5.9 Pathophysiology of the endocrine pancreas

The endocrine pancreas consists of about 1 million microscopic cellular units (the islets of Langerhans) accounting for about 1–2 % of the total weigh of the pancreas. In the human adult the islets consist of three major and three minor cell types. The three main types are B, A, and D cells making up about 95 % of the islet cell population. **The B cells** account for about 70 % of the islet cell population and produce insulin. **The A cells** account for about 20 % of the islet cell population and secrete glucagon. **The D cells** secrete somatostatin and make up about 5 % of the islet cell population. In immunohistochemical studies that employ specific antibodies to individual hormones, the existence of the three rare cell types has been proved. The three minor cell types are PP cells, D_1 cells, and G cells. **The PP cells** produce a unique pancreatic polypeptide (PP). **The D_1 cells** elaborate vasoactive intestinal polypeptide (VIP). **The G cells** synthesize pancreatic gastrin. According to their effect, pancreatic polypeptide, vasoactive intestinal polypeptide, pancreatic gastrin, and somatostatin belong to the group of gastrointestinal hormones.

The endocrine diseases of the pancreas include diabetes mellitus and tumors of the endocrine pancreas. The best known tumors of the islet cells include insulinoma, glucagonoma, gastrinoma, somatostatinoma, and VIPoma. Tumors of the endocrine pancreas may be also a part of the multiple endocrine neoplasia, type 1 (MEN 1), denoted as Wermer syndrome.

5.9.1 Diabetes mellitus

Diabetes mellitus is the most common endocrine disorder. However, it is not an individual nosological unit. This term denotes a diabetic syndrome comprising an etiologically and clinically **heterogenous group of pathological states**, the common and permanent symptom of which is hyperglycemia originating secondary to long-lasting absolute or relative insulin deficiency or to its insufficient effect in target tissues, usually in the presence of a relative or absolute excess of glucagon. Absolute insulin deficiency or its insufficient effect in peripheral tissues causes a disorder of glucose metabolism. When the insulin deficiency is extreme this hormonal abnormality is responsible for the tendency to develop ketoacidosis. The impaired glucose utilization is subsequently associated with the origin of disorder of fat and protein metabolism, as well as with the disorder of water and electrolyte metabolism. Therefore, **a complex metabolic disorder** originates. In the period of overt diabetes mellitus this complex metabolic disturbance is manifested by hyperglycemia, glycosuria, increased protein catabolism, and ketoacidosis. Due to nontreated evident insulin deficiency ketoacidosis may result in diabetic coma. Diabetes mellitus is hence considered not only as endocrine disorder, but also as metabolic disorder. In patients with long-lasting diabetes mellitus late complications develop, the most frequent and severest being degenerative changes of blood vessels and nerve system.

5.9.1.1 Etiology and classification of diabetes mellitus

The World Health Organization (WHO) defines diabetes mellitus as **a state of chronic hyperglycemia** caused by simultaneous affect of genetic and environmental factors including nutrition. This definition indicates that diabetes mellitus has **a multifactorial genesis**. Genetic, immunological, viral, toxicochemical, and nutritional factors participate in the origin of diabetes mellitus. Besides that diabetes mellitus is associated with other primary diseases or syndromes.

During the 70s and 80s a lot of new information on etiology and pathogenesis of diabetes mellitus was obtained. Therefore, in 1985 WHO accepted the following new classification of diabetes mellitus:

A. **Clinical groups**

1. INSULIN-DEPENDENT DIABETES MELLITUS (type 1 diabetes)
2. NON-INSULIN-DEPENDENT DIABETES MELLITUS (type 2 diabetes)
   (a) Non-obese
   (b) Obese

3. MALNUTRITION-RELATED DIABETES MELLITUS
   (a) Fibrocalculous pancreatic diabetes
   (b) Protein-deficient pancreatic diabetes
4. OTHER TYPES OF DIABETES MELLITUS associated with certain conditions or syndromes
   (a) Pancreatic disease
   (b) Disease of hormonal etiology
   (c) Drug-induced or chemical-induced conditions
   (d) Abnormalities of insulin or its receptors
   (e) Certain genetic syndromes
   (f) Other conditions or syndromes
5. IMPAIRED GLUCOSE TOLERANCE
   (a) Non-obese
   (b) Obese
   (c) Associated with certain conditions or syndromes
6. GESTATIONAL DIABETES MELLITUS

B. **Statistically dangerous groups**

1. POTENTIAL ABNORMALITY OF GLUCOSE TOLERANCE
2. PREVIOUS ABNORMALITY OF GLUCOSE TOLERANCE

The first two main clinical forms, i.e., insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) are most common (some authors consider them as two variants of primary diabetes mellitus). Insulin dependence in this classification is not equivalent to insulin therapy. Rather, it means whether endogenous insulin secretion is sufficient to prevent diabetic ketoacidosis. Other types of diabetes mellitus and gestational diabetes mellitus are rare. Malnutrition-related diabetes mellitus (MRDM) does not occur in our country.

In WHO classification the term insulin-dependent diabetes mellitus and type 1 diabetes are used synonymously, and the term non-insulin-dependent diabetes mellitus has been considered equivalent to type 2 diabetes. But a clinical practice that has been criticized, since some patients with apparent non-insulin-dependent diabetes may in fact be destined to become fully insulin-dependent and prone to ketoacidosis. Therefore, some authors apply the term insulin-dependent diabetes mellitus to all forms of diabetes in which exogenous insulin is required to prevent diabetic ketoacidosis, regardless of etiology. They apply the term type 1 only to diabetes resulting from autoimmune destruction of B cells regardless to whether the destruction is sufficiently complete to result in ketoacidosis. They use the term type 2 to denote all forms of diabetes mellitus which did not arise from autoimmune destruction of B cells. Thus in this formulation the terms type 1 and type 2 distinguish between autoimmune and nonautoimmune forms of diabetes (these terms refer to pathogenetic mechanism), whereas the terms insulin-dependent and non-insulin-dependent indicate only the absence or presence of B cell function, respectively describe pathophysiologic states (ketoacidosis-prone or ketoacidosis-resistant). Using such a classification, for example, if a patient with autoimmune diabetes were to pass through a transient non-insulin-dependent period during which B cell destruction is incomplete, he or she would be classified as having type 1 NIDDM until such time as insulin dependence appeared, whereupon the classification would change to type 1 IDDM. The type 1 NIDDM is an intermediate state of autoimmune destruction in which sufficient insulin remains to prevent ketoacidosis but not to maintain normal concentration of blood glucose (normoglycemia). The stage of type 1 NIDDM likely occurs when the autoimmune process begins at an older age and progresses at a slower rate. It is infrequently seen when IDDM appears in childhood or early adolescence.

5.9.1.2 Clinical groups of diabetes mellitus

According to WHO classification there are six following clinical groups of diabetes mellitus:

1. **Insulin-dependent diabetes mellitus**

Insulin-dependent diabetes mellitus (type 1 diabetes) is characterized by rather sudden onset of clinical symptoms, almost full or completely full deficiency of endogenous insulin, rapid development of diabetic ketoacidosis, and after the origin of ketoacidosis by vital dependence on therapeutical adminis-

tration of exogenous insulin. A severe, absolute lack of insulin is caused by a severe or complete reduction in the B cell mass due to autoimmunity. This form of diabetes may originate at any age, prevailingly, however, in childhood or adolescence (between the ages of 1 and 20), most frequently about 10 years of age. It accounts for about 10–15 % of all patients with diabetes mellitus.

Etiology and pathogenesis. Genetic and environmental factors share participation in the origin of insulin-dependent diabetes mellitus.

Genetic factors. The type 1 IDDM is thought to arise as a consequence of an autoimmune destruction of B cells in a genetically predisposed individuals. Genetic predisposition to IDDM is associated with the presence of certain **antigens of HLA system**. Approximately 95 % of patients with this type of diabetes carry the HLA-DR3 or HLA-DR4 or both antigens. In about 60 % of the patients both these HLA antigens can be found. If one of them is present, the risk of the origin of the type 1 IDDM is 5 times increased, however, the occurrence of both mentioned HLA antigens increases the risk of the origin of IDDM 40–50 times compared to the population without these HLA antigens.

Immunogenetic heterogenity of type 1 IDDM seems to exist. Some authors even assume that there are two diabetogenic genes responsible for genetic predisposition to type 1 IDDM. The first diabetogenic gene is made up of association of HLA-DR3, B8, Cw7, and A1 antigens. The second diabetogenic gene is made up of association of HLA-DR4, B15, Cw3, and A2 antigens. Recently the significance of HLA-DQ allele participation has been studied and strong associations are being reported with HLA-DQ allele. Today it is thought that HLA-DQb chain gene primarily determine susceptibility and resistance to autoimmune destruction of B cells. This finding may explain the observation that combinations of HLA-DR and HLA-DQ alleles confer higher risk than either alone. The participation of other genes not belonging to HLA area are also supposed. However, the information on them is controversial, and the mode of their inheritance is unknown.

In the patients with **HLA-DR3 antigene** circulating islet cell autoantibody titer is evidently increased, insulin antibodies are absent, other autoimmune endocrinopathies and nonendocrine autoimmune diseases also often occur (association of autoimmune endocrinopathies with IDDM is 30–50 times more frequent than their individual occurrence in rest of population). The carriers of this antigene are more commonly females, at onset of IDDM they are mostly of an older age, the degree of diabetic disorder is milder with less ketonuria at diagnosis, and diabetic disorder has a greater tendency for partial remissions. During the remissions exogenous insulin is not necessarily to be administered. The remissions are probably evoked by transient regenerations of B cells (a partial recovery of their function).

In the patients with **HLA-DR4 antigene** islet cell autoantibodies are not present in circulating blood, titer of insulin autoantibodies is increased, and these patients have little, if any, association with other autoimmune diseases. Subjects with this HLA antigene exhibit a male predominance, tendency to younger onset, and the degree of diabetic disorder is severer than that in the patients with HLA-DR3 antigene.

Environmental factors. The genetic contribution is necessary but ordinarily insufficient to cause the type 1 IDDM; usually an environmental factor is required as the trigger for its initiation. The most significant environmental factors inducing the clinical manifestation of genetic predisposition are considered **viral infections** evoked mainly by mumps virus, rubella virus, cytomegalovirus, coxackieviruses B4 and B5, retroviruses with type C particles, retrovirus with type A particles, reoviruses, and encephalomyocarditis virus. Presentation of the type 1 IDDM is more common in the spring and autumn than in the summer (its seasonal incidence), and it has been suggested that this might be related to the greater prevalence of viral infections at these times. The influence of **chemical substances** (betacytotoxins), mainly nitrosamines, is considered. Nitrosamines occur widely in small amounts in both natural and processed foodstuffs. They are found in variable amounts in fresh vegetables and in substantial quantities in foods high in nitrates and nitrites, e.g., some smoked or cured meats and fish. They are also formed in vivo from precursors in foods such as nitrates and nitrites, especially in the stomach at low pH, and even from certain medicaments. Some other, by now unknown environmental factors, may be a possible etiological agents triggering a clinical manifestation of type 1 IDDM as well.

Autoimmunity. A role of autoimmunity in the pathogenesis of type 1 IDDM is supported by sev-

eral morphological, clinical and experimental observations. Due to direct effect of triggering environmental agent originates an inflammatory response in the pancreatic islets (their early infiltration by activated T lymphocytes and macrophages) called **insulitis**. The mechanism, by which participation of genetic predisposition and environmental factors initiates an impairment of B cells and subsequent deficient insulin secretion, is not exactly known. However, from the etiopathogenetic point of view type 1 IDDM is considered as **an autoimmune disease** in the origin of which mechanisms of humoral and cell-mediated immunity participate.

A. **Humoral immunity**. The following two types of islet cell autoantibodies have been found in circulating blood of the patients: islet cell cytoplasmic antibodies and islet cell surface antibodies. The both kinds of these antibodies belong to IgG. Islet cell cytoplasmic and surface antibodies may be present simultaneously in the same patient, but either can occur alone.

The precise mechanism by which the environmental factors trigger production of islet cell antibodies in individuals with genetic predisposition to IDDM is not known. It is supposed that the exogenous agent might act in one of several ways. It has been suggested that an environmental factor might form a neoantigen in association with normal membrane structures. It is also possible that islet cell antibodies are secondary to the direct destruction of B cells by an environmental trigger, and are formed in response to liberated cellular constituents as a part of the polyclonal immune activation. This alteration or transformation of islet B cells leads to conversion of B cells from "self" to "nonself", which are no longer recognized as "self" but are acceptated by the immune system as a foreign cells or "nonself". The autoimmune system is, therefore, activated. Because the B cells of Langerhans islets are now considered "nonself" cytotoxic islet cell antibodies are produced by B lymphocytes and act in concert with cell-mediated immune mechanisms. It is supposed that islet cell antibodies evoke autoimmune inflammatory lesion of islet B cells, the evidence of which is early infiltration of islets by T lymphocytes and macrophages (autoimmune insulitis). The end result is the destruction of the islet B cells and later the appearance of diabetes.

