mation of 1,25-dihydroxycholecalciferol is also the result of damaged and shrunken parenchyma of the kidneys. Low serum 1,25-dihyroxycholecalciferol concentration leads to a reduction of intestinal absorption of calcium. Concentration of PTH in circulating blood increases also due to **decreased renal clearance of PTH**, which is caused by expressively decreased glomerular filtration rate. It is assumed that a further contributing factor to hypocalcemia is relative **skeletal resistance to PTH**.

Another, but less common cause of secondary hyperparathyroidism is **vitamin D deficiency**. Compensatory PTH oversecretion is due to hypocalcemia, which originates as a result of insufficient intestinal calcium absorption. This reduced calcium absorption is caused by underproduction of its protein carrier in enterocytes. Decreased production of this high-affinity calcium-binding protein of intestinal mucosal epithelia is induced by vitamin D deficiency (its active hormonal form, i.e., 1,25-dihydroxycholecalciferol), By PTH oversecretion hypocalcemia is being normalized. By simultaneous decreased reabsorption of phosphates in renal tubules (due to increased serum PTH level) hyperphosphaturia and hypophosphatemia develop.

The third main cause of secondary hyperparathyroidism is **intestinal calcium malabsorption**. Most commonly it originates due to intestinal lipid malabsorption caused by pancreatic lipase and bile acid deficiency, celiac sprue (gluten-induced enteropathy), and tropical sprue. Nonabsorbed fatty acids together with calcium form insoluble calcium soaps, and, therefore, excessive intestinal calcium loss appears. Decreased intestinal calcium absorption is also induced by fat-soluble vitamin D deficiency which is in patients with intestinal fat malabsorption caused by its insufficient intestinal absorption.

Clinical features. The clinical features of secondary hyperparathyroidism are analogous to those of primary hyperparathyroidism, however, usually milder. Nephrolithiasis and nephrocalcinosis are less common in the patients with secondary hyperparathyroidism. Ectopic calcifications appear mainly in subcutis, tissues of periarticular area, and in the wall of arteries. Besides the symptoms resulting from PTH overproduction, also the symptoms of primary disease which gives rise to the disorder of calcium homeostasis may be observed. The symptoms of primary disease are the most evident in the patients with chronic renal failure. Unlike the patients with primary hyperparathyroidism, in the patients with secondary hyperparathyroidism serum calcium concentration is slightly decreased, sometimes even normal, and serum phosphate concentration is increased. The symptoms of uremia are also present. The skeletal abnormalities include osteitis fibrosa cystica (caused by the excessive action of PTH on bones), osteomalacia (caused by impaired formation of 1,25-dihydroxycholecalciferol and by calcium deficiency), and generalized osteopenia. These bone abnormalities in patients with secondary hyperparathyroidism induced by chronic renal failure are usually termed **renal osteodystrophy**. Its expressive manifestations develop mainly in patients undergoing chronic hemodialysis. In this subjects generalized osteopenia may lead to a development of multiple pathological fractures. Any of the classic lesions of primary hyperparathyroidism can also occur, although bone cysts are less common. Clinically, osteodystrophy causes bone pain. In addition, proximal muscle weakness may be similar to that in primary hyperparathyroidism.

The clinical features of rickets develop with vitamin D deficiency in infancy or childhood. Vitamin D deficiency in the adults evokes the origin of the clinical features of osteomalacia.

5.6 Pathophysiology of the adrenal glands

The suprarenal glands are composed of two developmentally, morphologically, and functionally different parts, the cortex and the medulla. Cortical tissue is derived embryologically from the celomous mesoderm. Histologically it consists of three zones (zonae glomerulosa, fasciculata, and reticularis) and produces three kinds of functionally different corticosteroid hormones: glucocorticoids, mineralocorticoids, and androgens, and in small amounts also estrogen and progesterone. Medullary tissue is derived embryologically from neuroectoderm. Histologically it is rather homogenous and consists of chromaffin cells. The medulla produces catecholamines

(adrenaline, noradrenaline, and dopamine), the most important being adrenaline. The adrenal medulla and the sympathetic nervous system make up an anatomical and physiological unit that is often referred to as the sympathoadrenal system.

5.6.1 Pathophysiology of the adrenal cortex

There are two basic types of disorders of adrenal cortex, adrenocortical hypofunction and adrenocortical hyperfunction. According to the primary place of their origin the following types of disorders may be distinguished: primary adrenocortical hypofunction or hyperfunction (the cause of these disorders is within the adrenal cortex itself), secondary adrenocortical hypofunction or hyperfunction (the cause of these disorders is in the adenohypophysis), and tertiary adrenocortical hypofunction or hyperfunction (the cause of these disorders is in the hypothalamus).

5.6.1.1 Hypofunction of the adrenal cortex

Adrenocortical hypofunction includes all conditions in which adrenal steroid hormone secretion falls below the requirements of the body tissues. Isolated primary deficiency only of some kind of corticosteroid hormones is very rare. At present only primary hypoaldosteronism is known. Secondary hypoglucocorticoidism resulting from isolated ACTH deficiency or from its deficiency due to panhypopituitarism (a deficiency of all adenohypophyseal hormones) is also known. Tertiary hypoglucocorticoidism is quite common and originates as a result of inhibition of CRH secretion, respectivelly as a result of suppression of hypothalamic-adenohypophyseal function by chronic administration of pharmacological dosages of glucocorticoids. Deficiency of all kinds of corticosteroid hormones (adrenocortical insufficiency) is more common, deficiency of glucocorticoids and mineralocorticoids is decisive. According to clinical course chronic and acute adrenocortical insufficiency may be distinguished.

I. Chronic primary adrenocortical insufficiency

Chronic primary adrenocortical insufficiency (Addison disease) is a rare disease occurring in about 0.03–0.04 per mille of adult population. It is induced by deficiency of all three types of corticosteroid hormones due to gradually developing destruction of all three zones of adrenal cortex. As the functional reserve of adrenal cortex is large, deficiency of its hormones clinically appears not until at least 90 % of the functioning cortical cells have been destroyed. Initially secretion of adrenocortical hormones is enough for covering basal requirements of organism, however, it is insufficient in the situations of increased demands of body tissues. Therefore, it is clinically revealed only during various situations associated with stress. In this stage of decreased adrenal reserve the disease is denoted as relative adrenocortical insufficiency (**mild adrenocortical insufficiency** that results only in inadequate cortisol increase in response to stress). If the signs and symptoms of adrenocortical hormone deficiency appear already at rest (**severe adrenocortical insufficiency**), it is denoted as absolute adrenocortical insufficiency. Addison disease may occur at any age, more often in adults between 20 and 50 years of age, and usually affects more frequently women than men (2–3:1).

Etiology and pathogenesis. Addison disease results from progressive bilateral adrenocortical destruction, which must involve more than 90 % ot the parenchyma of the glands before signs and symptoms of adrenocortical insufficiency appear. **Tuberculous adrenalitis** was once the most common cause of Addison disease. Now it accounts for about 20 % of cases. The adrenal involvement is almost always a hematogenous dissemination from an active primary disease elsewhere in the body, most often the lungs but sometimes the genitourinary tract. With tuberculous adrenalitis the cortex and also the medulla are involved resulting in loss of all three types of corticoid hormones and catecholamines.

Today, the most common cause of Addison disease is **autoimmune adrenalitis** which accounts for about 75 % of cases. Autoimmune adrenalitis was previously known as idiopathic chronic primary adrenocortical insufficiency. It is characterized by destruction of glandular cells of parenchyma (diffuse atrophy) of all three zones, by diffuse lymphocytic infiltration and fibrosis of the cortex. An autoimmune process destroys exclusively the cortex, the adrenal medulla is unaffected. Circulating antiadrenal antibodies that react with all three zones of the adrenal cortex are present in 60–70 % of patients with autoimmune adrenalitis. Besides humoral im-

munity, cell-mediated immune processes may also be important in the development of adrenocortical insufficiency. Decreased suppressor T lymphocyte function has been described in patients with idiopathic adrenocortical insufficiency. There is a well-defined increased incidence of certain histocompatibility antigens in patients with autoimmune adrenalitis, particularly HLA-DR3, HLA-DR4 and HLA-B8, suggesting some genetic predisposition.

The presence of antiadrenal antibodies seems to precede the development of adrenocortical insufficiency by several years. The first sign of adrenocortical insufficiency is an increase in plasma renin activity in association with a normal or low serum aldosterone level, which suggests that the zone glomerulosa is affected initially. After several months to years, zone fasciculata dysfunction becomes evident, first by a decreased plasma cortisol response to ACTH, later by an increased basal plasma ACTH level, and finally by a decreased plasma cortisol concentration and overt symptoms.

In about half of patients with autoimmune adrenalitis, the adrenal is the sole target of the autoimmune reaction (**isolated** autoimmune adrenocortical insufficiency), but in the remainder, other endocrine glands are concomitantly affected. In the patients of the latter also antibodies against tissue of other endocrine glands are usually present, and also other types of antibodies related to involvement to some of nonendocrine organs or tissues may be found. These disorders associated with autoimmune adrenocortical insufficiency are referred as **polyglandular autoimmune syndrome** (autoimmune adrenocortical insufficiency **associated** with polyglandular autoimmune syndrome). The polyglandular autoimmune syndromes have been subdivided into three types, but only the type I and the type II are associated with autoimmune adrenocortical insufficiency.

Autoimmune adrenocortical insufficiency may be **familial** or **nonfamilial**. It is less likely to be familial when it occurs alone, whereas about one half of patients with adrenocortical insufficiency as a part of polyglandular autoimmune syndrome type I or II have positive family histories.

Polyglandular autoimmune syndrome **type I** represents the combination of adrenocortical insufficiency, primary hypoparathyroidism and chronic mucocutaneous candidiasis. Other autoimmune diseases in these patients include nontropical sprue, pernicious anemia, chronic active hepatitis, alopecia, primary hypothyroidism, and primary hypogonadism. This syndrome is rare and usually presents during childhood. It is inherited in an autosomal recessive pattern, in which females are affected slightly more than men, but there is no HLA association. **Type II** polyglandular autoimmune syndrome marked by coexistence of adrenocortical insufficiency, chronic lymphocytic thyroiditis, type 1 diabetes mellitus, and primary hypogonadism, sometimes accompanied by nonendocrine autoimmune disorders, such as vitiligo, myasthenia gravis, immune thrombocytopenic purpura, rheumatoid arthritis and Sjögren's syndrome. The type II is the more common polyglandular syndrome than type I and usually expressed in adulthood. Women are affected three times more frequently than men. About half of the type II cases are familial, but various modes of inheritance (autosomal recessive, autosomal dominant, or polygenic) have been reported. Polyglandular autoimmune syndrome **type III** is not associated with adrenocortical insufficiency.

Rarely, **other lesions** can involve the adrenal glands and cause chronic primary adrenal insufficiency, such as disseminated fungal infections (histoplasmosis, blastomycosis, and coccidioidomycosis), bilateral infiltration by metastatic cancer as well as by malignant melanomas and lymphomas, bilateral amyloidosis, sarcoidosis, hemochromatosis, or bilateral total adrenalectomy. This rare lesions of the adrenal glands cause only about 5 % of all cases of Addison disease.

Addison disease is characterized by an insidious onset of slowly progressive nonspecific signs and symptoms. The most common of them are fatigability, tiredness, chronic weakness, lassitude, general malaise, anorexia, nausea, vomiting, weight loss, cutaneous and mucosal hyperpigmentation, arterial hypotension, and occasionally hypoglycemia. All the mentioned nonspecific manifestations, besides hyperpigmentations, are the direct consequence of glucocorticoid and mineralocorticoid deficiencies. In women the symptoms due to deficiency of adrenal androgens also gradually appear. Therefore, the clinical picture of frank Addison disease is formed by signs and symptoms resulting from deficiency of all three kinds of corticosteroid hormones, as well as by those secondary to compensatory hypersecretion of

ACTH and other proopiomelanocortin-derived peptides (POMC peptides).

The generalized **weakness, tiredness** and **fatigability** are in the early phase of gradual primary adrenocortical insufficiency transient and appear only after increased physical or psychical stress. They become gradually more intensive and in more advanced stages of chronic adrenocortical insufficiency they become permanent. The patient is continuously fatigued, necessitating bed rest. Diffuse **myalgias** and **arthralgias** are also common.

Abnormalities of gastrointestinal functions are often the presenting complaint. **Gastrointestinal symptoms** vary from mild anorexia, occasional vomiting, weight loss, abdominal pain, and diarrhea that may alternate with constipation, to fulminating nausea, vomiting, diarrhea, and ill-defined abdominal pain, which may also be so severe as to be confused with an acute abdomen. The mechanism of these gastrointestinal disorders is not exactly known. Decreased production of gastric acid and decreased activity of pepsin and other gastrointestinal enzymes are considered to participate. It is assumed that the deficiency of glucocorticoids and mineralocorticoids are responsible for the origin of gastrointestinal symptoms. The wight loss (asthenia) is due mostly to anorexia but partly to dehydration. Intensity of gastrointestinal symptoms correlates with the severity of adrenocortical insufficiency.

