in food, which inhibits synthesis of thyroid hormones, may be also a cause of endocrine disorder.

    D. **Iatrogenic causes**. Endocrine disorders may occur as a complication of various kinds of therapy (e.g., surgical intervention, radiotherapy, inadequate hormone treatment, or therapy with some non-hormone drugs).

    E. **Primary hyperplasia** of endocrine gland cells. As its consequence, a hyperfunctional endocrine syndrome develops.

    F. **Other acquired causes**. They are rather rare. They include, e.g., destruction of endocrine cells by hormone inactive neoplasma, various kinds of vascular disorders (mostly aneurysm or hemorrhage), cyst, trauma, degenerative process, metabolic defect, and by toxic influences.

2. **Genetic causes**

Relatively frequent genetic causes of endocrine disorders are defects of various enzymes (**enzymopathies**) taking part in a hormone biosynthesis. The other inherent cause can be the synthesis of a defective prohormone or hormone or the disorder of conversion of prohormone to active hormone. The existence of genetic **disorder of cell receptors** for hormones is assumed as well. Inborn causes of endocrine disorders can also include **hypoplasia** or **aplasia** of endocrine gland as well as **chromosome anomalies** concerning X or Y chromosomes (gonosomes).

5.3 Pathophysiology of hypothalamic-hypophyseal system

Hypothalamus has an important integrative influence on the function of vegetative nervous system and also it is a place of various vital centres. It has a key role in regulation of basic biological rhythms and it is the place of production of various hormones (hypothalamic releasing hormones, hypothalamic inhibiting hormones or factors, antidiuretic hormone, and oxytocin). Hypothalamus, therefore, has an important role in the regulation of endocrine system as well. In the hierarchy of endocrine glands hypothalamus has a role of a control centre and along with hypophysis it forms a functional unit. In the consequence of its organic or functional disorder, a hypothalamic syndrome develops. In the clinical picture of this syndrome only endocrine symptomatology is present, or its endocrine symptomatology may be combinated with neurovegetative symptomatology. These disorders are usually distinguished as: disorders of hypothalamic-neurohypophyseal system and disorders of hypothalamic-adenohypophyseal system.

5.3.1 Pathophysiology of hypothalamic-neurohypophyseal system

Antidiuretic hormone (ADH, vasopressin) and oxytocin are the hormones of hypothalamic-neurohypophyseal system. They are produced in the nuclei of the front hypothalamus, i.e., in nucleus supraopticus and in nucleus paraventricularis. They are transported to neurohypophysis via the axons of the cells of these nuclei, where they are stored and released into the circulation when needed. Clinical symptoms of deficiency or overproduction of ADH are known only in human being. Disorders of oxytocin secretion are unknown at present.

5.3.1.1   Central diabetes insipidus

Central diabetes insipidus (neurogenic diabetes insipidus, diabetes insipidus verus) is a rare disease caused by partial deficiency or total absence of ADH. The kidneys of a patient, therefore, are not able to produce hypertonic urine and thus to prevent excessive loss of water from the organism. Most often it develops in the consequence of the damage of front hypothalamus, namely of nucleus supraopticus, e.g., by severe head trauma, intracranial tumors (craniopharyngioma, Rathke's pouch tumor, germinoma, pinealoma, pituitary adenoma, and metastatic tumors), cysts, inflammatory lesions, vessel lesions (hemorrhage or aneurysm), sarcoidosis, or by surgical intervention in the area of hypothalamus. Diabetes insipidus, which is due to any organic lesion mentioned above, is called **symptomatic** (secondary)

diabetes insipidus. However, in about 45 % of cases the cause of ADH deficiency is not found out. It is **idiopathic** diabetes insipidus. In rare instances, central diabetes insipidus may be **inherited** as an isolated defect (autosomal dominant inheritance) or as a part of an autosomal recessive syndrome (Wolfram syndrome) consisting of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness.

From the point of view of etiopathogenesis **peripheral diabetes insipidus** (nephrogenic diabetes insipidus) can be also distinguished. It originates as a consequence of reduced sensitivity even of insensitivity of the distal tubules and mainly of the collecting ducts to ADH. It is caused by disorder or lack of cell receptors for this hormone. Peripheral diabetes insipidus is *hypofunctional pseudoendocrinopathy*. It may be inborn or acquired. **Hereditary** nephrogenic diabetes insipidus is the disease with X chromosome-linked inheritance. The abnormal gene is localized on the long arm of this chromosome. It is transmitted by heterozygous women and clinically manifested in man. **Acquired** nephrogenic diabetes insipidus has heterogeneous etiology. It may develop, e.g., due to chronic hyperkalemia, chronic renal insufficiency, nephrocalcinosis caused by chronic hyperparathyroidism, amyloidosis, multiple myeloma, or due to long-lasting therapy by some drugs, such as demeclocycline, methoxyflurane, and lithium (drug-induced nephrogenic diabetes insipidus).

Pathophysiology and clinical features. Diabetes insipidus refers to the passage through the body of a large quantity of dilute fluid. This state of excessive water intake (**polydipsia**) and hypotonic **polyuria** is due to failure of vasopressin (ADH) release in response to normal physiologic stimuli (neurogenic diabetes insipidus) or due to inability of renal tubules to respond to ADH (nephrogenic diabetes insipidus). Polyuria, **excessive thirst** and polydipsia are primary symptoms almost invariably present in the patients. Characteristically, they are sudden in onset. The patient may recall the precise day or hour when polyuria and thirst began.

Urine osmolality is below that of the serum (less than 290 mmol/kg). A urine specific gravity is from 1.001 to 1.005. **Persistent hypostenuria** is the hallmark of diabetes insipidus. In severe cases, the urine is pale color, and the volume may be immense (up to 16–24 litres per day), requiring micturition every 30 to 60 minutes through the day and night. More frequently, however, urine volume is only moderately increased (from 3 to 6 litres per day).

Polyuria is the most expressive objective symptom, and excessive thirst is the main subjective symptom. Polydipsia provides an adequate compensation for large volumes of excreted water. The slight rise in serum osmolality, resulting from hypotonic polyuria, stimulates thirst. Large volumes of fluid, therefore, are imbibed, and cold drinks are preferred.

For the patient excessive thirst is hard to control, and due to that he often awakes throughout night. During the sleeping hours he often drinks and micturates (**nycturia**). Interrupted sleep may cause the origin of **neuroasthenic syndrome**. If the patient did not take adequate quantity of fluids he would develop severe dehydration, hypernatremia, plasma hyperosmolality, fever, psychic disturbances, prostration, collapse, and towards the end oligemic shock and death may occur.

5.3.1.2 Syndrome of inappropriate ADH secretion

The syndrome of inappropriate ADH secretion (**Schwartz-Bartter syndrome**, primary vasopressin excess) is the term applied to persistent production of ADH or ADH-like peptide despite body fluid hypotonicity and an expanded effective circulating volume. These peptides are syntethized and released **autonomously**, i.g., independently from plasma osmolality. There is sustained release of ADH in the absence of either osmotic or nonosmotic (volume-mediated) stimuli. It means that simple feedback control mechanism between plasma osmolality and ADH secretion is broken (osmoreceptors of the front hypothalamus lost or cannot realize their control function).