Islet cell cytoplasmic antibodies generally react with all islet cell types. However, only the B cells are destroyed (selective destruction of the insulin-secreting cells). The other cell types are normal. In the subjects with genetic predisposition to type 1 IDDM they appear alredy several months or even several years before the clinical manifestation of diabetes. These antibodies are detected in circulating blood of 70–90 % of newly diagnosed patients with the type 1 diabetes. They are still present in about 20–30 % of the patients 1 year after onset of the IDDM and persist in 10–15 % of the patients 2–3 years after the diagnosis of the IDDM.

In the patients with persistence of islet cell cytoplasmic antibodies in circulating blood simultaneously with the type 1 IDDM also other autoimmune diseases occur, such as Hashimoto thyroiditis, Graves-Basedow disease, Addison disease, pernicious anemia, myasthenia gravis, vitiligo, rheumatoid artritis, and collagen diseases. Islet cell cytoplasmic antibodies persist in their circulation even 10 years after onset of the IDDM. In plasma of these patients or in circulation of some members of their families cell cytoplasmic antibodies against the cells of other endocrine glands or other tissues simultaneously occur. These patients exhibit a female predominance and frequent association with HLA-DR3 and HLA-B8 antigens. In subjects with HLA-DR3 and HLA-B8 antigens the IDDM is clinically manifested at older age (about 30 years of age and later) than in individuals with HLA-DR4 and HLA-B15 antigens.

Islet cell surface antibodies are reported to be present in about 90 % of new-onset IDDM patients. They persist in about 38 % of patients five years after the clinical manifestation of diabetes. The islet cell surface antibodies have a cytotoxic effect. They predominantly (selectively) lyse B cells in the presence of complement. Thus if any of the islet cell antibodies are responsible for B cell destruction, it is more likely that surface rather than cytoplasmic antibodies play the critical role.

B. **Cell-mediated immunity**. The increased number of cytotoxic T lymphocytes (natural killer cells – NK cells) and the decreased number or defective function of suppressor T lymphocytes are the evidence of participation of cell-mediated immunity in the pathogenesis of type 1 IDDM. Decline in number or decrease of suppressor T lymphocyte activity probably activates helper T lymphocytes which play an important role in pathogenesis of IDDM.

They produce interleukin-2 (IL-2) which activates cytotoxic T lymphocytes, the number of which is increased in about 50–60 % of the patients in the time of diagnosis of the diabetes. It is supposed that in response to viral or other exogenous stimuli IL-2 and also interferon-γ (IFN-γ) are secreted by lymphocytes and macrophages which infiltrate the pancreatic islets (insulitis). Under the influence of these cytokines, macrophages and NK cells are activated to produce IL-1 and tumor necrosis factor-α (TNF-α). IL-1 has a selective cytotoxic effect on B cells of Langerhans islets leading to destruction of the B cells. This action of IL-1 is strongly potentiated by TNF-α. It has been postulated that cytotoxic effect of IL-1 on the B cells is mediated by oxygen-derived free radicals. The B cells are exquisitely sensitive to free radicals and have the lowest free radical scavenger potential of any cell in the body. Therefore, when production of free radicals exceeds the capacity of the antioxidant defences, impairment of cell membrane and membrane of intracellular organels, and also disorganization of intracellular enzymes will originate.

In summary, on the basis of the mentioned data the following hypothesis for the pathogenesis of the type 1 IDDM may be postulated. It is a progressive autoimmune disease which is clinically manifested when the destruction of more than 90 % of B cells of Langerhans islets originates. Macrophages, B lymphocytes, helper T lymphocytes, suppressor T lymphocytes, and cytotoxic T lymphocytes participate in its origin. It is now recognized that type 1 diabetes usually proceeds through the following sequence: genetically susceptible people begin their lives without any detectable abnormality (prediabetes). A triggering factor causing minimal destruction of islet B cells is followed by autoimmunity. This is reflected in positive tests for islet cell antibodies. Although B cell mass decreases, the functional reserve of B cells is more than enough to mantain normal plasma glucose level. Continual injury results in sufficient loss of B cell mass to cause diminution in glucose stimulated insulin secretion (impaired glucose tolerance). As the destruction of B cells continues, fasting glucose levels will rise above normal. Later, a mild persistent hyperglycemia appears (type 1 NIDDM). In this phase of diabetes, C-peptide in circulating blood of the patients is present, but its concentrations are decreased. The presence of C-peptide in the blood indicates that some B cells have survived. The classic clinical manifestations of type 1 diabetes appear when more than 90 % of the B cells have been destroyed. C-peptide is still present, but its concentrations are exremely low. When the total destruction of all B cells of islets originates, C-peptide level will become unmeasurable (type 1 IDDM). Hence, plasma C-peptide concentrations may provide a useful index of the degree of functional reserve of B cells. The pathogenetic process is slow and several months even several years may elapse from the time anti-islet immunity can be detected until type 1 IDDM becomes clinically manifest.

2. Non-insulin-dependent diabetes mellitus

Non-insulin-dependent diabetes mellitus (type 2 diabetes) is characterized by relative deficiency of endogenous insulin and by absence of tendency to the origin of ketoacidosis. The patients are not dependent on administration of exogenous insulin. Although in the patients with this type of diabetes there is no danger of the origin of ketoacidosis under circumstances of usual life style, it may be evoked by various stress situations (e.g., intercurrent infection, trauma, surgical intervention, and the like). Under these circumstances administration of exogenous insulin is almost always inevitable.

Non-insulin-dependent diabetes mellitus is **the most common type** of diabetic syndrome. It accounts for about 80–85 % of all patients with diabetes mellitus. It may originate at any age, but it mostly develops not before 30 years of age. Its incidence increases markedly with age. The clinical symptoms of this type of diabetes usually develop slowly. The affected subjects may be asymptomatic for several years. This disease is often discovered casually.

Etiology and pathogenesis. The precise etiology of the type 2 diabetes is unknown. Both genetic factors and environmental factors are supposed to participate in the origin of NIDDM. By contrast, however, with IDDM it is clear that B cell destruction is minimal, that autoimmunity does not play a role, and that insulin action is defective.

Genetic factors. They are of greater importance than in IDDM. Genetic basis of the origin of NIDDM is, however, different to that of IDDM. There is no association with HLA antigens in the patients with NIDDM. From genetic studies it has been known for many years that NIDDM is **a familial disease**. The

genetic contribution is illustrated by the fact that even 85 % of the patients' parents with NIDDM have also had diabetes, while only 11 % of the patients' parents with IDDM have had diabetes (IDDM is not a familial disease). The identical twin of a patient with NIDDM has an almost 100 % chance of developing the diabetes, whereas the identical twin of a patient with IDDM has only a 30–50 % chance of developing the diabetes.

Despite the strong influence of genetic factors their precise nature in etiology of NIDDM remains elusive. Mutations in insulin gene, insulin receptor gene, or glucose transporter genes (genes for glucose transport protein units – GLUTs – which transport glucose across the cell membrane) are considered. It has not been known yet, whether inheritance of NIDDM is monogenic or polygenic. Polygenic inheritance is usually preferred.

It is generally accepted that **the pathogenic basis** for NIDDM is made up by the defect in B cell function (dysfunction of B cells) and insulin resistance in peripheral tissues. For the present, however, it is not exactly known, whether the genetic defect primarily affects B cell function or peripheral insulin resistance, or whether one defect causes the other, or at least precedes the other.

A. **The defect in the function of B cells** is a qualitative and not quantitative defect. Normal subjects have a biphasic insulin response to intravenous glucose. In the patients with NIDDM the most characteristic defect is loss of the first phase insulin response to an intravenous glucose challenge. The second phase release of insulin is not as severely altered, although it cannot be considered truly normal. Insulin secretion in response to oral glucose is delayed and exaggerated. This impaired insulin secretion is due in part to a reduction of GLUT-2 glucose transporter that facilitates glucose entry into the B cells (it facilitates rapid equilibration of glucose between extracellular and intracellular compartments).

Current interest is also focused on the role of amyloidogenic peptide of islets in etiopathogenesis of type 2 diabetes. This material is 37-amino acid peptide termed **amylin**. Amylin is normally copackaged with insulin in secretory granules of B cells and is cosecreted to insulin secretagogues. However, in patients with NIDDM, amylin tends to accumulate autside the B cells, in close contact with their cell membranes. Isled amylin deposits are seen in about 70–90 % of patients with type 2 diabetes. A role for amylin deposition in the islets of subjects with NIDDM is not precisely established. Amylin may accumulate, either because of a primary defect of B cell function or because of abnormal B cell function secondary to prolonged hyperglycemia (which is secondary to the insulin resistance). It is possible that progressive accumulation of amylin disrupts islet architecture and leads to impaired B cell function and so it might contribute to the late failure of insulin production in patients with long-standing NIDDM. Whether extracellular deposits of amylin contribute also to early disturbance in insulin secretion is controversial. In animals, amylin has been reported to induce also insulin resistance. Hyperamylinemia may impair insulin action mainly in skeletal muscle cells.

B. **Insulin resistance** is the other prime characteristic of NIDDM. Patients with overt NIDDM undoubtedly have marked insulin resistance in target tissues. Insulin insensitivity may be a primary deffect (genetically conditioned) or is secondary to hyperglycemia. Most authorities believed that insulin resistance in patients with type 2 NIDDM is primary, with hyperinsulinemia being secondary, i.e., insulin secretion increases to compensate for the resistance state. However, it is possible that hypersecretion of insulin (and probably also amylin) causes insulin resistance, i.e., a primary islet cell defect causes insulin hypersecretion, and insulin hypersecretion, in turn, leads to insulin resistance. The insulin resistance can have many distinct mechanisms including a reduced number of seemingly normal receptors, receptors which function abnormally (due to abnormal insulin binding to the alpha subunit of the insulin receptor, or due to defective tyrosin kinase activity in the beta subunit of the insulin receptor), and postreceptor defects associated with normal insulin binding. More important postreceptor defects include impaired postreceptor signaling or reduced synthesis and/or translocation (from the Golgi apparatus to the plasma membrane) of the glucose transporter molecules of GLUT-4 in muscle and fat cells. Primary or secondary insulin resistance may cause a secondary defect in the B cells via their exhaustion or direct damage due to long-lasting hyperglycemia.

At the present time, it is not possible to assign primacy to either process, i.e., B cell dysfunction or peripheral insulin resistance. One must state that both a defect in the function of B cells and peripheral

insulin resistance are present in patient with overt type 2 NIDDM and that both are probably required for the appearance of clinical diabetes.

Environmental factors. Although environmental factors are extremely important in the genesis of type 2 NIDDM, it is likely that they can only lead to diabetes in genetically predisposed individuals. The following environmental factors (risk factors) are those which are currently suspected of being precipitants of NIDDM: obesity, physical inactivity, and psychosocial stress.

A. **Obesity.** It is the most frequent and most studied of all the risk factors for NIDDM. While in the whole population prevalence of diabetes mellitus has been somewhere between 3–6 %, in the population having obesity the prevalence of diabetes has been estimated at 20 %. With regard to importance of obesity in pathogenesis, type 2 NIDDM is divided into non-obese and obese variants. The latter form is more common and accounts for approximately 80 % of all cases of type 2 NIDDM. The risk of clinical manifestation of NIDDM shows a close relationship to the degree and duration of obesity. In most obese persons insulin secretion is excessive (from the begining mainly postprandial hyperinsulinemia is present). In spite of it, however, it is insufficient for increased demands of insulin evoked by peripheral insulin resistance. In theory hyperinsulinemia could induce secondary insulin resistance by down-regulation of insulin receptors. This results in hyperglycemia. It is possible that in some individuals prolonged hyperglycemia could lead to the increase of insulin resistance and to the impairment of B cell function. It gradually leads to B cell exhaustion and their irreversible damage. This hypothesis is supported by the finding that after the reduction of excess body wight the clinical and laboratory symptoms of diabetes are reduced. Insulin resistance in patients with type 2 NIDDM may be the result of two separate factors. Because insulin insensitivity occurs in obesity without hyperglycemia, increased adiposity undoubtedly plays an important role in the insulin resistance of obese patients with NIDDM. However, nonobese relatives of persons with NIDDM may have hyperinsulinemia and diminished insulin sensitivity, proving that obesity is not the sole cause of insulin resistance.