The loss of gluconeogenic effect of cortisol is manifested by the origin of **hypoglycemia** which appears mainly after prolonged fasting (usually in the morning) or, rarely, several hours after a high-carbohydrate meal. As the secretion of insulin is normal, contraregulatory effect of cortisol is missing in these situations. Hypoglycemia is infrequent in adults, but in children with primary adrenocortical insufficiency is common. In adults it usually appears after infection, fever, or alcohol ingestion. Hypoglycemia is thought to be due to increased peripheral glucose utilization associated with increased sensitivity to insulin and impairment of gluconeogenesis, hepatic glucose production, and glycogen synthesis. Patients with chronic adrenal insufficiency may tolerate greater degree of hypoglycemia without developing symptoms. Therefore, the development of hypoglycemic coma is rare.

Deficiency of mineralocorticoids is the cause of the origin of **hyponatremia** and **hyperkalemia**. The hyponatremia is due to both loss of sodium into the urine and movement into the intracellular compartment. The hyperkalemia is due to a combination of aldosterone deficiency, impaired glomerular filtration rate, and acidosis. Extravascular sodium loss deplets extracellular fluid volume, reduces circulating blood volume, and accentuates **hypotension**. Initially only postural hypotension may be evident, but later in most patients the blood pressure is low permanently and is usually associated with postural dizziness or syncope. The electrocardiogram may show nonspecific changes of the T wave, QRS complex, and QT interval. Hyperkalemic cardiac arrhythmias may also occur.

Mild to moderate **eosinophilia**, relative **lymphocytosis**, and **anemia** are common. The normocytic, normochromic anemia, which may initially be masked by hemoconcentration, is probably a direct effect of glucocorticoid deficiency. Some patients have also neutropenia, which is presumably caused by increased sequestration of neutrophils in the marginal pool. Splenomegaly and **lymphoid tissue hyperplasia**, particularly of the tonsils, may occur.

Hyperpigmentation of the skin and mucous membranes, which is evident in most patients with chronic primary adrenocortical insufficiency, is one of the characteristic physical findings. It is caused by an increased content of melanin in **the skin**, which is thought to be due to the melanocyte-stimulating activity of the increased circulating proopiomelanocortin (POMC) peptide level (POMC peptide is precursor of ACTH, MSH and beta-lipotropin). ACTH, MSH and beta-lipotropin have probably a direct effect on epidermal melanocytes as well. The resulting hyperpigmentation is generalized and it commonly appears as brown, tan, or bronze darkening of the skin, particularly of sun-exposed areas, such as the face, neck, and backs of the hands, and areas exposed to chronic mild trauma or pressure, such as the elbows, knees, knuckles, spine, waist (belt), and shoulders (brassiere straps). Unlike the insolation, hyperpigmentation is also prominent in the palmar and finger creases, and in areas that are commonly hyperpigmented, such as the arealae and perineum. Bluish black patchy **buccal pigmentation** occurs on the inner surface of lips and the buccal mucosa along the line of dental occlusion, the site of repeated trauma. It may also occur on or under the tongue, along the gingival border, and on the hard

palate. Scars acquired during untreated Addison disease are permanently pigmented. Scars acquired before the onset of primary adrenocortical insufficiency remain unpigmented, and those acquired after treatment do not become pigmented.

The hair and nails may become darker, the nails showing longitudinal bands of darkening. Darker nails are due to hyperpigmentation of nail-bed. Patchy, often bilaterally symmetrical areas of depigmented skin (**vitiligo**) occur on the trunk or extremities in 10 to 20 % of patients with autoimmune adrenocortical insufficiency. Their surroundings is hyperpigmented.

Psychiatric symptoms are present in most patients with severe or long-lasting Addison disease. Patients frequently have personality changes, usually excessive irritability, negativism, social withdrawal, hallucinations, and paranoid delusions. Sometimes apathy, depression, lack of initiative, and impairment of memory that can progress to confusion, delirium, and stupor, occur.

Deficiency of androgens is clinically manifested only in women, because the decisive source of androgens in them are the adrenal glands. Decreased axillary and pubic hair and loss of libido are typical. In about 25 % of women with Addison disease secondary amenorrhea may occur and it may be due to the effects of chronic illness, weight loss, or autoimmune-mediated primary hypogonadism.

Basal concentrations of plasma cortisol and aldosterone are subnormal and fail to increase following ACTH administration. ACTH and other POMC-derived peptides, such as beta-lipotropin, are elevated. The serum testosterone level is normal in men, because it is produced largely by the testes, but is low in women, in whom it is derived almost entirely from peripheral conversion of adrenal androgens. The volume depletion resulting from aldosterone deficiency causes increased plasma renin concentration and activity. Glucocorticoid deficiency reduces angiotensinogen level, but plasma concentration of angiotensin II is increased and, because of a direct peripheral vasoconstriction effect, plays an important role in maintaining blood pressure in Addison disease.

The patients with Addison disease have diminished resistance to infections and other stress situations. The course of intercurrent infection in them is severer than in healthy subjects. Patients may exhibit extreme sensitivity to some drugs, such as narcotics, anesthetics, and sedatives.

Untreated Addison disease has usually slow and progressive clinical course and in its final stage acute adrenal insufficiency (adrenal crisis) may develop. However, if this disease is adequately treated, it has a favourable prognosis, especially if the physician manages also therapy of intercurrent infections and other stress situations.

II. Secondary and tertiary adrenocortical insufficiency

Secondary adrenocortical insufficiency is due to insufficient pituitary ACTH secretion and subsequent insufficient adrenal cortisol secretion. Tertiary adrenocortical insufficiency results from deficient hypothalamic secretion of CRH and subsequent pituitary ACTH hyposecretion.

Chronic secondary adrenocortical insufficiency

Chronic secondary adrenocortical insufficiency related to natural causes, like chronic primary adrenocortical insufficiency, is also uncommon. ACTH deficiency may rarely occur alone, but in common instances, it is only one part of panhypopituitarism.

Etiology and pathogenesis. Any process that involves the adenohypophysis and interferes with the ability to secrete ACTH may cause secondary adrenocortical insufficiency. Large pituitary tumors or craniopharyngiomas, lymphocytic hypophysitis, head trauma, infectious diseases (such as tuberculosis or histoplasmosis), infiltrative diseases, pituitary metastases, large intracranial artery aneurysms, and pituitary infarction can destroy the pituitary tissue. In these patients secondary adrenocortical insufficiency occurs **in association** with multiple pituitary tropic hormone deficiencies (panhypopituitarism). ACTH deficiency may also be selective. However, this **isolated** ACTH deficiency is rare. The defect probably is at the pituitary level because there is no ACTH-secretory response to CRH, as usually occurs in hypothalamic disorders. Selective corticotrope absence (their atrophy due to anticorticotrope antibodies) and disability of corticotropes to respond to CRH stimulation are considered.

In secondary adrenocortical insufficiency, cortisol production is inadequate because of deficient pituitary ACTH secretion. As a result of decreased cortisol negative feedback inhibition, hypothalamic CRH

synthesis and secretion and plasma CRH concentrations are increased. The clinical presentation is one of pure glucocorticoid deficiency and, in women, loss of adrenal androgen secretion. Because ACTH secretion is decreased, patients are not hyperpigmented. Mineralocorticoid secretion usually remains normal because it is regulated by the renin-angiotensin system.

As in a patient with chronic primary adrenocortical insufficiency, the development of chronic secondary adrenocortical insufficiency is usually gradual, going first through a stage of partial (relative) ACTH deficiency that results only in inadequate ACTH and cortisol responses to stress. With prolonged and more profound ACTH deficiency, the adrenal fasciculata and reticularis atrophy and lose their ability to respond acutely to ACTH. Depending on the extent of ACTH lack, the adrenals may be moderately to markedly reduced in size. However, the adrenal cortex can recover the ability to produce cortisol in response to continuous maximal ACTH stimulation over a period of a few days to a week.

The clinical features of chronic secondary adrenocortical insufficiency are similar to those of chronic primary adrenocortical insufficiency with two major exceptions. First, hyperpigmentation is not present because plasma ACTH and other POMC peptides concentrations are not increased. On the contrary, plasma ACTH and related peptide levels are low, which may be manifested by hypopigmentation or depigmentation of skin. Therefore, the skin may have alabaster pale local colour. Second, dehydration and hyperkalemia are not present.

Weakness, fatigability, myalgias, arthralgias, and psychiatric changes are as common as in chronic primary adrenocortical insufficiency, indicating that most of these symptoms are due to glucocorticoid rather than mineralocorticoid deficiency. However, gastrointestinal symptoms are less common, suggesting that electrolyte disturbances may be involved in their etiology. Hypoglycemia occurs more frequently in chronic secondary adrenocortical insufficiency. In these patients secondary adrenocortical insufficiency often occurs in association with signs and symptoms of hyposecretion or sometimes hypersecretion of other anterior pituitary hormones.

Chronic tertiary adrenocortical insufficiency

Any process that involves the hypothalamus and interferes with CRH biosynthesis and secretion can cause tertiary adrenocortical insufficiency. Such processes include tumors, infiltrative diseases (e.g., sarcoidosis), and cranial irradiation. In patients with primary pituitary deffect, the ACTH-secretory response to CRH is inappropriately low or absent, whereas in those with primary hypothalamic defect, this response is usually exaggerated and prolonged.

Suppression of hypothalamic-pituitary-adrenal function by chronic administration of pharmacological dosages of glucocorticoids is the most common cause of tertiary adrenocortical insufficiency (iatrogenic tertiary adrenocortical insufficiency). It decreases CRH synthesis and secretion from the hypothalamus and blocks its tropic and secretagogue actions on the pituitary corticotropes. This results in decreased synthesis of ACTH by the anterior pituitary corticotropes, which decrease in size. Eventually, the number of corticotropes decreases. Therefore, plasma ACTH concentration is low. In the absence of ACTH stimulation, the adrenal zonae fasciculata and reticularis atrophy and can no longer secrete glucocorticoids and androgens. However, the adrenals retain nearly normal mineralocorticoid secretion. If chronic administration of glucocorticoids suddenly stops, acute adrenocortical insufficiency may originate.

Tertiary adrenocortical insufficiency also occurs in those patients who are cured of Cushing's syndrome by removal of a pituitary or nonpituitary ACTH-secreting or adrenal cortisol-secreting tumor, but who are left without an adequate cortisol therapy. The chronic endogenous hypercortisolemia suppresses the hypothalamic-pituitary-adrenal axis in the same manner as exogenous glucocorticoids.

The clinical features and the laboratory findings of chronic tertiary adrenocortical insufficiency are nearly similar to those of chronic secondary adrenocortical insufficiency.

III. Acute adrenocortical insufficiency

Acute adrenocortical insufficiency (adrenal crisis, Addisonian crisis) is a life-threatening acute illness, which requires prompt adequate therapy. It is an uncommon clinical state that may appear as **a result of several processes**, as follows:

1. In patients with chronic primary adrenocortical insufficiency precipitated by any form of stress that requires an immediate increase in corticos-

teroid hormone output from adrenals incapable of responding.

2. As a result of some massive destruction of parenchyma of both adrenal glands by hemorrhage or acute ischemia in subjects without chronic primary adrenocortical insufficiency.

3. In patients with chronic secondary adrenocortical insufficiency precipitated by any form of major stress.

4. From too rapid withdrawal of corticosteroid therapy in patients whose adrenals have been suppressed by long-term corticosteroid administration (patients with chronic tertiary adrenocortical insufficiency), or from failure to increase the level of administered steroids during stress in a bilaterally adrenalectomized patient.

Acute adrenocortical insufficiency is most common in the patients with chronic primary adrenocortical insufficiency who have been subjected to infection, trauma, surgical intervention, or other stress. Its clinical picture is developed in the course of several hours or days. Intensive nausea, vomiting, diarrhea, weakness, fatigue, and lethargy appear from the beginning. Later, nausea, vomiting, diarrhea, and abdominal pain may become intractable. Repeated intensive vomiting and diarrhea gradually lead to **severe dehydration**. Fever is often present, is usually due to a precipitating infection, and may be exaggerated because of the hypocortisolemia. The abdominal pain and fever may lead to incorrect diagnosis of an acute surgical abdomen and potentially catastrophic surgical exploration without corticosteroid replacement. Hypoglycemia rarely may be the presenting manifestation. By laboratory examination the presence of evident hyponatremia, hyperkalemia, hemoconcentration, metabolic acidosis, and hyperazotemia are found. Hyperazotemia is the result of acute renal failure which is secondary to **hypovolemic shock**. Lethargy deepens into somnolence and confusion. Without appropriate therapy, hypovolemic shock progresses to coma and death.

It is assumed that the major pathophysiology precipitating adrenal crisis is mineralocorticoid, not glucocorticoid deficiency. However, glucocorticoid deficiency can contribute to the hypotension, perhaps resulting from decreased sensitivity to angiotensin II and norepinephrine, and decreased synthesis of angiotensinogen.

Adrenal crisis may also occur as a result of **sudden hemorrhagic destruction** of both adrenal glands. Extensive hemorrhages are usually present within the cortex and the medulla. These patients do not have evidence of pre-existing chronic adrenocortical insufficiency. In children this is usually associated with septicemia with Pseudomonas aeruginosa or meningococcemia (Waterhouse-Friderichsen syndrome). The basis for the adrenal hemorrhage in patients with Waterhouse-Friderichsen syndrome is uncertain but could be attributed to direct bacterial seeding of small vessels in the adrenals, the development of disseminated intravascular coagulation (DIC), endotoxin-induced vasculitis, or some form of hypersensitive vasculitis. Because other small vessels in organism are affected as well, widespread purpura, particularly of the skin, is also present. Occasionally extensive bilateral adrenal hemorrhage in neonates results from prolonged and difficult delivery, with considerable birth trauma and hypoxia. Newborns are particularly vulnerable because they are often deficient in prothrombin for at least several days after birth. In adults, anticoagulant therapy (especially in postsurgical patients who develop DIC), or a coagulation disorder may result in massive bilateral adrenal hemorrhage. Hemorrhage has been very rarely observed following adrenal vein thrombosis after a back injury.