The syndrome of inappropriate ADH secretion originates by numerous causes. Its most frequent cause is an **ectopic** ADH or ADH-like peptide production from *neoplastic tissue* (small cell bronchogenic carcinoma, pancreatic carcinoma, lymphosarcoma, Hodgkin's disease, reticulum cell sarcoma, thymoma, and carcinoma of duodenum or bladder), and from lung cells during *inflammatory pulmonary diseases* (tuberculosis, lung abscess, pneumonias, empyema). In other cases the cause of this syndrome is **organic disorder** of hypothalamic-neurohypophyseal system (skull fracture, subdural or subarachnoid hematoma, cerebral vascular trom-

bosis, encephalitis, and purulent meningitis). Such cases are, however, very rare.

The symptoms of permanent inadequate antidiuresis may also result from **drug therapy**. Some drugs, such as vincristine, cyclophosphamide, clofibrate, carbamazepine, metoclopramide, and beta-adrenergic agents, may stimulate excessive ADH release from the neurohypophyseal system, and other drugs, as chlorpropamide and nonsteroidal antiinflammatory agents, potentiate the antidiuretic action of ADH, what is the result of increase of sensibility of renal tubule receptors to ADH. In this second case it is, however, *hyperfunctional pseudoendocrinopathy.*

The persistent production of ADH or ADH-like substances, or increased sensibility of renal tubules to ADH result in excessive retaining ingested water and in the excretion of concentrated urine. The excretion of concentrated urine (urine osmolality is usually over 300 mmol/kg) exists despite of subnormal plasma osmolality and decreased plasma sodium concentration. In a patient, the dilution of extracellular fluid develops. And so, the ADH excess is considered to be inappropriate because it occurs in the presence of plasma hypoosmolality. Water retention and consequent dilution of body fluids lead to hypotonic hyperhydration. The patient becomes **hyponatremic**, modestly volume expanded, and his body weight increases by 5 to 10 %. In spite of **hypervolemia** there is no hypertension and no edema (for an unknown reason).

Because of permanently increased concentration of ADH in circulating blood superfluous water cannot be excreted by the kidneys as free water (without solutes). Therefore, by urine only water linked to solutes excretes because ADH has no influence upon this water. In the clinical picture, therefore, symptoms of water intoxication and symptoms of blood dilution are dominant.

Symptoms of water intoxication. The extracellular hypotonicity, mainly if it is severe or acute at the onset, leads to intracellular edema. Therefore, especially severe symptoms of **cerebral edema** and following intracranial hypertension occur and become predominant. They include nausea, vomiting, restlessness, irritability, headache, desorientation, confusion, letargy, somnolence, convulsions, and coma.

Symptoms of blood dilution (hemodilution). The most expressive of these symptoms are reduced serum osmolality and dilutive **hyponatremia**. Hyponatremia is paradoxically connected with increased excretion of natrium by urine (**inadequate natriuresis**), so that urine osmolality is higher than plasma osmolality. In paradoxically increased glomerular filtration rate, decreased aldosterone secretion and increased production of atrial natriuretic peptide take part. These changes arise secondary to increased plasma volume.

5.3.2   Pathophysiology of hypothalamic-adenohypophyseal system

From the knowledge regarding the role of the hypothalamus in regulating anterior pituitary function, it seems likely that some diseases may actually be due to disordered function of the hypothalamus rather than at the level of the adenohypophysis or the target endocrine gland. Therefore, from the point of view of pathophysiology of hypotalamic-pituitary system we distinguished between disorders of hypothalamus with endocrine symptomatology and endocrine disorders of adenohypophysis.

5.3.2.1   Disorders of hypothalamus with endocrine symptomatology

Some of the disorders of hypothalamus are connected with endocrine symptomatology because hypothalamus regulates secretion of adenohypophyseal hormones by means of releasing hormones (liberins) and by means of inhibiting hormones or factors (statins). As hypothalamus has a key role also in regulating of basic biological rhythms, it takes part in regulation of the onset of puberty and also of sexual functions, endocrine disordes may also originate as the consequence of changes of these regulatory functions of the hypothalamus. Hypothalamus is sexually differentiated and regulates the sexual functions through its own biorhythm, which regulates secretion of gonadotropins (it is a monophasic type of their secretion in a man, but cyclical one in a woman). Hypothalamus plays an important role in regulation of lactation, too, which starts by combination of nerve and several hormonal influences.

From the point of view of etiology the disorders of hypothalamus with endocrine symptomatology can be divided to *functional* or *organic*, and *inborn* or *acquired*. Most often they are manifested by various disorders of hypothalamic-pituitary-gonadal

axis. As for intracranial organic disorders the following are most frequent: tumors (craniopharyngioma, pinealoma, glioma, meningioma, metastases), cyst, traumatic lesions, lesions after neurosurgical interventions, inflammatory lesions (meningitis, encephalitis, tuberculosis), sarcoidosis, and vascular lesions (ischemic lesions, local hemorrhage, aneurysm) in hypothalamus or in its neighbouring region.

A. Anorexia nervosa (anorexia mentalis)

Anorexia nervosa is an eating disorder of young, previously healthy women who develop a paralyzing fear of becoming fat. The driving force is the pursuit of thinness, all other aspects of life being secondary. This aim is achived primarily by radical restriction of caloric intake, the end result being emaciation. Anorexia nervosa is **psychoneurosis**, or rarely it is **purposeful reaction**. It is connected with remarkable lowering of body weight and with amenorrhea.

This disease occurs primarily in **young women** (to 25 years of age), mainly in **neurotic adolescent girls**. The most common time appearance is 4 to 5 years after menarche.

In **etiology** of this disease the combination of psychoemotional factors and behavioral characteristics of the patient (e.g., mentally unbalanced personality, anxiety, depression, perfectionism, inadequate ambition) takes place. The onset of the desease frequently follows a stressful event in the subject's life. The frequent cause of its origin is psychical stress, bad relation between mother and daughter, improper family relations, inappropriate and frequent comments on body weight or body proportions. It may be also an abnormal reaction to adolescence (a refusal of the role of adult woman and at the same time demand for independence from the family influence and parent's authority). Its prevalence is 0.5–1.5 per 100 000 inhabitants (involves approximately 1 % of girls and young women between ages 14 and 25, generally from middle to upper socio-economic families).

The causes and pathogenesis of anorexia nervosa are not fully explained. It has been argued that hypothalamic dysfunction is primary, but the evidence appears persuasive that the disorder is a psychiatric one. The psychodynamic mechanisms are not clear and in fact may not be fixed. Whatever other factors operate in the genesis of the disease, the families tend to be "enmeshed": they are blurred generational boundaries so parents and children are constantly involved in each other's problems. Although family structure appears to play a primary role in the genesis of anorexia nervosa, cultural issues and occupation are also important.

How the psychodynamic dysfunction is translated into biological disease remains a mystery. Numerous neurotransmitter systems may play a mediating role. The role of hypothalamus, in which centres of controlling food intake are situated, and which is the place of gonadotropins releasing and inhibiting hormones as well, in the pathogenesis of anorexia nervosa is not known. We do not know whether there is a certain predispose weakening of hypothalamic function (its latent dysfunction), or it is only a dysfunction of various internal interactions of the hypothalamus evoked by the influence of external factors.

The patients **permanently refuse food intake** (drastically restrict their own food intake) and later they gradually lose appetite. Sporadic dieting usually begins about a year before the start of the proper disease, often at the point at which maximal weight was reached. If social circumstances require them to eat more than usual, **vomiting is induced** as soon as possible, often in a public restroom. As noted, episodic binge eating may occur and also followed by emesis. The patient secretly self-induces vomiting most often by putting her fingers or tooth-brush into the pharynx, later she vomits reflexively. She may use enormous doses of laxatives. In the consequence of this considerable **loss of body weight** may be seen, as a rule from 15 to 25 % of the original body weight. In spite of significant cachexia the patient is often *physically and psychically overactive*, and ritualized excercise is common. Despite profound weight loss patients deny hunger, thinness or fatigue.