B. **Physical inactivity.** It is possible that in genetically predisposed subjects a sedentary life style associated with physical inactivity may participate in the clinical manifestation of type 2 NIDDM by the origin of insulin insensitivity in cells of skeletal muscles. Some studies suggest that an excercise training in subjects with an initially high insulin secretion leads to improvement in peripheral insulin sensitivity, decrease of insulin secretion, and improvement of glucose tolerance.

C. **Psychosocial stress.** A role of psychosocial stress in the development of NIDDM in genetically predisposed individuals is not exactly known at present. It has been suggested that a long implicated psychoemotional stress may participate in the clinical manifestation of type 2 NIDDM by means of increased secretion of hormones which are insulin antagonists (mainly glucocorticoids).

Relationship of NIDDM with some chronic diseases. Recently increased attention is paid to the relationship of NIDDM with some diseases, mainly with primary arterial hypertension and primary hypercholesterolemia. Rather frequent coexistence of these diseases with NIDDM may indicate common genetic influence, cooperation of common environmental factors, a causal sequence among these conditions themselves, or to existence of random chronology in realization of the mentioned endogenous and exogenous factors (overeating, physical inactivity, and psychosocial stress). Insulin resistance and hyperinsulinemia are often associated with obesity, arterial hypertension, hypertriacylglycerolemia, and hyperuricemia. The complex of these disorders has been termed "syndrome X" or **the Modan-Reaven syndrome**.

To summarize, the type 2 NIDDM appears to be a disease of complex etiology. It is probably caused by the interaction of several different genetic and environmental factors. Although specific genetic markers for the disease have yet to be defined, there is clear evidence for genetic predisposition. The most plausible environmental precipitants appear to be the inter-related triad consisting of obesity, low levels of habitual physical excercise, and psychosocial stress. On the basis of present knowledge the following hypothesis for the pathogenesis of the type 2 NIDDM may be postulated: By the influence of the risk factors in a subject with genetic predisposition to B cell dysfunction and/or genetically determined

predisposition to insulin resistance at first impaired glucose tolerance originates. Later, mild persistent hyperglycemia appears. Long-lasting moderate hyperglycemia intensifies the impairment of islet B cells and simultaneously leads to the origin of secondary insulin resistance in target tissues. The result is overt type 2 NIDDM.

3. Malnutrition-related diabetes mellitus

Malnutrition-related diabetes mellitus (MRDM) occurs only in tropical equatorial countries of Africa, Asia, and South America. Therefore, it is also termed **tropical diabetes**. It is characterized by an onset before the age of 30, a history of severe malnutrition and severe malnutrition on presentation, and by fluctuating insulin dependence and insulin resistance. However, ketoacidosis does not develop when insulin is withdrawn. There are two variants of this disorder:

(a) **Fibrocalculous pancreatic diabetes**. It is associated with exocrine pancreatic deficiency, pancreatic fibrosis which often leads to calcification, and the presence of stones in the pancreatic duct. Its etiology is not exactly known.

(b) **Protein-deficient pancreatic diabetes**. This form appears to be caused directly by malnutrition. Unlike fibrocalculous pancreatic diabetes, there is no impairment of exocrine pancreatic function, and no evidence of pancreatic fibrosis or calcification.

In both forms of tropical diabetes, insulin secretion is preserved, although impaired. This is the likely explanation for the resistance to ketoacidosis. Alternatively, malnourished individuals may have so little stored fat that free fatty acids cannot be released in sufficient quantities to fuel the process of ketogenesis.

4. Other types of diabetes mellitus

In the previous classification these forms of diabetes were termed secondary diabetes mellitus. At present this classificatory category includes diabetes mellitus associated with other basic diseases, syndromes, or certain conditions. It is divided into following six subgroups:

(a) **Diabetes mellitus associated with pancreatic disease**. It is caused by traumatic, infectious, toxic, or other form of damage of pancreas. It may occur in patients with chronic pancreatitis, cystic fibrosis, hemochromatosis, carcinoma of the pancreas, and pancreatectomy.

(b) **Diabetes mellitus associated with other endocrine disease**. It is mostly induced by overproduction of insulin antagonists (growth hormone, cortisol, or glucagon). It appears most often in the patients with Cushing syndrome, acromegaly, or gigantism. Glucagonoma, somatostatinoma, thyrotoxicosis, or pheochromocytoma may be a rare cause of its origin. Diabetes is usually mild and without tendency to ketoacidosis.

(c) **Diabetes mellitus induced by administration of some hormones, drugs, and chemicals**. The origin of diabetes depends on the amount of administrated substance, on the duration of its administration, and on sensitivity of the subject to administrated substance. The disorder of glucose metabolism is mostly transient and after a withdrawal of the administrated substance it becomes normal. If diabetes persists, it is probably a manifestation of prediabetes and the administrated substance was only a factor provoked its clinical manifestation. The most common diabetogenic drugs include: hormones (ACTH, synthetic glucocorticoids, and growth hormone), thiazide diuretics, β-adrenoceptor blocking drugs, drugs blocking ovulation, and tricyclic antidepressants. The most common diabetogenic chemicals are alloxan and streptozotocin having cytotoxic effect on islet B cells.

(d) **Diabetes mellitus due to an abnormal insulin or insulin-receptor abnormalities**. Abnormal insulin (e.g., insulin Chicago) originates due to mutation in the insulin gene. The usual clinical picture is mild hyperglycemia with hyperinsulinemia and decreased binding of the mutant insulin to target tissues (prereceptor insulin resistance). The response to normal insulin is intact.

At present two abnormalities of insulin receptors are known:

1. A defect due to mutation in the insulin receptor itself which is manifested by de-

creased affinity of receptor to insulin or by decreased number of insulin receptors (in the patients with congenital lipodystrophy or with acanthosis nigricans).

2. An existence of antibodies against insulin receptors (e.g., in women with androgen excess, particularly in those with polycystic ovary disease) which are the cause of insulin resistance.

(e) **Diabetes mellitus associated with some genetic syndromes**. This form of diabetes originates mainly as a result of combination of some genetic syndromes with various factors, as e.g., nutrition disorders, physical inactivity, obesity, immunological disorders, and the like. They are the following genetic syndromes:

- inborn metabolic disorders (glycogenosis type I, hyperlipoproteinemia, and acute intermittent porhpyria);
- syndromes with insulin resistance (hereditary ataxia-teleangiectasia, myotonic dystrophy, and lipoatrophic syndrome);
- hereditary neuromuscular disorders (muscular dystrophy and Friedreich's ataxia);
- syndromes associated with obesity (Prader-Willi syndrome and achondroplasia);
- cytogenetic disorders (Down syndrome, Klinefelter syndrome, and Turner syndrome).

(f) **Diabetes mellitus associated with other conditions or syndromes**. This category is poorly defined and is meant to include any condition associated with diabetes which does not belong to any of previous five subgroups. Such condition may by **potassium depletion** which originates due to primary hyperaldosteronism or during a long-time treatment by diuretics. Potassium deficit in islet B cells causes the disorder of the first phase of insulin secretion.

Other pathological state associated with diabetes is **cirrhosis** of the liver. However, the relationship between cirrhosis and diabetes mellitus has not been unambiguously explained yet. It has not been proved whether corrhosis causes diabetes or whether diabetes is prior to cirrhosis. Diabetes occurs 3 times more frequently in the patients with cirrhosis compared to those with normal liver. Similarly, in diabetics cirrhosis of the liver is 2–3 times more frequent than in the persons without diabetes. In the patients with cirrhosis hyperinsulinemia, hyperglucagonemia, and peripheral insulin resistance are often proved. Increased insulin and glucagon concentrations in circulating blood of the patients with cirrhosis can be explained by their decreased degradation in the cirrhotic liver.

5. Impaired glucose tolerance

Impaired glucose tolerance (IGT) is an intermediate category between normal glucose tolerance and diabetes mellitus. The persons with IGT are not considered to be diabetics, but probability of the origin of diabetes is higher in them than in the rest of population. This category is extremely heterogenous. Some subjects with IGT are obese or non-obese, some have liver disease, some are on medication that impairs glucose tolerance, and in others IGT is associated with other certain conditions or syndromes. About 20 % of the patients with IGT may progress to overt diabetes mellitus, about 50 % of them may spontaneously fall back to normal glucose homeostasis, and in about 30 % of the patients IGT persists during the whole life. Individuals with IGT have a substantially increased risk of atherosclerotic disease, but are not at risk of developing the specific microvascular late complications of diabetes. The development of atherosclerosis is fast mainly in those subjects whose IGT is associated with obesity and hyperlipoproteinemia.

6. Gestational diabetes mellitus

The term gestational diabetes mellitus (GDM) denotes diabetes or impaired glucose tolerance that develop in the course of pregnancy. Women with diabetes who became pregnant are not included in this group. This type of diabetes is typically asymptomatic and is demonstrated biochemically on the basis of random testing or an oral glucose tolerance test. Multiple investigations have shown that fetal malformations during pregnancy are not induced only by existence of diabetes, but also by presence of impaired glucose tolerance in a pregnant women. Fetal macrosomia, neonatal hyperglycemia, and an increased perinatal mortality rate are frequent. However, by increased health care and ap-

propriate therapy of pregnant women with diabetes, the origin of the mentioned consequences may be prevented. Approximately half the mothers who develop gestational diabetes revert to normal after delivery. But gestational diabetes may reappear with subsequent pregnancies and there is a higher incidence of NIDDM later in the life (even 5–10 years after delivery). It has been found that the higher degree of impaired glucose tolerance during pregnancy is associated not only with higher risk of the origin of NIDDM, but also with the shortening of the period during which NIDDM develops after delivery. In dependence on an actual state of glucose tolerance (glucose metabolism disorder) and on etiology of its impairment, gestational diabetes has to be reclassified after delivery in some of the types of diabetes or in impaired glucose tolerance. If the glucose tolerance test after delivery normalises, gestational diabetes mellitus is reclassified in previous abnormality of glucose tolerance.

5.9.1.3 Epidemiology of diabetes mellitus

Diabetes mellitus is a relevant medical and social problem in the most countries of the world. In well-developed countries its occurrence has approximately 10 times multiplied during the last fifty years. In Slovakia its prevalence in 1965 was 0.33 % and at present it is about 3.7 %. In the group of population over 65 years of age prevalence of diabetes is even 16 %. In the first years of life diabetes mellitus is rare. However, children are affected between 10–15 years of age most frequently. In our country in the first decade of life in two children per 100,000 inhabitants diabetes mellitus is supposed to be newly diagnosed anually. In each of the following decades diabetes mellitus is doubled. To the age of 40 diabetes occurs in both sexes equally, later it is a little more frequent in women. Probability of the origin of diabetes mellitus is doubled in those individuals whose body weight is 20 % higher than normal.

5.9.1.4 Pathophysiology and clinical features of diabetes mellitus

Characteristic symptoms of clinically manifested diabetes mellitus are polyuria, polydipsia, decrease in body activity, and wieght loss. They occur in most of patients with both basic types of diabetes mellitus. **Rate and intensity of the development of the symptoms** are, however, different. In the patients with type 1 IDDM the onset of these symptoms often occurs over a short period, mostly in the course of several few days or weeks. Diabetic ketoacidosis also originates in a short period, and without administration of exogenous insulin it gradually leads to ketoacidotic coma. This does not mean that the pathological process leading to overt type 1 IDDM is brief or that the symptoms always appear suddenly. As discussed previously, destruction of the B cells usually requires more than a year. In the patients with type 2 NIDDM these characteristic symptoms develop slowly, usually in the course of several months or years. They are milder, weight loss is often absent. The typical patient is overweight. Most patients are asymptomatic, hyperglycemia may be detected on a routine examination. In some cases the presence of type 2 NIDDM in women may be indicated by the origin of Candida vulvovaginitis with a pruritus vulve. In men the presence of NIDDM may be indicated by the origin of Candida balanitis. Neither tendency to ketoacidosis is present. In the decompensated metabolic state they are susceptible to the syndrome of hyperosmolar nonketotic coma. Occasionally the presenting symptom of type 2 NIDDM may be one of the late diabetic complications that leads the physician to test for hyperglycemia or perform a glucose tolerance test. Only rarely the onset of symptoms of type 2 NIDDM is as acute as in type 1 IDDM. When this occurs it is usually the result of the stress of an acute intercurrent illness. In the individuals with the Modan-Reaven syndrome diabetes mellitus is often diagnosed on medical examination initiated by the origin of symptoms of arterial hypertension or ischemic heart disease.

