viral interactions. Recently **the pathomechanism of MG is related to immunological mechanism**.

Because MG is known from the year 1672 when the disease was described by T. Willis (the doctor of Charles the 2nd in England), we have a quantity of clinical observations, that reflect the development of openion about the pathogenesis of this disease. The first theory, the deficiency of the living energy was replaced with openions about the microbial origin of the disease. After the year 1900 MG was related to diseases of **thymus**. **Thymectomy** that is used up to date really improves the patientd̈s situation. In 1932 Loewi described ACH as a transmitter in the neuromuscular junction and two years later a symptomatic treatment with physostigmin was used. From the 60s long acting blockers of ACHE were used. It was shown that serum of patients with MG had a depressive effect on the transmission of impulses in the neuromuscular apparatus of the frogs. A positive therapeutic effect of the corticosteroids confirmed the immunological pathogenesis of MG that was pointed to by the clinical experience with thymectomy. The proven immunological alteration of the post synaptic part of the neuromuscular junction and the common association of MG with other autoagresive diseases but mainly the experimentally evoked autoimmune MG, lead to the present opinion about the pathogenesis of this discase.

From the neuromuscular junction functional point of view in cases of MG many authors wrongly thought that there was an altered function of the presynaptic part and hence the synaps contained low amount of ACH. Some precise calculations could prove that the production of ACH on the neuromuscular junction in patients with MG is similar to normal individuals. Some marked changes were found in the sensitivity of postsynaptic membrane and hence the acetylcholin receptors for the acetylcholin. In patients with MG this decrease was up to 80 % compared with the normal value. The lower postsynaptic sensitivity can be caused by many factors:

- lower number of the ACH – receptors
- an abnormal acetylcholin-receptor binding
- disturbed function of the ion channels, that provide the occurance and the continuation of the stimulation on the muscle.

The last possibility was not proven yet. On the other side many clinical and experimental studies showed that, the postsynaptic membrane is the target of the autoimmune reaction in cases of the experimental autoimmune MG in animals and the functional as well as the morphological changes are markedly similar to the human MG The result of both cases is a lower number of functioning acetylcholin receptors, which is most probably the most important factor of the disturbed neuromuscular transmission.

The role of thymus in the pathogenesis of MG is yet not much understood. The hypothesis, claiming, that thymopoetin, that has got a role in the transformation of lymphoid cells into T-lymphocytes, at the same time has an inhibitory effect on the neuromuscular junction was left nowadays. A new concept about the initiation of autoimmune aggressive process in MG came upon the exploration of the thymic myoid cells. These cells compose acetylcholin receptors on their surface and we assume that exactly here the reaction between ACH-receptor proteins with T-lymphocytes can occur for the first time (e.g. during a viral infection) and this could initiate the formation of antibodies. This hypothesis says that thymus is the primary site of autoimmunization, where the T-lymphocytes after sensitization by the ectopic acetylcholin receptors, the myoid cells act as inductors for the production of pathological IgG in the B-lymphocytes. The T-lymphocytes at the same time act as helpers to maintain the pathological process.

If we want to understand the pathogenesis of the disease completely, we have to know which pathophysiological moment is the most important in the course of the disease: whether it is the autoaggressive immunity pathway itself, or it is an immunity defect that released those autoimmune processes from the controlling effects.

6.24 Autonomous (vegetative) nervous system

Most pathologic conditions do not represent a simple change of some organ function. They mostly evoke a secondary alteration of activity in the autonomous nervous system. A non-causal therapy of diseases often represents an intervention into the autonomous nervous system. Thus, from the pharmacological point of view it is often not the pathologically altered organ that is influenced but the autonomous nerves that control its activity.

The **autonomous nervous system** is the component of the nervous system supervising the vegetative (autonomous) functions of the organism by controlling the activity of smooth muscle cells, myocardial cells, endocrine and exocrine glands as well as parenchymatous organ cells. It contributes to the organisms homeostasis. Its typical traits are not to be influenced by free will and not to be directly connected to consciousness.

The autonomous nervous system is a subsystem of the nervous system, controlling the very basic activities of the body and assuring that the state variables of the organism are maintained in that part of the phase space that defines life. It is autonomous in the sense that it is able to perform its activities in an independent way. If the central nervous system is affected (as a consequence of traumatism, CVA, tumor or other factors), concomitantly the motor functions in the corresponding part of body can be completely lost (plegia). In this case any output of the so called somatic nervous system is blocked, but the vegetative functions remain conserved. We can take the physiological condition of sleep as another example. During the sleep, the motor functions are to an on rest important degree due to insufficient activity of reticular formation. The latter is responsible for such a level of excitation of the cortex that an additional input from other regions of the central nervous system (CNS) will induce activity (spike generation) in the corresponding cortical area. In the case of sleep, as well, the homeostasis in conserved. Eventually, the most striking example is that of an animal decerebrated above the hypothalamus. Such an animal shows no signs of disturbances in autonomous functions.