Adrenal crisis is uncommon in patients with secondary or tertiary adrenal insufficiency, because normal renin-angiotensin-aldosterone physiology is usually maintained and hypovolemia is rare. Hypoglycemia is the more common presentation in these patients, who often also have signs and symptoms of deficiency of other anterior pituitary hormones. Because glucocorticoids have a role in maintaining peripheral vascular adrenergic tone, sudden loss of ACTH secretion particularly in conjunction with other serious illness, can lead to hypotension and circulatory shock.

IV. Isolated mineralocorticoid deficiency

Isolated mineralocorticoid deficiency states are characterized by isolated aldosterone deficiency accompanied by normal glucocorticoid and androgen production. They include inherited enzymatic defects in aldosterone biosynthesis, acquired primary aldosterone deficiency, and acquired secondary aldosterone deficiency. Pseudohypoaldosteronism, a rare

salt-wasting syndrome caused by an abnormal mineralocorticoid receptors, is also included among these states.

The feature common to all patients with hypoaldosteronism is the inability to increase secretion appropriately during salt restriction. In severe cases, urine sodium wastage occurs on a normal salt intake, whereas in milder forms, excessive losses of urine sodium occur only during salt restriction.

A. Congenital primary hypoaldosteronism

It is a rare inherited disorder transmitted as an autosomal recessive trait. The defect is in the activity of one of the terminal enzymes in the aldosterone biosynthetic pathway, i.e., corticosterone 18-methyl oxidase (CMO) or corticosterone 18-methyl isomerase (CMI). These enzymes catalyze two terminal steps in aldosterone biosynthesis. Both these enzymes are present only in zona glomerulosa. Congenital defect of 18-methyl isomerase is more frequent. CMO refers to the enzymatic activity responsible for hydroxylation of corticosterone at C-18 (Fig. 5.1,374). Deficiency of this enzyme would be expected to produce low plasma levels of products derived from corticosterone, i.e., 18-hydroxycorticosterone and aldosterone. CMI activity converts 18-hydroxycorticosterone to aldosterone (the C-18 methyl group of corticosterone to the C-18 aldehyde of aldosterone). Its deficiency should be associated with high plasma 18-hydroxycorticosterone level and low plasma aldosterone level. These patients have elevated plasma renin activity (**hyperreninemic hypoaldosteronism**). This disorder is clinically manifested already in the early childhood. The clinical picture reveals hyponatremia, hypochloremic metabolic acidosis, dehydration, retardation of the linear body growth, and failure to thrive of a child. Hyperkalemia is not usually part of this syndrome. Patients with this disorder have a high mortality rate (about 80 %).

B. Acquired primary hypoaldosteronism

This disorder is characterized by aldosterone biosynthetic defect or a selective unresponsiveness to angiotensin II. Long-lasting **heparin therapy** suppresses aldosterone synthesis, leading to a compensatory rise in plasma renin activity (hyperreninemia), which in most subjects is sufficient to prevent aldosterone deficiency. However, the compensatory mechanism apparently is insufficient in some individuals because of an impaired renin-angiotensin system, as might exist in diabetes mellitus. **Persistently hypotensive, critically ill patients** also have inappropriately low plasma aldosteron concentration relative to the activity of the renin-angiotensin system. The defect is at level of the adrenal but is not associated with any particular disease state or therapy. The mechanism is unknown, however, a selective insensitivity to angiotensin II is considered.

C. Acquired secondary hypoaldosteronism

This disorder occurs in the patients with a deficiency in renin production, and, therefore, is denoted as **hyporeninemic hypoaldosteronism**. It is seen most commonly in adults with mild renal failure and diabetes mellitus in association with hyperkalemia and metabolic acidosis out of proportion to the state of renal impairment. The pathogenesis is uncertain. Possibilities include impairment of a juxtaglomerular apparatus (most likely) or a defect in conversion of renin precursors to renin. Plasma renin activity and aldosterone concentrations are low.

D. Pseudohypoaldosteronism

It is a rare salt-wasting syndrome caused by **tubular unresponsiveness to aldosterone** (pseudoendocrinopathy). Patients may have absent or greatly reduced numbers of mineralocorticoid receptors. In the patients with this disorder real aldosterone deficiency does not originate. Plasma aldosterone concentration is even increased. Hypothalamic-pituitary-adrenal function is normal.

Inherited and acquired forms of pseudohypoaldosteronism may be distinguished. **Inherited form** is a rare salt-wasting syndrome of infancy with autosomal recessive transmission. It is present more frequently in boys and is manifested already during the first year of life. **Acquired form** is due to obstructive uropathy or may be present in a premature infant or follows renal transplantation.

Clinical hallmarks of pseudohypoaldosteronism are those of aldosterone deficiency: hyponatremia, hyperkalemia, and renal salt wasting. However, plasma aldosterone level is elevated. Plasma renin activity is also increased (hyperreninemia).
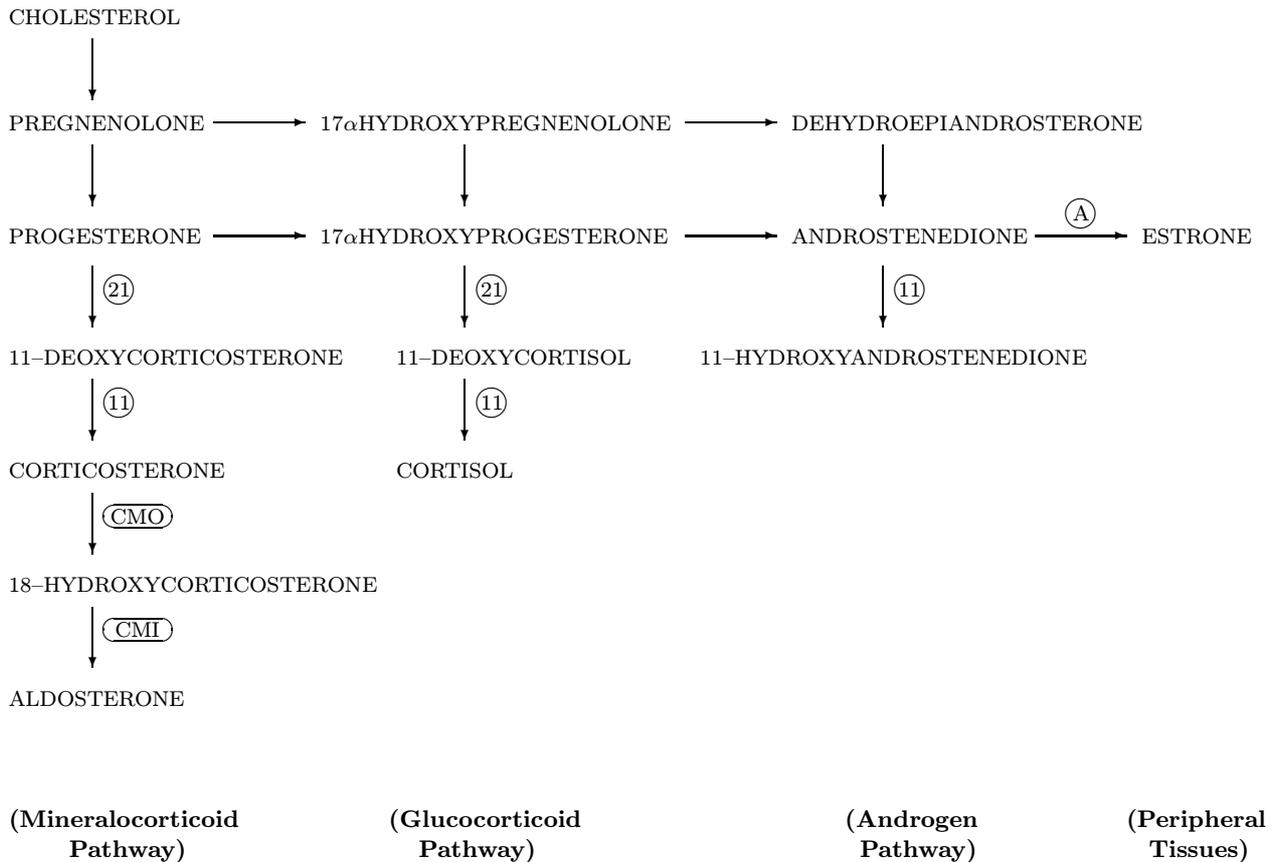
CHOLESTEROL

  ↓

PREGNENOLONE ⟶ 17αHYDROXYPREGNENOLONE ⟶ DEHYDROEPIANDROSTERONE

  ↓   ↓   ↓

PROGESTERONE ⟶ 17αHYDROXYPROGESTERONE ⟶ ANDROSTENEDIONE ⟶(A)⟶ ESTRONE

  ↓(21)   ↓(21)   ↓(11)

11–DEOXYCORTICOSTERONE   11–DEOXYCORTISOL   11–HYDROXYANDROSTENEDIONE

  ↓(11)   ↓(11)

CORTICOSTERONE   CORTISOL

  ↓(CMO)

18–HYDROXYCORTICOSTERONE

  ↓(CMI)

ALDOSTERONE

(Mineralocorticoid   **(Glucocorticoid**   **(Androgen**   **(Peripheral**
Pathway)   **Pathway)**   **Pathway)**   **Tissues)**

Figure 5.1: Steroid biosynthetic pathways in the adrenal cortex.
(11 = 11β–Hydroxylase;   21 = 21–Hydroxylase;   CMO = Corticosterone 18-methyl oxidase;
CMI = Corticosterone 18-methyl isomerase;   A = Aromatase)

5.6.1.2   Hyperfunction of adrenal cortex

Hyperfunction of adrenal cortex may be manifested by oversecretion of any kind of corticosteroid hormones: glucocorticoids (mainly cortisol), mineralocorticoids (mainly aldosterone), adrenal androgens, and rarely also estrogens. **Selective** (isolated) overproduction of one kind of the mentioned steroid hormones may originate. However, their **combinated** hypersecretion is more common. Overproduction of aldosterone is typically isolated, while overproduction of cortisol and androgens is being mixed quite often. Combination of hyperproduction of androgens and

mineralocorticoids is also known. Some carcinomas of adrenal cortex may be manifested by oversecretion of all kinds of corticosteroid hormones.

The clinical picture of adrenal cortex hyperfunction may be rather variable and depends partly on the kind of overproduced hormones, and partly on intensity of their hypersecretion. The clinical features are also influenced by the fact that effect of individual kinds of corticosteroid hormones partly coincide, e.g., cortisol, the most important glucocorticoid in men, has also weak mineralocorticoid effect and some of its metabolites have a slight androgenic effect.

I. Cushing's syndrome (hypercortisolism)

In the past this term denoted only primary hypercortisolism. Nowadays this term denotes each pathological state induced by the chronic increased plasma cortisol concentration, regardless of a cause of its origin. If it is evoked by oversecretion of cortisol, it is termed **endogenous** Cushing's syndrome. If it originates as a result of long-term pharmacotherapy by synthetic glucocorticoids, rarely also by ACTH, it is denoted as **exogenous** (iatrogenic) Cushing's syndrome. Endogenous Cushing's syndrome is rare, occurring in about 1 per mille of adult population. It is more common in women that in men (4:1), especially between 25 and 45 years of age. However, it may occur at any age. Occurrence of neoplastic and paraneoplastic forms is increasing after the age of 50.

Classification and pathogenesis. Basically Cushing's syndrome is usually classified from two viewpoints. According to whether it is induced by overproduction of cortisol or by administration of excessive amounts of potent synthetic glucocorticoids **endogenous** and **exogenous** forms of Cushing's syndrome are distinguished. According to the role of ACTH in its pathogenesis **ACTH-dependent** Cushing's syndrome and **ACTH-independent** Cushing's syndrome are distinguished.

ACTH-dependent Cushing's syndrome is caused by oversecretion of hypothalamic CRH, oversecretion of pituitary ACTH, ectopic production of CRH, ectopic production of ACTH, and rarely by administration of excessive amounts of ACTH. ACTH-independent Cushing's syndrome is induced by primary adrenocortical neoplasms, bilateral ACTH-independent macronodular adrenocortical hyperplasia, bilateral ACTH-independent micronodular adrenocortical dysplasia, and by administration of excessive amounts of synthetic glucocorticoids.