The insulin lack reduces glucose utilization and increases glucagon secretion. Therefore, the metabolic derangements of diabetes are due not only to relative or absolute deficiency of insulin but also to relative or absolute excess of glucagon. A fall in the insulin/glucagon ratio causes increased production of glucose by the liver while the absolute decrease in plasma insulin concentration reduces glucose utilization in peripheral tissues. Insulin deficiency block glucose utilization by insulin-requiring tissues, activates lipolysis in adipose tissue, enhances proteolysis in skeletal muscles, causes hyperglucagonemia, and intensifies glucagon effects on the liver. Glucagon, when unoposed by a normal insulin response, is pri-

marily responsible for the hepatic components of diabetic decompensation, i.e., increased glycogenolysis, gluconeogenesis, and ketogenesis. In other words, insulin deficiency is the cause of augmented delivery to the liver of the substrates for glucose and ketone production (mainly amino acids and free fatty acids, respectively) and glucagon is the switch that activates the hepatic production machinery for glucose and ketones. Therefore, a further decrease in the insulin/glucagon ratio leads to more serious syndromes of diabetic decompensation, i.e., diabetic ketoacidosis and hyperosmolar nonketotic coma.

The first and direct consequence of absolute or relative insulin deficiency is the disorder of glucose metabolism, the most evident biochemical manifestation of which is **hyperglycemia**. The rising of glucose concentration in circulating blood and in extracellular fluid is due to sharply diminished or abolished glucose utilization by insulin-requiring tissues (mainly by muscle, fat, and liver cells). Lipogenesis (conversion of glucose to fatty acids) decreases in adipose tissue. Glycogenolysis (glycogen breakdown) and gluconeogenesis (synthesis of glucose from noncarbohydrate sources, mainly from amino acids) increase in the liver. Glucose is, therefore, to a higher extent released from the liver into circulating blood. Thus, insulin deficiency does not lead only to underutilization of glucose in peripheral tissues but also to hepatic glucose overproduction. The result of both a reduction of transmembrane glucose flow into the cells of insulin-requiring tissues and hepatic glucose overproduction is the origin of a state which is characterized by excess of extracellular glucose and by deficiency of intracellular glucose.

When the level of circulatig glucose exceeds the renal threshold (about 10 mmol/L) a capacity of glucose reabsorption of the least efficient nephrons is exceeded. Non-reabsorbed glocose from these nephrons is excreted by urine, **glycosuria** ensues. If the capacity of glucose reabsorption of all nephrons is exceeded, the whole quantity of filtered glucose exceeding maximum tubule glucose transport (350 mg/min) is lost by urine. As glucose is an osmoticly active substance, the excessive glycosuria induces an osmotic diuresis and thus **polyuria** (usually also nocturia). In more advanced cases the volumes of urine may reach 5–10 litres per day. Due to evident polyuria a profound loss of water and electrolytes may originate and so the danger of **extracellular dehydration** may occur. Affected patient suffers from dryness in mouth and **intense thirst** causing excess drinking (**polydipsia**).

Rather early symptoms of diabetes mellitus are decreasing of physical activity, intensifying of overall **weakness** and fatigue. Simultaneous **weight loss** appears (despite polyphagia which is sometimes present) in the consequence of:

a) Decrease of muscle tissue mass (due to enhanced catabolism of proteins);

b) Decrease of fat tissue mass (due to activation of lipolysis in adipocytes);

c) Increased loss of water and electrolytes.

At the onset of diabetes increased appetite, even **polyphagia** are less common. With grading metabolic derangements of diabetes appetite gradually decreases.

Because insulin deficiency blocks glucose utilization by insulin-requiring tissues, free fatty acids and in less extent amino acids are utilized as a source of energy. Free fatty acids (FFA) become the main energetic source, because the increased protein catabolism cannot be sufficient to cover energetic demands of body tissues. Activation of **lipolysis** in adipose tissue and successively enhanced FFA release from adipocytes results in **hyperlipidemia**. Plasma FFA, triacylglycerols, and rarely cholesterol concentrations are increased. Plasma HDL concentration is usually decreased. The increased lipolysis is marked by an accompanying rise in glycerol release into circulating blood which is then used in the liver as a gluconeogenic substrate.

Increased oxidation of FFA within the liver is associated with increased production of ketone bodies (β-hydroxybutyric acid, acetoacetic acid, and acetone). Glucagon is the hormone that accelerates such FFA oxidation. The rate at which ketone bodies are formed may gradually exceed the rate at which accetoacete and β-hydroxybutyrate are oxidised in extrahepatic tissues, mainly in skeletal muscles, myocardium, and other tissues. Thus increasing ketogenesis leads to **hyperketonemia**. As the renal threshold for ketone bodies is low, their urinary excretion originates rather soon leading to **ketonuria**. Acetone is used for gluconeogenesis although most is excreted in the urine or by the lung. Some ketones may be

esterified to triacylglycerols leading to hypertriacylglycerolemia. Triacylglycerols are to a high extent stored in the hepatocytes (steatosis originates).

Acetoacetic acid and β-hydroxybutiric acid are weak (but fully disociated at physiological pH) and nonvolabile organic acids which cannot be freely excreted by the kidneys, and, therefore, are buffered by plasma bicarbonate. Gradually, plasma bicarbonate concentration decreases, plasma hydrogen ion concentration increases, and systemic **metabolic ketoacidosis** results. From the beginning ketoacidosis is compensated, later, even maximum utilization of compensatory mechanisms cannot prevent the evident decrease of pH in blood and extracellular fluid (decompensated metabolic acidosis). Due to the decrease of pH in extracellular fluid the respiratory centre is intensively stimulated which gives rise to mildly accelerated and evidently deep respirations termed **Kussmaul respiration**. This form of respiration partially compensates the metabolic acidosis by blowing off carbon dioxide (i.e., by respiratory alkalosis). Evident metabolic decompensation (ketoacidosis) is often associated with **vomiting** which further exacerbates the water and salt depletion.

Insulin deficiency also grossly affects protein metabolism, what is manifested by **increased proteolysis**, hyperaminoacidemia, and increased urinary nitrogen loss. In more advanced degree of insulin deficiency protein synthesis is also decreased. The overall increase in proteolysis is probably quantitatively more important than a decrease in protein synthesis in determining the effects of insulin deficiency. The result of increased protein catabolism and decreased proteosynthesis is the origin of evidently negative nitrogen balance and reduction in body proteins (body protein depletion) what is manifested mainly by reduction of skeletal muscle mass. This disorder of protein metabolism contributes to slow healing of wounds. Protein depletion in diabetics decreases also resistance of organism to infection. The increased glucose concentration in extracellular fluid is a convenient environment for microorganisms, what may also contribute to the increased suspectibility of diabetics to bacterial or fungal infections. Glycation of circulating immunoglobulins and glycation of proteins of leucocyte membrane also participate in decreased resistance of diabetics to bacterial infections. Glycation of the leucocyte membrane proteins probably results in inhibition of chemotaxis, diapedesis, phagocytosis, and bactericidal activity of leucocytes.

Extracellular dehydration and increased glucose concentration in extracellular fluid (the both causing hyperosmolarity of extracellular fluid), as well as increased protein breakdown and metabolic acidosis lead to the origin of **intracellular dehydration**, increased intracellular depletion of potassium and to the increased urinary potassium loss. Finally it leads to a severe **total body deficit of potassium**. Extracellular dehydration, which is gradually increased not only by polyuria but also by vomiting and hyperventilation, in insufficiently treated or in nontreated patients may result in hypovolemia, arterial hypotension, and later even in hypovolemic shock.

5.9.1.5 Acute metabolic complications of diabetes mellitus

The patients with diabetes mellitus, mainly those with inadequate therapy, are susceptible to two major acute metabolic complications: hyperglycemic diabetic coma with ketoacidosis and hyperosmolar nonketotic diabetic coma. The former is a complication of IDDM, while the latter usually occurs in the setting of NIDDM. Lactacidotic coma and hypoglycemic coma are less common acute metabolic complications of diabetes. All these four acute metabolic complications of diabetes are a lifethreating clinical states requiring prompt hospitalization and adequate intensive therapy.

A. Hyperglycemic diabetic coma with ketoacidosis

It is the severest degree of complex metabolic disorder induced by absolute or almost absolute insulin deficiency. It originates in insufficiently treated subjects with type 1 IDDM, or rarely in individuals with type 2 NIDDM due to stress load (e.g., intercurrent infection or other illness, trauma, surgery, psychoemotional stress). The increased need of insulin during stress load is conditioned by the increased secretion of stress hormones which are insulin antagonists (cortisol, growth hormone, and adrenalin which is in stress the operative stimulus for glucagon release). Also hypovolemia, which is the consequence of increased diuresis, directly increases the secretion of glucagon, catecholamines, and other hormones of stress and, via decreasing renal blood flow, reduces glucagon degradation by the kidneys. The result is marked hyperglucagonemia and hyperglycemia. Hy-

perosmolality thus becomes a factor and water moves out of cells (intracellular dehydration).

Hyperglycemic diabetic ketotic coma is very relevant, life-threatening clinical state, evoked mainly by hyperosmolality, dehydration and ketoacidosis. Hyperosmolality of extracellular fluid is caused by high concentration of glucose in circulatoing blood and in extracellular fluid (16–41 mmol/L) and by extracellular dehydration. In the consequence of hyperosmolality and toxic effect of ketoacidosis on CNS, decreased consciousness gradually develops in the diabetic patient (somnolence, disorientation, sopor, stupor, and confusion), and later frank coma occurs. Skin and mucous membranes of the patient are dry, skin turgor is decreased, eyballs may be soft (intraocular pressure is usually decreased) and sunken into the sockets, and breathing is typical acidotic (Kussmaul respiration). A high plasma acetone level imparts a fruity odor to the breath. Rigidity of the abdominal wall is a common finding due to increased tonus of abdominal muscles which is secondary to the loss of water and electrolytes from the organism (pseudoperitonitis diabetica). Body temperature is normal or lowered in uncomplicated ketoacidosis by infection, extremities are cold. Pulse is soft and accelerated (thready pulse), arterial blood pressure is decreased. Polyuria is replaced by oliguria even by anuria what leads to prerenal azotemia. With greater degrees of volume depletion a frank oligemic shock may occur. Without early adequate intensive terapy diabetic coma may, therefore, lead to death.

B. Hyperosmolar nonketotic diabetic coma

It is the characteristic acute metabolic complication of type 2 NIDDM, analogous to ketotic diabetic coma in type 1 IDDM. It is also termed a syndrome of glucose hyperosmolarity or a syndrome of extreme hyperglycemia and dehydration. The clinical picture of hyperosmolar nonketotic diabetic coma develops slowlier (during several days even weeks) than ketotic diabetic coma. It is characterized by extreme hyperglycemia (usually above 56 mmol/L), hyperosmolality of extracellular fluid, and volume depletion. Prerenal hyperazotemia and extremely high glycosuria have been found out. As the concentration of ketones in circulating blood is not increased, Kussmaul respiration, a fruity odor of the breath, and ketonuria are absent. Central nervous system dysfunction is presumably the consequence of intracellular dehydration.

This type of diabetic coma may originate mostly in elderly patients with type 2 NIDDM in whom an intercurrent illness increases glucose production secondary to stress hormones and impairs the capacity to ingest fluids (the patients are unable to drink sufficient water to keep up with increased urinary fluid losses evoked by increased osmotic diuresis). The mortality rate in hyperosmolar nonketotic diabetic coma is high (over 50 %).

C. Lactacidotic coma

It is a very rare acute metabolic complication in diabetics. It may originate in the diabetics suffering from evident tissue hypoxia associated with insufficient removing of lactic acid by the liver and kidneys (mainly in diabetics with cardial and respiratory hypoxia and in diabetics-alcoholics). Blood lactic acid concentration is higher than 6–8 mmol/L (the norm is 1.6 mmol/L). Glycemia need not be much increased. Neither ketonemia and ketonuria are present. In some cases, however, concentrations of ketone bodies in blood and urine are slightly increased. Blood bicarbonate concentration and pH are low.

D. Hypoglycemic coma

It can occur in diabetics treated by insulin, for example, when insulin doses are excessive or poorly timed, when meal is missed or food intake is delayed after administration of insulin, when endogenous glucose production is impaired (as after alcohol ingestion), or when glucose utilization is increased (as during excercise). Symptoms of hypoglycemic coma originate when blood glucose concentration falls to about 2.5 mmol/L. Breathing of a patient is normal, dehydration is not present. Urine does not contain ketones or glucose.

5.9.1.6 Late complications of diabetes mellitus

Better diagnostic possibilities, insulin treatment, and increased care of diabetics have prolonged their lives. At the same time, however, this resulted in more frequent occurrence of late (mainly degenerative) complications of diabetes mellitus. Some of them originate only in diabetics, and therefore, are considered as **specific late complications** of diabetes mellitus. They include diabetic microangiopathy and diabetic

neuropathy. Others are **nonspecific late complications** of diabetes mellitus. Nonspecific complications can be also present in the rest of the population (in nondiabetic persons with other diseases), but less frequently than in diabetics. They include mainly atherosclerosis and its sequalae (myocardial infarction, cerebral stroke, and gangrene of low limbs), various infections, and cataract.