Considering all these facts we can imagine the autonomous nervous system as an independent entity. We might divide the nervous system into two subsystems: the somatic nervous system and the autonomous nervous system. We can conclude that the autonomous nervous system (ANS) can independently control the life-inevitable functions of the organism (obviously, in relation to the higher centers of the CNS).

The ANS is under regulatory influence of higher centers in the CNS. These centers can modulate the reacting capacity of the autonomous nervous system on the vegetative afferentation. The resulting activity of the ANS is so a consequence of its intrinsic activity, the vegetative afferentation (interoreceptors) and the directing signals from CNS.

The resulting activity is further transformed into efferent signals, led by several **efferent pathways**. We mean the sympathetic, parasympathetic, dopaminergic nervous fibers and a supposed fourth type of output (see below). These pathways are defined qualitatively (the effect of sympathetic NS is different - "opposite" - to that of parasympathetic NS) as well as anatomically, and by their transmitters. In the case of sympathetic NS the transfer from the nervous fibers to the effector is assured by catecholamine, whereas in the parasympathetic NS this happens by means of acetylcholine. While dopamine acts as neurotransmitter in the dopaminergic pathway, in the fourth pathway the transmitter role is being attributed to nitric oxide (NO). The description of these two latter pathways is still rather imprecise.

The sense of such **multichannel output** consists in a reciprocal combination of several individual information channels enabling to widen the spectrum of the organisms reactions (i.e. an increased information capacity of the ANS output). As a consequence of sympathetic activation a given organ can e.g. behave in different ways corresponding to different possible activities of the parasympathetic fibers. It is important to keep this in mind and on the other hand to realize that e.g. a block of the sympathetic activity can theoretically be compensated by a diminution of the parasympathetic tonus or by a complex modification of the activity of the resting 3 autonomous output channels. Obviously, the corresponding functions have to be regulated (and not simply controlled, with absent feedback).

6.24.1 The architecture of the ANS

The anatomy of the dopaminergic and fourth (above mentioned) vegetative output channels are not precisely defined yet. We shall therefore concentrate on the sympathetic and parasympathetic NS in this section.

Principally, the efferent channels are composed of 3 neurons. The first of them (called **preganglionic**) connects the ANS centers located in the CNS to the peripheral ganglia. The axon of the preganglionic neuron is myelinated. In the ganglion area this preganglionic neuron is connected to a **postganglionic** neuron. The axon of the latter is no longer myelinated. There are more postganglionic then pregan-

glionic neurons and this gives a divergent character to this neural network. Sometimes a third, s.c. **intramural** neuron is described, located directly in the wall of the innervated organ. The latter population of neurons is being currently designed as intramural autonomous system.

6.24.1.1 Sympathetic NS

The efferent sympathetic output channel originates in the spinal intermediolateral nucleus. Following the way of white rami (rr. communicantes albi) it reaches the ganglia of the sympathetic chain (truncus sympaticus, paravertebral ganglia), located along the sides of the spine. These form, as a result of their interconnections by means of longitudinal interconnecting fibers, a united system. Within this chain preganglionic fibers synapse with sympathetic neurons in ganglia at the same, higher, or lower levels. After integrative processes involving dopaminergic neurotransmission they send postganglionic axons either back to the spinal nerves as gray rami (gray because unmyelinated), or to prevertebral plexuses or ganglia in the abdominal cavity. A part of the mentioned nervous fibers pass through these ganglia without being interrupted. These fibers form synapses in ganglia placed around vessels (ganglia plexorum autonomicum) or in prevertebral ganglia. The last neuron of the sympathetic pathway ends on the effector.

6.24.1.2 Parasympathetic NS

The preganglionic parasympathetic fibers run in the cranial nerves and in the sacral spinal roots. Their interconnections take place in the plexi located in the proximity of these roots or directly in the organ plexi. Cranial nerves containing parasympathetic neurons are the following: the oculomotor nerve, facial nerve, glossopharyngeal nerve and the vagus. Other parasympathetic neurons are included in the nerve fibers of the sacral plexus. The mentioned nerves take their origins either in the corresponding nuclei of the cranial nerves, in the Edinger-Westphali nucleus, or in the spinal areas representing a continuation of the intermedial nucleus.

