline (Gothic type). It is probably due to the stimulative effect of thyroid hormones to resorption of glucose in intestine. Pre-existing diabetes mellitus is aggravated by thyrotoxicosis, perhaps as a result of increased degradation of insulin.

Cardiovascular symptoms of thyrotoxicosis. They are the most frequent and most prominent manifestations of thyrotoxicosis. They are present almost in every patient with Graves-Basedow disease. Hypermetabolism and increased heat production give rise to the increased demands of tissues for oxygen supply and thereby also for circulation. These changes lead to the origin of syndrome of hyperkinetic circulation. Thyroid hormones in excess also have a direct cardiostimulatory action, possibly mediated by changes in the state of contractile proteins (mainly myosin) or in the function of sarcoplasmic reticulum. However, increased cardiac sensitivity to catecholamines in hyperthyroid subjects is also considered.

The most characteristic cardiovascular symptom of thyrotoxicosis is **sinus tachycardia** (pulse rate greater than 90 beats/min). It is almost always present, even at rest and during sleep. Respiratory arrhythmia is not present. During excercise heart rate is increasing disproportionately to the degree of physical load. Also dyspnea usually appears.

Cardiac **arrhythmias** are common with thyrotoxicosis. They are almost invariably supraventricular. In some patients, paroxysmal supraventricular tachycardia may also occur. Approximately 10 % of the patients with thyrotoxicosis manifest **atrial fibrilation**. Ventricular arrhythmias are unique. **Palpitations** may be rather common subjective symptom.

At rest, peripheral vascular resistance is decreased, and **cardiac output is increased** as a result of an increase in both stroke volume and heart rate. Systolic **blood pressure** is slightly increased due to the increased stroke volume. Diastolic blood pressure is decreased due to peripheral vasodilatation. The pulse pressure is widened as a result of both an increase in systolic pressure and a decrease in diastolic pressure.

As a result of a direct effect of increased concentrations of thyroid hormones on myocardium is long-term increased oxygen consumption in cardiomyocytes. Persistence of increased oxygen consumption and increased energy consumption (due to increased cardiac work) may lead to the origin of hypoxic changes in the myocardium. Also increased degradation of protein has a negative effect on myocardium. Due to the noted hypoxic and metabolic changes in some patients **thyrotoxic cardiomyopathy** (cor thyreotoxicum) may occur after a long period of persisting of thyroid hormone overproduction. It is clinically manifested by severe forms of arrhythmia and by a congestive heart failure. The response of such heart to digitalis is decreased.

Ocular symptoms of thyrotoxicosis. These symptoms are a very frequent manifestation of all forms of thyrotoxicosis, regardless of the underlying cause. Spasm and retraction of the upper eyelids (increased tonus of musculus levator palpebrae), which lead to widening of the palpebral fissure, are most common. These changes of the eyelids are evident as the presence of a rim of sclere between the upper lids and the superior margin of the iris (**Dalrympl symptom**). It is responsible for the bright-eyed, staring appearance of the patient with thyrotoxicosis. Accompanying lid retraction are the phenomena of **lid lag**, in which the upper lid lags behind the globe, exposing more of the sclera, when the patient is asked to gaze slowly downward. Therefore, the presence of a rim of sclera is constant (**Graefe symptom**). When the patient gazes slowly upward the globe often lags behind the upper lid. The movements of the lids are jerky and spasmodic. A fine tremor of the lightly closed lids can often be observed (**Rosenbach symptom**). The patients blink rarely, 1–2/min, while the norm is 3–5/min. This infrequent blinking is termed **Stellwag symptom**. Due to the increased lacrimation in the patients with thyrotoxicosis, expressive shiny eyes can be observed. These ocular manifestations appear to be the result of increased adrenergic activity and usually subside when the thyrotoxicosis is corrected. It is important to distinguish these ocular manifestations, which occur in all forms of thyrotoxicosis, from those of the infiltrative ophthalmopathy, which are characteristic of Graves-Basedow disease.

Skin symptoms of thyrotoxicosis. Thyrotoxicosis leads to a variety of changes in the skin and its appendages. Most characteristic is **the warm moist feel** of the skin that results from cutaneous vasodilatation and excessive sweating as part of the hyperdynamic circulatory state. Skin is, therefore, fine with a velvety texture. The hands are usually warm and moist, **palmar erythema** is common. The complexion is rosy and the patient blushes readily. Increased diffuse pigmentation is formed occasionally, which may result from hypersecretion of ACTH secondary to accelerated turnover of cortisol. **Hair** is fine and friable, does not retain a wave and some may fall out. **Nails** are often soft and friable. A characteristic finding is **Plummer nails**, especially on the ring finger. This term is applied to separation of the distal margin of the nail from the nailbed with irregular recession of the junction (**onycholysis**).

Psychic and nervous symptoms of thyrotoxicosis. These symptoms are an almost invariable accompaniment of thyrotoxicosis. The patients complain of nervousness, irritability, psychic and motor restlessness, anxiety, emotional tension, emotional lability, insomnia, and hyperkinesia. **Nervousness** may manifest as a feeling of apprehension and inability to concentrate. **Emotional lability** and irritability may lead to difficulty in interpersonal relationships and to inappropriate spells of crying and laughing, or euphoria and depression. The patients are scared without apparent reason. Their speech is fast and exciting, trains of thoughts are accelerated. They respond quickly to questions or commands. Their behaviour is hyperactive and they are always in a hury. During the interview the patient cannot sit still, drums on the table, taps a foot, or shifts positions frequently. Movements are quick, jerky, exaggerated, and often purposeless. Examination reveals **a fine rhythmic tremor** of stretched finger tips of the arms stretched forward (it is better inspected by touch than by sight). The fine rhythmic tremor of put out tongue and lightly closed eyelids is also present. **Tendon reflexes** are rapid, mainly Achilles' jerk. The physiological basis of the findings refer-

able to the nervous system is not well understood. In part, they may reflect increased adrenergic activity.

Symptoms of thyrotoxicosis due to alterations of skeletal muscles. Weakness and fatigability are frequent. Often the weakness is most prominent in the proximal muscles of the limbs (mainly extensor of the legs) and is manifested by difficulty in climbing stairs or in maitaining the leg in an extended position. The patient is also unable to climb the chair (**Plummer symptom**) or to rise from a sitting. Thyrotoxicosis may lead to degeneration of skeletal muscle fibres. The mentioned disorders of skeletal muscles are termed **thyrotoxic myopathy**.

Other symptoms of thyrotoxicosis. The commonest of them are referable to the alimentary tract, mainly those related to **bowel function**. Diarrhea is rare. More often stools are less well formed, and the frequency of bowel movements is increased. Thyrotoxicosis is generally associated with increased excretion of calcium and phosphorus in urine and stool. Excessive loss of mineral is sometimes associated with **demineralization of bones** and occasionally with pathological fractures, especially in elders. Thyrotoxicosis in early life may be associated with delayed sexual maturation, although general physical development is normal and skeletal growth is often accelerated. In adults an **increase in libido** sometimes occurs in both sexes. In women menstrual function is usually disturbed. The change in menstrual pattern usually takes the form of **oligomenorrhea** with a variable intermenstrual period, occasionally progressing to amenorrhea.