In some patients several chronic complications occur simultaneously, in others one late complication is prevailing in the clinical picture of diabetes. Though, the long-term complications accur in both main types of diabetes mellitus, some of them are more common in one type, and others in the other type. Chronic renal failure resulting from diabetic microangiopathy is the most frequent cause of death in type 1 IDDM. The consequences of macroangiopathy occur equally in the both basic types of diabetes mellitus. Diabetic neuropathy is much more frequent in the patients with diabetes type 1. Due to late complications the health of diabetics becomes essentially impaired. Chronic complications cause their more frequent and longer working incapacity, the change of working place, or precocious invalidism of diabetics. Therefore, late complications give rise not only to health problems, but also to social and economic ones.

Patogenetic mechanisms. Most ot the available experimental and clinical evidences suggest that the chronic complications of diabetes mellitus are a consequence ot the metabolic derangements, mainly hyperglycemia. Because due to insulin deficiency in diabetics, glucose is not metabolized by normal way, metabolic processes in which insulin is not necessary for glucose metabolism are activated. Glycosylated proteins, sorbitol, and fructose are produced. These products of aberrant glucose metabolism play an important role in pathogenesis of specific late complications of diabetes mellitus.

Currently following two mechanisms linking hyperglycemia to the complications of long-standing diabetes mellitus are considered important: nonenzymatic glycosylation (glycation) and activation of the polyol pathway.

(a) **Nonenzymatic glycosylation**. When a protein is exposed to a high glucose concentration, nonenzymatic incorporation of glucose can occur, resulting in unregulated glycosylation. Nonenzymatic glycosylation refers to the process by which glucose chemically attaches to the amino group of proteins without the aid of enzymes. Lysine and valine amino groups are the primary sites of glucose addition. The level of glycation of protein is determined by the level of hyperglycemia and by the duration of protein contact with a given level of hyperglycemia. Glusose forms **chemically reversible glycosylation products** with protein (named Schiff bases or aldimines) that may rearrange to form more stable Amadori-type early glycosylation products (ketoamines), which are also chemically reversible. The early glycosylation products with protein undergo a slow series of chemical rearrangements to form **irreversible advanced glycosylation end-products** (AGE), which accumulate over the life-time.

AGE formation occurs on proteins, lipids, and nucleic acids. On proteins, such as collagen, they cause *cross-links between polypeptides* of the collagen molecule and also trap nonglycosylated plasma or interstitial proteins. Glycated collagen is more insoluble and resistant to digestion (degradation by collagenase) than native collagen because of increased intramolecular cross-linking, which decreases its degradation. **In large vessels**, trapping LDL, for example, retards its efflux from the vessel wall and enhance the deposition of cholesterol in the intima, thus accelerating atherogenesis in diabetics. **In small vessels** (especially in capillaries) plasma proteins such as albumin bind to the glycosylated basement membrane, accounting in part for the increased basement membrane thickening characteristic of diabetic microangiopathy. AGE cross-linked proteins are resistant to proteolytic digestion. Thus, cross-linking decreases protein removal while enhancing protein deposition. AGE-induced cross-linking in collagen type IV in basement membrane may also impair the interaction of collagen with other matrix components (proteoglycans, laminin) resulting in structural and functional defects of the basement membranes.

AGEs are found in increased amounts not only in connective tissues, but have been also demonstrated **in cardiac myosin** from diabetic subjects. AGEs also bind to **receptors on many cell types**, such as endothelium, monocytes, macrophages, lymphocytes, and mesangial cells. Binding induces a variety of biologic activities, including: monocyte emigration, release of cytokines and growth factors from macrophages, increased endothelial permeability, in-

creased procoagulant activity, enhanced proliferation of fibroblasts and smooth muscle cells, and enhanced synthesis of extracellular matrix by fibroblasts and smooth muscle cells. All these effects can potentially contribute to chronic diabetic complications.

Proteins in plasma that turn over slowly, such as albumin, LDL, HDL, immunoglobulin G, antitrombin III, red blood cell membrane, hemoglobin, and von Willebrand factor become also significantly glycosylated in diabetics. It has been found that also **lens and myelin proteins** are glycated. Glycosylated proteins react in the presence of metal ions to produce superoxide. The action of oxygen-derived free radicals is potentially enhanced by the reduced levels of antioxidants found in diabetics. Increased activity of the polyol pathway (see below) depletes NADPH, making scavenging of free radicals less efficient. Cytosolic superoxide dismutase has been found decreased in diabetes mellitus.

In comparison to original nonglycosylated proteins, glycated proteins have different physicochemical properties what is manifested by the change of their function. Long-term persistence of metabolic derangement (mainly hyperglycemia) of diabetics, therefore, to a high degree participates in the origin of late complications of diabetes mellitus. Relationship between the severity of late complications and cumulative hyperglycemia (metabolic imbalance of diabetes) is significant from the point of view clinical practice (long-term attendance of correction of the metabolic and hormonal abnormalities of diabetes). It points out the possibility of utilization of long-lasting normoglycemic compensation in diabetics for delay of the onset and for the relief of consequences of late complications of diabetes mellitus. However, there is no evidence that meticulous control of diabetics (correction of the metabolic and hormonal abnormalities) reverses clinically established microangiopathic complications.

(b) **Activation of the polyol patway**. It is a second general mechanism possibly underlying late complications of diabetes mellitus. In some tissues (e.g., nerve, retina, lens, kidney, and endothelial cells, pericytes and mesangial cells) that do not require insulin for glucose transport, hyperglycemia leads to an increase in intracellular glucose content. The excess glucose is metabolized to **sorbitol**, a polyol, under the influence of the enzyme aldose reductase with NADPH as cofactor. Sorbitol can then be oxidized to **fructose** by the enzyme sorbitol dehydrogenase with NAD^+ as coenzyme. The accumulated sorbitol and fructosa lead to increased intracellular osmolarity and influx of water (osmotic cellular swelling) and, eventually, to osmotic cell injury. Intracellular sorbitol accumulation is associated with a decrease in myo-inositol content, resulting in decreased phosphoinositide metabolism, and a subsequent fall of protein kinase C and Na^+/K^+–ATPase activity. This mechanism may be responsible for damage to Schwann cells and to pericytes of retinal capillaries. In the lens, osmotically imbibed water causes swelling and opacity.

Nonenzymatic glycation of proteins and the polyol pathway may not be unrelated mechanisms. It is known that fructose generated in the polyol sequence can nonenzymatically bind to protein (called fructation). It is thus possible that an active polyol pathway contributes significantly to nonenzymatic glycation (fructation) of proteins. The rate of glycation with fructose is seven or eight times faster than with glucose.

Pathophysiology and clinical features of individual forms of specific and nonspecific late complications of diabetes mellitus:

A. Diabetic angiopathy

Diabetic angiopathy is the severest and most common late complication of diabetes mellitus. At present it determines the prognosis in diabetics. This long-term complication considerably increases invalidity and mortality of diabetics. About 75 % of diabetics die of the consequences of cardio-vascular disorders. Diabetic angiopathy is traditionally divided into two forms, which are pathogeneticly and clinically different: diabetic microangiopathy and diabetic macroangiopathy. Diabetic microangiopathy is a specific and macroangiopathy is a nonspecific late complication of diabetes mellitus.

1. Diabetic microangiopathy

Diabetic microangiopathy is a generalized disease of small vessels causing various disorders of microcirculation. Although it is a generalized disease, pathological changes preferentially affect retinal vessels and renal glomeruli. However, they also participate in the disorder of microcirculation in myocardium, brain, and peripheral tissues, but less significantly. Diabetic microangiopathy invalides a great number

of diabetics already in their productive age. In diabetics, incidence of renal failure is 17 times and incidence of blindness is 25 times more frequent, in comparison with nondiabetic population. Severity of microangiopathy and mortality depend mainly on the age at which diabetes originates, on the period of its duration, and on the level of management for the metabolic control of diabetes.

Morphological changes affect arterioles, capillaries, and venules. They are characterized by diffuse thickening of basement membrane, which is caused by a large accumulation of PAS-positive material. Chemically, this substance resembles advanced glycosylation end-products which are the result of glycosylation of structural proteins. However, thickening of basement membranes is also conditioned by the increased binding of glycated plasma proteins (particularly albumins) to its components, and also by the decrease of catabolism of AGE cross-linked proteins of basement membrane.

In **chemical constitution** of basement membrane of capillaries also other abnormalities have been found, e.g., the decrease in content of sialic acid and heparan sulphate (the main proteoglycan). They are negatively charged molecules influencing filtration of negatively charged molecules of plasma, e.g., albumins. As a result of the mentioned changes, permeability (porosity) of basement membrane is increasing. The change of electrical properties of basement membrane may be conditioned also by glycosylation of its own proteins, especially by the origin of glycated collagen type IV. It has been found that synthesis and amount of collagen type IV are increased that results in the decrease of elasticity and distensibility of capillaries. The content of collagen-related components (e.g., glycine, hydroxyproline, and hydroxylysine) is increased. All the mentioned changes in chemical constitution and morphologic features of the basement membrane are the cause of the origin of **the increased permeability** and **decreased reactibility** of the terminal vascular bed.

The disorders of microcirculation in patients with diabetic microangiopathy are caused not only by morphological, but also by functional changes. **The functional changes** concern partly the decreased reactibility and the increased permeability of the terminal vascular bed (already mentioned), and partly some blood components. The best known functional changes of blood components include the increase of the amount of glycosylated hemoglobin (HbA_{1c}), the decrease of deformability and increase of adhesivity of the red cells, and the increase of platelet aggregation.

Glycosylated hemoglobin originates by nonenzymatic addition of glucose to hemoglobin over the life span of the red blood cell. Glucose is attached to α-amino group of the terminal valine of the β-chains of globine. Glycosylation of hemoglobin block the reaction of 2,3-diphosphoglycerate with positively charged residues on the β-chains, causing a slight increase in oxygen affinity. Impaired release of oxygen from hemoglobin results from the combined effect of increased hemoglobin A_{1c} and reduced 2,3-diphosphoglycerate level. In the patients with evidently increased blood level of HbA_{1c} the tissue hypoxia can, therefore, originate in spite of normal pO_2 in arterial blood, what is most evidently manifested in tissues with increased demands for oxygen supply, e.g., mainly in retina.

With regard to a relatively long life span of the red blood cells the amount of glycated hemoglobin is the indicator of the level of metabolic compensation of diabetes minimally during the last 4–6 weeks before the examination. Glycated hemoglobin constitues up to about 5 % of total hemoglobin in normal adults. The diabetics with a very good metabolic compensation exhibit the value of glycated hemoglobin of about 8 %, those with satisfactory metabolic compensation exhibit its value less than 12 %. The higher values are the evidence of insufficient metabolic compensation of diabetes.

It has been reported that glycosylation of the red cell membrane decreases elasticity and fexibility of erythrocytes, and their increased adhesivity has been also observed in poorly controlled diabetes. Normal red blood cells pass easily through capillaries with luminal diameters smaller than their own because they are deformable. The loss of erythrocyte deformability deteriorates their pass through capillaries and can cause sludging of blood and contribute to retinal and renal ischemia in diabetics. Overglycosylation of von Willebrand factor could contribute to the increased platelet aggregation what makes conditions for the origin of multiple microthrombi in microcirculation. The decreased activity of fibrinolytic system in diabetics also contributes to their origin, probably as a consequence of the decreased release of plasminogen activator from endothelial cells. These changes

also contribute to tissue ischemia in diabetics with insufficient metabolic control.

The accumulation of sorbitol in endothelial cells of capillaries, in pericytes, and mesangial cells causes their osmotic swelling. The successive obliteration of small blood vessels lumen contributes to the tissue hypoxia. The small blood vessel closure is most characteristic in the retina. Later, injury even destruction of these cells can originate what leads to the formation of capillary microaneurysms and to the increase of permeability of capillaries. It is manifested by their increased readiness to produce exudates and later also hemorrhages into adjacent interstitium. In the retina after vascular occlusion formation of new blood vessels (neovascularization) appears. Retinal neovascularization is the result of the effect of angiogenetic factor (a local capillary growth factor) produced by hypoxic retina. The new vessels and microaneurysms are fragile, and, therefore, hemorrhages are more frequent and extensive. These changes and contraction of fibrous proliferations are the principal mechanisms leading to a higher probability of retinal detachment and subsequent visual loss (blindness).