The central regulatory structures of the ANS: several structures of the CNS have a close relationship to the ANS. First of all, this is the case of the hypothalamus and medulla oblongata. Whether or to what extent these represent the central part of the ANS itself has not been well concretized in all cases. It has however been possible to define several concrete centers of the ANS, like the respiratory centers, vasomotor centers, cardioacceleratory or inhibitory centers, the center of cough reflex, the vomitus center or the regulatory center of the body temperature.

The **afferent information** of the ANS follows several pathways. Most of them originate in the visceral receptors and in chemoreceptors. The axons of afferent neurons can be found for example in the vagus, glossopharyngeal nerve, in the splanchnic nerves, but also in somatic nerves. The afferent compartment is not negligible, e.g. for vagus it represents to four fifths of all its fibers. A part of the afferent axons synapse with the preganglionic fibers of the ANS. At the recent level of knowledge the afferent part of the ANS can not be divided in a similar way as its efferent (output) part. This is interesting in that it underlines the reality of a conception of integrated ANS structures, a sort of centers analyzing the afferent information (feedback signal) and, at the same time, controlling the activity of efferent pathways. It is also interesting to mention here that the visceral afferentation does not only condition the vegetative nervous system, but also the somatic efferent system and vice versa. We can give several spinal reflexes as an example: there are pathological processes in the splanchnic regions that are accompanied by a redness of the dermatomes innervated by the same spinal segments.

In this case the visceral afferentation probably exerts a direct influence on the activity of the sympathetic efferent fibers in the given segment leading to dilatation of blood vessels of the corresponding dermatome **(viscerocutaneous reflexes)**. In the s.c. **viscerosomatic reflexes** the activity spreads from the ANS to the somatic nervous system – e.g. an augmented tonus of the abdominal muscles can be observed in the corresponding area of the abdomen following increase of autonomous afferent activity. Clinical practice offers us still more examples, e.g. the **cutanovisceral reflexes**, where the warming up of certain areas of the skin leads to a diminution in the motility of the intestines. Surgeons describe the postoperative ileus, an event sometimes complicating postoperative care following an operation in abdominal cavity. Here visceral afferentation from intestine, as a consequence of mechanical manipulation, activates its own sympathetic efferentation **(intestinoin-**

testinal reflexes). The intestinal ANS is corresponsible for this reflex. Identical causal mechanisms are implied in the **Ogilvie's syndrome**, which is an acute intestinal pseudoobstruction. Except for a surgical abdominal intervention it can be induced by sepsis, myocardial infarction, respiratory insufficiency, all of them sharing a hyperactivity of the sympathetic NS leading to the a dilation of intestinal wall. However, the precise pathomechanism of these phenomena has not been elucidated yet. All these reflexes become more apparent after a transversal spinal lesion above the corresponding spinal segments. Then a mechanical stimulation of the skin can lead to a profuse sweating and to an excessive vascular reactivity of the skin. This is explained as a consequence of the interruption of the continually active descendent inhibitory pathways.

6.24.2 The sympathetic nervous system and the adrenal medulla. The dopaminergic system.

As we have already mentioned, among the characteristics of the efferent pathways of the ANS the function and the type of transmitter play an important role. If we simplify we can say that the sympathetic NS is most often activated in situations requiring mobilization of the organism, like in danger. The role of this activation is then to provide the necessary oxygen and nutrients supply to the organs responsible for the safeguard of life and to switch the functioning of the latter over to a more economic alternative. It activates the cardiovascular and respiratory system and assures a sufficient perfusion of the heart and brain.

In the human body three **catecholamines** occur naturally: epinephrine (adrenaline), norepinephrine and dopamine. They function as neurotransmitters in the CNS as well as in the ANS. For the sympathetic NS epinephrine and norepinephrine are the most important.

Principally one can say that norepinephrine is rather locally acting, while epinephrine, a product of adrenal medulla, exerts its effect after passing into the blood circulation, i.e. globally.

The catecholaminergic receptors, localized on the postsynaptic membranes of the effectors, can be stimulated either by a catecholamine eliminated from the innervating nerve ending or by catecholamine diffusing from the circulation, if this is possible with regard to local conditions. In a similar way pharmaceuticals diffusing from the circulation can stimulate a receptor (or, in an opposite case, block the effect of its stimulation).

Catecholamines are **synthesized** from the amino-acid tyrosine. This is first hydroxylated to dihydroxyphenylalanine (dopa), then decarboxylated to dopamine and finally hydroxylated on the beta position of its lateral chain with norepinephrine as a result. The regulated link in this chain (the rate-limiting step of this process) is the hydroxylation of tyrosine. Norepinephrine (the reaction product) induces a modification in the activity as well as the mass quantity of the enzyme tyrosine-hydroxylase, which is responsible for the mentioned step. The described metabolic process is followed by methylation of norepinephrine to epinephrine by the phenylethanolamine-N-methyltransferase in adrenal medulla.