3. Infiltrative ophthalmopathy

Infiltrative ophthalmopathy (infiltrative orbitopathy, exophthalmic syndrome) is characteristic only for Graves-Basedow disease. It occurs in about 50 % of patients and is induced by a specific immunoglobulin. In some patients it may appear in the course of thyrotoxicosis, most frequently, however, occurs simultaneously with thyrotoxicosis. Occasionally, infiltrative ophthalmopathy occurs in the absence of diffuse toxic goiter, an entity that is termed euthyroid ophthalmic Graves-Basedow disease.

In the patients with infiltrative ophthalmopathy, the volume of orbital contents is increased because of both an increase in retrobulbar connective tissue and an increase in mass of the extraocular muscles. This increase in both retrobulbar tissues is due to edema resulting from the increased content of the glycosaminoglycans and also due to an inflammatory infiltrate. Glycosaminoglycans are very hydrophilic substances, and, therefore, the water content in retrobulbar tissues is increased. The inflammatory infiltrate consists of lymphocytes, mast cells, and plasma cells. Also augmentation of connective and fat tissues participates in increased volume of the orbital contents. The fibres of extraocular muscles show degeneration and loss of striations, with ultimate fibrosis.

The symptoms associated with infiltrative ophthalmopathy are diverse and may appear in varying combinations. The most evident symptom is protruding of the globe (**exophthalmos**, proptosis), which is usually bilateral and frequently asymmetrical, and may be accompanied by a feeling of pressure behind the globes. The cause of protruding of the globes is the increased volume of the orbital contents. When exophthalmos is pronounced, the patient may sleep with the eyes partly open (**lagophthalmos**).

Edematous and infiltrative changes give rise to **myopathy of the extraocular muscles**. Patients frequently report that their vision is blurred and that their eyes tire easily. Double vision (**diplopia**) may occur. Weakness of the extraocular muscles is most commonly evident in an inability to achieve or maintain convergence (**Moebius symptom**). Limitation of upward gaze and especially of superolateral gaze may be present. Sometimes the paralysis of some extraocular muscles may occur. It is manifested by permanent anomalous position of more often both globes, but sometimes only one of them. Various forms of bilateral or unilateral **strabismus** originate. The ocular muscle weakness that results in impaired upward gaze and convergence and strabismus with varying degrees of diplopia is termed **exophthalmic ophthalmoplegia**.

Severe and long-standing lagophthalmos promotes drying and corneal damage with subsequent ulceration of the cornea, **keratitis ulcerosa** develops. When exophthalmos progresses rapidly it is termed **progressive exophthalmos**. In untreated patients infectious inflammation of all orbital structures may occur (**panophthalmitis**), which may lead to destruction of one or both eyes and thereby to loss of vision (**amaurosis**). Ophthalmopathy connected with such severe complications is termed **malignant exophthalmos**.

4. **Infiltrative dermopathy**

It occurs in about 5–10 % of patients with Graves-Basedow disease. It is almost always accompanied by infiltrative ophthalmopathy, usually of a severe degree. Pathological immunoglobulins probably participate in its origin. Skin is infiltrated by glycosaminoglycans and by the cells characteristic for chronic inflammatory process. This dermopathy is usually localized over the pretibial area (**pretibial myxedema**) and over the dorsa of the feet. Rarely it is seen on the face or dorsa of the hands. The skin of the affected areas is thickened, raised, and has a peau d' orange appearance. The indurations are usually discrete, assuming a plaquelike or nodular configuration but in some instances are confluent.

Severe complications of Graves-Basedow disease

Besides the both, congestive heart failure and malignant exophthalmos already mentioned, the third dangerous complication is thyrotoxic crisis.

Thyrotoxic crisis (crisis thyreotoxica)

Thyrotoxic crisis is an extreme accentuation of thyrotoxicosis. It is an uncommon but serious complication of Graves-Basedow disease. Crisis is almost always of abrupt onset and occurs in patients in whom pre-existing thyrotoxicosis has been treated either incompletely or not at all. It is almost always evoked by **a precipitating factors**, such as infection, trauma, surgical operations, surgical emergencies, radiation thyroiditis, toxemia of pregnancy, and parturition. The mechanism whereby such factors lead to an accentuation of thyrotoxicosis has not been ascertained. It does not appear to be an acute increase in the severity of thyroid hyperfunction. Rather, it may represent a shift from protein-bound to free thyroid hormones. It is manifested by extreme hypermetabolism and by fulminating increase in all characteristic symptoms of thyrotoxicosis.

The clinical picture of thyrotoxic crisis is dominated by hyperpyrexia (40–41°C), marked tachycardia (over 140/min), even tachyarrhythmia associated with atrial fibrilation, extreme irritability and restlessness, diarrhea, vomiting, profuse sweating, and dehydration. As the crisis progresses, apathy, prostration, stupor, and coma may supervene, but with only slight elevation of temperature. The blood pressure, which initially is well maintained, may fall to hypotensive levels. Mortality of the patients with thyrotoxic crisis is high, usually up to 50 %.

B. Hyperthyroidism due to nonimmunogenic thyroid autonomy

There are two forms of hyperthyroidism due to nonimmunogenic (intrinsic) thyroid autonomy: toxic multinodular goiter and toxic adenoma. In the past both these forms were included in a common term toxic nodular goiter. With regard to their different pathogenesis and histopathology they are distinguished as separate nosologic entities.

a) **Toxic multinodular goiter**

Toxic multinodular goiter is an occasional consequence of a long-standing simple goiter, although the proportion of cases in which this complication arises is uncertain. The symptoms of hyperthyroidism usually originate after the age of 50 in patients who have had nontoxic multinodular goiter for many years. It is many times more common in women than in men.

The cause of gradually originating autonomy of certain areas of thyroid parenchyma (their independence from TSH stimulation), which causes transition from nontoxic to toxic multinodular goiter, is not precisely known. It is probably the result of functional heterogenity of epithelial cells of follicles. Sometimes, hyperthyroidism may appear abruptly, but this almost always results from exposure to increased quantities of iodine in the patients with a nontoxic multinodular goiter (iodine-induced hyperthyroidism, jodbasedow). Administration of iodides permits autonomous foci to increase their rate of hormone biosynthesis and secretion to truly excessive levels.

From the histopathological and functional viewpoint two types of toxic multinodular goiter can be distinguished:

1. **The first type** of toxic multinodular goiter is more common. It is characterized by a diffuse small focal (patchy foci) distribution of radioisotope in scintillation scaning. This distribution is not usually altered by administration of exogenous thyroid hormone. Histopathological examination reveals multiple aggregates of small follicles with hyperplastic epithelium (micronodules), interspersed with variably sized inactive nodules. It is very likely that some of these inactive nodules may preserve the ability of hormone

production. They are inactive because TSH secretion is suppressed by the increased concentration of thyroid hormones in circulating blood. Thyroid hormones are produced by numerous autonomous micronodules.

2. **The second type** of toxic multinodular goiter is less common. The accumulation of radioiodine is localized only in one or more discrete nodules within the gland, the remainder appearing to be essentially nonfunctional (suppressed). No further suppresion is produced by exogenous thyroid hormone, but administration of TSH stimulates accumulation of radioiodine in the areas previously inactive. Histopathological examination reveals that the hyperfunctioning areas resemble adenomas in being reasonably well demarcated from surrounding tissue. They produce hormones autonomously. They consist of large follicles, sometimes with hyperplastic epithelium. The remaining tissue appears inactive. Zones of degeneration are usually present in both hyperfunctioning and nonfunctioning areas.