The best known manifestations of diabetic microangiopathy are diabetic nephropathy and diabetic retinopathy. The microvascular kindney disease is characterized by thickening of the capillary basement membrane and increased deposition of extracellular matrix components, while formation of microaneurysms, obliteration and loss of microvessels with subsequent neovascularisation are predominat in the retina of diabetics.

a) **Diabetic nephropathy**

Diabetic nephropathy (nodular Kimmelstiel-Wilson glomerulosclerosis) is one of the severe chronic complications of diabetes mellitus. In about 30 % of the patients with type 1 IDDM it is clinically manifested after 15–20 years of the duration of diabetes. Its incidence in the patients with type 2 NIDDM is evidently lower than in those with type 1. The following five stages of development of diabetic nephropathy are distinguished:

- **The first stage** is characterized by hyperfunction and hypertrophy of glomeruli which are probably the result of chronic renal hyperperfusion (increased flow and pressure). One important factor in the induction of hyperperfusion may be renal hypoxia, presumably the consequence of interactions among increased levels of glycosylated hemoglobin, decreased levels of red blood cell 2,3-diphosphoglycerate, increased blood viscosity, and diminished red blood cell deformability (the hemodynamic hypothesis). Hyperperfusion leads to shear stress and tangential pressure on the microvascular wall. This results, with the interaction of advanced glycosylation of proteins, in changes of basement membrane and in the increased production of extravascular matrix proteins (by the microvascular endothelium) that contribute to the expansion of mesangium. Glomerular filtration rate is increased (*supernormal function*), the kidneys are usually enlarged. Low microalbuminuria, which is detectable only by special techniques, may appear, however, only during long standing insufficient metabolic compensation of diabetes. It is termed *transient microalbuminuria*. Blood pressure is not increased.

- **The second stage** is characterized by thickening of glomerular basement membrane and by expansion of the mesangium (a diffuse increase in the mesangial matrix between the glomerular capillaries). Microalbuminuria (30–300 mg/day) is reversibly increasing only during insufficient metabolic compensation or due to increased physical activity (usually after a provocative exercise test). Glomerular filtration rate is normal. Blood pressure is also normal, but in elderly it may be slightly increased.

- **The third stage** is denoted as incipient diabetic nephropathy. Microalbuminuria is permanently increased (later the *high microalbuminuria* is present). Glomerular filtration rate is normal, later, however, it may be slightly decreased. Arterial blood pressure is gradually increasing, and during increased physical activity blood pressure is increased inadequately to the degree of the physical load.

- **The fourth stage** is denoted as manifest diabetic nephropathy. At the onset of this stage intermittent nonselective proteinuria is present. Later, the persistent nonselective proteinuria (*macroproteinuria*) originates (proteinuric period). Proteinuria is greater than 550 mg/day. Arterial hypertension is present. Progression of

diabetic nephropathy is accelerated by arterial hypertension. A progressive loss of glomeruli appears. Since the reduction in the number of functioning nephrones is increasing, the glomerular filtration rate is gradually decreasing and serum creatinine concentration increases (the beginning of an azotemic period).

- **The fifth stage** is denoted as a terminal renal failure. It is characterized by a massive reduction in the number of functioning glomeruli (nephrones) what is clinically manifested by the symptoms of uremia (uremic period). The kidneys are reduced in size. Long-standing arterial hypertension together with hypervolemia may lead to heart failure. The duration of interval from the onset of persistent proteinuria to the origin of overt renal failure varies in individual diabetics. Its average length is about 10 years.

b) **Diabetic retinopathy**

It is characterized by progressive pathological changes of retinal vessels leading to the damage of retina what is manifested by gradual impairment of vision which may result in blindness. Three following forms of diabetic retinopathy are distinguished: nonproliferative (background; simple), preproliferative, and proliferative diabetic retinopathy. They probably represent different stages of the same pathophysiological process.

- **Nonproliferative diabetic retinopathy** is characterized by dilatation, constriction, and tortuosity of vessels; hard exudates (they are rich in lipids and proteins which leakage from hyperpermeable capillaries); arteriovenous shunts; microaneurysms; and by causal small inner retinal hemorrhages. Macular edema is not present.

- **Preproliferative diabetic retinopathy** is characterized by occurrence of the increased number of hard exudate spots, capillary microaneurysms, and dot-shaped inner retinal hemorrhages. It is also characterized by cotton-wool spots (they are patches of retinal edema) which represent microinfarctions, and by dot-blot, linear, or flame-shaped preretinal hemorrhages. Hard exudates are arranged in horseshoe or circular fashion around the central and lateral part of the macula. Macular edema is common. Therefore, this stage is also denoted as **diabetic maculopathy**. Maculopathy can lead to serious disturbances or even to loss of vision.

- **Proliferative diabetic retinopathy** is characterized by new vessel formation, proliferation of connective tissue and scarring, vitreal hemorrhage, and retinal detachment. New vessels may be found anywhere in the retina, but often occur on or near the optic disc. They lie on the retinal surface or extend to the vitreous. This leads to fibrosis and scarring. A bleed into vitreous causes partial or complete loss of vision in the affected eye. Fibrous proliferation gives rise to traction bands that contract with the course of time, producing retinal detachment, which usually also leads to blindness.

Diabetic retinopathy need not be developing in the both eyes simultaneously. Several factors influence its origin and course. The frequency of diabetic retinopathy appears to vary with the age of onset as well as the duration of the diabetes. The younger the individual at the onset of diabetes is, the later retinopathy originates. In older patients it develops earlier. The occurrence of retinopathy increases with the duration of diabetes. If diabetes persists more than 15 years every patient has at least incipient structural abnormalities in the retina. An adequate metabolic compensation of diabetes delays the origin of retinopathy, but it cannot absolutely prevent its origin. If the diffuse retinal ischemia or the incipient proliferative retinopathy originates neither a perfect metabolic compensation is sufficient to prevent further progression of proliferative retinopathy. Blindness is reported to occur within 5 years after the onset of proliferative retinopathy. The course of diabetic retinopathy is unfavourably influenced by high arterial blood pressure and smoking.

2. **Diabetic macroangiopathy**

Diabetes mellitus is a risk factor for the development of atherosclerosis, particularly in women. Diabetic macroangiopathy is the disease of middle and large arteries, mainly coronary, cerebral and lower extremity arteries, and aorta. It is the severest nonspecific complication of diabetes mellitus. Diabetic atherogenesis neither morphologically nor by its distribution differs from atherosclerosis in nondiabetics. However, atherosclerosis in diabetics occurs more extensively and earlier than in the general

population, it is twice more frequent, its course is accelerated and it is more common in women than in men. Diabetic atherosclerotic lesions faster undergo to changes leading to complicated atherosclerotic lesions, that is, ulceration, calcification, hemorrhage, and superimposed tromboses. Therefore, its prognosis is worse and mortality rate is evidently higher than in persons without diabetes.

The enhancing susceptibility of diabetics to atherosclerosis is due to several factors. The significant place is occupied by hyperlipidemia, especially increased concentration of LDLs (mainly oxidized and glycosylated) in poorly metabolic controlled diabetic patients. Plasma HDL level (HDLs protect the arterial wall against the development of atherosclerosis) is reduced, therefore, a high LDL/HDL ratio also favours atherogenesis. The increased glycosylation of the LDL apoprotein reduces its cellular recognition. Glycated LDL is not recognised by the normal LDL receptor, and its plasma half-life is increased. Uptake and degradation of LDLs are reduced, therefore, their plasma concentration is high. The magnitude of reduction in glycosylated LDL uptake and degradation is related to the degree of their glycosylation. Both processes of LDL modification, i.e., oxidation and glycosylation, contribute to the acceleration of atherosclerosis in diabetic patients. HDL in diabetics is also glycated. Glycated HDL unlike glycated LDL, has an accelerated catabolism what contributes to the reduced plasma HDL concentration. It is also possible that glycosylation of HDL may be responsible for the ineffective removal of cholesterol from cholesterol-overloaded cells. Both these effects concerning of HDL enhance atherogenesis.

Other factors of potential importance for accelerated atherosclerosis in diabetes mellitus are: alteration of macrovascular endothelial function, reduced synthesis and release of prostacyclin, increased platelet adhesiveness and aggregation, enhanced tromboxane A_2 synthesis and release, and decreased fibrinolytic activity. Most patients with type 2 NIDDM tend to be obese and hypertensive, so that other contributing influences are present.

A clinical consequence of diabetic macroangiopathy is the origin of ischemic heart disease, cerebral stroke, or diabetic foot syndrome. However, atherosclerosis in diabetics may also induce aneurysmal dilatation, seen most often in the aorta, with the grave potential of rupture.

a) **Ischemic heart disease**
It is one of the most common causes of death of diabetics. Myocardial infarction is 3–5 times as common in diabetics than in non-diabetic subjects. Myocardial infarction in diabetics is characterized by certain peculiarities. Silent myocardial infarction is thought to occur with increased frequency in diabetics, what is probably due to the presence of diabetic neuropathy. Myocardial infarction is often associated with congestive heart failure which is usually severer than in nondiabetics with myocardial infarction. Sometimes congestive heart failure occurs also in the diabetics with the absence of coronary atherosclerosis. The common complication of myocardial infarction in diabetics is the origin of cardiogenic shock. Mortality rate of the diabetics with myocardial infarction is 3 times higher than in nondiabetics, extremely high is in women. Unfavourable prognosis of myocardial infarction in diabetics suggests that in diabetic patients along with coronary atherosclerosis also the other pathological changes participate in pathogenesis of myocardial damage. Microangiopathy has a significant role. Interstitial and perivascular fibrosis has been also observed, associated with PAS-positive deposits (glycated proteins), what negatively influences diastolic properties of myocardium, i.e., decreases diastolic compliance (distensibility) what restricts diastolic filling of ventricles. Changes in cardiac myosin and an intracellular Ca^{2+} overload have been observed in diabetes mellitus. With regard to the fact, that myocardial disease in diabetics is characterized by certain histological, biochemical, functional, pathogenetic, and clinical peculiarities, it is denoted as **diabetic cardiomyopathy** by some authors. However, increasingly diabetic cardiomyopathy is being accepted as a clinical reality, although the pathogenesis of this putative entity is varied and multifactorial.

b) **Cerebral stroke**
Cerebrovascular accidents in diabetics are also characterized by some peculiarities. The strokes are prevailingly due to ischemic cerebral infarction. In spite of the fact that diabetes mellitus is frequently associated with arterial hypertension, the strokes due to brain hemorrhage in diabetics are rather rare. Not only atherosclero-

sis of larger intracranial and extracranial arteries, but also pathological changes of small cerebral vessels (microangiopathy) and multiple microtrombi participate in the pathogenesis of severe ischemic focal changes in the brain of diabetics. Mortality rate in diabetics with cerebral stroke is three times higher than in nondiabetic subjects.

c) **Diabetic foot syndrome**
The diabetic foot syndrome is the consequence of coexisting vascular insufficiency and diabetic neuropathy. The vascular insufficiency involves large vessels of the lower limbs (atherosclerosis), and small vessels (diabetic microangiopathy). There is also an extensive arteriovenous shunting at the precapillary level. The neuropathy is predominantly sensory and is characterized by a diminution or even absence of pain. Diabetic dermopathy (mainly severe trophic changes located on feet or over the anterior tibial surface) and diabetic sensory neuropathy cause that also minimal, casual, and often unknown wounds are dangerous for a diabetic. They result in the origin of the skin lesions, even in the development of diabetic ulcers, the infection of which is common (often with multiple microorganisms). The ulcer may be initiated by illfitting shoes or by other forms of trivial trauma. If the capacity to sweat is lost because of diabetic autonomic neuropathy, the resulting dryness of the skin may lead to spontaneous cracking, supperficial inflammations or to the development of ulcers as well. The final consequence of these changes may be the origin of **the gangrene**, which is 15 times more common in diabetics than in nondiabetics. Moist gangrene is typical for diabetics while dry gangrene for nondiabetics with atherosclerosis of lower limb arteries. Amputation of a foot for gangrene is 50 times more common in diabetics than in nondiabetic subjects.

The clinical picture of diabetic foot syndrome includes also night muscle spasms, severe night burning pain, and diabetic osteopathy. Bone demineralization and later even deformation of small joints of the metatarsophalangeal region originate (Charcot joints). These changes are denoted as **neuropathic osteoarthropathy**. Autonomic neuropathy (functional sympathectomy) causing extensive opening of arteriovenous shunts plays probably an important role in its pathogenesis. Successive abnormal blood flow distribution which is associated with increased blood pressure in veins is probably the cause of the origin of osteolysis in the metatarsophalangeal region.