Interestingly it has been observed that the enzyme phenylethanolamine-N-methyltransferase is inducible by glucocorticoids. When we look at the anatomy of the organ we see that the blood supply entering adrenal medulla is already enriched by glucocorticoids, originating in the adrenal cortex. Thus this further enhances the adrenomedullar synthesizing capacity.

The **degradation** of catecholamines is performed by the catechol-O-methyltransferase (O-methylation) that takes place in the liver and the kidney. It permits a removal of the active catecholamines from the blood circulation. A second catecholamine-degrading enzyme is the monoaminooxidase (MAO), which is located in the nerve endings (and synaptic clefts), playing a role in the inactivation of catecholamines in the nervous system. The products of the catecholamine degradation are the metanephrines and the vanilmandelic acid (there are two forms of MAO, a central form, acting in the CNS, and a peripheral form). In the dopaminergic system, the degradation product is the homovanilic acid. Catecholamines are being stored in vesicles and are released by exocytosis. Both in the adrenal medulla and in the sympathetic nerve endings, there are important stores of catecholamines, interpreted as a reserve for situations requiring a massive stimulation of sympathetic NS.

This localization of catecholamines inside vesicles

has a key meaning also from another point of view – the free monoaminooxidase, present in the cytoplasm, would otherwise lead to a rapid degradation of the synthesized catecholamines. In this way the catecholamine compartment represented by the vesicles is a compartment protected from intracellular degradation.

The **adrenal medulla** occupies a highly specific place in the ANS. It can be characterized as a transformed sympathetic ganglion composed of modified postsynaptic neurons. The adrenal medulla produces a mixture containing approximately 80 % of epinephrine and 20 % of norepinephrine. Once this mixture is released into the blood circulation, it can potentiate the effect of a sympathetic activation on the corresponding effectors, but in fact, its role is providing the function of a metabolic hormone. Adrenaline mobilizes oxidable substances (glucose and fatty acids) from their stores. This could be interpreted as the providing for fuel to the organism that, due to a longer lasting sympathetic activation, works at a higher speed.

The neuro-sympathetic communication: An important process taking place on the peripheral ending of the sympathetic NS is the s.c. reuptake of catecholamines from the extracellular space into the presynpatic neuron by means of a special transport system. This mechanism becomes evident in several physiological processes. On one hand, it protects the stores of catecholamines (to some extent, however, the catecholamines transported in this way are degraded by the cytoplasmatic fraction of the MAO), on the other hand, it is one of the classical mechanisms enabling an activation of the postsynaptic membrane at high-frequency.

In order to clarify these events we must go back to the fundamentals of neurophysiology. The neural system recognizes basically 2 distinct codes: the anatomical code and the frequency code. The frequency code is based on the capacity of neurons to carry several action potentials (spikes) in a rapid sequence. We know that this ability is not equal for all neural cells. Generally, the value of 1000 Hz is taken as the upper limit for the spike frequency. That means that the spikes run on the neural axon with a speed of 1 to 1000 per second. The neural pathways can this effectively use only if the chemical processes on the synapses run at least at the mentioned speed. This means that the synapse must be capable of activation 1000 times a second. After every single activation, however, a state of peace must be restituted. The biochemical processes taking place at the synapse must fit well with the elimination speed and with short duration of the transmitter effect at the postsynaptic membrane. These synaptic processes must be extremely short-lasting (at a speed of 1000 Hz less than 1 ms), allowing the next spike to be transferred to the postsynaptic neuron. This is made possible so that the quantity of the eliminated transmitter is small (about 10^{-13} mol/impulse), by removal of the transmitter by reuptake, by its degradation by MAO that finds itself in the synaptic cleft and by internalization of the occupied receptors at the postsynaptic membrane.

Let us now give a description of the complex event called the activation of sympathetic NS. The sympathetic pathway can be activated either by a local reflex (e.g. intestino-intestinal reflex) or by an activation of the central control structures (e.g. vasomotorical center). Under basic conditions, every nerve fiber is characterized by a basal (spontaneous) activity, where the spikes run along the axons with a rather low frequency. If the nerve fiber is activated, this frequency becomes higher. This situation is designed as an increase of tonus. An inhibition of the corresponding neuron on the contrary, leads to a diminution of this frequency.