Clinical features. The extent of overproduction of thyroid hormones in toxic multinodular goiter is usually mild compared with that in Graves-Basedow disease. Therefore, the serum T_4 and T_3 concentrations are only slightly above normal. TSH secretion is inhibited. The symptoms of infiltrative ophthalmopathy and infiltrative dermopathy are never present, because toxic multinodular goiter is not a disease with autoimmune pathogenesis.

The clinical picture of thyrotoxicosis due to toxic multinodular goiter is usually oligosymptomatic. **Cardiovascular manifestations** tend to predominate, possibly because of the age of the patients in which this form of hyperthyroidism may be often acompanied by ischemic heart disease. These manifestations may include tachycardia, arrhythmias, atrial fibrilation, or congestive heart failure. Weakness, tiredness and wasting of muscles are common. The nervous manifestations are usually mild or absent, but emotional lability may be pronounced. As the thyroid tissue due to toxic multinodular goiter is of tougher consistency and the goiter is often retrosternal, the symptoms of mechanical local syndrome may be also present.

b) **Toxic adenoma**

Toxic adenoma (Plummer disease) is less common as toxic multinodular goiter. It occurs in a younger age group than does toxic multinodular goiter, often between the ages of 30 and 40. Thyrotoxicosis is usually caused by a solitary hyperfunctional autonomous nodule (**toxic uninodular goiter**). Occasionally, two or three adenomas of similar character are present.

From the point of view of histopathology it is true follicular adenoma being well encapsulated (demarcated from surrounding tissue). Its pathogenesis is unknown. In anamnesis the patient often reports that the nodule (lump) in the neck has grown slowly over many years. The nodule becomes capable to produce thyrotoxicosis if it has achieved a diameter of 2.5 to 3 cm. Initially it is present as a small nodule the function of which is insufficient to disturb hormonal equilibrium, though its capacity to accumulate radioiodine is evident in scintiscans as an area of increased density within the still-functioning extranodular tissue (**warm nodule**). With time, the nodule grows larger, its function increasing until it is sufficient to suppress TSH secretion. Consequently, the remainder of the gland undergoes relative atrophy and complete loss of function. The scintiscan reveals radioiodine accumulation only in the adenoma (**hot nodule**). At this time frank thyrotoxicosis usually sepervenes. Hyperthyroidism is not caused by the whole parenchyma of the thyroid gland, as it is in the patients with Graves-Basedow disease, but it is induced only by its relatively small encapsulated area.

Clinical features. The clinical picture of toxic adenoma is similar to that of toxic multinodular goiter. The peripheral manifestations of thyrotoxicosis due to toxic adenoma are also generally milder than those of diffuse toxic goiter. The symptoms of infiltrative ophthalmopathy and infiltrative dermopathy are never present. **Cardiovascular symptoms** may be prominent, and their relevance increases with the age of the patient. Toxic adenoma in some patients secrete T_3 predominantly, therefore, serum T_4 concentration is normal and serum T_3 concentration alone is increased. Relative to its overall rate of occurrence, toxic adenoma is the most frequent of T_3 **toxicosis**. Secretion of TSH is suppressed, its serum concentration is low. On palpation, the nodule is usually felt as a smooth, well-defined, round or ovoid mass that is firm and moves freely on swallowing.

C. Hyperthyroidism due to nonimmunogenic abnormal thyroid stimulator
This form of hyperthyroidism may be also termed hyperthyroidism due to **trophoblastic tumors**, because malignant tumors arising from trophoblastic tissue (hydatidiform mole, choriocarcinoma, or metastatic embryonal carcinoma of the testis) may be sometimes accompanied by the symptoms of thyrotoxicosis. The increased production of T_4 and T_3 is induced by a circulating thyroid stimulator, which is not, however, identical with TSH. It is probably human chorionic gonadotrophin (hCG), or a protein closely related to it (**chorionthyrotrophin**). It has been found out that alpha subunits of TSH and gonadotropins are identical.

Serum T_4 and T_3 concentrations are increased only slightly, serum TSH concentration is decreased. Thyrotoxicosis is mild, goiter is absent.

D. Hyperthyroidism due to increased TSH production
Rarely, hyperthyroidism and thyrotoxicosis are the result of sustained hypersecretion of TSH (central hyperthyroidism). The cause of overproduction of TSH may be TSH-secreting pituitary adenoma, selective resistance of pituitary to thyroid hormones, or increased secretion of hypothalamic TRH. All these varietes are associated with a diffuse hyperfunctioning goiter. Features of autoimmune thyroid disease are absent in the patient and in the patient's family. Serum TSH concentration, as well as serum T_4 and T_3 concentrations are increased. In the clinical picture of TSH-secreting pituitary adenoma some local symptoms, secondary to compression of surrounding structures, may be present.

Hyperthyroidism due to ectopic (paraneoplastic) production of TSH is extraordinarily rare. Its production in bronchogenic carcinoma is most common.

E. Iodine-induced hyperthyroidism
For some time it has been known that administration of supplemental iodine to subjects with endemic iodine-deficiency goiter can result in overproduction of thyroid hormones. This response has been termed **jodbasedow**. It usually occurs in the patients with nontoxic multinodular goiter, some areas of which have autonomous function. This autonomous areas of its tissue, however, has not appeared before administration of iodine. Since such patients tend to be elderly with the danger of serious cardiovascular manifestations thyrotoxicosis should ensue, large doses of iodine should not be given to those with the multinodular goiter. The jodbasedow phenomenon can seldom occur in younger individuals with the diffuse goiter, and here thyroid-stimulating immunoglobulins are often present. Thyrotoxicosis is induced by random administrations of pharmaceuticals containing iodine, such as expectorants, x-ray contrast media, or any other forms. It seems that jodbasedow occurs only in thyroid glands in which function is independent of TSH stimulation and refers to the induction of thyrotoxicosis in a previously euthyroid patients as a result of exposure to administration of larger doses of iodine. Mechanism of inducing hyperthyroidism by iodine is not exactly known. In these patients, serum T_3 concentration is quite often normal, but serum total and free T_4 concentrations are increased (T_4 **toxicosis**).

5.4.3.2 Thyrotoxicosis without hyperthyroidism

Thyrotoxicosis not associated with hyperthyroidism is rare. It may have a iatrogenic origin, it may be associated with various forms of inflammatory disease of the thyroid gland, or the source of excess of thyroid hormones may be outside of the thyroid gland itself.

A. Thyrotoxicosis factitia
This term designates temporary thyrotoxicosis that arises from ingestion, usually chronic, of excessive quantities of exogenic thyroid hormone (exogenous, iatrogenic thyrotoxicosis). It occurs rarely. The symptoms are typical of thyrotoxicosis and may be severe. If thyrotoxicosis is induced by an excessive intake of T_4 , its symptoms persist several weeks after the intake of this hormone has been finished. However, after finishing of an excessive intake of T_3 , the symptoms of thyrotoxicosis will disappear much more faster. Due to long-standing intake of exogenic thyroid hormone, endogenous thyroid function is suppressed and thyroid parenchyma may become atrophic (serum TSH is decreased, therefore, the stimulation of thyroid parenchyma is suppressed).