From the point of view of endocrinology anorexia nervosa is manifested by **secondary amenorrhea** (menstruation was present for a variable time and then ceases), which is one of its basic and an almost constant symptoms. It is now generally accepted that the primary cause of its origin is localized in the hypothalamus and operates via impaired (insuficient) secretion of luteinizing hormone-releasing hormone (**LHRH deficiency**), also termed gonadotropin-releasing hormone (GnRH). Functional **gonadotropic hypopituitarism** is formed. Why the hypothalamus is unable to release LHRH is not known, although abnormalities in norepinephrine and dopamine me-

tabolism in the central nervous system (CNS) have been postulated.

In the origin of secondary amenorrhea psychoemotive stress and significant body weight loss take part. About one half of patients with anorexia nervosa develop amenorrhea consominant with the onset of dieting. However, up to 40 % of girls cease menses before significant body weight loss. The latter one points out to the fact that amenorrhea origin is likely not to be only a simple consequence of malnutrition. Presumably, early amenorrhea is due to emotional stress antedating clinical illness.

Plasma levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estrogens are low. However, there is no evidence for primary dysfunction of the pituitary gland or gonads. Plasma prolactin level is usually normal. Female secondary sexual characteristics (breasts and pubic hair) are properly developed.

In the consequence of long-lasting malnutrition anemia, hypoproteinemia and hypokalemia may be developed. Anemia and occasional pancytopenia appear to be due to hypocellularity (hypoplasia) of the bone marrow. Later **peripheral edema** (mainly on extremities) may apear. It is due to a failure to mobilize the normal extracellular fluid volume proportionately with body mass during starvation and probably due to hypoalbuminemia. If vomiting is severe and prolonged, hypochloremic alkalosis may occur. Basal metabolic rate is decreased.

By **clinical examination** bradycardia (persistent resting pulse of 60 beats per minute or less), arterial hypotension (less than 70 mmHg systolic), bradypnea (less than 15 breaths per min), hypothermia, and cold intolerance are found. These changes develop as a response of circulation to cachexia. Skin is usually pale and dry, hands and feet are cold. Anorexic patients may develop excessive vasoconstriction, and Raynaud phenomenon has been noted. Hair is dry and soft. The patients often suffer from obstipation. Sometimes also psychical depression occurs. In the consequence of long-term and severe malnutrition, various **complications** may develop (symptoms of vitamin deficiency, osteoporosis and intercurrent infections). If the treatment is delayed till the body weight falls under 50 % of patient ideal weight, this disease may end lethally. Mortality is about 4–7 %.

B. Hypothalamic amenorrhea

All types of amenorrhea of the hypothalamic origin, with the exception of amenorrhea at anorexia nervosa, rank among this tittle. They are secondary amenorrheas caused by various functional or organic disorders of the hypothalamus, which result in disorder of LHRH secretion.

Among **functional amenorrheas** of the hypothalamic origin are included:

- psychogenic amenorrhea after psychic stress;

- amenorrhea at false pregnancy (pseudocyesis, pseudogravidity);

- exercise-induced amenorrhea, which is associated with intense and prolonged physical exertion, such as long-distance running, swimming, gymnastic, and ballet dancing. The patients are always below ideal body weight and have low stores of fat. The mass of fat may be a regulator of LHRH secretion;

- long-term starvation;

- amenorrhea at hyperprolactinemia mediated by decreased hypothalamic dopamine (prolactin-inhibiting factor – PIF). Hyperprolactinemia causes amenorrhea by inhibition of LHRH release.

Organic causes of hypothalamic amenorrhea can be head trauma, tumor, inflammatory lesion and vascular lesion in the hypothalamic gonadotropin-regulating area.

C. Hypothalamic disorders of the onset of puberty

Some functional or organic disorders of hypothalamus may cause true precocious puberty or true delayed puberty. Puberty is considered precocious if the symptoms of sexual maturity begin to apear prior to age 8 in girls and age 10 in boys. Puberty is considered delayed if its spontaneous beginning appears in both sexes by age 16 or older.

True precocious puberty (pubertas praecox vera). **In girls** this type of puberty has mostly functional origin (primary hypothalamic). The cause of the precocious onset of hypothalamic regulatory mechanisms (precocious secretion of LHRH), and thus also precocious gonadotropic hormone secretion from

adenohypophysis is not known (idiopathic true precocious puberty). **In boys** true precocious puberty occurs more rarely than in girls. Its cause is usually organic, especially hypothalamic tumors (e.g., hamartoma) or tumor of epiphysis (pinealoma), internal hydrocephalus or consequences of encephalitis.

True delayed puberty (pubertas tarda vera). In boys and girls it is mostly constitutional deviation with familiar occurence in some members of the family (**constitutional delayed puberty**). By the age of 18 it is usually spontaneously settled. It is caused by the delayed onset of hypothalamic mechanism (delayed secretion of LHRH, and thus by delayed gonadotropic hormone secretion of adenohypophysis.

D. Adipose genital dystrophy (Babinski-Fröehlich syndrome)
Adipose genital dystrophy is a rare **organic disorder** of hypothalamus affecting mostly boys. It is characterized by obesity and by symptoms of hypogonadotropic hypogonadism. This disorder may be caused by a wide variety of organic lesions of the hypothalamus, such as tumors, various degenerative or inflammatory changes in hypothalamus and its surrounding area.

Besides this organically conditioned, so called true adipose genital dystrophy, also so called **benign type** of adipose genital dystrophy (false adipose genital dystrophy, Fröehlich like type), which occurs more often, is known. It develops in boys in the consequence of wrong regimen (inadequate alimentary and locomotor habits, inappropriate upbringing in a family, i.e., overeating, mainly sweets, drinking sweet juices and limonades, not sufficient physical activity, and too much protective influence from mother). The course of puberty in boys with benign type of adipose genital dystrophy is usually spontaneously settled when regimen becomes normal. On the other hand, in organically conditioned true adipose genital dystrophy the disorder of the hypothalamus is permanent without surgical therapy and its prognosis is serious.

Dominant symptom of Fröehlich syndrome is **obesity** with typical deposition of fat mostly in the subcutaneous tissue of abdomen, thighs, and gluteal area. Fat can deposit also in the subcutaneous tissue of chest and suras. The presence of obesity implies that there is damage of the food-regulating region of the hypothalamus.

Besides obesity, Fröehlich syndrome is characterized by symptoms of **hypogonadotropic hypogonadism** (sexual infantilism) and by **shortness of stature**. Gonadotropic deficiency is due to LHRH deficiency, which is caused by damage of crucial area of hypothalamus that regulates synthesis and secretion of gonadotropins. In the patient some of the symptoms caused by compression of the hypothalamus and its surrounding structures may occur, e.g., epileptic attacks, visual field defects, diabetes insipidus, and headache. This compression is secondary to expansive growing tumor.

E. Laurence-Moon-Biedl-Bardet syndrome
This syndrome is an inborn disease with autosomal recessive type inheritance. It is characterized by a set of various **abnormalities** and **anomalies**, e.g., hypogonadotropic hypogonadism (delayed puberty and sexual infantilism), obesity, short stature, retinitis pigmentosa (visual impairments or blindness), mental retardation, polydactyly, syndactyly, and defective hearing even deafness. The basis of the origin of the above mentioned abnormalities is diencephaloreticular degeneration. Hypogonadism and obesity are thought to be hypothalamic in origin.