6.24.2.1 The receptor theory. Sympathoadrenal and dopaminergic receptors.

Every organ reacts on stimulation of the corresponding part of the ANS in a different way. This is very important, according to different roles different organs play in the maintaining of the functional equilibrium of the organism. In a life-saving situation, some organs are necessary to be stimulated while others, less important in such situation, can be inhibited due to an energy-economizing requirement. In such situations it is very important that the organ reactions may be greatly diversified. Here, two mechanisms are involved. First, every organ has its innervating autonomous fibers differently active. This is a consequence of an integration of different influences on the ANS at different levels of control (e.g. spinal vegetative reflexes). The degree of activation of single sympathetic fibers depends also on the character of the stimuli responsible for this activity. Besides this, it is important that the organ's reaction to the

release of adrenaline from adrenal medulla is a specific one, characteristic for the given organ. For this, the organs are equipped with a specific spectrum of receptors. This enables a more complex organ reaction to a rather general (uniform) answer of the ANS (especially of the adrenal medulla) to stimulation, so that eventually, the vegetative reaction in a given situation can be more general (and more economic).

The diversity is also achieved on the periphery as different structures and organs express different receptors for the same mediators. Hypothetically we must consider an additional factor: the answer of an organ to its vegetative stimulation should rely on the particular state of this organ or on the concrete status of the whole organism at a given moment. The receptor molecules are proteins. As such, their structure, similarly to the structure of all other proteins of the organism, is encoded in the DNA of the cell nucleus under the form of genes. The moment and the extent of the activation of these genes is a strictly controlled process. It means that **the number of receptors expressed on the cell membrane is not constant and undergoes a regulation.** Like this a cell (an organ) disposes of a modification possibility of its answer to vegetative influences according to local factors.

Let us close this subject by saying that the diversity of the organism reactions to a particular state of the organism functional equilibrium can be achieved in several ways. First, by the existence of a multichannel output from the ANS, second, by the fact that the organs are innervated by vegetative fibers the activity of which is not necessarily uniform, third, due to the fact that the effectors of ANS present a diversity of receptors associated with different types of responses, more or less specific to the given organ. In this way, with exceptional economy and a very short reaction time (almost immediately) the ANS reaction is started, leading to an adaptation of the organism to changed conditions, with respect to its stability.

The reactions of the ANS change inside a large spectrum, from very discrete, sometimes at a limit of recognition (change in body position, food intake, change of vigilance, mental activity, physical exercise) to whole-body extensive reactions (like the "fight and flight" reaction after Cannon, triggered by a life danger). This system is highly effective and fails only if so intervention to the organism's integrity is such excessive (like in the case of shock) that the ability to keep the regulated variables in a stable area is lost so that a desired progression of the pathological process appears.

The receptor has a binding component to which different substances can bind. If the latter respond to certain criteria, they induce such a modification of the 3-dimensional structure of the receptor that an intracellular receptor-dependent cascade is triggered. We call the so behaving substances the **agonists** of the receptor function. Contrary to them, the **antagonists** of the receptor function are substances able to block the mentioned effect. Two basic origins can be recognized for the agonists: the **synaptic button** of the innervating fiber and the **circulation**. The agonists appearing in the circulation can be of endogenous origin (e.g. epinephrine synthesized in adrenal medulla) or of an exogenous origin (e.g. drugs).

6.24.2.1.1 Adrenergic receptors We have already mentioned that the effect of the efferent pathways on the effector is chemically mediated. The effector is equipped by the same receptors to which the neurotransmitter liberated from the synaptic button of the innervating nerve fiber is bound. In order to react to the control signals from the sympathetic NS the tissues must be equipped by receptors susceptible to react to the corresponding transmitter. In the case of sympathetic NS these are the adrenergic receptors. Those can be found first of all in the cardiovascular system, but also in the splanchnic area, in the respiratory system, urogenitary tract, etc. We recognize several types of adrenergic receptors. Their differences mean in fact a differentiated influence on different functions, mediated through different mechanisms at the cellular level. The corresponding biochemical structures of the receptors are also different, so that there is a possibility of a selective activation or blocking of these different receptors. We divide adrenergic receptors in alpha and beta receptors.

Alpha adrenergic receptors: In general we can say that the activation of the alpha receptor induces vasoconstriction, relaxation of the intestine and mydriasis. Epinephrine and norepinephrine bind to alpha receptors and their effect is approximately the same. Alpha receptors are divided in alpha_1 and alpha_2 receptors.

The **alpha_1** receptor was originally considered a receptor of the postsynaptic membranes. The main

effect mediated through these receptors are vasoconstriction and mydriasis.

The **alpha$_2$** receptor was, according to the original conception, a receptor of the presynaptic membrane of the sympathetic nerve ending. As in the case of the alpha$_1$ receptor so for the alpha$_2$ receptor several new functions have been discovered. The alpha$_2$ mediated effects include the inhibition of the norepinephrine secretion from the adrenergic nerve endings, the inhibition of the acetylcholine release from the cholinergic nerves, the inhibition of lipolysis in the fat tissue, the inhibition of the insulin secretion, the stimulation of the platelet aggregation and vasoconstriction of some vessels.