B. Transient thyrotoxicosis associated with thyroiditis
The symptoms of thyrotoxicosis may appear in the

early phase of **subacute thyroiditis**. The episode of thyrotoxicosis may also occur in the patient with a painless form of thyroiditis in which biopsy of the thyroid reveals the histopathological changes of chronic lymphocytic thyroiditis that, however, differs from that of Hashimoto thyroiditis. Circulating antithyroid antibodies, when present, are in low titer. This form of thyroiditis has been variously designated as painless thyroiditis, silent thyroiditis, or chronic thyroiditis with spontaneously resolving thyrotoxicosis. At present the term **chronic thyroiditis with transient thyrotoxicosis** is preferred.

In the both above mentioned forms of thyroiditis the thyrotoxicosis is usually of a mild degree, only in some instances its symptoms may be severer. The clinical features of thyrotoxicosis reflect the extent of elevation of serum T_4 and T_3 concentrations. It is supposed not to be induced by the increase biosynthesis and secretiom of thyroid hormones. The cause of its origin is presumably larger destruction of thyroid parenchyma (**disruption of follicles**) which appears suddenly in the course of inflammatory process. Due to the disruption of a large number of follicles the extensive nonregulated depletion of thyroid hormone stores into circulating blood occurs. Low or undetectable serum TSH concentration (suppression of its secretion by the increased concentrations of thyroid hormones in blood), as well as decreased accumulation of radioiodine in the thyroid gland are the evidence of this assumption. Later, as glandular hormones are depleted, the patient may pass through a hypothyroid phase, in which serum T_4 and T_3 concentrations are low and serum TSH concentration is increased. After this hypothyroid phase, duration of which is several months, the patient usually returns to an euthyroid state.

C. Thyrotoxicosis due to ectopic production of thyroid hormones

The symptoms of thyrotoxicosis may be rarely induced by hyperfunctioning distant **metastases of thyroid carcinoma** (mostly follicular carcinoma) in lung or bones. Ectopic thyroid tissue may also be present in teratomas, especially in the ovary. About 3 % of the whole number of ovarian teratomas are hyperfunctioning. The tissue of such teratomas produces thyroid hormones, and, therefore, it may evoke mild thyrotoxicosis (**struma ovarii**). A severer degree of thyrotoxicosis can appear due to the origin of autonomous adenoma of this ectopic thyroid tissue.

5.4.4 Inflammations of the thyroid gland (thyroiditis)

Inflammations of the thyroid gland (thyroiditis) are rather common. From the etiological point of view several forms of thyroiditis are distinguished. Thyroid biopsy and histopathological examination of obtained specimens has an important role in the diagnosis of their certain types. The most common are lymphocytic thyroiditis, chronic thyroiditis with transient thyrotoxicosis, and subacute thyroiditis. They are notable for their different clinical courses and for the fact that each can be associated, at one time or another, with an euthyroid, thyrotoxic, or hypothyroid state. Acute thyroiditis, chronic fibrosing thyroiditis, and the other types of thyroiditis are rare.

5.4.4.1 Acute thyroiditis

Acute thyroiditis (**pyogenic thyroiditis**) is rare. It is due to an infection of the thyroid gland by pyogenic microorganisms, most frequently by staphylococci, streptococci, or pneumococci. Less commonly it may be due to salmonellae or E. coli. Infectious agents may come from infectious focus located in the close area of the thyroid and get into it by lymphatic or vascular vessels. Sometimes it may be the result of hematogenous dissemination from distant primary septic foci, or it may be the complication of infectious disease. If pyogenic thyroiditis is nontreated abscesses may develop in the thyroid.

Clinical features. The clinical picture of acute thyroiditis is characterized by sudden origin of evidently painful goiter. Usually only one lobe of the thyroid gland is enlarged. The overlying skin is red and warm. The goiter is tender and painful spontaneously and on palpation. The pain is aggravated by swallowing (dysphagia is present), yawning, and by turning the head. On the affected side, the pain characteristically radiates to the ear, jaw, or occiput. Fever, malaise, leukocytosis, and increased erythrocyte sedimentation rate are present. Serum thyroid hormone concentration is normal. In scintiscan abscess, if present, is usually manifested as a cold nodule. In circulating blood antithyroid antibodies are not present.

5.4.4.2 Subacute thyroiditis

Subacute thyroiditis (**de Quervain thyroiditis**) is considered viral in origin (**viral thyroiditis**). The specific virus which would be the cause of its origin, however, has not been found out. The viral infection of the thyroid gland usually follows a cataral upper respiratory infection, or influenza. A tendency to a seasonal and geographic aggregation of cases has been noted. The mumps virus, influenza virus, Coxackie B viruses, echoviruses, and adenoviruses are considered the etiological agents of subacute thyroiditis. Women are more frequently affected than men. The maximal incidence is in the fourth and fifth decades. In about 70 % of the patients the leukocyte antigen HLA-Bw35 is present, what indicates possibility of existence of genetic predisposition to this disease.

Histopathological examination reveals that the parenchyma of affected area is infiltrated with cells predominantly of the mononuclear type. Many of the follicles show disruption of epithelium with partial or complete loss of colloid. The colloid is found in the interstitium and is surrounded by the multinucleate giant cells (**giant cell thyroiditis**). The follicular changes may progress to form granulomas (**granulomatous thyroiditis**).

Pathophysiology. Destruction of follicular epithelium and loss of follicular integrity are the primary events in the pathophysiology of subacute thyroiditis. Preformed hormones are released into circulating blood, often in quantities sufficient to produce thyrotoxicosis (**the thyrotoxic phase**). Later in the disease, when stores of preformed thyroid hormones are depleted, the patient may pass through a period of mild transient hypothyroidism (**the hypothyroid phase**). Ultimately, as biosynthesis of hormones resumes and their stores are repleted, the thyroid function usually becomes normal.

Clinical features. The characteristic feature of subacute thyroiditis is the gradual or sudden appearance of pain in the region of the thyroid, which is slightly to moderately enlarged. One lobe generally being more severely affected than the other. Less commonly it may be unilateral. The goiter is painful spontaneously and on palpation. The pain is aggravated by swallowing (dysphagia is present), yawning, and turning the head. The pain characteristically radiates to the ear, teeth of the lower jaw, or occiput. A painless form of subacute thyroiditis may occur only rarely. On palpation, the enlarged thyroid is firm and often nodular.

The origin of painful goiter is usually accompanied by fever, but in some cases the body temperature in the morning is increased only slightly. The most striking laboratory finding of subacute thyroiditis is a high erythrocyte sedimentation rate (usually>100). The leukocyte count is normal or, at most, moderately increased. Antithyroid antibodies are not present.

In the early phase of subacute thyroiditis in some patients the clinical symptoms of mild transient thyrotoxicosis (e.g., tachycardia, palpitation, nervousness, lassitude, and weakness) may occur. They are evoked by depletion of larger quantities of preformed thyroid hormones due to the disruption of a larger number of follicles. The thyrotoxic phase lasts about one month and results in spontaneous withdrawal followed by return of serum thyroid hormone concentrations to normal (**the phase of transient euthyroidism**). Duration of this phase is about 1–3 weeks. Later in the disease serum thyroid hormone concentrations sometimes decrease below normal level. The hypothyroid phase lasts 2–5 months. In this phase the goiter gradually diminishes.