F. Kallmann's syndrome (dysplasia olfacto-genitalis)
This disease is a rather rare form of isolated hypogonadotropic hypogonadism with familiar occurence, which is connected with impaired sense of smell and sometimes also with other anomalies. It is a heterogenous genetic disorder with X-linked as well as autosomal inheritance with incomplete exppressivity (it affects boys).

Kallmann's syndrome is characterized by congenital **hyposmia** or **anosmia** (central type), due to the olfactory bulb disorder (hypoplasia or agenesis). The olfactory bulbs (rhinencephalon) and the hypothalamic defects originate in embryonic life and are due to failure of olfactory receptor neurons and LHRH-synthetizing neurons migration from the olfactory placode, where they arise, into the brain, along with the olfactory and other nerves. **Hypogonadotropic hypogonadism** is due to LHRH deficiency. In this disorder, the young males fail to undergo puberty. They enter adulthood with an eunuchoid habitus and other evidences of androgen lack, such as immature genitalia (hypogenitalism), cryptorchidism (the size

of testes correlates with the extent of the LHRH deficiency), gynecomastia, imperfect or absence of facial hair, feminine body contour, and the absence of libido and potentia. Plasma FSH, LH, and testosterone levels are below the normal male range. The secretion of other pituitary hormones is normal. Less commonly, these patients may have other congenital anomalies, such as cleft lip, cleft palate, deafness, and daltonism.

G. Hypothalamic hyperprolactinemia

Hyperprolactinemia of hypothalamic origin is rare. It arises in the consequence of decreased secretion of prolactin inhibiting factor (dopamine) or due to disorder of its transport from hypothalamus to adenohypophysis. Weakening or absence of inhibitory influence of dopamine causes permanent production of prolactin by anterior lobe of pituitary.

Hypothalamic hyperprolactinemia has many causes. It can be **organic lesion** in the hypothalamic area or pituitary stalk (e.g., by tumor, inflammatory or vascular lesions, trauma, sarcoidosis, and by stalk section) or hypothalamic disorder caused by **long-lasting drug therapy** (phenothiazines, thioxanthenes, metoclopramide, methyldopa, reserpine, cymetidine, estrogens, oral contraceptives, and opiates). This disease may be also of **unknown origin** (an idiopathic form of the disease).

In women hypothalamic hyperprolactinemia is manifested by **non-puerperal galactorrhea** (continual milk secretion in non-puerperal period), by **secondary amenorrhea**, and by atrophy of gonads and uterus. The set of these symptoms is called hyperprolactinemic syndrome. From the point of view of endocrinology the clinical picture is the same as at adenohypophyseal hyperprolactinemia. And, therefore, its detailed description is given in the chapter on endocrine disorders of adenohypophysis.

If hypothalamic hyperprolactinemia develops post partum, it is so-called **Chiari-Frommel syndrome**. It is defined as galactorrhea and amenorrhea persisting more than 6 months post partum in the absence of nursing and without an evident pituitary tumor. Some of these patients probably harbor occult microadenomas stimulated by the hormones of pregnancy that may later become radiologically evident. In about half, menses eventually return over a period of months or years. This syndrome is often connected with psychotic symptoms (depression and somnipa-

thy), which may sometimes be similar to those at schizophrenia.

If hypothalamic hyperprolactinemia occurs in young women, who are not and have never been pregnant, it is defined as **Ahumad-de Castill syndrome** (some authors call it Forbers-Albright syndrome).

H. Other hypothalamic disorders of adenohypophyseal regulation

As a result of primary disorder of production of hypothalamic releasing or inhibiting hormones or factors is the origin of increased or decreased function of adenohypophysis. This disorder is defined as **central hypothalamic hyperpituitarism or central hypothalamic hypopituitarism**. However, if the disorder of adenohypophyseal hormone production is not the result of the change of production of hypothalamic releasing or inhibiting hormones, but it is the result of a pathologic process which affects adenohypophysis primarily, **central adenohypophyseal hyperpituitarism or central adenohypophyseal hypopituitarism** develops. It is rather difficult to make the difference between the primary hypothalamic disorders and the primary adenohypophyseal disorders.

Primary hypothalamic and primary adenohypophyseal endocrinopathies may be manifested either by the disorder of production of one type of adenohypophyseal hormones (**isolated** hyperpituitarism or hypopituitarism), or by the disorder of production of several types of adenohypophyseal hormones (**combinated** hyperpituitarism or hypopituitarism). These combinated primary hypothalamic endocrinopathies are, however, very rare.

The cause of primary hypothalamic endocrine disorder may be hypothalamic adenoma overproducing one of the releasing hormones, hormonally nonfunctioning tumors situated in the surroundings of hypothalamus, or a disorder of production of one of the releasing or inhibiting hormones of unknown etiology (idiopathic primary hypothalamic endocrinopathy).

Following four types of isolated primary hypothalamic endocrine disorders may be distinguished:

1.   **Isolated TRH deficiency**.   Undersecretion of thyrotropin-releasing hormone (TRH, thyroliberin) leads to decreased thyroid-stimulating hormone (TSH, thyrotropine) synthesis by the pituitary and thus gives rise to **the syndrome of hypothalamic hypothyroidism**, also called tertiary hypothyroidism.

Its clinical picture is usually milder than the one of primary hypothyroidism.

2. **Isolated CRH oversecretion**. Corticotropin-releasing hormone (CRH, corticoliberin) causes the origin of **tertiary hyperglucocorticoidism** (Icenko-Cushing's disease). Some authors assume that CRH overproduction is probably the cause of **Nelson's syndrome** development, which appears in about 10–15 % patients with hyperglucocorticoidism after bilateral total adrenalectomy realized for the purpose of the therapy of hyperglucocorticoidism. Despite permanent adequate substitute glucocorticoid therapy in patients with Nelson's syndrome, significant ACTH (adrenocorticotropin hormone) oversecretion henceforth continues and increasing skin pigmentation is present. This presence of ACTH excess is caused by **hyperplasia or adenoma** (Nelson's adenoma) of corticotrope cells of the pituitary gland. This hyperplasia or even adenoma develops secondary to permanent stimulation of corticotrope cells by CRH. Production of CRH in hypothalamus is primarily autonomously increased, and, therefore, feedback inhibition of its secretion by exogenous cortisol, administrated for the purpose of substitute therapy, is not realized. Some other authors assume that exogenous cortisol is not equivalent to endogenous cortisol, therefore, its inhibiting influence upon the CRH secretion via feedback mechanism is weaker. This fact is considered to be the cause of continual CRH overproduction, as well as Nelson's syndrome.

Nelson's adenomas sometimes grow more rapidly, are frequently invasive, and some of them even border malignity (agressive ACTH-secreting pituitary adenomas). In the clinical picture progressive **skin hyperpigmentation** (similar to that of Addison's disease) dominate. ACTH and MSH (melanocyte-stimulating hormone) partake in its origin. Stimulative ACTH effect on skin melanocytes equals 1/3 of MSH effect. It is due to the fact that the sequence of the first seven amino acids of ACTH and MSH molecules is identical. Besides that, the cells of the adenohypophyseal adenoma along with ACTH oversecretion usually also overproduce MSH.

In the clinical picture visual disturbances and visual field defects (due to compression of the optic chiasm by adenoma), severe headache, respectively further symptoms of intracranial hypertension often apear.