A. Endogenous Cushing's syndrome

All cases of endogenous Cushing's syndrome are due to increased production of cortisol by the adrenal glands. According to the place of primary cause and according to the histological finding in the adrenal cortex, following five forms of endogenous Cushing's syndrome may be distinguished:

1. Central form of Cushing's syndrome

It is the most common form of hypercortisolism accounting for about 70 % of the total number of patients with Cushing's syndrome. The cause of its origin may be in adenohypophysis or hypothalamus. The older term for adenohypophyseal disorder is **Cushing's disease (secondary hypercortisolism**, pituitary Cushing's syndrome). The hypothalamic disorder was denoted as Icenko-Cushing's disease (**tertiary hypercortisolism**, hypothalamic Cushing's syndrome). In the patients with adenohypophyseal disorder the source of excessive ACTH production is primary neoplasia of corticotrophs (usually basophilic microadenomas or sometimes solitary macroadenoma). In the patients with hypothalamic disorder isolated CRH oversecretion occurs probably due to overstimulation of hypothalamus from higher centers of CNS or due to CRH-secreting gangliocytoma of the hypothalamus. Hypersecretion of CRH causes corticotrope hyperplasia. The hyperplastic corticotropes secrete excessive amounts of ACTH. It is also supposed that this primary oversecretion of CRH would lead to hyperstimulation of the pituitary, resulting in adenoma formation. As the pituitary microadenoma grows, it may become independent of the regulating influence of CNS factors and/or circulating cortisol levels.

In both cases of central form of Cushing's syndrome, the result of permanently increased ACTH secretion is the origin of **bilateral diffuse hyperplasia of adrenal cortex** (the zonae fasciculata and reticularis) and successive overproduction of cortisol. In some patients production of adrenal androgens may be also increased. Plasma ACTH and cortisol concentrations are elevated. Other POMC-derived peptides parallel ACTH. The zona glomerulosa is normal. In about 20 % of patients with long-standing central Cushing's syndrome bilateral macronodular adrenocortical hyperplasia may be present.

2. Paraneoplastic form of Cushing's syndrome

It is also denoted as ectopic form of Cushing's syndrome (ectopic ACTH syndrome). It accounts for about 10 % of the total number of the patients with Cushing's syndrome. It is induced by extrahypophyseal and extrahypothalamic hormonally active tumors which produce ACTH or CRH. The presence of tumor producing ACTH and CRH simultaneously is quite common. Isolated ectopic CRH production is very rare.

The most frequent cause of paraneoplastic form of Cushing's syndrome are **malignat tumors**, e.g., small cell lung carcinoma (accounts for about half of all

these malignant tumors), thymic carcinoma, pancreatic carcinoma, malignant pheochromocytoma, thyroid medullary carcinoma, ovaric carcinoma, and prostatic carcinoma. Some carcinoids (bronchial and gastrointestinal) may be less common cause of ectopic ACTH and CRH secretion.

These malignant nonendocrine tumors secrete polypeptides that are biologically, chemically, and immunologically indistinguishable from either ACTH or CRH and that cause bilateral adrenal hyperplasia. The ectopic production od ACTH is also accompanied by secretion of other POMC-derived peptides, which is associated with intense skin pigmentation.

The development of bilateral diffuse adrenocortical hyperplasia is secondary to the permanent ectopic ACTH or CRH production. In spite of ectopicly conditioned autonomous secretion of cortisol the loss of regulation of its production by feedback mechanism is not usually total.

Central and paraneoplastic forms of Cushing's syndrome are denoted as Cushing's syndrome due to bilateral ACTH-dependent diffuse adrenocortical hyperplasia. In the patients with long-standing persistence of these both forms of Cushing's syndrome adenomatous changes of diffusely hyperplastic cortex of the adrenals may occur. Bilateral ACTH-dependent micronodular or macronodular adrenocortical hyperplasia originates. Macronodularly changed adrenal cortex may manifest various degree of autonomy.

3. Cushing's syndrome due to bilateral ACTH-independent macronodular adrenocortical hyperplasia

From the histopathological point of view it is characterized by presence of the large nodules in the adrenal cortex which is between these large nodules hyperplastic. It occurs very uniquely. The pathogenesis of this disorder is unknown. There is no evidence that ACTH hypersecretion is involved. Plasma ACTH concentration is very low even undetectable. Participation of local growth factor in the pathogenesis of bilateral ACTH-idependent macronodular hyperplasia is considered.

4. Cushing's syndrome due to bilateral ACTH-independent micronodular adrenocortical dysplasia

From the histopathological point of view it is characterized by the presence of numerous nodules in both adrenal glands. The nodules consist of large cells containing brown lipofuscin pigment. The colour of these nodules is, therefore, brown or black (hence the synonym "pigmented" micronodular adrenal disease). The ultrastructure of the cells resembles that of fasciculata cells. The intervening non-nodular cortex consists of small cells with clear cytoplasm characteristic of adrenal atrophy. The nodules function autonomously, the cortisol they secrete suppresses ACTH secretion, and, therefore, the remainder of the cortex atrophies.

Sporadic and **familial forms** of this disease are distinguished. About half of the patients with this disorder have no distinctive clinical presentation other than being young, always less than age 30 (sporadic form of the disease). Median duration of the symptoms before diagnosis is usually one year. The other half of the patients have a familial form of the disease that is a dominant trait and accompanied by pigmented lentigines and blue nevi on the face (including the lips, conjuctiva, or sclera), neck, and trunk. These patients may also have cutaneous, mammary, and atrial myxomas, testicular tumors, and other tumors. Only 20 % of the patients have Cushing's syndrome, and none has all features of the syndrome. Plasma cortisol concentration is usually moderately elevated. Plasma ACTH concentration is low or undetectable.

This disease occurs very rarely. Together with bilateral ACTH-independent macronodular adrenocortical hyperplasia accounts less than 1 % of all cases of Cushing's syndrome, but macronodular hyperplasia is rarer than micronodular dysplasia. Pathogenesis of this disorder in unknown. But, it is assumed that circulating immunoglobulin (IgG) which stimulates steroidogenesis and adrenal cell growth may be involved. However, it is unclear why the cells that form the nodules, but not the intervening cells, should be susceptible to stimulation by these autoantibodies.

5. Peripheral form of Cushing's syndrome

Peripheral (primary, adrenal) form of Cushing's syndrome originates due to primary adrenocortical neoplasms with autonomous secretion of cortisol. It accounts for about 15 % of the whole number of patients with Cushing's syndrome. Adrenocortical cortisol-secreting tumors generally predominate in children and young adults. **Adenomas** are more common than **carcinomas** (2:1). These tumors are usually unilateral and solitary, their bilateral and multi-

ple occurrence is less common. Pathogenesis of these tumors is not known.

The adrenocortical adenomas and carcinomas produce excessive cortisol. Its increased plasma concentration inhibits hypothalamic-adenohypophyseal system by feedback mechanism (secretion of CRH and ACTH is inhibited, pituitary corticotropes are atrophic). As pituitary ACTH secretion is suppressed, the remaining cortex of the adrenals is atrophied (the zonae fasciculata and reticularis).

Plasma ACTH concentration is low or often undetectable. Plasma cortisol level is inappropriately high. As ACTH and other POMC-derived peptides production is suppressed, signs of hyperpigmentation are absent. Adrenal adenomas usually produce only cortisol. Therefore, patients with adrenal adenoma usually have only gradual onset of hypercortisolism. Hirsutism and other androgenic effects are absent. In contrast, patients with adrenocortical carcinoma tend to have a more acute and progressive course, and hyperandrogenic effects may predominate. Markedly elevated adrenal androgen secretion often leads to virilization in the female. The adrenocortical carcinoma may also produce estrogens. Besides that, the adrenocortical carcinomas usually secrete increased amounts of androstenedione which is peripherally converted to the estrogens, estrone and estradiol. Feminizing estrogens usually present with gynecomastia in the male and dysfunctional uterine bleeding in the female. Approximately 30 % of adrenocortical carcinomas are hormonally nonfunctional or produce biologically inactive steroid precursors.

B. Exogenous Cushing's syndrome

Exogenous form of Cushing's syndrome is usually caused by long-lasting administration of excessive amounts of potent **syntetic glucocorticoids**, rarely by long-term **ACTH administration**. Therefore, it is usually termed **iatrogenic Cushing's syndrome**.

Iatrogenic (factitious) Cushing's syndrome associated with chronic administration of synthetic glucocorticoids (such as dexamethasone or prednisone) is ACTH-independent. Excessive amounts of exogenous glucocorticoids inhibit synthesis and secretion of CRH, suppress pituitary ACTH synthesis and secretion, resulting in bilateral adrenocortical atrophy. Plasma ACTH and usually cortisol concentrations are low. Hirsutism is absent and arterial hyperten-

sion occurs only if the patient is taking hydrocortisone or cortisone. The severity of iatrogenic Cushing's syndrome is related to the duration of the therapy and to the total corticosteroid dose.

Iatrogenic Cushing's syndrome caused by prolonged administration of exogenous ACTH for therapeutic reason is rare. It is one of the variants of the ACTH-dependent Cushing's syndrome. In spite of inhibition of pituitary ACTH synthesis and secretion, bilateral adrenocortical hyperplasia and cortisol hypersecretion are present. The clinical signs and symptoms in these patients are similar to those with endogenous ACTH hypersecretion (tertiary hypercortisolism).

The clinical picture of Cushing's syndrome depends on both the degree and duration of hypercortisolism. Many of the signs and symptoms of this syndrome logically follow the known action of glucocorticoids, but some probably reflect concominant hypersecretion of androgens. The clinical picture of Cushing's syndrome is characterized mainly by the symptoms resulting from the increased protein catabolism, increased hepatic gluconeogenesis, and increased fat deposition and redistribution. The disease develops slowly. For a long time it may produce oligosymptomatic clinical form (signs and symptoms are present in less number, sometimes also slight Cushing's habitus may be observed). Later symptomatology of fully developed Cushing's syndrome originates.

Subjectively the patients usually complain of fatigability, muscle weakness, back pain, facial changes, increased susceptibility to infections, and poor wound healing. Women also complain of menstrual abnormalities.

The most evident somatic symptom is the change of general appearance of the patient, which is conditioned partly by progressive obesity with a peculiar distribution of adipose tissue (its deposition in characteristic sites), and partly by the decrease of muscular mass (**Cushing's habitus**). Obesity is characterized by typical centripetal (truncal, disproportional) fat redistribution manifested by rounded face, dorsocervical fat pad (buffalo hump), enlarged fat pads characteristically fill the supraclavicular fossae, and fat accumulation about trunk and abdomen. On the other hand gluteal area is inadequately slim in comparison to prominent abdomen and enlarged chest. The extremities, mainly lower, are thin, spared,

or even wasted (spider-like figure). Slenderness of gluteal area and extremities is conditioned not only by the decreased amount of adipose tissue in these sites, but also by the loss of muscular mass, mainly of proximal muscles of the limbs. The loss of muscular mass is due to proteocatabolic effect of cortisol and also due to its antianabolic effect (amino-acids are to a higher extent used for gluconeogenesis, and, therefore, they are not in a sufficient amount at a disposal for proteosynthesis). The muscular atrophy of lower limbs, mainly the gluteus maximus and the quadriceps, in severe cases of the disease, is usually manifested by muscle weakness even muscle wasting, which is denoted as **proximal myopathy**. Most patients cannot rise from a squatting position without assistance, and those with severe disease may be unable to climb stairs or get up from a deep chair (this state is similar to thyrotoxic myopathy).

The origin of obesity in the patient with Cushing's syndrome has been explained by the increased gluconeogenesis which displaces sources of energy to fat tissue. Fat redistribution is probably the result of the origin of different local sensitivity of fat tissue to cortisol (causing lipolysis) and to insulin (causing lipogenesis). Unlike adults, children with Cushing's syndrome often develop generalized obesity.

The result of the increased protein catabolism is not only the loss of muscular mass, but also atrophy of skin, osteoporosis, and involution of lymphatic tissue. The skin is fine, thin, and fragile as a result of mobilisation of peripheral supportive tissue and weakening of collagen fibers in the dermis. Due to its increased transparency subcutaneous blood vessels can be seen. Facial skin over the cheeks is, therefore, plethoric, and together with rounded face is typical of the facial appearance of patients with Cushing's syndrome, and is termed a **moon face** (facies cushingoides). Bizarre type of obesity in patients with Cushing's syndrome is, therefore, along with prominent abdomen, evidently thin extremities, and buffalo hump, characterized also by moon face.

In places with excessive fat accumulation the fragile skin is stretched, therefore, rupture of collagen fibers in the dermis originates producing **cutaneous striae**. Unlike the striae of pregnant women (striae albi), they appear purplish or reddish (**striae rubrae**) because the thin, transparent skin reveals the color of venous blood in the dermis. The striae rubrae are also more numerous and often wider. Such

striae are most frequent on the lower flanks and sides of lower abdomen but can be also found on the breasts, hips, buttocks, shoulders, and upper thighs. They occur more frequently in younger patients. Increased proteocatabolic effect of cortisol causes also loss of perivascular supportive tissue probably resulting in increased fragility of vessels. Therefore, in a patient **increased bruisability** is present. Easy bruising can appear after minimal, unremembered trauma, mainly on the forearms and shins. Extensive ecchymoses at venipuncture are common.

A very significant and frequent clinical symptom of Cushing's syndrome is **osteoporosis**. It originates rather quickly and affects diffusely the whole skeleton. It is clinically manifested by pain in bones (low-back pain is common), excessive kyphosis, and pathologic fractures (most frequent are vertebral compression fractures, spontaneous rib fractures, and, less commonly, long bone fractures). Osteoporosis is the result of the effect of hypercortisolism on metabolism of proteins and calcium (stimulation of proteocatabolism in bones, antianabolic effect, decrease of intestinal calcium absorption, and decrease of calcium reabsorption in renal tubules). Hypercalciuria may result in nephrolithiasis (in about 15 % of cases). In children Cushing's syndrome is manifested by body growth impairment (linear growth is slowed or arrested). Excessive diffuse osteoporosis is usually present, too.