In the phase of transient thyrotoxicosis serum T_4 and T_3 concentrations are slightly increased, serum TSH concentration is decreased. The scintiscan reveals that radioiodine accumulation in the affected area is low. In the hypothyroid phase serum thyroid hormone concentrations are decreased below normal and serum TSH concentration is appropriately elevated. In the hypothyroid phase radioiodine accumulation may be temporarily increased. With recovery the normal values for serum thyroid hormones and TSH concentrations are restored.

Occasionally, the locus of maximal involvement migrates over the course of a few weeks to other parts of the thyroid gland. This is usually manifested by the change of physical findings and by a relapse in other clinical symptoms and laboratory findings as well. The disease usually subsides spontaneously within a few months, leaving no residual deficiency of the thyroid function. Usually only very mild, functionally non-significant, residual fibrosis has been left. The goiter usually completely disappears. Rarely recidivation of subacute thyroiditis may occur, mainly after some viral diseases. In rare cases, the subacute thyroiditis may smoulder with re-

peated exacerbations over many months, permanent hypothyroidism being the result.

5.4.4.3 Chronic thyroiditis with transient thyrotoxicosis

Chronic thyroiditis with transient thyrotoxicosis (**painless thyroiditis, silent thyroiditis**) is a disease in which a self-limited episode of thyrotoxicosis is associated with a histologic picture of chronic lymphocytic thyroiditis that differs from that of Hashimoto thyroiditis. It occurs in patients of any age, women are more frequently affected than men.

Etiology and pathogenesis of this disease are unclear. Viral antibody titers show no characteristic pattern. Lymphocytic infiltration and presence of plasma cells within the thyroid could suggest an autoimmune basis. However, the absence of high titers of circulating antithyroid antibodies and the permanent resolution in most would argue against this.

The thyroid gland is enlarged in only about 50 % of the patients. The thyroid enlargement is usually mild and unaccompanied by nodularity. Thyrotoxicosis is rarely severe, and elevation of serum T_4 and T_3 concentrations is consonant with a degree of thyrotoxicosis. Conventional essays reveal antithyroid antibodies in only about one half of the patients. Unlike subacute thyroiditis, the erythrocyte sedimentation rate is normal or near normal.

It is presumed that thyrotoxicosis results from leakage of preformed hormones from the thyroid gland (due to the destruction of follicular epithelium and loss of follicular integrity), as in subacute thyroiditis. The thyrotoxic phase lasts usually two manths. About one half of the patients return to an euthyroid state and remain well. The remaining half patients pass through a short transient euthyroid phase to hypothyroid phase. This phase of self-limited hypothyroidism varies in duration from 2 to 9 months. The tendency of the disorder to pass through a hypothyroid phase is not surprising in view of the extensive depletion of glandular hormone stores that must occur while hormones are leaking from the gland and new hormone synthesis is reduced. This phase gives way to a restoration of euthyroidism, but in about 5 % of the patients permanent hypothyroidism develops years later. In some patients recurrence (sometimes multiple recurrences) of thyrotoxicosis may occur months or years after restoration of an euthyroid state.

The postpartum thyroiditis syndrome is similar in presentation, course, and pathophysiology. Transient thyrotoxicosis may occur some time within a few months (usually 2–4) after delivery. The thyrotoxicosis phase is often followed by the phase of hypothyroidism which lasts several months. The phase of self-limited hypothyroidism may be only component of the disease that is diagnosed because the thyrotoxic phase may be very brief. After the hypothyroid phase the patient usually returns to an euthyroid state. The postpartum thyroiditis syndrome may occur in 4–8 % of pregnant women. Very likely, it has **an autoimmune** basis. Most patients have a small goiter and positive tests for antithyroid peroxidase antibodies (formerly called antimicrosomal antibodies), although titers are low. There is a strong association with the HLA-DR3 and HLA-DR5 haplotypes. The postpartum occurrence of this syndrome is probably due to a rebound of immune activity after its suppression during pregnancy.

5.4.4.4 Lymphocytic thyroiditis (Hashimoto disease)

Lymphocytic thyroiditis (Hashimoto thyroiditis, struma lymphomatosa) is the most common type of inflammations of the thyroid gland. About 3–5 % of population are affected, women more frequently than men. It may occur at any age, most often between the ages of 30 and 50. It often develops also at puberty participating in more than one half of goiters originated in this period. Hashimoto thyroiditis is **an autoimmune disease** characterized by chronic course (chronic autoimmune thyroiditis), painless goiter, and by gradual development of hypothyroidism. The evidence of autoimmunity includes the lymphocytic infiltration of the thyroid tissue and the presence in the serum of high titers of antibodies against several components of epithelial cells of follicles.

Etiology and pathogenesis are not exactly known. It is assumed that autoimmunity in Hashimoto disease reflects genetically determined defect in the function or deficiency of suppressor T cells (probably of autosomal dominant inheritance). This defect allows the emergence and persistence of forbidden clones of helper T cells directed against the thyroid antigens. The thyroid-sensitized helper T lymphocytes cooperate with B cells in the thyroid to produce a constellation of the specific antithyroid autoantibodies. In patients with Hashimoto thyroiditis, unlike those with Graves-Basedow disease, the number

of cytotoxic T lymphocytes, damaging epithelial cells of follicles, is increased.

Lymphocytic thyroiditis, primary idiopathic hypothyroidism, and Graves-Basedow disease often occur familially. Therefore, it is generally agreed that the noted diseases are various variants of the same autoimmune disease. Mechanisms responsible for the development of individual clinical forms of the mentioned triad of autoimmune thyroid disorders are not, however, known.

Hashimoto thyroiditis coexists in some frequency with other diseases of an autoimmune nature, including type 1 diabetes mellitus, Addison disease, primary idiopathic hypoparathyroidism, pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, chronic active hepatitis, myasthenia gravis, Sjögren syndrome, vitiligo, early graying of the hair, and others. These diseases, as well as Hashimoto disease, also occur frequently in family members of the patients with Hashimoto diesease. A significant association between Hashimoto disease and the human leukocyte antigens HLA-DR3, HLA-DR5, and HLA-B8 also exists.

Histopathologic examination of the thyroid gland reveals destruction of epithelial cells and fibrosis which is more evident especially in the older lesions. The most characteristic finding is an abundant diffuse lymphocytic infiltration of the interstitial tissue. Interfollicular infiltration by plasma cells may be often present. More of the remaining epithelial cells may be larger and show oxyphilic changes in the cytoplasm. They are called **Askanazy cells** and are considered pathognomic for this disease. In some cases epithelial hyperplasia may be prominent.

From the histopathologic point of view two variants of Hashimoto thyroiditis may be distinguished. The more common is **oxyphilic variant** which is characterized by more evident exyphilic changes in the cytoplasm of epithelial cells, less fibrosis, and more prominent infiltration with lymphocytes. **The fibrous variant** is characterized mainly by evident infiltration with plasma cells and display of more fibrosis.

Hashimoto thyroiditis usually begins with discovering of **a small painless goiter**, which enlarges gradually over many years, especially if left untreated. It is often found during examination for some other complaint. Goiter is the outstanding clinical feature of Hashimoto disease. It is usually diffuse and firm in consistency and moves freely when the patient swallows. Its surface is either smooth or scallopes, but well-defined nodules are unusual. Therefore, compression of adjacent structures, such as trachea, esophagus, and recurrent laryngeal nerves, occurs rarely. Both lobes of the thyroid are enlarged, but one is often larger than the other. In occasional instances, however, the thyroid enlarges rapidly, and when accompanied by pain and tenderness the disorder may mimic subacute thyroiditis.