3. **Isolated GHRH deficiency**. Undersecretion of growth hormone-releasing hormone (GHRH, somatoliberin, somatocrinin) in childhood causes **hypothalamic hyposomatotropic nanism**. GHRH deficiency, resulting in the growth hormone (GH, somatotropin) deficiency, appears in most patients with **idiopathic dwarfism**. The hypothalamic hyposomatotropic nanism is sometimes **combined** with hypothalamic hypogonadotropic hypogonadism. The clinical picture of hypothalamic hyposomatotropic nanism is the same as that of adenohypophyseal hyposomatotropic nanism.

Special cause of isolated GHRH deficiency origin may be **emotional** (psychosocial) **deprivation** of a child. It is mostly secondary to insufficient care of the child in a family with improper relations. Decreased production of GHRH results in STH deficiency. Compared to his/her age group, the child's growth is, therefore, retarded (**psychosocial dwarfism**). If the psychosocial relations in the family improve, the child begins to grow evidently faster and the growth retardation is gradually compensated.

4. **Isolated GHRH oversecretion**. It is now known that excess GHRH can be induced (though rarely) by **neurogenic tumors** of the hypothalamus (GHRH-secreting gangliocytomas, gliomas, and hamartomas), or by **non-endocrine neoplastic tissue** (most common by GHRH-secreting tumors of the bronchi or pancreas, by medullary thyroid carcinoma, and by carcinoids of small intestine and thymus). In the latter case it is **ectopic GHRH production**.

GHRH hypersecretion causes somatotropes hyperplasia and thus excessive secretion of growth hormone. GH overproduction, dependent on the pacient's age in which arises, causes **gigantism** or **acromegaly** of hypothalamic origin. But, they are clinically indistinguishable from gigantism and acromegaly of primarily adenohypophyseal origin.

5.3.2.2 Endocrine disorders of adenohypophysis

From the point of view of intensity of hormonal activity endocrine disorders of adenohypophysis can be classified as **adenohypophyseal hyperfunction** (hyperpituitarism) and **adenohypophyseal hypofunction** (hypopituitarism). They are clinically manifested by endocrinological symptoms, which are conditioned

by the change of secretion of one or more adeno-hypophyseal hormones. If they are caused by the tumors in the area of Turkish saddle (sella turcica), in the clinical picture local symptoms, resulting from compression of intrasellar or parasellar structures which is secondary to expansive tumor growth, may occur. Manifestation of these local symptoms depends on speed, range, and direction of tumor expansion.

I. Adenohypophyseal hyperfunctions

Hypersecretion of one or more hormones of the anterior lobe of the pituitary gland is called as hyperpituitarism. There is usually **isolated hyperpituitarism** which originates by oversecretion of only one adenohypophyseal hormone (monohormonal hyperpituitarism). Isolated somatotropin oversecretion, isolated prolactin oversecretion, and isolated adrenocorticotropin oversecretion most often occur. Isolated thyrotropin hypersecretion, and isolated gonadotropin (FSH or LH) hypersecretion are very rare. In some cases **combinated hyperpituitarism**, e.g., simultaneous hyperproductions of STH and prolactin (PRL), or simultaneous hyperproductions of ACTH and MSH (bihormonal hyperpituitarism), may develop.

A. Somatotropic hyperpituitarism

This disorder is relatively rare and mostly caused by primary acidophilic (eosinophilic) **adenoma** (somatotrope adenoma), or less frequently by chromophobic adenoma of adenohypophysis. These adenomas have autonomous STH secretion. Over 99 % of cases of somatotropic hyperpituitarism result from a primary pituitary adenoma. As a rule this adenoma grows slowly. Whether development of somatotrope adenoma is primarily a pituitary disease or the result of hypothalamic dysregulation is unresolved. However, the majority of evidences suggest that it is a primary pituitary disease. STH overproduction may be caused also by **hyperplasia** of acidophilic cells (somatotrophs) of the anterior pituitary. It is assumed that somatotropic hyperpituitarism caused by hyperplasia of somatotrophs has a hypothalamic origin. In fact it is hypothalamic somatotropic hyperpituitarism caused by isolated GHRH overproduction induced by a tumor or by other organic lesion in the hypotalamic region. In rare instances **ectopic** GHRH secretion has been described. Ectopic STH production is very rare.

Permanent GH overproduction gives rise to the excess growth of long bones of extremities, and thereby accelerated and excessive linear body growth in the youth, as well as overgrowth of soft tissues. After puberty, respectively in adulthood it results in excessive growth of acral parts of the body.

Dependent on the age in which GH oversecretion occurs two clinical forms of somatotropic hyperpituitarism originate. They are gigantism and acromegaly.

Gigantism – It is the clinical form of somatotropic hyperpituitarism characterized by **statural overgrowth** (giant's growth), eunuchoid proportions resulting from lower concentrations of gonadotropins and thereby lower concentrations of sex hormones. Atrophy of gonadotrope cells caused by expansive growth of somatotrope adenoma partakes in decreased secretion of gonadotropins and sex hormones. If STH overproduction starts at the onset of puberty and continues also in adulthood, epiphyseal closure is delayed and finishes around the age of 30. Therefore, by the end of 3rd decennium, besides the giant's stature also acromegalic features begin to apear and the clinical picture of **gigantoacromegaly** originates.

The increased GH concentration does not influence longitudinal growth of bones directly, but through the stimulation of **insulin-like growth factor I** (IGF I, also called somatomedin C) production in liver (its main source), kidneys, muscles, chondrocytes, and may be also in other tissues. IGF I (a 70-amino acid basic peptide) is the important mediator of GH action. It stimulates deposition of chondroitin sulphate in epiphyseal cartilage of long bones, and so increases chondrogenesis followed by longitudinal growth of bones.

In the clinical picture of gigantism some **local symptoms** (secondary to compression of intracranial structures) induced by expansive growth of adenohypophyseal tumor (expansive adenoma) can be also observed. Prognosis of the disease, especially if it develops in the early childhood, is usually bad. If the patients are not given a successful therapy, they mostly die prematurely, in the first years of adulthood. However, today, gigantism has become vanishingly rare.

Acromegaly – It is a clinical form of somatotropic hyperpituitarism characterized by enlargement of acral parts of the body, and by overgrowth of inner organs (generalized organomegaly). It is the en-

largement of the acral parts that gives the name to this disease. It develops if STH overproduction begins during adulthood, i.e., after epiphyseal growth plates are closed. Therefore, excessive GH production does not induce exessive longitudinal growth of bones, but causes only **widening of bones** by periostal apposition, and **overgrowth of soft tissues**, especially of skin, subcutis, and inner organs.

In the clinical picture **the enlargement of acral parts** of the body dominates. The result of widened phalanges, and skin and subcutis thickening is gradual enlargement of fingers and toes, and hands and feet, leading to the need of larger gloves, rings, and shoes. The increased hand and finger size may cause difficulty with performing fine task, e.g., picking up a pin. Head size increases because of the increase in both soft tissue and skull mass (the need of a larger hat). The mandible enlargement is manifested by expressive protrusion of the lower jaw (prognatism), and by increased spaces between the teeth. Supraorbital ridges, and cheek bones are made more expressive. Physical examination demonstrates **the typical facial appearance** with soft tissue thickening, greasiness of skin, increased breadth of the nose, enlarged ears, protruding chin, and thickening of the lips. These changes gradually lead to coarsening of the facial features. In patients **generalized organomegaly** is usually present, including enlargement of the tongue (macroglossia), and inner organs (visceromegaly), mainly enlargement of heart (cardiomegaly), liver (hepatomegaly), spleen (splenomegaly), and kidneys (nephromegaly). Laryngeal hypertrophy, vocal cords thickening, and sinus enlargement result in a characteristically deep, resonant, and hollow-sounding voice.