Disturbed metabolism of glucose is one of the main manifestations of Cushing's syndrome. Due to increased hepatic gluconeogenesis and tissue insulin resistance, **impaired glucose tolerance** originates. Overt diabetes mellitus occurs in about 15 % of the patients (probably in individuals with a familial predisposition to diabetes).

One of the most common symptoms of Cushing's syndrome is moderate **arterial hypertension**. It occurs in about 80–90 % ot the patients. Several factors participate in the mechanism of its origin. The most important of them is moderate mineralocorticoid effect of glucocorticoids resulting in hypernatremia and hypervolemia (volume mechanism). The change of natrium distribution between intracellular and extracellular fluid owing to cortisol may have a supportive role. The result of this change is the increase of natrium content in myocytes of vascular wall followed by their increased sensitivity to angiotensin II and norepinephrine (resistant mech-

anism). Glucocorticoids also induce hepatic production of angiotensinogen (renin substrate). Increased circulating levels of angiotensinogen probably result in increased angiotensin II generation.

Long-lasting evident hypernatremia results in the origin of metabolic alkalosis. Increased natrium retention is associated with increased depletion of potassium with successive **hypokalemia** which may aggravate muscular weakness.

Profund **emotional changes** or psychiatric complications are rather frequent symptoms of Cushing's syndrome of all etiologies (in about 70–75 % of patients). Sometimes they may appear even at the beginning of the disease. Insomnia is often an early symptom and is presumably caused by high plasma cortisol levels during sleep. Some patients appear euphoric or manic, particularly during the early course of the disease. Irritability, emotional lability, agitated depression, panic attacks, and mild paranoia are most common. Occasional patients may be suicidal. Hallucinations and delusions, or even frank psychosis are rare. Psychiatric complications occur in the patients with ACTH-dependent and ACTH-independent Cushing's syndrome. Therefore, it is assumed that high plasma cortisol concentration at least partially participates in their origin by its psychotropic effect.

In women with Cushing's syndrome mild **hypertrichosis** or even evident **hirsutism** often occur. In both sexes manifestations of **hypogonadism** are also present. Increased plasma cortisol concentration, causing the decrease of testosterone-binding globulin synthesis in liver, is probably responsible for the origin of mild hypertrichosis. Because of decreased synthesis of testosterone-binding globulin the free fraction (the biologically active form) of testosterone in circulating blood is increased. More evident hirsutism, increased sebaceous gland activity, acne, and thinning scalp hair are usually present in those patients with Cushing's syndrome which manifest simultaneous hypersecretion of adrenal androgens. In women they cause masculinization and virilization. Fast developing virilization is usually the result of adrenocortical carcinoma. Hypogonadism in women is manifested by oligomenorrhea even secondary amenorrhea, decreased libido, and infertility. Hypogonadism in men is manifested by decreased libido and impotence. It is assumed that hypogonadism is evoked by the disorder of hypothalamic-hypophyseal system which is probably conditioned by chronic hypercortisolism.

In patients with Cushing's syndrome susceptibility to bacterial and fungal infections is increased. Migratory ability of leukocytes is decreased. Production of antibodies is also decreased. The most common intercurrent infections are those of skin and urinary tract.

Red blood cell number is usually mildly increased what contributes to plethoric skin. The leukocyte number, mainly neutrophils, is also elevated. Eosinopenia and lymphopenia are usually present as well.

Basic clinical picture of individual pathogenetic forms of Cushing's syndrome is rather similar to each other. Hyperpigmentation of Addison's type is the evidence of central or paraneoplastic Cushing's syndrome. The clinical picture of those forms of Cushing's syndrome which are induced by tumors in hypothalamic-hypophyseal area, by malignant tumors with ectopic ACTH or CRH production, and by adrenocortical carcinoma partly depends on the rate of tumor growth and on its degree of malignity. In the clinical picture of Cushing's syndrome due to tumors in hypothalamic-hypophyseal area some local symptoms secondary to compression of intracranial structures can be observed. In patient with Cushing's syndrome evoked by malignant neoplasm, mainly by a small cell carcinoma of lung producing ACTH, centripetal obesity is usually missing, because of cachexia and rapid dissemination of the tumor. In patients with iatrogenic Cushing's syndrome only signs from glucocorticoids excess are present because of usual administration of synthetic glucocorticoids having very weak mineralocorticoid effect and no androgenic effect. Therefore, arterial hypertension and hirsutism do not occur in their clinical picture.

II. Hyperaldosteronism

Hyperaldosteronism is a chronic pathological state induced by overproduction of aldosterone by the cells of zona glomerulosa. Hypersecretion of aldosterone may be autonomous (primary hyperaldosteronism), or it is a response to other basic disease (secondary hyperaldosteronism) associated with formation of peripheral edema. Primary hyperaldosteronism signifies that the stimulus for the excessive aldosterone production resides within the adrenal gland; in sec-

ondary hyperaldosteronism, the stimulus is extraadrenal.

A. Primary hyperaldosteronism

Primary hyperaldosteronism (**Conn's syndrome**, primary aldosteronism) is a clinical syndrome characterized by high plasma aldosterone concentration associated with suppressed plasma renin activity. Plasma cortisol and adrenal androgen levels are normal. **Low plasma renin activity** is the evidence of autonomous aldosterone hypersecretion, e.i., chronic excess aldosterone secretion is independent of the renin-angiotensin system. Low plasma renin activity is the main criterion to distinguish between primary and secondary hyperaldosteronism.

The most common cause of primary hyperaldosteronism is **solitary unilateral adenoma** composed of glomerulosa cells. Aldosterone-producing adrenal adenoma is present in about 65 % of all cases. It is more often found on the left. In about 30 % of cases primary hyperaldosteronism is caused by **bilateral idiopathic hyperplasia** of zona glomerulosa. The pathogenesis of zona glomerulosa hyperplasia is unknown.

Besides bilateral idiopathic hyperplasia there are also two rare types of bilateral adrenal hyperplasia. **The first type** is dexamethasone-suppressible hyperaldosteronism (dexamethasone inhibits secretion of ACTH). Aldosterone level falls also after glucocorticoid administration and remains suppressed during the course of administration, indicating the dependence of aldosterone secretion on ACTH stimulation. Therefore, it is also called glucocorticoid-suppressible hyperaldosteronism. It is supposed that its origin is the result of the failure of normal differentiation of transitional zone cells to zona fasciculata cells (the transitional zone is found between zona fasciculata and zona glomerulosa during embryonal development). This mutation leads to the origin of hybrid cells which do not lose the activity of terminal enzymes in the aldosterone biosynthetic pathway, i.e., 11β-hydroxylase, corticosterone 18-methyl oxidase, and corticosterone 18-methyl isomerase Fig. 5.1, 374). The postulated defect results in ACTH-response cells that retain the ability to synthesize aldosterone and 18-hydroxycorticosterone. The first type of bilateral adrenal hyperplasia is more common than the second type. It occurs familially, mainly in young subjects, and has autosomal dominant inheritance. **The second type** of bi-

lateral adrenal hyperplasia is occasional. It is denoted as primary adrenal hyperplasia because subtotal adrenalectomy (75 %) apparently results in permanent cure. Its pathogenesis is unknown.

Adrenal **carcinoma** is also a rare cause of primary hyperaldosteronism. **Unilateral adrenocortical hyperplasia** is even a rarer cause. Its pathogenesis is unknown, too. A solitary cause of primary hyperaldosteronism may be **an ectopic secretion of aldosterone**, mainly by ovarian carcinomas.

The data on occurrence of primary hyperaldosteronism rather vary. The most frequent information is that primary hyperaldosteronism is the cause of about 0.5–2 % of all arterial hypertensions. Primary hyperaldosteronism may appear at any age, however, the peak incidence occurs between ages 30 and 50. It tends to occur in women more often than men (2:1).

The clinical picture of primary hyperaldosteronism is characterized mainly by arterial hypertension, hypokalemia, mild metabolic alkalosis, and suppressed plasma renin activity. However, adrenocortical adenoma tends to produce severer hyperaldosteronemia, with consequent severer hypertension, more profound hypokalemia, and more complete renin suppression.

The clinical symptomatology of primary hyperaldosteronism of all etiologies results from the disorders of electrolyte metabolism due to chronic hyperaldosteronemia. As a consequence of persisting hyperaldosteronemia renal distal tubular **sodium reabsorption** and renal distal tubular **potassium depletion** are increased. The continual hypersecretion of aldosterone increases the renal distal tubular exchange of intraluminal sodium for secreted potassium and hydrogen ions, with progressive depletion of body potassium and development of **hypokalemia**. The electrochemical gradient generated by excessive sodium retention also causes hydrogen ion loss in the distal tubules. As hypokalemia increases, so does renal ammoniagenesis, contributing to the metabolic alkalosis. The increased tubular sodium reabsorption is associated with the increased **water retention**, so serum sodium concentration remains normal, or tendency to hypernatremia is present. Total body sodium content, and thereby also total extracellular fluid volume are increased. Therefore, mild **hypervolemia** originates. Unlike the secondary hyperaldosteronism, the patients with primary hyperaldosteronism do not have edema. It is caused by so-

called **escape phenomenon** of the renal tubules from the sodium-retaining action of aldosterone. In the patients with primary hyperaldosteronism this phenomenon originates due to long-lasting effect of excessive amount of aldosterone on the renal tubules. Escape phenomenon is possibly mediated by a compensatory increase in atrial natriuretic factor (ANF) secretion, but renal hemodynamic changes may also play a role in the escape. Inhibition of sodium retention prevents futher expansion of extracellular fluid volume, and thereby also futher increase of circulating blood volume. There is no evidence of escape from the potassium-lossing effect of aldosterone, therefore, depletion of potassium continues despite hypokalemia.

Arterial hypertension is the main objective symptom of primary hyperaldosteronism. It is usually not of marked severity, but most patients have an evident systolic hypertension. Characteristic feature of the hypertension is its **stationary** (fixed) **course**. The presence of escape phenomenon and mainly the increase of diastolic pressure indicates that it is not only volume expansion (hypervolemia) that participates in its pathogenesis. Increased peripheral vascular resistance seems to be simultaneously involved. Increased vascular sensibility to vasoactive substances is secondary to the increase of intracellular vascular smooth muscle cell sodium content. Approximately half of the patients with arterial hypertension have severe headaches (mainly frontal). Later, consequences of hypertension may appear, especially left ventricle hypertrophy and atherosclerosis. However, fatal complications of hypertension and atherosclerosis are rare, and occur only in the untreated patients.

Hypokalemia (usually less than $3.5\,\mathrm{mmol/L}$) is almost regular finding. In some patients it may be severe, less than $3\,\mathrm{mmol/L}$. The origin of hypokalemia is the result of permanently increased potassium loss in the distal renal tubules (**hyperkaliuresis**). Evident hypokalemia may evoke striking **muscular weakness** and fatigue, sometimes even flaccid paralysis. Tonus of smooth muscles is also decreased and is especially manifested by **constipation** and by disorders of urinary bladder discharge. Tendency to **cardiac arrhythmias** may also appear. Electrocardiographic signs of hypokalemia, such as flattening or inversion of the T wave and prominent U wave, are usually present. Common consequence of evident chronic

hypokalemia is the origin of **hypokalemic nephropathy** (tubulopathy). It is manifested by diminishing of renal concentrating capacity (hyposthenuria even isosthenuria), diminishing of acidification ability of the renal tubules (urine pH is alkaline), polyuria, polydipsia, and nycturia. The polyuria results from impairment of concentrating ability and is often associated with polydipsia. Those are the signs of peripheral (symptomatic) diabetes insipidus, which is resistant to ADH therapy, because the renal tubules have lost sensitivity to ADH.

Laboratory examination reveals metabolic alkalosis, increased plasma aldosterone concentration, low plasma renin activity, low plasma angiotensin II concentration, and glucose tolerance impairment.

Low plasma renin activity is the result of inhibition of the juxtaglomerular apparatus by hypernatremia, hypervolemia, and arterial hypertension. **Metabolic alkalosis** (hypokalemic and hypochloremic) originates secondary to increased hydrogen ion loss into the urine and hydrogen ion migration into potassium-depleted cells. The alkalosis is perpetuated by potassium deficiency, which partly increases the capacity of the proximal tubules to reabsorb filtered bicarbonate and partly increases renal ammoniagenesis. Metabolic alkalosis may be associated with fall of plasma ionized calcium concentration what is manifested by paresthesias and signs of tetany. **Glucose intolerance** originates probably only in genetic predisposed individuals. Evoking factor, causing the disorder of insulin secretion, is potassium depletion from the B cells of islets of Langerhans due to long-lasting hyperkaliuresis.

B. **Secondary hyperaldosteronism**

The term secondary hyperaldosteronism denotes the state of a chronic aldosterone hypersecretion evoked by primary extraadrenal causes. Primary disease begins outside zona glomerulosa and aldosterone overproduction is only one of the symptoms of this primary disease. Therefore, it is also termed **symptomatic hyperaldosteronism**. Aldosterone overproduction is a response to activation of the renin-angiotensin system included to pathogenetic process only secondary as a compensatory mechanism (**secondary hyperreninemia**). An overproduction of renin is secondary to a decrease in renal blood flow and/or a decrease in renal perfusion pressure. These changes of renal hemodynamics are caused by primary disease. The aim of this compensatory hyper-

secretion of aldosterone is to restore the changed renal hemodynamics to normal by increased natrium retention and by successive expansion of circulatig blood volume.