The goiter is usually the only feature of Hashimoto thyroiditis for a long time. It is manifested as an eufunctional goiter, and, therefore, the patient is metabolically normal. However, clinical symptoms of **hypothyroidism gradually appear** and become more evident over several years. Slowly appearing symptoms of hypothyroidism may be from the beginning of the disease understood as growing old. In about 20 % of the patients, especially those with the fibrous variant, the symptoms of hypothyroidism may be observed already at the first detection of the Hashimoto thyroiditis in the patient.

Occasionaly, patients with Hashimoto disease present with hyperthyroidism in association with the thyroid gland that is unusually firm and with high titers of circulating antithyroid antibodies, a combination which suggests, probably correctly, the concurence of Graves-Basedow disease and Hashimoto thyroiditis. In these patients, usually in midcourse of Hashimoto thyroiditis, develops hyperthyroidism, sometimes called "**Hashitoxicosis**". In other patients with Hashimoto disease, hyperthyroidism may supervene presumably due to the emergence of clones of lymphocytes that produce stimulatory anti-TSH receptor antibodies. However, in some patients with Hashimoto thyroiditis only **transient thyrotoxicosis** without evidence of thyroid hyperfunction may develop. Symptoms of transient thyrotoxicosis may appear either during initial stage of the disease or as a consequence of rarely occurring exacerbation of chronic inflammatory process. In this phase of transient thyrotoxicosis serum thyroid hormone concentrations increase as a result of more extensive destruction of the follicles, and not as a result of increased synthesis of the thyroid hormones. The evidence of this is low radioiodine accumulation in scintiscan.

Titers of **antithyroid antibodies** (antithyroglobulin and antimicrosomal) are high already from the onset of the Hashimoto disease. Circulating autoantibody

titers tend to be higher in patients with the fibrous variant than in those with the oxyphilic variant.

The results of the tests of thyroid function depend on the stage of the disease. At initial stage serum T_4 and T_3 concentrations are normal, the patient is eumetabolic. As the disease progresses, thyroid failure, at first subclinical, may supervene owing to progressive replacement of the thyroid parenchyma by lymphocytes or fibrosis. Although damage of the thyroid gland is the obvious cause of **the failing thyroid function**, a contributing influence may be the presence of TSH receptor-blocking antibodies. With the passage of time, thyroid function decreases gradually. Ability of the thyroid tissue to respond to TSH progressively diminishes. Therefore, the serum TSH concentration progressively rises and the serum T_4 concentration falls to subnormal values. The thyroid failure is evident first in the rise in serum TSH concentration. At this stage, the serum T_3 concentration remains normal for some time. However, with time, serum T_3 concentration may slightly increase, reflecting in all likelihood maximal stimulation of the failing thyroid by the increased serum TSH concentration. The foregoing sequence of symptoms (concerning serum TSH, T_4 and T_3 concentrations) in the evolution of complete thyroid failure has been termed **diminished thyroid reserve** or **subclinical hypothyroidism**. Ultimately, the serum T_3 concentration also declines to subnormal values, and **frank hypothyroidism** supervenes. Autoimmune thyroiditis may account for as many as 90 % of cases of hypothyroidism.

5.4.4.5 Chronic fibrosing thyroiditis

Chronic fibrosing thyroiditis (**Riedel thyroiditis**) is rare and is observed chiefly in middle-aged women. The etiology is unknown. From the histopathological point of view it is characterized by extensive fibrosis of the thyroid gland which gradually becomes unusually hard (a woody gland). Infiltrative growth of fibrous tissue into adjacent structures, including adjacent vessels, nerves, and muscles, is typical, too. Successive compression of the esophagus, trachea, and recurrent laryngeal nerves gives rise to the symptoms of local mechanical syndrome. The goiter is mild in size, usually asymmetrical, fixed, and stony hard. The patient is usually euthyroid, hypothyroidism occurs only occasionally.

5.4.4.6 Other types of thyroiditis

They are very rare. These miscellaneous types of thyroiditis include post-irradiation thyroiditis and trauma thyroiditis. They also include chronic nonpyogenic bacterial thyroiditis, which may originate due to some specific infections (e.g., brucellosis, tuberculosis, and syphilis). Occasionally thyroiditis may occur also due to sarcoidosis, amyloidosis, and systemic mycosis.

5.4.5 Thyroid neoplasms

Tumors of the thyroid gland are the most frequent among the tumors of the endocrine system. They are traditionally classified to benign and malignant neoplasms. They may arise from epithelial cells (follicular cells or parafollicular cells), also from the cells of connective tissue or from lymphoreticular cells. Therefore, epithelial, nonepithelial, or miscellaneous primary neoplasms of the thyroid gland may be distinguished. Secondary neoplasms (metastases of extrathyroid tumors to the thyroid) of the thyroid gland may also occur.

5.4.5.1 Benign neoplasms

Benign neoplasms of the thyroid gland (**benign goiter**) include predominantly **follicular adenomas** (the more highly differentiated adenomas) being hormonally active (toxic adenomas) or hormonally inactive. True adenomas are well encapsulated nodules of the thyroid gland, which do not invade adjacent tissues, and do not metastase.

The patients often report that the nodule has grown slowly over many years. Initially, if it is a hormonally active adenoma, its function is insufficient to disturb hormonal equilibrium, though its capacity to accumulate radioiodine is evident in scintiscans as an area of increased density within the still-functioning extranodular tissue (**warm nodule**). With time, the nodule grows larger, its function increasing until it is sufficient to suppress TSH secretion. Consequently, the remainder of the gland undergoes relative atrophy and loss of the function, and the scintiscan reveals intensive radioiodine accumulation only in the region of the nodule (**hot nodule**). Frank thyrotoxicosis usually supervenes. Relatively to its overall rate of occurrence, hyperfunctioning adenoma is a frequent cause of T_3 toxicosis. The function of toxic

adenoma is autonomous, independent of TSH stimulation.

About 95 % of adenomas are afunctional. Scintiscans reveal no accumulation of radioiodine (**cold nodule**). Epithelial cells of afunctional adenoma lost the iodide-trapping mechanism, and, therefore, they cannot produce hormones.

Up to the present time it is not known whether adenomas arise de novo or arise from hyperplastic perenchyma of the thyroid which is stimulated by TSH for a long time. Toxic adenomas never undergo malignant transformation. It has not been exactly known whether malignant transformation of afunctional adenomas is possible.

From the histopathological view point structure of adenomas is not uniform, but it is variable. Therefore, thyroid adenomas are classified into following histopathological types: embryonal adenoma, fetal adenoma, microfollicular adenoma, macrofollicular adenoma (colloid adenoma), papillary cystadenoma, and Hürthle cell adenoma (it is composed of large acidophilic cells). In the thyroid gland various histopathological types of adenomas may be found in the same time, even in the same adenoma several of the above mentioned histopathological structures may occur.