The patients with acromegaly have a gradual progression of all above mentioned symptoms. Thus the diagnosis is often delayed for as many as 15–20 years. The symptoms usually begin inconspiciously and insidiously, therefore, they are unnoticed until complications develop.

Along with bone thickening, **osteoporosis** (probably as a result of hypogonadism) also develops. It gives rise to bone deformations. The disease is, therefore, associated with dorsal kyphosis or kyphoscoliosis. Joint pain resulting from accelerated osteoarthrosis may also be the presenting symptom. The osteoarthrosis is secondary to articular cartila-

ges thickening followed by their degenerative changes.

Hypersecretion of GH induces **insulin resistance** and glucose intolerance in about 50 % and diabetes mellitus in about 20 % of patients.

In some patients, more often in acromegalic women, **combination** of hypersomatotropinemia and hyperprolactinemia is present. The cause of this combinated endocrine disorder may be the presence of somatotrophs and lactotrophs in adenohypophyseal adenoma, respectively adenoma consists of bihormonal somatolactotrophs. Probably, in the consequence of antagonistic effect of hyperprolactinemia to gonadotropin production, in men decreased libido, and impotence, gynecomastia, and galactorrhea may occur. In acromegalic women gonadal dysfunction is manifested by loss of libido, oligomenorrhea, even secondary amenorrhea, and infertility.

At progressive adenoma expansion some of the **local symptoms** secondary to compression of intracranial structures may gradually appear, too. These symptoms are: chronic cephalalgia usually accompanied by nausea and vomiting, diminished visual acuity, diplopia, visual field defects, sometimes even complete blindness, symptoms resulting from nerve damage of oculomotor muscles, changes in eyeground from optic nerve compression (paleness of optic nerve papilla, respectively even papilloedema), parosmias, epileptic attacks, and symptoms from damage of hypothalamic centres (disorder of body temperature regulation, somnipathy, obesity, emaciation). In x-ray film changes of size or configuration of sella turcica can be seen.

B. Prolactic hyperpituitarism

Prolactic hyperpituitarism (adenohypophyseal hyperprolactinemia) is the most frequent among hyperpituitarism. The cause of its origin are almost always lactotrope adenomas (**prolactinomas**), belonging among the most often occuring hypophyseal tumors (30–40 % out of their total number). Women are affected 5–8 times more often than men. The adenomas can appear at any age, however, the most frequently from 20 to 40 years of age. If they occur in children, their puberty is delayed. In women simultaneous occurrence of more small adenomas (microadenomas) are prevailingly present. In men mostly one larger adenoma (macroadenoma) occurs, which gives rise to local symptoms from its expansive growth.

The cause of prolactinomas is not known. Primary hypothalamic disorder in the sense of insufficient production of prolactin-inhibiting factor (PIF), or disorder of its transport to adenohypophysis are considered. In unique cases prolactic hyperpituitarism may arise as a result of decreased perception of lactotrophs to PIF. But, this disorder is associated with pituitary lactotroph hyperplasia.

The clinical picture of prolactic hyperpituitarism is characterized especially by the symptoms of **hypogonadism** and by **galactorrhea**. It is diferent in both sexes.

In women the main symptom is a disturbance of menstruation (oligomenorrhea or secondary amenorrhea) which is accompanied by infertility. Concentrations of estrogen and progesterone in blood are decreased. Galactorrhea is present in 30–80 % of these women and may be related to the duration of gonadal dysfunction. Women with long-standing amenorrhea are less likely to have galactorrhea, which probably reflects prolonged estrogen deficiency. In some women patients (20–30 %) other features of estrogen deficiency may occur, such as decreased libido, vaginal dryness, dyspareumia, mastalgia, and hirsutism and tendency to obesity may be also present.

In men hyperprolactinemia is manifested by decrease or loss of libido, partial or complete impotence, disorder of spermatogenesis (oligospermia or azoospermia), and decreased plasma testosterone level, sometimes by gynecomastia, and rarely galactorrhea.   As to the fact that in men the cause of adenohyphyseal hyperprolactinemia is mostly macroadenoma, in the clinical picture also local symptoms from its expansive growth are present.

In both sexes the hypogonadism associated with hyperprolactinemia appears to be due to inhibition of hypothalamic release of LHRH by hyperprolactinemia, resulting in decrease of LH and FSH secretion. Besides that, hyperprolactinemia decreases the effect of gonadotropins at the gonad level (hypofunctional pseudoendocrinopathy). The damage of pituitary gonadotrophs by macroadenoma compression may be also considered.

C. Adrenocorticotropic hyperpituitarism

Adrenocorticotropic hyperpituitarism (central adenohypophyseal hyperglucocorticoidism, Cushing's disease) is the most frequent form of hyperglucocorticoidism. It represents 75 % of the total number of the cases of hyperglucocorticoidism.   This disease is mostly caused by corticotrope **microadenomas** (in 90 % of patients) and by a corticotrope **macroadenoma** in most of the rest.   Microadenomas and macroadenoma autonomously overproduce ACTH resulting in hyperplasia of adrenal cortex. Therefore, the adrenal glands overproduce glucocorticoids, mainly cortisol. The microadenomas are often small (3 to 6 mm or less) and may be difficult to find.

Central adenohypophyseal hyperglucocorticoidism (secondary hyperglucocorticoidism) represents 90 % of the total number of cases of central hyperglucocorticoidism, and the rest 10 % represents central hypothalamic hyperglucocorticoidism (tertiary hyperglucocorticoidism). The result of ACTH excess, which is common phenomenon of the both forms of the central hyperglucocorticoidism, is the origin of hyperplasia of adrenal cortex (mainly zona fasciculata), and thus the origin of glucocorticoid oversecretion with its subsequent clinical symptoms. The cause of origin of ACTH-secreting pituitary adenomas is not known.

Cushing's disease is seldom (5–10 %) caused by **ectopic ACTH production** (ectopic ACTH syndrome). A unique possibility of ectopic CRH production is also admitted. Ectopic production of both these hormones is usually caused by malignant tumors, mostly by lung carcinoma, thymic carcinoma, duodenal carcinoma, pancreatic carcinoma, thyroid medullary carcinoma, and rarely bronchial carcinoid or neuroblastoma.

Cushing's disease occurs 4 times more in women than in men, prevailingly from 25 to 45 years of age.

Pathophysiology and clinical features of Cushing's disease (secondary hyperglucocorticoidism) are almost the same as those of the primary hyperglucocorticoidism (Cushing's syndrome). Therefore, they are detailed in the chapter on pathophysiology of adrenal cortex. They differ from Cushing's syndrome only by the presence of **skin hyperpigmentation**, which originates because the corticotrope adenomas, as well as the cells of malignant tumors with ectopic ACTH secretion, also produce MSH. The moderate stimulative effect of ACTH on skin melanocytes also participates in the origin of the skin hyperpigmentation.

D. Other types of hyperpituitarism

The occurrence of **gonadotropic hyperpituitarism** is unique. It is caused mainly by macroadenoma of

gonadotrophs (**gonadotropic adenoma**), which over-produces gonadotropins (usually FSH or FSH in conjunction with LH, rarely LH alone). It can be observed before puberty more often than in adulthood, five times more frequent in girls than in boys. In both sexes it results in true precocious puberty. Although in men LH plasma concentration is elevated, testosterone level is often low. The reason for this subnormal serum testosterone concentration is unclear, but by some authors it is attributed to secretion of biologically inactive gonadotropins. In postmenopausal women with macroadenomas, it may be difficult to ascertain whether the increased plasma gonadotropin concentration is due to normal menopause or due to a gonadotropin-secreting adenoma.