Increased plasma renin activity and angiotensin II concentration differ secondary hyperaldosteronism from primary hyperaldosteronism. Plasma concentrations of both these components of the renin-angiotensin-aldosterone system are low in the patients with primary hyperaldosteronism. Secondary hyperaldosteronism usually occurs on the basis of the disease states associated with formation of peripheral edema, in association with the accelerated phase of hypertension, or in association with malignant hypertension. However, unlike primary hyperaldosteronism, in secondary hyperaldosteronism the sodium-retaining effect of aldosterone persists because the mechanism of escape is not activated. Its activation is prevented by the fact that the cause of the decrease in effective circulating blood volume persists, and, therefore, the fluid retained by the kidneys does not remain in circulation, but transudation of intravascular fluid into extravascular sites continues. Homeostasis occurs as late as the edema is stabilized. In the time of stabilized edema the activity of the renin-angiotensin-aldosterone system becomes normal. In patients with secondary hyperaldosteronism neither hypokalemia is usually so evident nor arterial hypertension is necessarily always present as it is in the patients with primary hyperaldosteronism.

Besides secondary hyperaldosteronism caused by the mentioned secondary hyperreninemia, rare form of secondary hyperaldosteronism which is the result of a primary overproduction of renin (**primary hyperreninemia**, primary hyperreninism) also exists. This rare form of secondary hyperaldosteronism, caused by primary hyperreninism, occurs with or without arterial hypertension.

From the point of view of etiopathogenesis following causes of secondary hyperaldosteronism are distinguished:

1. **Diseases associated with hypovolemia** and/or with arterial hypotension. These diseases include mainly those associated with the origin of edemas, such as congestive heart failure, cirrhosis of the liver (respectively portal hypertension with ascites), and nephrotic syndrome. This group of diseases may also include the states associated with dehydration and large loss of blood (hemorrhage). In patients

with all the mentioned states activation of the renin-angiotensin-aldosterone system is common compensatory response to the decrease of effective circulating blood volume. This decrease is evoked by transudation of intravascular fluid into extravascular space, by reduced cardiac output, or by a large loss of fluid or blood. Reduced renal perfusion is the major stimulus to the increased renin secretion, angiotensin II production and aldosterone secretion, and thus to sodium and water retention. In patients with cirrhosis of the liver, decreased degradation of aldosterone also participates in the increase of its plasma concentration.

2. **Hereditary renal tubular acidosis** and **Bartter syndrome**. They are pathological states with secondary hyperreninemia but without edemas and arterial hypertension. They are salt-wasting nephropathies.

Hereditary renal tubular acidosis of both, proximal or distal tubules, is associated with urinary depletion of sodium and potassium and with successive activation of the renin-angiotensin-aldosterone system. In the clinical picture besides hyperreninemia, hyperaldosteronemia and hypokalemia, hyperchloremic metabolic acidosis is present. Hyperchloremic acidosis makes renal tubular acidosis different from Bartter syndrome.

Bartter syndrome is a rare hereditary disease of the kidneys. Inheritance is autosomal recessive, and manifestations commonly begin in childhood. It is characterized by renal potassium wasting, secondary hyperreninemia, hyperaldosteronemia, hypokalemia, and metabolic alkalosis without hypertension or edema. In the patients also hyponatremia, hypochloremia, and hyporesponsiveness of blood pressure to infused angiotensin II may be found. Hyperplasia of the granular cells of the juxtaglomerular apparatus of the kidneys is observed. Hyperplasia of renal medullary interstitial cells, which produce prostaglandins E and F, has been also described. The disease is usually manifested by evident muscular weakness or periodic paralysis, occasional cramps, frequent vomiting, urinary frequency and polyuria, and by developmental impairment. The patients are, therefore, of short stature.

A number of primary defects have been proposed to account for Bartter's syndrome, but the cause is unknown. The main defect seems to be reduced NaCl reabsorption by the thick ascending limb of

Henle's loop. Volume depletion stimulates the renin-angiotensin-aldosterone system. The combination of high plasma aldosterone levels and increased delivery of NaCl and water to the distal part of nephron causes kaliuresis and hypokalemia. The hyperaldosteronism presumably is not the cause of the hypokalemia because bilateral adrenalectomy does not correct the kaliuresis. Magnesuria and hypomagnesemia occur, perhaps because the thick ascending limb of Henle's loop is a main site for magnesium reabsorption. Hypomagnesemia enhances kaliuresis. Hy-

pokalemia futher increases aldosterone production by stimulating release of prostaglandins E_2 and I_2, which promote increased secretion of renin. Both angiotensin II and aldosterone increase renal kallikrein, which increases plasma bradykinin. Elevated level of bradykinin could participate in the origin of arteriolae hyporesponsiveness to angiotensin II, stimulate production of prostaglandin E_2 and stimulate natriuresis. The normal blood pressure probably reflects an interaction between the vasodepressor actions of prostaglandin E_2 and bradykinin and vasoconstrictive effect of elevated level of angiotensin II. Excessive production of prostaglandin E_2 resulting from hypokalemia is probably a secondary consequence. In some cases blockade of prostaglandin E_2 production with indomethacin lowers renin level and restores vascular response to angiotensin II infusion but does not reduce potassium wasting.

3. **Diseases associated with a local decrease in renal blood flow**. Secondary hyperreninism and thereby also secondary hyperaldosteronism originate as a result of renal ischemia occurring in the patients with a narrowing of one or both of the major renal arteries (renal artery stenosis) either by an atherosclerotic plaque or by fibromuscular hyperplasia. Overproduction of renin from both kidneys also occurs in association with severe arteriolar nephrosclerosis (malignant hypertension) or secondary to profound renal vasoconstriction (accelerated phase of hypertensive disease).

4. **Primary hyperreninism** (Robertson syndrome). It is a rare disease induced by autonomous renin-secreting renal or extrarenal neoplasm. Plasma concentration of renin is high. Renin-secreting tumor, made up of juxtaglomerular cells or hemangiopericytes, occurs most commonly in young patients with severe arterial hypertension. Secondary hyperaldos-

teronism is manifested by hypokalemia. Paraneoplastic autonomous production of renin may rarely occur in bronchogenic carcinoma or ovarian tumor (ectopic renin secretion).

III. Adrenal androgen excess

Adrenal androgen excess (**adrenal hyperandrogenism**) is the cause of the origin of **adrenal virilization**, which is the common term for all virilizing syndromes induced by hypersecretion of adrenal androgens (**adrenogenital syndromes**). The principal adrenal androgens are dehydroepiandrosterone (DHEA), androstenedione, and 11-hydroxyandrostenedione. However, adrenal androgens are biologically weak androgens. Therefore, they are not a direct cause of virilizing changes. But, they are converted to the potent androgen testosterone and dihydrotestosterone in extraglandular tissues. Only elevated levels of these biologically more active androgens are the main cause of the origin of virilization and other androgenic effects. In general, the degree of virilization reflects both the duration and the degree of excess androgen secretion. With regard to the heterosexual character of the hormonal disorder, virilization in girls and in women means partly predominance of male sexual characteristics (hirsutism, male habitus, deepening of voice, and clitoral enlargement), and partly absence or withdrawal of female sexual characteristics (oligomenorrhea even amenorrhea, breast atrophy, and loss of female body contours) denoted as defeminization. The term **hirsutism** is limited to females and means hair growth in a male pattern of distribution. Hair grows in those areas which are typical for males, such as the face, upper pubic triangle, chest, areolae, back, buttock, thighs, ears, nose, and back of the hands and feet.

According to the period of ontogenesis in which adrenal androgen overproduction originates, prenatal and postnatal forms of adrenal virilization are distinguished. Adrenal androgen hypersecretion may be either selective or may be associated with the secretion of smaller or greater amounts of other adrenocortical hormones. In patients with congenital form it may be associated with decreased production of glucocorticoids and simultaneosly with increased or decreased secretion of mineralocorticoids. In patients with acquired form of adrenal androgen hypersecretion, adrenal virilization may be associated with excessive production of glucocorticoids and some characteristics of Cushing's syndrome.

A. **Prenatal form of adrenal virilization**

Prenatal form of adrenal virilization (**congenital adrenal hyperplasia**, congenital adrenogenital syndromes) is a disease owing to inherited enzymatic defects (inherited enzymopathy) in cortisol biosynthetic pathway. Any of the enzymes participating in cortisol synthesis can be affected (a defect in enzyme quantity or activity) and, therefore, cortisol production is permanently insufficient. Since cortisol is the principal adrenal steroid regulating ACTH synthesis, and since the ACTH stimulates both cortisol and andrenal androgen production, an enzymatic interference with cortisol synthesis may result in the enhanced synthesis of adrenal androgens. Namely, due to low plasma cortisol concentration, pituitary ACTH secretion is increased by feedback mechanism. ACTH overproduction results in adrenal cortex hyperplasia and excessive secretion of precursor steroids that are synthetized before the defective enzyme step. Some of these cortical precursor steroids belong to precursors of adrenal androgens (pregnenolone and 17α-hydroxyprogesterone). Production of precursor steroids and thereby also adrenal androgens is, therefore, permanently increased, which is clinically manifested by the origin of virilization.

According to the place of enzymatic defects in cortisol biosynthetic patway, synthesis of mineralocorticoids may be normal, insufficient, or excessive. Synthesis of steroid hormones located behind the defective enzyme step, especially synthesis of cortisol, is in spite of permanently increased ACTH secretion still insufficient. The degree of glucocorticoid deficiency and simultaneous adrenal androgen excess depend on the degree of the enzyme deficiency. Due to the severe degree of enzymopathy (a total lack of a particular enzyme involved in the biosynthesis of cortisol) hypocorticolism and virilization originate, already prenataly or in the early childhood (**classic forms**). In patients with partial adrenal enzyme deficiency, symptoms of cortisol deficiency need not be present at all. Only the symptoms of virilization can be clinically manifested, however, only after adolescence (**nonclassic forms**, delayed virilizing steroid enzymopathies).

Prenatal form of adrenal virilization is clinically manifested in three variants depending on the enzyme of adrenal steroidogenesis the deficiency of

which is present. The three following distinctive syndromes may be segregated:

- Simple virilization (simple virilizing adrenogenitalism)

- Virilization with sodium depletion (salt-wasting adrenogenitalism)

- Virilization with sodium retention (salt-retaining adrenogenitalism)

The first two clinical syndromes are due to **21-hydroxylase deficiency** occurring in about 95 % of all patients with prenatal form of adrenal virilization. The third clinical variant is evoked by **11β-hydroxylase deficiency** and occurs in about 5 % of all patients with prenatal form of adrenal virilization.

21-hydroxylase deficiency

It is a rare disorder. Incidence of its classic form (prenatal form) in our country is approximately 1 to 6 000 to 8 000 live births. The deficiency of 21-hydroxylase is transmitted as a single-gene autosomal recessive trait linked to the major histocompatibility complex locus on the short arm of chromosome 6. It occurs more frequently in persons with HLA-A3, DR7, B14, B35, BW47, B51, and B60 alleles. 21-hydroxylase deficiency has two following clinical variants:

1. **Simple virilization**
   In the clinical picture of simple virilizing form of 21-hydroxylase deficiency (simple virilizing congenital adrenal hyperplasia) only symptoms of virilization (without salt-wasting symptoms) are present. It accounts for only about 35 % of cases of 21-hydroxylase deficiency. The defect of this enzyme is present in zona fasciculata and zona reticularis. Conversion of 17α-hydroxyprogesterone to 11-deoxycortisol and thus also synthesis of cortisol stagnate (Fig. 5.1, 374). Accumulation of cortisol precursors, that are synthetized before the defective enzyme step, is present. Accumulated precursor steroids, mainly 17α-hydroxyprogesterone and 17α-hydroxypregnenolone are in increased extent converted to adrenal androgens. In extraglandular tissues adrenal androgens are converted to the potent testosterone which is the main cause of virilization.

2. **Virilization with sodium depletion**

   It accounts for about 65 % of cases of 21-hydroxylase deficiency. In the clinical picture, besides the symptoms of virilization, the symptoms resulting from the increased sodium loss from organism also occur (salt-wasting congenital adrenal hyperplasia). The defect of 21-hydroxylase is present not only in zona fasciculata and zona reticularis, but also in zona glomerulosa. The consequences of 21-hydroxylase defect in fascicular and reticular zones are the same as those of previous variant, i.e., virilization originates. However, the defect of 21-hydroxylase in zona glomerulosa causes the block of progesterone conversion to 11-deoxycorticosterone (Fig. 5.1, 374). Production of 11-deoxycorticosterone and thus also production of succeeding mineralocorticoids, i.e., corticosterone, 18-hydroxycorticosterone, and aldosterone, stagnate. In spite of compensatory increased plasma renin activity, the deficiency of mineralocorticoids causes the salt depletion (salt-lossing form of congenital adrenal hyperplasia).