Beta receptors: Through the activation of the beta receptors the heart frequency acceleration as well as an augmented myocardium contractility are achieved and at the same time vasodilation and lipolysis are favored. We recognize 2 subtypes of receptors:

Beta$_1$ receptor is equally sensitive to both epinephrine and norepinephrine, it exerts influence on the heart action and is responsible for lipolysis in fat tissue (recently the lipolytic effect has been ascribed to **beta$_3$** receptors).

Beta$_2$ are more sensitive to epinephrine. They trigger vasodilation and bronchodilation regulate hepatic glycogenolysis and gluconeogenesis, skeletal muscle glycogenolysis and other metabolic processes.

6.24.2.1.2 Dopaminergic receptors Dopaminergic receptors can be found in a large variety of tissues, mainly in the CNS and the peripheral NS, but also elsewhere. Their classification is very complex. For the sake of simplicity let us divide the dopaminergic receptors into two types (the effect of dopamine on both of them is equal):

D-1 receptor induces vasodilation in the following vessel beds: cerebral, coronary, renal and mesenteric.

D-2 receptor inhibits the conductivity in sympathetic ganglia, inhibits the release of norepinephrine from the sympathetic nerve endings, inhibits the secretion of prolactin from the pineal gland and induces vomiting.

6.24.2.1.3 The structure of adrenergic and dopaminergic receptors In the following text we shall try to elucidate the intracellular mechanisms implied in the mediation of the effects of adrenergic and dopaminergic receptors. The biochemistry of these receptors teaches us that the binding of the corresponding transmitter to the receptor leads to a modification of the receptor structure, initiating further biochemical processes inside the cell. The receptor molecule is associated with a regulatory protein called **G protein** (G, because as soon as it is activated, the GTP binds to it) that will decide the further character of the response. Alpha$_2$ and D-2 receptors are associated with the G_i protein, the activation of which leads to a decrease of cAMP level. The information passed further by this second messenger then mediates the effect on the cAMP-dependent proteinkinases. It is relevant to mention that not all responses to an alpha$_2$ receptor stimulation can be exclusively explained by this mechanism and that, actually, a modification in the permeability of some ion channels is being considered.

The alpha$_1$ receptor is associated with a G_p-protein (not precisely identified yet) that activates the phospholipase C. This enzyme induces a decomposition of the phospholipids that find themselves bound to the cellular membrane, mainly of the phosphatidylinositol-4,5-biphosphate, having the consequence of the formation of inositol-1,4,5-triphosphate and 1,2-diacylglycerol. Both these products act as second messengers. The inositol-1,4,5-triphosphate liberates calcium from its intracellular stores and, acting on the calcium/calmoduline dependent proteinkinases, mediates the transmitter's effect on the cell. This pathway is further potentiated by the entry of calcium into the cell, due to a longer-lasting stimulation by an agonist of alpha$_1$ receptor (the mechanism of this elevated uptake of calcium is not yet well known). The 1,2-diacylglycerol stays in the cell membrane and activates the proteinkinase C, which acts on substrates other than the calcium/calmoduline dependent proteinkinase. The effects mediated by proteinkinase C (which phosphorylates proteins) have still not been clearly elucidated.

The beta$_1$, beta$_2$ and D-1 receptors are associated with the s.c. G_s protein. The latter enhances the activity of the adenylatecyclase with a consecutive rise in cAMP. Due to this, the cAMP-dependent proteinkinases are activated. These on their turn induce the phosphorylation of proteins, responsible for the final cellular effect attributed to the activated receptor.

6.24.2.1.4 Influencing the sensitivity to the adrenergic effects It has been discovered that the sensitivity to the adrenergic effects is rather variable than constant. We shall mention two kinds of processes taking place at the receptor level: the homologous and heterologous regulations.

Homologous influences. It is a well-known fact that a long-lasting exposition of receptors to their agonists induces a decrease in their number (it is an opposite process to the long-term potentiation in the CNS during engram formation, where the efficiency of synaptic transmission is increased). The mechanism of such s.c. down-regulation is not well understood for the ANS. It is possible that the internalization of the occupied receptors plays a role in it, it could be so in the case of beta receptors. Besides this it is supposed that the receptors associated with the adenylatecyclase (beta and alpha$_2$) might alternate between two states: one with high affinity to its agonist and a second, with low affinity to this agonist. One of the existing theories on this subject is that a long-lasting exposition of a receptor to its agonist leads to a changed ratio between the two components in favor of the low-affinity state of the receptor. The kinase, phosphorylating the beta receptor, is probably involved in this phenomenon. Even if the exact mechanisms of these events are still but hypothetical, it is doubtless that the s.c. tachyphylaxy (diminished responsiveness of a tissue following its long-lasting stimulation) indeed appears in the ANS.