5.4.5.2 Malignant neoplasms

Malignant neoplasms of the thyroid gland (**malignant goiter**) account for about 1 % of all malignant tumors of the population. Women are affected aproximately twice more frequently than men. From the point of view of histopathology primary malignant neoplasms are divided into epithelial, nonepithelial, and miscellaneous. Rarely, metastases of extrathyroid cancers to the thyroid may occasionally occur (secondary malignant neoplasms). Breast cancer, bronchogenic carcinoma, renal cell carcinoma, malignant melanoma, and malignant lymphomas metastase to the thyroid gland most frequently.

Epithelial malignant neoplasms of the thyroid gland arise from follicular cells or parafollicular cells (C cells). Follicular carcinoma, papillary carcinoma and anaplastic carcinoma originate from the follicular cells. The parafollicular cells give rise to medullary carcinoma.

Nonepithelial malignant neoplasms and **miscellaneous** malignant neoplasms of the thyroid gland occur very rarely. Fibrosarcoma is the best known of nonepithelial malignant neoplasm of the thyroid gland. Miscellaneous malignant tumors include mainly carcinosarcoma. The thyroid gland also may be the site of lymphoproliferative disease, namely thyroid lymphoma. The relative risk of thyroid lymphoma is 67-fold higher in patients with Hashimoto thyroiditis than in the thyroid glands with colloid nodules.

Primary thyroid carcinomas

Primary thyroid carcinomas are the most common endocrine malignancies, accounting for more than 99 % of all thyroid malignancies. It occurs prevailingly as a nodular goiter, most commonly as a solitary nodule. In the thyroid scintiscans malignant nodules very often appear as a cold area, warm or hot nodules are less common. About 80 % of thyroid carcinomas apear in the patients between the ages of 25 and 65. In children and young adults before the age of 40 mostly papillary carcinoma occurs, accounting for about two thirds of all thyroid carcinomas occurring in this period of life. Anaplastic carcinoma is very rare before the age of 40. In adults after the age of 40, follicular carcinoma is more common. At the same time the occurrence of anaplastic carcinoma is also significantly increased. Medullary carcinoma occurs mainly in elders.

Etiology and pathogenesis of the thyroid carcinomas are not exactly known. It is assumed that several factors participate in their origin and development. The best known are:

1. **Genetic factors**. They have not been explored precisely. However, the existence of familial type of medullary carcinoma has been considered proved (autosomal dominant inheritance).

2. **Ionizing irradiation**. It is the best known and most significant external factor causing the origin of malignant goiter. Its effect depends on greatness of radiation dose applied to the area of the thyroid gland or its vicinity, usually for diagnostic or therapeutic purposes, as well as on the age in time of radiation. X-ray radiation is considered of a greater importance than radiation by radioactive isotopes. Radiation during infancy or childhood is considered decisive. Carcinomas usually appear 6–8 years after radiation of the neck area, but they may originate as late as 20 or even more years after the radiation exposure. At present, it is assumed that

in most instances only microcarcinoma develops. As this microcarcinoma stops growing, it is so-called "sleeping carcinoma". The microcarcinoma may start growing again and later metastase only when further stimulating and promotional factors are involved (e.g., long-lasting excessive stimulation of the thyroid gland by TSH and suppression of the immune system are considered). It is assumed that also some goitrogens and iodine deficiency may play a pathogenetic role in the origin of thyroid carcinoma.

Primary thyroid carcinomas are classified into two varieties depending on whether the lesion arises in the thyroid follicular epithelium or from the parafollicular cells forming calcitonin. Three histopathological types of carcinomas of follicular epithelium are distinguished: follicular, papillary and anaplastic carcinomas. Parafollicular cells give rise to medullary carcinoma.

A. **Follicular carcinoma**

Follicular carcinomas tend to be slow growing and account for 10–15 % of all thyroid cancers. In regions with iodine deficiency they occur more often than papillary carcinomas. Follicular carcinoma occurs in an older age group than papillary carcinoma, most cases arising after the age of 40. Women are affected two to three times more commonly than men. The degree of malignancy varies but generally exceeds that of papillary carcinoma. Follicular carcinoma seldom spreads to the regional lymph nodes, but undergoes early hematogenous spread to distant sites, particularly bone, lung, liver, or CNS.

Follicular carcinoma histopathologically resembles normal thyroid epithelium, is encapsulated, and differs from benign follicular adenoma only by the presence of capsular and/or vascular invasion. Histopathological examination reveals the presence of various size follicles containing subnormal amounts of colloid. The cells exhibit mitoses to a varying degree. Invasion of blood vessels and adjacent thyroid parenchyma is often observed. The degree of invasiveness is greatest in the older age group of patients. The follicular carcinoma usually consists of a single nodule. The regional lymph nodes are seldom enlarged. Pain and invasion of the adjacent structures manifest later than in papillary carcinoma.

Unlike other types of the thyroid carcinomas, follicular carcinoma may accumulate radioiodine, but only to a small extent. Its metastases are sometimes hyperfunctional and may be sufficient to produce clinical thyrotoxicosis, including T_3 toxicosis. However, its response to administration of suppressive doses of thyroid hormone (regression of the primary tumor and its metastases due to inhibition of TSH secretion by administrated thyroid hormone) is weaker than that of papillary carcinoma.

B. **Papillary carcinoma**

Papillary carcinoma accounts for about 60–75 % of all thyroid carcinomas. It may occur at any age but is seen more frequently in children and young adults. Women are affected 2–3 times more commonly than men. Papillary carcinoma is the most common thyroid malignancy originating after X-ray radiation exposure to the neck during childhood. In general, papillary carcinoma is the slowliest growing one of all thyroid carcinomas. Clinically, it usually appears as an asymptomatic nodule, which varies in size and is usually uncapsulated. It tends to spread via the intraglandular lymphaties from its primary site to other parts of the thyroid and to the pericapsular and regional lymph nodes, where it may remain localized for years. Hematogenous spread to distant sites is uncommon. Its clinical course is relatively the most benign of all thyroid carcinomas. Papillary carcinoma has a tendency to become more malignant with advancing age. Invasion of adjacent structures and distant metastases may appear only as late manifestations. Papillary carcinoma may sometimes dedifferentiate to the highly malignant anaplastic carcinoma.

Histopathological examination reveals that papillary carcinoma is composed of columnar epithelium that is thrown into folds, forming papillary projections with connective tissue stalks. There may be gross or microscopic foci of carcinoma in other parts of the thyroid gland, resulting from spread via the intraglandular lymphaties.

Papillary carcinoma accumulates iodine less efficiently than does follicular carcinoma. However, its response to administration of suppressive doses of thyroid hormone is better than that of follicular carcinoma (regression of the primary tumor and its metastases is more evident).

C. **Anaplastic carcinoma**

Anaplastic carcinoma accounts for about 5–10 % of all thyroid carcinomas. It occurs after the age of 50, usually in the sixth to seventh decade of life. It is slightly more common in women. It is a highly malignant tumor, rapidly invading adjacent structures and metastasizing extensively throughout the body. Invasion of adjacent structures, such as skin, muscles, nerves, blood vessels, larynx, and esophagus causes the origin of symptoms of local mechanical syndrome. Tumor mass is often fixed to adjacent structures, therefore, moves poorly on swallowing.