Virilization. It is present in the clinical picture of the both variants of classic form of 21-hydroxylase deficiency, i.e., in the patients with simple virilization and in those having virilization with sodium depletion. Virilization is usually apparent at birth in the female and within the first 2 to 3 years of life in the male.

Female fetus with 21-hydroxylase deficiency may be virilized in utero, if adrenal androgen production is evidently increased already during intrauterine development. Congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency is the most common cause of ambiguous external genitalia in the newborns. Hypertrophy of the clitoris, partial or complete labial fusion, and formation of a urogenital sinus result from androgen effect on the development of the external genitalia. Genital ambiguity may be so profound that inappropriate sex assignment may be made at birth. In untreated girls the change of external genitalia may gradually resemble male external genitalia (**female pseudohermaphroditism**). Complete fusal majus labia resemble scrotum, minus labia remain infantile, and enlarged clitoris resembles a penis. Pubic and axillary hair appears already in childhood. Coarse voice, infantile mammary glands,

hirsutism, virilization, and male habitus are typical for affected adolescent girls.

The excessive androgens result in accelerated linear growth already in childhood (usually before the age of 10), with bone age exceeding chronologic age. Since epiphyseal closure is hastened by excessive androgens, growth of the long bones stops (usually before the age of 13), but truncal development continues, giving the characteristic appearance of an affected subject, whose **stature is short and disproportional** (well-developed trunk and short extremities). High plasma concentrations of progesterone and androgens inhibit hypothalamic-hypophyseal system. Secretion of GTHs is, therefore, reduced resulting in atrophy of ovaries and disorder of maturation of ovarian follicles (**hypogonadotropic hypogonadism**). Uterus remains infantile, menarche does not appear, primary amenorrhea and infertility originate (sexual infantilism).

At birth there may be enlarged genitalia in **the male infant** with 21-hydroxylase deficiency. In the postnatal period, congenital adrenal hyperplasia is associated with isosexual precocity in the male (**precocious masculinization**). High plasma androgen concentration in untreated boys accelerates growth of penis in childhood and causes also premature pubic and axillary hair (already at age 3 to 7). Their voice starts to break and facial hair appears approximately at the age of 10. The clinical picture of **precocious pseudopuberty** originates (pseudopubertas praecox). This state is also denoted as macrogenitosomia praecox. Due to inhibition of GTH secretion, testes are atrophic and spermiogenesis is absent. Linear body growth disorder of the boys is the same as that of the girls. The excess of androgens accelerate both linear growth and epiphyseal closure, so despite the early accelerated growth velocity, bone age advances rapidly and ultimate adult height is diminished. Therefore, affected adult men are of a short stature with disproportionally short limbs.

Sodium depletion. Unlike virilization occurring in the both classic variants of 21-hydroxylase deficiency, sodium depletion occurs only in the patients with the second variant (salt-wasting congenital adrenal hyperplasia). If the severer degree of aldosterone deficiency is present, the symptoms of sodium depletion appear already during the first 2-3 weeks of postnatal life. In a short time life threatening **disturbance of water and electrolitic metabolism** may develop.

The increased natriuresis causes the origin of hyponatremia, volume depletion, arterial hypotension, metabolic acidosis, and hyperkalemia. This disturbance of water and electrolitic metabolism become severer due to vomiting and diarrhea occurring already at the onset of the disease. Later, the affected child develops severer dehydration, finally resulting in hypovolemic shock. If the aldosterone deficiency is milder, only anorexia, retardation in normal increasing of body weight, and overall failure to thrive of a child are present.

The clinical picture of the both classic variants of 21-hydroxylase deficiency is supplemented by the symptoms of **hypocortisolism** and **hyperpigmentation**. Hyperpigmentation is the result of increased secretion of ACTH and other POMC-derived peptides.

Some individuals with inherited 21-hydroxylase deficiency do not manifest the symptoms of virilization at birth or during childhood, but only at the time of puberty, or at the onset of adolescence or even in adulthood. This form of 21-hydroxylase deficiency with late-onset adrenal hyperplasia is denoted as **delayed virilizing adrenal enzymopathy** (nonclassic form of 21-hydroxylase deficiency). It is probably a special group of homozygous carriers of combination of genic mutations with different degree of expressivity. It seems that the nonclassic disease is much more common than the classic one. The first symptom in adolescent girls may be premature pubarche or persisting acne. In affected women menstrual abnormalities and hirsutism of various intensity may appear. However, virilization, if present, is minimal. In adolescent boys and adult men with delayed virilizing adrenal enzymopathy gynecomastia, hypotrophy of testes, azoospermia, and infertility may originate. In either, female and male individuals with nonclassic form of 21-hydroxylase deficiency, sodium depletion does not originates, plasma ACTH concentration is not increased, symptoms of hypocortisolism are not present, and hyperpigmentation does not occur.

11β-hydroxylase deficiency

Inborn 11β-hydroxylase deficiency is the cause of the origin of the third variant of prenatal form of adrenal virilization, i.e., **virilization with sodium retention** (the hypertensive form of congenital adrenal hyperplasia). 11β-hydroxylase deficiency is rarer than 21-hydroxylase deficiency. Its precise incidence is not known, because it is usually diagnosed only in individuals with the severest defect of this enzyme. According to some authors, incidence of 11β-hydroxylase deficiency is 1 in 100 000 live births, and it accounts for about 5 % of all cases with prenatal form of adrenal virilization. This disease is inherited as an autosomal recessive disorder without evidence of linkage to the HLA locus. **The classic form** of 11β-hydroxylase deficiency (presented already at birth or in childhood) is more frequently diagnosed than its **nonclassic form** (with the later-onset and milder symptomatology). The defect of 11β-hydroxylase is present in zona fasciculata and zona glomerulosa.

In the zona fasciculata 11β-hydroxylase catalyses the terminal step of cortisol biosynthesis, i.e., hydroxylation of 11-deoxycortisol (Fig. 5.1, 374). Due to 11β-hydroxylase deficiency conversion of 11-deoxycortisol to cortisol stagnates. Therefore, plasma cortisol concentration is low. Because of low cortisolemia hypothalamic-adenohypophyseal system is chronicly stimulated to increased ACTH secretion. The result of permanently increased plasma ACTH level is excessive synthesis of cortisol precursor steroids. 11-deoxycortisol, 17α-hydroxyprogesterone, and 17α-hydroxypregnenolone accumulate proximally to the 11β-hydroxylation step. These accumulated precursor steroids, especially 17α-hydroxyprogesterone and 17α-hydroxypregnenolone, are being shunted into the androgen biosynthetic pathway. The increased substrate flow through the androgen biosythetic pathway results in an excess adrenal androgen secretion. Therefore, in an affected subject virilization originates (usually already in female fetus). Unlike 21-hydroxylase deficiency conversion of androstenedione to 11-hydroxyandrostenedione is inhibited, because 11β-hydroxylase catalyzes this conversion as well (Fig. 5.1, 374).

In the zona glomerulosa the conversion of 11-deoxycorticosterone to corticosterone, and thereby also synthesis of aldosterone stagnate due to 11β-hydroxylase deficiency (Fig. 5.1, 374). However, this disorder results in the accumulation and excess secretion of 11-deoxycorticosterone, a weak mineralocorticoid. The increased plasma 11-deoxycorticosterone concentration gives rise to the increased retention of sodium and water resulting in arterial hypertension despite low plasma renin activity and low plasma aldosterone concentration. Therefore, 11β-

hydroxylase deficiency is also denoted as the hypertensive form of congenital adrenal hyperplasia.

In **the clinical picture** of the classic form of 11β-hydroxylase deficiency **virilization** dominates. Depending on the sex and age, the virilization is manifested equally as it does due to 21-hydroxylase deficiency. Simultaneously the symptoms resulting from the increased plasma 11-deoxycorticosterone are present. Due to the increased retention of sodium and the increased depletion of potassium, hypervolemia, **arterial hypertension**, metabolic alkalosis, and hypokalemia originate. In the clinical picture of the disease the symptoms of hypercortisolism and hyperpigmentation may be also observed.

In some individuals with inherited 11β-hydroxylase deficiency the symptoms of virilization may appear as late as at puberty or even later. This form of 11β-hydroxylase deficiency belongs to the group of delayed virilizing adrenal enzymopathies (**the nonclassic form** of 11β-hydroxylase deficiency, late-onset form of the disorder). In the clinical picture of the nonclassic form of 11β-hydroxylase deficiency only the symptoms of overproduction of adrenal androgens are present. In both sexes they are analogous to the nonclassic form of 21-hydroxylase deficiency, i.e., they are milder than those of classic form and virilization is minimal. Plasma ACTH concentration is not increased, and, therefore, increased production of 11-deoxycorticosterone, sodium retention and arterial hypertension do not develop.

B. Postnatal form of adrenal virilization

Postnatal form of adrenal virilization (**postnatal adrenogenital syndrome**) is caused by **an androgen-secreting adrenocortical tumors**. These neoplasms may appear in childhood or adulthood. They may be in the form of virilizing adrenal adenomas or carcinomas. Virilizing adrenal adenomas are rare and are most common in adults. Virilizing adrenal carcinomas are the most common adrenal tumors causing virilization and appear more frequently in childhood.

Adrenal adenomas usually cause a pure virilizing syndrome (an androgen-secreting adenomas). Adrenal adenomas which may simultaneously produce also cortisol are very rare.

Adrenal carcinomas usually cause a mixed virilizing syndrome because they secrete not only adrenal androgens, but also intermediate products of other adrenocortical steroid hormones.

The clinical features of postnatal adrenogenital syndrome depend on the sex and age of a patient. Sudden onset of progressive hirsutism and virilization suggests adrenal carcinomas. In the patients with virilizing adrenal adenomas symptoms of virilization develop gradually.

In **the girls**, virilizing adrenocortical tumors evoke manifestations analogous to those originating due to congenital form of adrenal virilization. Female pseudohermaphroditism, having milder manifestations than that of congenital form, originates.

In **the boys**, the clinical picture of precocious pseudopuberty originates. Its manifestations resemble those observed in boys with congenital adrenogenital syndrome.

In **the adult women**, with regard to heterosexual hormonal disorder, menstrual irregularities, infertility, hirsutism, breast atrophy, and coarse voice originate. In the affected women defeminization gradually develops and male habitus originates.

In **the adult men**, with regard to isosexual hormonal disorder, hirsutism need not be striking. Adrenal androgen excess may be unnoticed for a long time. The disorder is often diagnosed only when atrophy of testes, azoospermia, and infertility appear. These symptoms are the consequence of inhibited GTH secretion due to increased plasma adrenal androgen concentrations. Though testicular androgen secretion is reduced, sexual potence of affected men has not been usually changed because of the effect of adrenal androgens.

5.6.2 Pathophysiology of adrenal medulla

The most common and most significant disease of the adrenal medulla is pheochromocytoma being the cause of its hyperfunction. While this hyperfunctional state of the adrenal medulla is exactly defined, its hypofunctional states are not precisely defined and their existence is even considered speculative. Idiopathic orthostatic hypotension, occurring in middle-aged and elders is sometimes considered a manifestation of hypofunction of the adrenal medulla.

5.6.2.1 Pheochromocytoma

Pheochromocytoma is a catecholamine-producing tumor derived from chromaffin cells. It arises

most commonly from adrenomedullary chromaffin cells (**intraadrenal pheochromocytoma**). If a catecholamine-producing tumor arises from extraadrenal chromaffin cells (usually from the sympathetic chain in the abdomen), it is denoted as **extraadrenal pheochromocytoma** or paraganglioma. Chromaffin cells of pheochromocytoma synthesize, store, and secrete excess catecholamines (norepinephrine and epinephrine). They may be released into circulating blood continually or intermittently (in paroxysmal attacks) causing the origin of severe hemodynamic disorders and also evoke series of metabolic changes.

In the patients with pheochromocytoma the most evident and severest hemodynamic disorder is the origin of **arterial hypertension** (secondary hypertension). It is induced by excess stimulation of α-adrenergic receptors of vessels by intermittently or permanently increased plasma noradrenaline concentrations. Pheochromocytoma occurs in approximately 0.1–0.2 % of the hypertensive population. Some authors assume that its real incidence is higher (0.5–0.6 %). Pheochromocytoma may occur at all ages but is most common in young to midadult life.

Similar clinical manifestations may occur in patients with **other tumors** of sympathetic and adrenomedullary origin, such as ganglioneuroma, neuroblastoma, and ganglioneuroblastoma. These tumors, like pheochromocytomas, are derived from the neural crest and are located in the adrenal medulla or sympathetic ganglia. Therefore, like pheochromocytomas, they are often associated with excessive production of catecholamines and their metabolites. **Ganglioneuroma** is a benign tumor consisting of mature cells derived from the sympathetic ganglia. **Neuroblastoma** is the most immature and malignant of these tumors and is considered derivative of primitive sympathetic cells or neuroblasts which are intermediate grade in the process of differentiation of primitive sympathetic cells into mature cells of sympathetic ganglion. **Ganglioneuroblastoma** is partially differentiated neuroblastoma containing also certain amount of mature ganglion cells. Its malignity is not so severe as that of neuroblastoma, therefore, its prognosis is better than that for neuroblastoma. Neuroblastomas almost exclusively occur in individuals younger than 18 years of age, 85 to 90 % are found in children younger than five years of age. Ganglioneuroma also occurs mainly in childhood.