Heterologous influences. There are more heterologous factors that influence the sensitivity of a synapse. A drop of the ambient temperature augments the affinity of the alpha receptor to its agonist. Thyroidal hormones augment the number of beta receptors and make the cellular response to beta receptor stimulation more effective. Estrogens and progesterone modify the sensitivity of the myometrium to catecholamines (by means of the alpha receptor). Glucocorticoids prevent from the tachyphylactic effect on the adrenergic receptor level.

6.24.2.2 Central regulation of the sympathoadrenergic system

We can trace the output from the sympathetic NS starting with the **reticular formation** in the pons and medulla oblongata. There is also a part originating in the **hypothalamus**. Descendent fibers then end in the **intermediolateral nucleus** of the medulla, where the preganglionic sympathetic neuron originates.

The activity of the mentioned centers depends on numerous factors. Among the most important are activities arising from the cortex, limbic system and hypothalamus. We can further enumerate afferentations communicating with sympathetic NS directly at the brainstem level, and, equally, the qualitative variations of the extracellular fluid composition. The role of the higher centers is to coordinate the effects of the sympathetic system with mental functions, emotional reactions and with homeostasis.

At this place it is important to attract the attention to the difference between the neural and humoral component of the sympathetic NS. The neural component reflects itself in the rapidity of reaction, while the humoral component has a prolonged and slightly different effect. Different stimuli activate the sympathetic NS at different points and to a different extent. Upright posture activates the neural component, while hypoglycemia first acts on the humoral component.

6.24.2.3 Modification of the transmitter release on the presynaptic membrane

The effect of a sympathetic stimulus on a given organ is determined by the extent of activation of the corresponding efferent pathway. The mediation of the effect is realized by a neurotransmitter. The greater its quantity released into the synaptic cleft, the more receptors of the postsynaptic membrane are activated and the more intense signal is achieved inside the cell.

Not only the activity of the efferent pathway, but also other mechanisms affect the quantity of the transmitter released. There is an important number of these factors. We speak about **presynaptic modulation**. Among the less specific these are e.g. fall in body temperature or acidosis, both reducing the quantity of the released norepinephrine. Other factors are more specific and their effects pass in the most cases through a receptor on the synaptic membrane. Such a receptor probably triggers a cascade of events in the presynaptic area, that have not been sufficiently precised yet. The consequence of these events is a modification of the transmitter quantity that will be released in response to the passage of the spike through the presynaptic button. The release of a transmitter can be either subjected to facilitation or to inhibition. The catecholamines themselves have

an inhibitory effect on the release of norepinephrine (by the alpha$_2$ receptor). Such negative feedback assures a very small amount of the transmitter to be released, which contributes to a shortening of the synaptic passage time. Acetylcholine (muscarinic receptor), dopamine (D-2 receptor), histamine (H-2 receptor), serotonin, enkephalines and prostaglandins act also in an inhibitory way, while catecholamines (beta$_2$ receptor !), acetylcholine (nicotinic receptor !) and angiotensin II have **facilitating effects** at this level. Even if we knew the effects of the enumerated substances, the modulation of this pathway as a whole still needs further clarification.

The ambivalent effects of catecholamines and acetylcholine (inhibitory as well as facilitating) require a more detailed analysis.

Presynaptic adrenergic receptors: As for the ambivalent effect of catecholamines no explanations are available, however, two hypotheses are being evoked. The first one suggests that the effect on beta receptors dominates within a range of lower concentrations of the ligand, while higher concentrations are required to trigger an alpha receptor effect. At a lower firing rate less transmitter is released and by means of a positive feedback on the beta receptor, this quantity is augmented. If, on the contrary, large amount of transmitter is released (due to an intense stimulation of the sympathetic NS, i.e. to a high discharge rate), the alpha effect will predominate, leading to a decrease of this quantity by a negative feedback.

The second hypothesis suggests that the beta receptors are more sensitive to epinephrine than to norepinephrine and that, therefore, the circulating epinephrine increases the effect of the neural sympathetic component. The alpha receptor then only functions as the above mentioned negative feedback on the transmitter release.