B. Diabetic neuropathy

Diabetic neuropathy is a very frequent specific late complication of diabetes mellitus. It occurs especially in the patients with type 1 IDDM affecting sensory, motor, and autonomic nerves. The prevalence of diabetic neuropathy parallels the duration and severity of hyperglycemia and it ultimately affects approximately 50 % of patients with long-lasting diabetes mellitus. It is rare before the 5th year of diabetes. There are three recognized forms of diabetic neuropathy: symmetrical peripheral polyneuropathy, mononeuropathy, and autonomic neuropathy.

Pathogenesis. Diabetic neuropathy is now generally considered to be a secondary consequence of insulin deficiency and/or hyperglycemia. Its pathophysiological and clinical expressions are thought to be influenced by various additional independent genetic and environmental factors. There are following three major hypotheses trying to explain the pathogenesis of diabetic neuropathy: vascular hypothesis, metabolic hypothesis, and axonal hypothesis. These major hypotheses, however, are clearly not independent of one another but are linked at one or more levels.

The vascular hypothesis postulates diabetic microangiopathy of the vasa nervorum as the prime cause. This seems likely in isolated mononeuropathy, but microvascular disease is also considered as a contributor to other forms of diabetic neuropathy.

The metabolic hypothesis is the best known and best-explored of all three mentioned hypotheses. The metabolic abnormalities are generally acknowledged as a primary cause of diabetic symmetrical peripheral polyneuropathy and diabetic autonomic neuropathy. Hyperglycemia leads to increased glucose concentration in Schwann cells. Due to activation of the polyol pathway formation of sorbitol and fructose in Schwann cells increases. Sorbitol, which diffuses poorly across cell membrane, accumulates intracellularly. **Osmotic swelling of Schwann cells**, secondary to intracellular sorbitol and fructose accumulation, has been considered as a cause of both functional and structural alterations in diabetic nerve. Metabolic

abnormalities in diabetic nerve, however, involve also decrease of myo-inositol content and decrease (Na^+, K^+)–ATPaze activity which are also initiated by hyperglycemia. Hyperglycemia lowers **the myo-inositol content** of Schwann cells and axons, probably by increasing the sorbitol-fructose content of the nerve via the polyol pathway. The decreased myo-inositol concentration in Schwann cells and axons may lead to the diminution of phosphoinositide metabolism, protein kinase C activity, and **(Na^+, K^+)–ATPaze activity**. These metabolic disorders lead to abnormal energy metabolism, subsequently to nerve dysfunction and finally to structural damage (the axonal demyelination or degeneration). The role of **glycosylated myelin** in the pathogenesis of diabetic neuropathy is not exactly known. Some authors suppose that glycated protein of myelin could be a signal for activation of macrophages. Activated tissue macrophages remove and degrade glycated myelin and by these processes may support segmental demyelination.

The axonal hypothesis supposes early functional changes, such as slow axonal transport, followed by structural degeneration. Impaired anterograde transport would produce defects in the most distal portions of axons, and altered retrograde transport might likely impair neurotrophic function. The mechanisms responsible for transport defects and the exact contribution of altered axonal transport to the pathogenesis of diabetic neuropathy are not well understood. However, recent studies indicate that some component of nerve (Na^+, K^+)–ATPaze is indeed carried by both antegrade and retrograde transport, rising the possibility that alterations in axonal transport, some of which are related to altered sorbitol and myo-inositol metabolism, may contribute to the derangement of (Na^+, K^+)–ATPaze in diabetic nerve.

Diabetic neuropathy can be classified into two distinct stages: subclinical neuropathy and overt or clinical neuropathy. The latter consists of the presence of symptoms and/or neurological deficits consistent with one or more of the clinical syndromes of diabetic neuropathy, while the former consists of demonstrable evidence of peripheral nerve dysfunction (e.g., slowed nerve conduction velocity or elevated sensory perception thresholds, and etc.) in the absence of clinical signs and/or symptoms of overt diabetic neuropathy. The earliest histological change is segmental demyelination, due to damage of Schwann cells. In the early stages axons are preserved, implying prospects of recovery, but at a latter stage irreversible axonal degeneration develops.

The following three varieties of diabetic neuropathy may occur:

1. **Diabetic symmetrical peripheral polyneuropathy**
   It is the most commonly recognized form of diabetic neuropathy prevailingly affecting the both lower limbs simultaneously. Its most common manifestation is symmetrical sensory loss in the distal lower extremities (distal symmetrical sensory neuropathy). Motor deficits and upper extremity involvement are less common, although deep tendon reflexes, especially the Achilles tendon reflex, may often be diminished or absent.

   At the beginning it is manifested by paresthesias (mainly tingling) and dysesthesias persisting several months or even years. Later, hyperesthesias (burning), pain (it may be deep-seated and severe) or lancinating originate which are worse at night. Lancinating may become extremely severe, and suicides are known to have occured because of it. This severe pain, however, is not permanent and will subside spontaneously within months to years as the involved neurons became destroyed.

   Sensory findings appear first in the most distal portions of the extremities, progress proximally in a "stocking-glove" distribution. The signs, symptoms, and neurological deficits of distal symmetric polyneuropathy vary depending on the classes of nerve fibers that are involved. A loss of large sensory and motor fibers diminishes light touch and proprioception (vibratory perception) and produces weakness of intrinsic muscles of the hands and feet, while a loss of small fibers diminishes pain and temperature perception, resulting in repeated injury due to an ill-fitting shoe, a hot water bottle, or embedded foreign bodies leading to ulceration, especially foot ulceration.

2. **Mononeuropathy**
   Diabetic mononeuropathy is a relatively uncommon late complication. Motor disorders (paresis) usually affects only single peripheral nerve, e.g., ulnar, median, proneus, femoral, or sciatic nerve (diabetic motor neuropathy; diabetic

asymmetrical neuropathy). Several peripheral nerves may be rarely affected at the same time (**mononeuropathy multiplex**).

Cranial nerve lesions (isolated or multiple) are more common in diabetics. Especially the third, fourth, sixth, or seventh cranial nerves are affected (**cranial diabetic mononeuropathy**).

Affection of the nerve roots (radiculopathy) is rare. In older patients with diabetes mellitus after 15–20 years of its duration **diabetic amyotrophy** may originate. This syndrome is characterized by weakness, painful wasting, and atrophy of muscles of the limbs, usually asymmetrical. The disorder is considered to be a severe manifestation of microangiopathy of peripheral nerves. Diabetic amyotrophy is usually associated with periods of poor glycemic control.

3. **Autonomic neuropathy**
Diabetic autonomic neuropathy affects the sympathetic and parasympathetic nervous systems and may be presented in a variety of ways.

Cardiovascular autonomic neuropathy usually initially involves cardiac parasympathetic nerves, producing asymptomatic absence of the normal sleep bradycardia, presence of tachycardia at rest, or diminished variation of the pulse rate with respiration (reduced sinus arrhythmia). More advanced sympathetic cardiac denervation (resembling a transplanted heart) is manifested by diminishing exercise tolerance, Q–T interval prolongation, and hypersensitizing the heart to circulating catecholamines, predisposing to tachyarrhythmias and sudden death. Cardiovascular reflexes, such as the Valsalva manoeuvre, are impaired. Cardiovascular autonomic neuropathy is also responsible for the high frequency of painless myocardial infarctions in patients with long-lasting diabetes. Baroreceptor insufficiency, reduction in catecholamine secretion (loss of sympathetic tone to peripheral arterioles), and inability to increase the pulse rate combine to cause orthostatic hypotension.

Gastrointestinal autonomic neuropathy can be manifested by esophageal dysmotility associated with difficulty in swallowing (dysphagia) and reflux, decreased vagally-mediated gastric acid secretion, and delayed gastric emptying, produce anorexia, nausea, and vomiting. Diabetic enteropathy encompasses the clinical symptom of diabetic constipation, which is usually intermittent and alternate with diabetic diarrhea, and fecal incontinence. Diarrhea often occurs at night accompanied by urgency and incontinence. Fecal incontinence reflects impaired sensation of rectal distension and sphincter dysfunction. Dysfunction of gallbladder and biliary tract may also appear.

Genitourinary autonomic neuropathy is manifested by diabetic cystopathy, neuropathic erectile impotence, and retrograde ejaculation. All these changes result from loss of coordination of the autonomic innervation of the genitourinary tract. Autonomic neuropathy of the bladder begins with the selective involvement of autonomic sensory afferents resulting in diminished sensation of bladder fullness and a resultant reduction in urinary frequency. With progressive efferent involvement, urination is incomplete, leading to poor stream, dribling and overflow incontinence, predisposing to urinary infection. Impotence ultimately occurs in up to 75 % of men with prolonged diabetes mellitus. It may be due to either diabetic neuropathy and vascular disease. The syndrome is particularly disturbing because the libido is intact.

Diabetic autonomic sudomotor dysfunction produces an asymptomatic distal anhidrosis (of the lower extremities). This diminished thermoregulatory reserve is usually associated with compensatory central hyperhidrosis (of the upper half of the body).

C. Other complications of diabetes mellitus

Infections in persons with diabetes mellitus, mainly if poorly controlled, occur more frequently than in normal subjects, and they tend to be severer. In diabetics **infections of urinary tract**, mainly chronic interstitial nephritis, are rather common. Chronic interstitial nephritis is 5 times more frequent in diabetics than in nondiabetics and is most commonly presented as a chronic pyelonephritis with casual exacerbations of acute pyelonephritis. Pyelonephritis in the patients with long-lasting poorly controlled diabetes can lead to acute necrotizing papillitis if not treated promptly.

Bacterial **infections of the skin**, mainly impetigo or furunculosis (pyoderma), are frequent. **Mucocutaneous candidiasis**, mainly epidermophytosis, Candida vulvovaginitis associated with vulvar pruritus, and Candida balanitis, are typical for diabetes mellitus. Mucocutaneous candidiasis and cutaneous pruritus in some cases may be the first symptoms of till then unknown diabetes mellitus.

Rather frequent nonspecific complication of diabetes mellitus is **parodontosis** which may originate already at a younger age period. It is sometimes the first symptom of diabetes. Bacterial stomatitis or fungal **infection of the mouth** may also occur. Malignant **external otitis**, usually due to Pseudomonas aeruginosa, tend to occur in older diabetics. Staphylococcal, pneumococcal, or Gram-negative **pneumonia** is also rather frequent in diabetics. The origin of **tuberculosis** in diabetics is evidently frequent. Intercurrent infections in diabetics tend to have severer course.

Senile cataracts develop some 10–15 years earlier in diabetic patients than in the remainder of the population. **Juvenile cataracts**, so-called "snowflake" cataracts are much less common and occur more often in type 1 IDDM. These are diffuse, rapidly progressive cataracts associated with very poorly controlled diabetes. Sorbitol accumulation, as well as aggregation and precipitation of crystalline glycated proteins of the lens, participate in the pathogenesis of cataracts.

5.9.2 Tumors of the endocrine pancreas

Pancreatic endocrine tumors may be benign or malignant. They may occur as a solitary adenoma or as multiple adenomas. They are usually composed of one type of Langerhans islet cells, sometimes, however, heterogenous population (several different types) of endocrine cells may occur in endocrine tumors of the pancreas (mixed pancreatic endocrine tumors). The predominant type of cell and the predominant hormone produced define the clinical syndrome of the multiple hormone-secreting pancreatic tumor. Rarely one type of tumor cells can produce several kinds of hormones simultaneously (a pluripotent capacity allows these cells to produce any polypeptide). It is the evidence that the cells of the pancreatic islets are derived from functionally multipotent cells of embryonal neuroectoderm and become a part of the diffuse neuroendocrine system. On the other hand, 20–40 % of islet cell tumors are nonfunctioning; that is they do not release hormones into the circulation despite the presence of functioning endocrine cells on histological examination.

The best known tumors of the cells of the pancreatic islets include: insulinoma, glucagonoma, gastrinoma, and somatostatinoma. Pancreatic endocrine tumors can also be a part of the syndrome multiple endocrine neoplasia type 1 (MEN type 1). Islet cell carcinomas are rare and can secrete hormones in addition to insulin, including ACTH, MSH, hCG, glucagon, somatostatin pancreatic polypeptide, gastrin, VIP, and serotonin.

5.9.2.1 Insulinoma

Insulinomas are the B cell tumors. Tey are the second most common functioning islet cell tumors. The hallmark of insulinoma is the development of symptomatic hypoglycemia from unregulated insulin hypersecretion leading to the origin of **endogenous hyperinsulinism**.

Insulinomas arise most frequently in the fifth to seventh decades, although cases have been reported at all ages. It is very rare in children to 10th year of life. About 90 % of the patients is older than 30 years. The majority of infants and children, and some adults do not have discrete tumor. Hyperinsulinemia in these cases has been attributed to the B cell hyperplasia termed **nesidioblastosis**.