More than 90 % of pheochromocytomas appear to be benign (adenomas), less than 10 % are malignant (carcinomas). Because benign and malignant pheochromocytomas may have an identical histologic appearance, the only criterion of malignancy is local invasion of surrounding tissues and mainly origin of distant metastases. The metastases occur more frequently to the related retroperitoneal lymph nodes, liver, lungs, and bones. Paraganglioma is more often malignant than intraadrenal pheochromocytoma.

In about 80 % of the patients with pheochromocytoma solitary and unilateral intra-adrenal tumor accurs. It is more common on the right side. About 10 % of cases are bilateral in the adrenals, and about 10 % are extra-adrenal. Extra-adrenal pheochromocytomas (paragangliomas) are most often located within the abdomen, mainly in the area of the organ Zuckerkandl (caudal to the origin of the inferior mesenteric artery, respectively close to the aortic bifurcation). Extra-adrenal pheochromocytomas are more rarely located in the thorax (mainly in the posterior mediastinum), in the neck, or within the urinary bladder.

In adults pheochromocytoma is more common than in children. Children account for about 10–12 % of the total number of cases, boys are affected more often than girls. In adults pheochromocytoma most often occurs between 40 and 50 years of age, with a slight female preponderance. It is rare after age 60.

Approximately 90–95 % of pheochromocytomas are considered as acquired disease with unknown pathogenesis, they occur sporadically. In about 5–10 % of cases, pheochromocytoma is inherited as an autosomal dominant trait either alone or in combination with familial multiple endocrine neoplasia (as a part of the MEN 2A and the MEN 2B). Most tumors in the familial syndromes are bilateral (70 %), but in the nonfamilial setting only 10–15 % are bilateral. In the patients with the MEN syndromes, the adrenal medullary involvement may take the form of diffuse or nodular hyperplasia accompanied by one or more neoplasms.

The clinical manifestations of pheochromocytoma are the result of intensified physiological and pharmacological effects of noradrenaline (norepinephrine) and adrenaline (epinephrine), the synthesis of which in its chromaffin cells is increased and autonomous. Unlike the normal adrenal medulla, adrenaline of

which is major product, pheochromocytoma usually secretes noradrenaline most predominantly. Most extraadrenal pheochromocytomas secrete noradrenaline exclusively, Rarely, pheochromocytomas produce adrenaline alone, particularly in association with the MEN. Prevailingly increased adrenaline secretion may be the evidence of intraadrenal localization of pheochromocytoma, because only in adrenal medulla phenylethanolamine N-methyltransferase, which catalyzes the N-methylation of norepinephrine to epinephrine, is present. Malignant pheochromocytomas usually produce increased amounts of dopamine.

The clinical symptomatology of pheochromocytoma is rather variable depending on the total amounts of released noradrenaline and adrenaline, as well as on the mutual ratio of their concentrations in circulating blood. The clinical symptomatology of some pheochromocytomas is also influenced by possible production of other substances, e.g., enkephalins.

In the clinical picture of pheochromocytoma combination of arterial hypertension and metabolic changes (symptoms of metabolic syndrome) is most common. However, the dominant clinical feature in patients with pheochromocytoma is arterial hypertension. According to the way of catecholamine release from pheochromocytomas (intermittent or continual) three types of the arterial hypertension are distinguished:

1. **Paroxysmal arterial hypertension**

2. **Sustained arterial hypertension with paroxysmal attacks**

3. **Sustained arterial hypertension**

In the both first types of the disease blood pressure is significantly elevated only during **the paroxysmal attaks**. The paroxysmal increase of blood pressure is pathognomonic for pheochromocytoma. It occurs in about 50 % of all patients with pheochromocytoma. Approximately in about half of these patients with the paroxysmal attacks it occurs as paroxysmal arterial hypertension and in the other half as sustained arterial hypertension with the distinct paroxysmal attacks. In some patients the blood pressure during the paroxysm may be so elevated that a hypertensive crisis occurs. In the periods between the paroxysms or crisis catecholamines are not being released from pheochromocytoma, therefore, blood pressure

is normal or sometimes slightly decreased. The other 50 % of all patients with pheochromocytoma have sustained arterial hypertension without the paroxysms or crises.

The paroxysmal release of catecholamines from pheochromocytoma and thereby successive paroxysmal blood pressure elevation may be **evoked** by physical (mechanical, termal, or cooling), chemical, or pharmacological influences. It may be initiated by vigorous palpation of the abdomen or by any activity that displaces the abdominal contents, respectively increases intraabdominal pressure (e.g., coughing, sneezing, lifting, straining, bending or strenuous excertion of any kind, defecation, micturition, coitus, delivery, or change of body position). The paroxysm may be also precipitated by trauma, surgical intervention, high or low temperature of the patient's surroundings, intake of hot or cold drink or meal, intake of alcohol or coffee, and smoking). Severe and occasionally even fatal paroxysm or crisis have been induced by some sedatives, opiates, histamine, and glucagon. These agents appear to release catecholamines directly from the pheochromocytoma. In some patients a particular stimulus may reproduce an attack in a characteristic manner. In other cases the paroxysmal release of catecholamines from pheochromocytoma may originate without clearly evident cause (**spontaneously**), even during sleep. Mental stress or psychological tension does not usualy provoke the paroxysm or crisis.

The paroxysm or crisis is the classic manifestation of pheochromocytoma. It is the consequence of catecholamine release from the tumor and the subsequent stimulation of adrenergic receptors. The paroxysmal attack of blood pressure elevation usually has a sudden onset. It may last from a few minutes to several hours. Most paroxysms subside within 40 minutes. Rarely, more prolonged episodes occur. The paroxysm is associated with several **symptoms**, most evident of which are: headache, palpitations, excessive sweating, and apprehension, often with a sense of impending doom. Headache may be severe, throbbing or steady. It is localized in frontal or occipital areas. Palpitations are usually the result of tachycardia or cardiac tachyarrhythmia, they may, however, occur without these changes of cardiac rhythm. In some patients other accompanying symptoms may occur during the attack. Chest pain and nervousness or anxiety may accompany the attack. Pal-

lor or flushing of the face is also frequent, with a flushed, warm feeling afterward. Hands and feet of some patients are cold and sometimes also cyanotic (acral cyanosis). Mydriasis accompanied by blurred and vague vision is rather common. Tachypnea and sometimes dyspnea are also present. Gastrointestinal symptoms, mainly epigastric pain, nausea, and vomiting are rarer. The decrease of intestinal motility due to catecholamines may result in constipation. Fine tremor of fingers and eye-lids is sometimes present. Feeling of fatigue, weakness or exhaustion may also appear. Occasional paresthesias and tetanic convulsions resulting from hyperventilative respiratory alkalosis are described. After the paroxysm the patient feels rather exhausted. After finishing the attack, profuse sweating and increased diuresis persist even for several hours.

During the severe paroxysm the systolic arterial pressure may be 250–300 mmHg. In these patients angina pectoris or even acute myocardial infarction may occur in the absence of coronary artery disease. Catecholamine-induced increase in myocardial oxygen consumption and, perhaps, coronary spasm may play a role in these ischemic events. During a very severe attack, mainly in the patients with sustained arterial hypertension with paroxysmal attacks, blood pressure may reach critical values associated with possible origin of a fatal complication (**fatal hypertonic crisis**). Due to such extreme increase of blood pressure there is a danger of cerebral hemorrhage, congestive heart failure, or ventricular fibrillation.

Duration, frequency, and intensity of the paroxysms are variable. At the onset of the disease, the attacks of arterial hypertension are usually shorter, milder and the intervals between them are usually quite long (several months or even several years). In some patients, as the disease progresses, the paroxysms tend to increase in frequency, severity, and duration. Later, the attaks may occur every day, or even several times a day. Untreated paroxysmal type of hypertension may persist lifelong or may be changed to sustained arterial hypertension without paroxysmal attacks.

Laboratory examination during the attack of hypertension reveals hyperglycemia, glycosuria, increased plasma concentrations of free fatty acids and lactic acid, and the increase of BMR. Sometimes the elevated hematocrit, secondary to diminished plasma volume, is present. Plasma volume depletion is the result of increased diuresis which is secondary to both the attack of arterial hypertension and glycosuria.

Sustained arterial hypertension (without paroxysmal attacks) occurs in about 50 % of all patients with pheochromocytoma. Permanently increased systolic and diastolic blood pressure is the result of continual releasing of catecholamines from pheochromocytoma and successive sustained increase of their concentration in circulating blood. If blood pressure lability is present, it may sometimes resemble essential hypertension. However, severe headaches, increased sweating, frequent palpitations, or also presence of symptoms of metabolic syndrome are the evidence of pheochromocytoma occurrence. It differs from essential hypertension also by its usual unsatisfactory response to conventional antihypertensive treatment.

Prognosis of sustained arterial hypertension is determined by the development of complications associated with high blood pressure, mainly by atherosclerosis and hemodynamic overload of the left ventricle. In a large number of patients so called **catecholamine cardiomyopathy**, being the result of a direct effect of catecholamines to myocardium, is developing. Histologically, numerous focal areas of myocytolysis, and occasionally myofiber necrosis and interstitial fibrosis, sometimes with mononuclear inflammatory infiltrates, are present. In patients with sustained hypertension the development of malignant hypertension is relatively fast. However, the prognosis of patients affected by sustained arterial hypertension with paroxysmal attacks is worst.

Metabolic syndrome is the result of an increased metabolic rate (glucose and lipid mobilisation), thermogenetic effect (mainly due to increased oxidation of free fatty acids associated with the increased oxygen consumption and heat production), and anti-insulin effect of catecholamines. **The increased heat production** is manifested by profuse sweating, heat intolerance, and slightly elevated basal body temperature even occasionally fever. **Hypermetabolism** may be manifested by weight loss, mainly in patients with continual releasing of catecholamines from pheochromocytoma. Suppression of insulin secretion (mediated by stimulation of α_2–adrenergic receptors) and increase of hepatic glucose output (mediated by stimulation of β–adrenergic receptors) are the cause of impaired carbohydrate tolerance and elevated plasma glucose concentrations. **Glucose in-**

tolerance and **hyperglycemia** may occur during the paroxysms, later after fasting are also present.

In untreated patients with sustained arterial hypertension **orthostatic hypotension** is often present. It is manifested by a significant postural fall in blood pressure (more than 30 mmHg in comparison with current values of the patient) accompanied by dizzinesses. In some patients with orthostatic hypotension collapse may sometimes originate. Hypotension may last several minutes. During trauma or surgical intervention in untreated patients with pheochromocytoma unexplained hypotension or circulatory shock may develop.

In the patients with untreated pheochromocytoma several factors probably participate in the origin of orthostatic hypotension. It may be partly a consequence of hypovolemia (as a result of increased diuresis which is secondary to arterial hypertension and glycosuria), and partly a consequence of blunted postural reflexes due to a prolonged excess of catecholamines. According to some authors orthostatic hypotension occurs mainly in the patients with oversecretion of adrenaline and enkephalins from pheochromocytoma.

5.7 Endocrine disorders of the ovaries

Endocrine disorders of the ovaries are the third most common endocrinopathy, more frequent are only the thyroid gland disorders and the disorders of the endocrine portion of the pancreas. Their classification has not been yet sufficiently transparent and uniform. At present **pathogenetic classification** has been considered most convenient. It is based on the following four criteria:

1. The type of intensity of hormonal secretion, i.e., hyposecretion or hypersecretion of ovarian hormones, respectively secretion of hormones atypical for ovaries.

2. The place of origin of an endocrine disorder, i.e., primary, secondary, or tertiary disorder of hormonal secretion.

3. The basic cause of endocrine disorder, i.e., inborn or acquired endocrine disorder.

4. Number of hormones of which secretion is impaired, i.e., disorder of only some or all ovarian steroid hormones.

5.7.1 Ovarian endocrine hypofunction

Hyposecretion of ovarian hormones is denoted as **female hypogonadism** (hypogonadismus femininus). Its etiopathogenesis is rather variable. The cause of ovarian hormone deficiency may be within the ovaries themselves (**primary** female hypogonadism), in the adenohypophysis (**secondary** female hypogonadism), or in the hypothalamus (**tertiary** female hypogonadism). The clinical picture of ovarian hypofunction depends on the age of a patient in the time of its origin. If the ovarian endocrine hypofunction originates prior to puberty in girls its consequences begin usually to appear at the time of expected onset of puberty. Insufficient sexual maturation (sexual infantilism) develops. If the ovarian endocrine hypofunction originates in adult female it is manifested by menstrual abnormalities and infertility.

5.7.1.1 Primary ovarian hypofunction

Primary (peripheral) ovarian hypofunction is **a complete disorder** of ovarian hormone secretion, i.e., the production of all ovarian steroid hormones is insufficient. Primary ovarian hypofunction can result from multiple causes, but principally it may be inborn or acquired. The menopause is a special form of primary ovarian hypofunction (physiological cessation of ovarian function). However, cessation of ovarian function can occur at any age, even in utero. If it occurs before puberty, the presentation is as primary amenorrhea; after pubertal development and menarche the presentation is as secondary amenorrhea. Due to decreased plasma ovarian hormone concentrations hypothalamic-adenohypophyseal area is stimulated to increased secretion of gonadotropins by feedback mechanism. The pituitary gonadotropin concentrations in circulating blood are, therefore, increased (**hypergonadotropic female hypogonadism**).