Thyrotropic hyperpituitarism (pituitary hyperthyroidism, secondary hyperthyroidism) is very rare. It is caused by macroadenoma (thyrotropic adenoma) of thyrotrophs which overproduces TSH (TSH-induced hyperthyroidism). In the patients the clinical symptoms of thyrotoxicosis are present, however, they are usually milder than in primary (peripheral) hyperthyroidism.

II. Adenohypophyseal hypofunctions

Decreased ability of the anterior lobe of the pituitary gland to produce one or more tropic hormones is called hypopituitarism. Insufficient secretion of only one pituitary hormone (**isolated hypopituitarism**, monohormonal hypopituitarism, monotropic hypopituitarism) occurs seldom and it is mostly STH deficiency. Dependent on the cause, the monohormonal hypopituitarism can be sometimes gradually changed to plurihormonal hypopituitarism (**combinated hypopituitarism**). However, the most frequent form of adenohypophyseal hypopituitarism is the disorder manifesting insufficient secretion of all adenohypophyseal hormones. This condition is called **panhypopituitarism**. If the adenohypophyseal hypofunction orriginates as a result of the pathological process of gradually destroying cells of its hormonally active tissue, isolated or combinated hypopituitarisms are only incipient phases of panhypopituitarism. Panhypopituitarism may occur also suddenly, without the two phases mentioned above.

A. Somatotropic hypopituitarism

In the patients with the somatotropic hypopituitarism STH deficiency is present or this hormone is totally absent. In about one third of cases it is **an isolated** GH deficiency. However, in the rest of the patients the deficiency of GH is **combinated** with the deficiency of gonadotropins.

In adults, STH deficiency is usually cryptic. Its presence in adults does not seem to be inevitable. But, the consequences of STH deficiency and replacement in adults are still being explored. Physiological production of GH is needed only in children during the whole period of body growth, i.e., till the epiphyseal growth plates are closed. Insuficient STH production in childhood or youth before epiphyseal closure leads to impaired growth and short stature, respectivelly gives rise to the origin of **hyposomatotropic dwarfism** (pituitary dwarfism, pituitary nanism). However, it is more often a consequence of hypothalamic GHRH deficiency than a consequence of primary disorder of STH production by pituitary somatotropes.

There are two forms of hyposomatotropic dwarfism: hypothalamic and pituitary. **Hypothalamic dwarfism** is usually caused by isolated STH deficiency, while **pituitary dwarfism** is mostly characterized by combinated disorder, e.g., by STH deficiency and gonadotropin deficiency.

The cause of the both mentioned forms of hyposomatotropic dwarfism can be found only in about 35 % of affected children. It may be an organic disorder, e.g., tumor, cyst, aneurysm, trauma, or other pathological process endamaging the cells of competent endocrine active tissue of hypothalamus or adenohypophysis. In about 65 % of patients the cause of GH deficiency can not be found (idiopathic hyposomatotropic dwarfism).

The both forms of hyposomatotropic dwarfism are necessary to differ from those forms of dwarfism in which plasma GH concentration is normal or even increased. The following forms of dwarfism must be distinguished:

1. Nanism caused by long-term severe **nutritional insufficiency**.

2. Nanism caused by some **chronic diseases**, e.g., malabsorption or chronic inflammatory intestine disease, chronic renal disease (renal nanism), severe congenital heart disease (cardial nanism), severe pulmonary disease, and severe hematological disease.

3. Dwarfism caused by **insensitivity to GH** at the

level of GH receptors. This disorder is due to absent or defective GH receptors. It is also widely known as **Laron-type dwarfism**, which probably represents only one form of insensitivity to STH (familial form of short stature). Due to STH receptors disorder IGF I (somatomedin C) is not produced in hepatocytes and in cells of other tissues. The serum IGF I concentration is low and does not increase in response to injection of human GH. Abnormalities of DNA restriction fragment length in some of these patients are consistent with defects in the gene encoding the GH receptor.

4. **Constitutional delay in growth and puberty**. Healthy individuals, who spontaneously enter puberty after the age of 12 for girls and 14 for boys, have constitutional delay in growth and adolescence. The syndrom of growth retardation with delayed puberty accounts for a high proportion of referrals for growth evaluation, particularly **in boys**. Height and bone age are usually delayed by 2 to 4 years, and onset of pubertal development is delayed by 2 years or more. In the patients adrenarche and gonadarche occur later than in their classmates for years. However, the patients undergo spontaneous puberty.

   GH secretion before the actual onset of puberty in these patients is suboptimal. However, their STH secretion and growth velocity return to normal after the onset of puberty. There is an interaction of IGF I and gonadotropins in the testis, and the relatively low secretion of GH (and presumably intragonadal IGF I) may impair the gonadal response to gonadotropins. Affected boys seem to be more distressed by short stature than by delay in sexual development.

   Final adult stature, which may not be reached until age 20 or more, is often in the low-normal range, and sexual development and fertility are normal. Anamnesis can show, that delay in growth and in pubertal development may have occurred in the father and other male relatives. This diagnosis of constitutional growth delay should be made only after the exclusion of other causes of delayed growth and puberty.

5. **Familial (genetic) short stature**. The patients with familial short stature do not have delayed

pubertal development. Plasma concentrations of STH and IGF I are usually normal. Familial short stature is a physiological variant of growth distance in which the velocity of bone age is normal, whereas constitutional delay in growth and adolescence is a disorder of growth and bone age tempo that secondarily impairs growth distance. Of course, some children may have a combination of genetic short stature and constitutional delay in growth and puberty.

Pathophysiology and clinical features of hyposomatotropic dwarfism. The most expressive symptom of this disease is a disorder of body growth. Children with hyposomatotropic hypopituitarism are of a short stature and exhibit growth curves that deviate progressively from normal. In idiopathic hypopituitarism, growth failure may not be obvious until patients are 2 to 4 years old. In retrospect, however, it is often possible to establish that growth failure began in the first few months of life. The growth disorder is most evidently manifested at the onset of puberty when the psychical problems from short stature of the pacient may appear.

Retardation or precocious cessation of body growth is the result of **longitudinal bone growth disorder**, while epiphyseal growth plates are open for longer than usual. Therefore, in the patient the slow growth may be prolonged until age 30–40 years. A bone age retardation in relation to chronological age (delayed skeletal maturation) is evident. Closure of the fontanelles and eruption of permanent teeth are delayed.

The final height of hypophyseal dwarf varies from 120 to 150 cm. The stature is, however, usually proportional (the patients exhibit normal body proportions). Overall look, especially facial appearance is infantile for quite a long time. On the contrary, in adulthood the facial appearance is progeric (precociously senile). There is no significant deviation of the patient intelect. In the first several years of life, approximately 10 % of children with somatotropic hypopituitarism have hypoglycemic convulsions. An additional 10 % or more have asymptomatic fasting hypoglycemia. Hypoglycemia is usually secondary to combined deficiencies of cortisol and GH.

Somatotropic hypopituitarism in children is usually associated with gonadotropin deficiency (combinated hypopituitarism). In that case along with dwarfism also sexual infantilism occurs. When

the hyposomatotropic dwarfism is due to expansive growing tumor, in the clinical picture of the disease also local symptoms from the damage of the surrounding intracranial structures can be present.