On histopathological examination, anaplastic carcinoma is composed of atypical cells that exhibit numerous mitoses. Spindle-shaped cells and multinucleate giant cells are usually predominant. In some cases, small cells are most prominent. Colloid absence is evident. Areas of necrosis and polymorphonuclear infiltration are frequently present. Sometimes elements of papillary or follicular carcinoma can be detected, suggesting that they may be the precursors of anaplastic carcinoma, probably originating by their malignant dedifferentiation. According to histopathological finding spindle-shaped cell, giant cell, and small cell types of anaplastic carcinoma are distinguished.

In general, anaplastic carcinoma does not accumulate radioiodine. Therefore, it is refractory to radioiodine therapy, and it also does not response to administration of suppressive doses of thyroid hormone.

D. **Medullary carcinoma**

Medullary carcinoma makes up about 2 % of all thyroid carcinomas. It arises from the parafollicular cells producing calcitonin. It usually occurs after the age of 40 and is slightly more common in women. Medullary thyroid carcinoma is more malignant than follicular carcinoma, and by its malignity it may approach anaplastic carcinoma. Initially it invades the intraglandular lymphaties, spreading to other parts of the gland and to the pericapsular and regional lymph nodes. In this phase it resembles papillary carcinoma, but unlike the latter, later it also spreads via the bloodstream to distant sites, particularly lung, bone, liver, and suprarenal gland. In the time of origin of distant metastases medullary carcinoma may resemble anaplastic carcinoma, but unlike the latter it usually grows slowlier. Medullary carcinoma is firm, hard, and usually unencapsulated and fixed nodule. It is sometimes bilateral, usually localized to the upper two thirds of the gland, which are the anatomical location of the parafollicular cells.

Histopathological examination reveals that medullary carcinoma is composed of the cells that vary widely in morphological features and arrangement. Round, polyhedral, and spindle-shaped cells form a variety of patterns. The cells may appear undifferentiated and exhibit mitoses. Unlike the anaplastic carcinoma, necrosis and polymorphonuclear infiltration are absent. There is an abundant hyaline connective tissue stroma that gives the staining reactions for amyloid (a distinctive amyloid stroma).

Medullary thyroid carcinoma occurs in both **sporadic** (80 %) and **familial** (20 %) forms. The familial variety, usually appears at a yonger age, is more often bilateral, is less likely to have associated cervical metastases when diagnosed, and has a better prognosis. The familial form may occur as a part of multiple endocrine neoplasia (MEN) types 2A or 2B, or in a familial non-MEN setting (medullary thyroid carcinoma unassociated with other endocrine disorders). The peak incidence of the sporadic form is in the sixth and seventh decades of life, and patients usually have cervical lymph node metastases at presentation.

Differing from all the previously described thyroid carcinomas, medullary thyroid carcinomas are neuroendocrine neoplasms of parafollicular cell origin. Neuroendocrine cells are widely dispersed in the body and are capable of elaborating a large variety of amine and polypeptide bioactive products. Therefore, in addition to calcitonin, medullary thyroid carcinoma may elaborate a variety of products. So, a variety of symptoms, other than those related to mass lesions, are present in patients with medullary thyroid carcinoma. The carcinoid syndrome (flushing, diarrhea, and bronchospasm) and Cushing syndrome may occur, owing to secretion of serotonin and ACTH, respectively. Prostaglandins, kinins, and vasoactive intestinal peptide (VIP) may also be secreted and are variously responsible for the attacks of watery diarrhea and circulation disorders.

Clinical manifestation of familial medullary carcinoma is antecedent by **a premalignant hyperplasia of the C cells** of the thyroid gland. This premalignant hyperplasia is the earliest demonstrable abnormality (after the administration of provocative agents) in

the thyroid gland of individuals with familial form of medullary thyroid carcinoma. Infusions of pentagastrin or calcium (and also having drunk alcohol) elicit secretion of calcitonin and successively increase calcitonin concentration in circulating blood. This is considered as **an early biochemical signal** of starting medullary thyroid carcinoma.

With time, premalignant hyperplasia of the C cells is followed by progression to nodular hyperplasia, microscopic medullary carcinoma, and finally frank medullary thyroid carcinoma. Basal plasma calcitonin concentration is elevated in about two thirds of patients with clinically developed medullary carcinoma. In these patients, however, hypercalcemia is usually not present.

In patients with the familial form of medullary thyroid carcinoma, there is often clinical or laboratory evidence of hyperparathyroidism and pheochromocytoma (MEN 2A, Sipple syndrome). Hyperparathyroidism is most commonly due to parathyroid hyperplasia, rather than adenoma. Pheochromocytomas are often bilateral. This **variant of the MEN 2A syndrome** is one in which medullary thyroid carcinoma, pheochromocytoma, and possibly parathyroid hyperplasia are associated with ganglioneuromas. If there are a marfanoid habitus, thickened corneal nerves, multiple mucosal neuromas, and typical facies simultaneously present in the patient, this disease is denoted as **the variant of the MEN 2B syndrome**. Mucosal neuromas may occur on the distal portion of the tongue, on the buccal mucosa, on the lips (thick bumpy lips), in subconjuctival areas (thickened and friable eyelids-margin), and throughout the gastrointestinal tract (ganglioneuromatosis of the GIT). In the patients with the variant of the MEN 2B syndrome tumors originate at younger age and metastase more frequently than in those with the variant of the MEN 2A syndrome.

5.5 Pathophysiology of parathyroid glands

Primary disorders of hormonal activity of the parathyroid glands are rare. The pathophysiological state resulting from undersecretion of parathyroid hormone (PTH) is denoted as **hypoparathyroidism**. The pathophysiological state resulting from oversecretion of PTH is called **hyperparathyroidism**. There is also a pathophysiological state similar to hypoparathyroidism in which secretion of PTH is normal. The disorder is on the level of target tissues, which are insensitive to PTH. It is in fact pseudohypofunctional endocrine disorder (pseudoendocrinopathy) denoted as **pseudohypoparathyroidism**.

5.5.1 Hypoparathyroidism

It is a pathophysiological state when the parathyroid glands are not able to maintain normal calcium concentration in circulating blood (normocalcemia) and thereby its homeostasis in organism. Hypoparathyroidism is characterized by low plasma PTH concentration, hypocalcemia, hyperphosphatemia, and increased neuromuscular excitability.

Etiology of hypoparathyroidism is heterogeneous. Organic and functional causes participate in its origin.

A. **Organic causes**. The most frequent organic causes are various iatrogenic influences, mainly postsurgical injuries or inadvertent removal of all parathyroid glands, respectively impairment of their vascular supply during thyroidectomy or during radical dissection in the neck for some form of malignant disease. **Postoperative hypoparathyroidism** originates when during surgical intervention more than 50 % of parenchyma of parathyroid glands is damaged. It occurs as a complication in about 1 % of patients after the mentioned operations. The risk of the origin of permanent hypoparathyroidism exists also in the patients after therapeutic subtotal parathyroidectomy for parathyroid hyperplasia. Acquired hypoparathyroidism is an extremely rare complication of radioactive iodine therapy (**postradiation hyperparathyroidism**). Its onset is generally between 5 and 18 months after radiotherapy. Most cases are associated with large doses of radioiodine in the patients with Graves-Basedow disease rather than in those with thyroid carcinoma. In the latter hypoparathyroidism often originates after the therapy by external irradiation.

Spontaneous origin of hypoparathyroidism due to organic lesion is rare. It is denoted as **idiopathic**