Single, benign insulinoma is present in 80–85 % of patients with excessive secretion of insulin. About 10 % of cases are multiple adenomas or microadenomas. An additional 5–10 % of insulinomas are malignant, with spread to the local lymph nodes and the liver. The metastases may be the cause of recidivation of hypoglycemia even after the surgical removal of primary pancreatic insulinoma. Insulinoma may be situated in any part of pancreas, most often in the body or tail of the gland. About 0.5–1 % of insulinomas occur ectopicly; ectopic insulinomas have been found in the areas of pancreatic heterotopia, including the wall of the duodenum, the porta hepatis, superior mesenteric artery, and the vicinity of the pancreas. Insulinomas may be also associated with MEN type 1, and such tumors are more likely to be multifocal.

Insulin secretion from insulinoma is usually peri-

odical, rarely continual. According to the way of insulin secretion from insulinoma and according to the origin of subsequent hyperinsulinemia either paroxysmal or permanet hypoglycemia originates. Sudden fall of glycemia appears mainly due to prolonged fasting (usually in the late morning or afternoon) or after increased physical activity.

The most consistent insulin secretory abnormality in patients with an insulinoma is a failure of the normal decrease in insulin secretion as the plasma glucose level declines in the postabsorptive state. This failure results in hyperinsulinism. Hyperinsulinism in the portal and peripheral circulations results in low rates of glucose production with high rates of glucose utilization that are not high in the absolute but are inappropriately high relative to the plasma glucose concentration. Thus the plasma glucose concentration declines progressively in the postabsorptive state. Hypoglycemia induces dysfunction of the CNS and the secondary release of catecholamines.

Symptoms of hypoglycemia in patients with insulinoma fall into two main categories:

- Symptoms induced by inadequate supply of the CNS by glucose termed neuroglycopenic symptoms, or neuroglycopenia;
- Symptoms induced by activation of sympathoadrenal system, mainly by an excessive secretion of adrenaline.

a) **Symptoms of acute neuroglycopenia** are the result of a sudden decline of ATP in cells of the CNS. These manifestations range from subtle impairment of mentation to coma (if glycemia falls under 2.5 mmol/L) and death. Between these extremes a variety of other expressions can occur, including visual symptoms (diplopia or blurred vision), weakness, lethargy, somnolence, confusion, behavioral changes, impaired performance of routine tasks, vertigo, paresthesias, incoordination, slurred speech, hunger, hemiparesis, and clonic convulsions. Convulsions are more frequent in children than in adults. Rarely, chronic hypoglycemia results in demention or psychosis.

b) **Symptoms of activation of sympathoadrenal system** (rapid adrenaline release) include sweating, paleness, anxiety, behavioral irritability, tremulousness, restlessness, tachycardia, cardiac arrhythmias, palpitations, and headache.

5.9.2.2 Glucagonoma

Glucagonoma is the A cell tumor of the islets of Langerhans causing overproduction of glucagon. It occurs rarely. The two thirds of glucagonomas are malignant and have metastasized to the liver, regional lymph nodes, and bones. They are more frequent in women, especially after menopause. Glucagonomas are characteristically single, large, and slow-growing. Glucagonomas have been also reported in association with MEN type 1.

Pathophysiology and clinical features. The glycogenolytic and gluconeogenic actions of glucagon result in mild hyperglycemia. The levels of hyperglycemia and plasma glucagon are poorly correlated, possibly because of down-regulation of glucagon receptors but more likely because of the ability of intact the B cells to counteract the hyperglycemic effect of glucagon by releasing insulin.

The clinical picture of glucagonoma is characterized by impaired glucose tolerance or by **diabetes mellitus**. The diabetes is usually mild or asymptomatic. Ketoacidosis has not been reported.

The disorder of glycoregulation is associated with a characteristic skin rash, **necrolytic migratory erythema**, which is frequently the major manifestation of the glucagonoma. Erythematous lesions are raised (with a moving edge), scaly, sometimes bullous, sometimes psoriatic, and ultimately encrusted. They are located primarily on the face, abdomen, buttocks, perineum, and thighs. After resolution, the regions of the acute eruption usually remain indurated and hyperpigmented. The rash disappears promptly when the plasma glucagon level (hyperglucagonemia) returns to normal after the complete tumor resection.

Glucagon excess causes increased hepatic conversion of amino acid nitrogen to urea nitrogen, resulting in decreased blood amino acid concentration (**hypoaminoacidemia**). Enhanced protein catabolism is associated with **weight loss**. In patients with glucagonoma **other manifestations** are also present. They include: glossitis, stomatitis, angular cheilitis, diarrhea, venous thrombosis, anemia, depressions, dystrophic nails, hair thinning, hypocholesterolemia, hypoproteinemia, and hyperinsulinemia.

5.9.2.3 Gastrinoma

Pancreatic gastrinoma (**Zollinger-Ellison syndrome**) is a tumor arising from the G cells of pancreatic islet and generating high serum gastrin levels (hypergastrinemia), leading to hypersecretion of gastric acid and consequent peptic ulcer. Therefore, it is also denoted as ulcerogenic tumor of pancreas. Gastrinomas are the most common of the hormone-secreting tumors of the pancreatic islets. They are usually small and multiple. The tumors are most common in the head of the pancreas. Gastrinomas, like most other islet cell tumors, are generally slow-growing. Approximately 60 % of gastrinomas are malignant with metastases in the lymph nodes and the liver, and less frequently in bones. Between one-fourth and one-half of gastrinomas occur in association with the MEN 1, an autosomal dominant disorder with a high degree of penetrance and great variability in expressivity. Gastrinomas in non-MEN 1 patients are considered to be usually sporadic. Multiple gastrinomas are usually present in patients with MEN 1 and are usually smaller than sporadic gastrinomas.

Approximately 80 % of gastrin-secreting tumors arise in pancreatic islets, including nearly all those associated with MEN type 1. Another 10–15 % arise from G cells in the duodenum (duodenal gastrinoma), and the remainder are located in other sites, such as the hilum of the spleen and rarely in the stomach. The Zollinger-Ellison syndrome may occur most commonly between the ages 30 and 60.

In patients with gastrinoma, *gastric acid hypersecretion* is caused by excessive production of gastrin by tumor cells. Due to high rate of gastric acid secretion **peptic ulceration** of the gastrointestinal tract develops in 90–95 % of patients with gastrinoma. The anatomic site of the peptic ulcer in patients with gastrinoma is similar, but not identical, to that of patients with common type of peptic ulcer. About 75 % of gastrinoma patients have ulcers in the first portion of the duodenum or in the stomach. These ulcers are usually single but may be multiple. When multiple ulcers occur, they are frequently located in the remainder of the duodenum or even the jejunum. Especially early in the course of the disease, symptoms are usually similar to those of patients with typical peptic ulcer. In gastrinoma patients, however, ulcer symptoms may be more fulminant, progressive, and persistent.

Clinical features other than peptic ulcer include diarrhea and steatorrhea. **Diarrhea** occurs in about 40 % of patients and may precede peptic ulcer symptoms. The major cause of diarrhea is the large amount of hydrochloric acid entering the duodenum. The excessive acid has been shown to reduce also the pH of the content of the jejunum. **Steatorrhea**, which is less common than diarrhea, results from inactivation of pancreatic lipase by large concentrations of hydrochloric acid in the proximal small intestine and from decrease in luminal bile acids. The decrease in intraluminal bile acid concentration is caused by precipitation of the major bile acids at low pH. This leads to impaired micelle formation, which, in turn, reduces intestinal absorption of fatty acids and monoglycerides.

5.9.2.4 Somatostatinoma

Pancreatic somatostatinoma is the D cell tumor of the islets of Langerhans. It is a somatostatin-secreting tumor, therefore, plasma somatostatin concentrations are high. Somatostatinoma is usually a single and a large tumor. It is often malignant tumor which metastasizes to the liver. Somatostatinomas have been reported in association with MEN 1 only rarely.

The classic triad of somatostatinoma comprises diabetes mellitus, steatorrhea, and cholelithiasis. The diabetes is usually mild. In some patients with somatostatinoma only impaired glucose tolerance may be present. Other features include indigestion (dyspepsia), hypochlorhydria, diarrhea, and weight loss. All these symptoms derive from the widespred inhibitory actions of somatostatin, including inhibition of insulin and glucagon release, pancreatic enzyme and bicarbonate secretion, gallbladder motility, and gastrointestinal function, respectively.

5.9.2.5 Multiple endocrine neoplasia, type 1

The multiple endocrine neoplasia (MEN) syndromes are classified into two broad categories, MEN type 1 (MEN 1) and MEN type 2 (MEN 2). The MEN 2 syndrome has been subcategorized into two variants called MEN 2A and MEN 2B (formerly MEN 3). Hormonally active tumors arise from the cells of the APUD system (the diffuse neuroendocrine system). The APUD cell type is thought to derive embryologically from neuroectoderm. Pancreatic endocrine tumors can be a part of MEN 1 syndrome only.

Multiple endocrine neoplasia type 1 (**Wermer syndrome**) is the association of neoplastic transformation of parathyroid, pancreatic islet, and pituitary cells. Hyperplasia is the initiating lesion, followed later by adenomatous or carcinomatous changes. The syndrome is inherited as an autosomal dominant trait. The MEN 1 locus has been mapped to a specific region on chromosome 11, but the gene itself has not been identified. The MEN 1 syndrome generally evolves over a 30- to 40-year period. Its pancreatic neoplasm includes: pancreatic polypeptide producing tumor (in 75–85 % of cases), gastrinoma (60 %), insulinoma (25–35 %), glucagonoma (5–10 %), VIPoma (3–5 %), and somatostatinoma (from 1 to 5 percent of cases). The growth of the parathyroid, pancreatic islet, and pituitary tumors is usually slow and not of the same rate.

Pathophysiology and clinical features. The clinical picture of the MEN 1 syndrome is usually various and depends on the types of hormones overproduced by individual tumors of the parathyroid glands, the pancreatic islets, and the anterior pituitary.

a) **Hyperparathyroidism** is the most common manifestation of the MEN 1 syndrome. It is present in 90–95 % of cases. The general clinical features of hyperparathyroidism in MEN 1 are not different from those associated with other forms of hyperparathyroidism. Parathyroid hyperplasia is the most common cause of hyperparathyroidism in MEN 1, although single and multiple adenomas have been described. Hyperplasia of one or more parathyroid glands is common in younger patients; adenomas are generally found in older patients or those with long-standing disease.

b) **Neoplasia of the pancreatic islet cells** is the second most common manifestation of MEN 1 syndrome, and these abnormalities tend to occur parallel with parathyroid abnormalities. The islet cell tumors produce various hormonal manifestations and can undergo malignant transformation and metastasis. Although a pancreatic islet cell tumor is frequently identified by the clinical syndrome caused by a single hormone product, most of these tumors demonstrate hyperplasia of multiple cell types and produce several different peptides and biogenic amines. The syndromes of pancreatic islet cell hormone excess, associated with MEN 1, include:

- **Zollinger-Ellison syndrome** caused by excessive production of gastrin (hypergastrinemia) by pancreatic gastrinoma.
- **Fasting hypoglycemia** with inappropriately elevated serum insulin and C peptide concentrations caused by insulinoma. The tumor may be benign or malignant. The clinical features do not differ from those associated with sporadic insulinoma.
- **The glucagonoma syndrome** consisting of hyperglycemia, a characteristic skin rash termed necrolytic migratory erythema, and other symptoms typical for glucagonoma.
- **The watery diarrhea syndrome** (Verner-Morrison syndrome) consisting of watery diarrhea, hypokalemia, hypochlorhydria, and systemic acidosis. Patients with this syndrome have elevated plasma VIP levels. Excessive production of VIP is caused by VIPoma. The major clinical manifestation of VIPoma is a large-volume secretory diarrhea, which is termed **pancreatic cholera** because the diarrhea results from the massive intestinal secretion of fluid.
- **Overproduction of pancreatic polypeptide**. Its plasma concentration is frequently elevated in MEN 1 patients, but does not appear to cause clinical manifestations. Whether the elevated pancreatic polypeptide level is always related to a pancreatic islet cell tumor is not clear.

c) **Pituitary tumors** occur in more than half of patients with MEN 1. The most common manifestation is **the galactorrhea-amenorrhea syndrome** caused by prolactinoma. Tumors that produce growth hormone are the second most common pituitary tumors in patients with MEN 1 (25 % of pituitary adenomas). Therefore, **acromegaly** is a frequent syndrome in patients with MEN 1. **Cushing syndrome** due to an ACTH-producing pituitary tumor also can occur in patients with MEN 1 syndrome.