In adults the clinical syndrom due to STH deficiency is not known. In the patients only tendency to hypoglycemia resulting from the increased sensitivity of tissues to insulin is observed. GH is insulin antagonist, and, therefore, its deficiency is connected with the increased sensitivity of tissues to insulin.

B. Gonadotropic hypopituitarism

Forms and intensity of symptoms of gonadotropic hypopituitarism (gonadotropic hypogonadism, secondary hypogonadism) depend not only on **the degree** of gonadotropin deficiency, but also especially on the age and sex of a patient in **the time** of the origin of gonadotropin deficiency. Isolated type of gonadotropic hypogonadism is very rare. Combinated gonadotropic hypogonadism, characterized by simultaneous deficiency of gonadotropins and GH, is more frequent.

Isolated gonadotropic hypogonadism is usually inborn (see Kallmann's syndrome). However, it is a primary hypothalamic disorder (deficiency of GnRH secretion). It can be caused also by a functional disorder, mainly in the female, e.g., by chronic psychoemotional stress.

Combinated gonadotropic hypogonadism, i.e., simultaneous gonadotropin and GH deficiency, is more often caused by organic disorder (see somatotropic hypopituitarism). This organic disorder destroys the hypothalamic cells producing GnRH and GHRH, or destroys adenohypophyseal gonadotrophs and somatotrophs.

The clinical picture of secondary hypogonadism depends on sex and the age of a patient in the time of the origin of this disease. Prepubertal or postpubertal hypogonadotropic hypogonadism can be distinguished. Their clinical picture depends on the sex of a patient. Therefore, the following four types of hypogonadotropic hypogonadism may occur:

1. **Prepubertal hypogonadotropic hypogonadism in boys**.

   In an affected child the sexual development ceases, the symptoms of spontaneous onset of puberty do not appear. Secondary sexual characteristics are not developed (sexual infantilism). Axillary and pubic hair is missing, break-

ing of the voice does not occur and facial appearance remains infantile for a long time. Development of muscles is insufficient and sometimes gynecomastia is present. The testes are small and soft, and scrotum is not pigmented. Sometimes cryptorchism may be present. Spermiogenesis is absent what leads to infertility. The size of the penis remains the same as in childhood. If STH production is normal (isolated gonadotropic hypopituitarism), epiphyseal fusion is retarded, and growth of long bones of extremities continues also after 20 years of age. Therefore, eunuchoid body proportions (excessive and disproportional body growth, characterized by too long extremities in relation to the trunk) develop in the patient. But, if STH secretion is decreased (combinated disorder) not only sexual infantilism, but also hypophyseal nanism appears in the patient.

2. **Prepubertal hypogonadotropic hypogonadism in girls**

   In affected girls any symptoms of spontaneous onset of puberty are absent, sexual infantilism continues. The main symptom of the disease is primary amenorrhea. Neither primary nor secondary sexual organs are being developed like in women. Also secondary sexual characteristics are not developed. If STH secretion is normal, epiphyseal closure is retarded leading to disproportional body growth (eunuchoid habitus). But, if in the patient STH deficiency occurs, hypophyseal dwarfism originates.

3. **Postpubertal hypogonadotropic hypogonadism in men**

   This disorder is very rare, and sometimes it can be the first symptom of development of panhypopituitarism. It is manifested by gradual regression of secondary sexual characteristics, diminished libido and impotence appear. Axillary and pubic hair becomes thinner, and growth of facial hair decelerated. Moderate atrophy of epididymides may occur, spermatogegenesis becomes insufficient and leads to infertility. Muscle flaccidity and atrophy are present, female like type of subcutaneous fat distribution appears. Chronically untreated hypogonadism may result in the origin of osteoporosis. Some psychical

changes may appear as well, e.g., loss of aggressivity.

4. **Postpubertal hypogonadotropic hypogonadism in women**

   Postpubertal hypogonadotropic hypogonadism is more frequent in women than in men. It may be only the initial phase of gradually developing panhypopituitarism. The most evident symptoms of hypogonadotropic hypogonadism in women are the secondary amenorrhea and infertility. Gradually the symptoms of different degree of defeminization (atrophy of the breast, uterus and ovaries) appear. Inhibition of orgasmic function may appear. When hypogonadism is untreated for a long time, the symptoms of osteoporosis may be gradually developed in the patients.

C. Other types of hypopituitarism

Due to primary disorder of adenohypophysis **isolated TSH deficiency** or **isolated ACTH deficiency** can occur very rarely. Damage of thyrotropes or corticotropes is more frequently present in the patients with panhypopituitarism, when also other trope cells are damaged. Secondary hypothyroidism as well as secondary hypoglucocorticoidism have essentially the same pathophysiology and clinical features as primary hypothyroidism or primary hypoglucocorticoidism. The symptoms of secondary hypothyroidism are, however, usually milder than the symptoms of primary hypothyroidism.

D. Panhypopituitarism

The term panhypopituitarism signifies a deficiency of all anterior pituitary hormones. Its symptoms originate either suddenly or are developing gradually (even several years). It is caused by various organic disorders of adenohypophysis. **Sudden** form of panhypopituitarism in the past often occured in some women as a result of postpartum necrosis of adenohypophysis (pituitary infarction at the time of delivery), the clinical picture of which is known as **Sheehan's syndrome**. Adenohypophyseal necrosis induces sudden occurrence of symptoms of panhypopituitarism. This syndrome usually originated in women with a long-lasting and complicated delivery accompanied by excessive blood loss as a sequel of hemorrhagic shock at the time of delivery.

Pathogenesis of Sheehan's syndrome is not exactly known. But, mainly spasm of arterioles of portal vessel bed during obstetric posthemorrhagic shock is supposed to participate in the origin of adenohypophyseal necrosis. Other pathogenic mechanism, however, may be involved, such as intravascular thrombosis or increased sensibility (vulnerability) of the anterior lobe of pituitary gland to hypoxia in parturient women.

Other causes of sudden origin of panhypopituitarism are: adenohypophyseal hemorrhage (pituitary apoplexy), severe head trauma, hypophysectomy, and ionizing irradiation applied in the area of sella turcica.

The cause of **gradually** developing panhypopituitarism may be expanding adenohypophyseal tumor (mainly from chromophobic cells), craniopharyngioma, pinealoma, large artery aneurysm, metastases, cyst, infiltrative diseases, infectious diseases, and lymphocytic hypophysitis (autoimmune pituitary destruction). Because the functional capacity of the adenohypophyseal tissue is rather large, pituitary hypofunction is unlikely to be manifested until at least 75–85 % of anterior lobe is destroyed. In most instances, there is destruction of 95–99 % of the anterior lobe. Secondary to chronic deficiency of adenohypophyseal tropic hormones, atrophy of individual target endocrine glands (multiglandular atrophy) gradually develops.

The clinical picture of panhypopituitarism depends on the age and sex of the patient in the time of the origin of this disease, and also on the degree of deficiency of individual adenohypophyseal hormones. Prepubertal and pospubertal panhypopituitarism can be distinguished.

Prepubertal panhypopituitarism

This disease is manifested especially by the symptoms resulting from STH and gonadotropic hormone deficiency. Deficiency of STH prior to epiphyseal fusion leads to retardation in bone age and in body growth resulting in **pituitary dwarfism**. Central adenohypophyseal hypothyroidism may to a certain extent also participate in the body growth disorder. GTH deficiency leads to absence of pubertal development (sexual infantilism), the clinical picture of which depends on sex of the patient. As there is a certain spontaneous basal production of the thyroid hormones, TSH deficiency in the dwarfish children is not usually expressively manifested. Therefore,

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 defi-**

ciency (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