Presynaptic cholinergic receptors: Despite the fact that two types of presynaptic cholinergic receptors exist and, as a result of this, two different effects of acetylcholine on the presynaptic ending, it is presumed that the muscarinic receptor plays the preponderant role. Its effect is the inhibition of the catecholamine release from the presynaptic area, achieved at lower concentrations of acetylcholine. This is considered to be an important component of the functionally often reciprocal reactions between sympathetic and parasympathetic NS.

6.24.3 Parasympathetic NS

Parasympathetic NS represents the 2nd output channel of the ANS. Its effect (being contrary to the sympathetic effect, roughly speaking), is evident e.g. during sleep, in a resting state or during digestion. Of course, here, for didactic reasons, we are presenting examples with a high degree of simplification. It is important to know that in reality, also the parasympathetic NS is participating in the enumerated situations.

We have already mentioned the anatomical particularities of the sympathetic NS. Acetylcholine acts as a transmitter in its postganglionic neuron (it also plays the role of neurotransmitter in all vegetative ganglia and in the postganglionic sympathetic neurons innervating the sweat glands).

Acetylcholine is synthesized from choline actively extracted from the extracellular space by the neuron and from CoA (a product of the neuron itself). The mentioned synthesis is catalyzed by the enzyme cholinacetyltransferase. The reaction product acetylcholine is then stored in the synaptic vesicles until it is liberated due to passage of an action potential.

Acetylcholine binds to more receptor types that can be divided into two groups. They have been discovered during a series of pharmacological experiments where nicotine and muscarine were administered in experimental animal models leading to the finding of distinct reactions due to each stimuli. Later the corresponding subgroups of parasympathetic receptors were successfully identified.

The first, referred as **nicotinic receptors**, include receptors that can be activated by nicotine. For most of them, they are located in the adrenals, in the autonomic ganglia, as receptors of the neuromuscular junction and in the CNS. The second type, **muscarinic receptors**, can be activated by muscarine and they are mainly located on the membranes of the effector cells of the parasympathetic NS and in the CNS.

The muscarinic receptors can be further divided into two subtypes: the **M_1 receptor** (found mainly in the CNS and probably also in the parasympathetic ganglia) and the **M_2 receptor** (a non neural receptor) detectable on the effectors like the smooth muscle, cardiomyocyte or the glandular epithelium.

The M_1 receptor, like the alpha$_1$ receptor, is associated with a G_p protein, so that the subsequent intracellular cascade is the same as was described for

the alpha$_1$ receptor. The M_2 receptor is associated with a G_i protein and the mechanism of the cellular effect includes the same biochemical steps as in the case of the alpha$_2$ and D_2 receptors.

The acetylcholine is **inactivated** in the synaptic cleft by acetylcholineesterase. This enzyme is not identical with the serum acetylcholinesterase, the latter having any influence on the mentioned physiological reactions.

6.24.3.1 Parasympathetic NS at the organ level

The parasympathetic fibers innervate the cardiovascular system, the GIT and the urogenitary system, including the kidneys, liver, thyroid gland, pancreas and other organs and tissues. This explains why it might intervene in a lot of metabolic events. Such interventions have, however, not been concretized in detail yet.

The parasympathetic NS reaches the **cardiovascular system** by means of vagus. It leads to a decreased automaticity in the sinoatrial node and by this to a decrease in heart rate (negative chronotropic effect). Additionally, it slows down the conduction (negative dromotropic effect). Not only it slows down the conductivity, but it also shortens the refractory phase of the myocyte, an association of effects predisposing to arrhytmias. The right vagus primarily affects of the function of sinoatrial node while the left vagus acts primarily on the atrioventricular node. These facts may be exploited in clinical practice.

Acetylcholine decreases the conductivity and prolongs the refractory phase in the atrioventricular node. The negative inotropic effect is attributed to the presynaptic inhibition of the sympathetic fibers by acetylcholine, as well as to the decrease of the rapidity of excitatory conduction. This leads to a gentle desynchronisation of myocardial contraction, diminishing its efficiency. The ventricular myocardium is but very little influenced, as its parasympathetic innervation is not extensive. It seems rather improbable that the parasympathetic NS could have a direct effect on blood vessels. It is supposed, actually, that its only effect consists in presynaptic inhibition of the sympathetic fibers.

The **GIT** is the organ system, in which the effect of parasympathetic NS is the most evident. The parasympathetic innervation reaches this organ system through vagus nerves and the sacral plexus. The parasympathetic message to the GIT leads to an increase in the smooth muscle tonus, increase in peristaltic motility and the relaxation of sphincter muscles. Additionally, the parasympathetic NS stimulates the exocrine secretion of gastrin, secretin, insulin and the production of gastric mucine.

As for the **urogenital system** acetylcholine here leads to an increase in the urethral peristaltics, a contraction of the detrusor muscle of the urinary bladder (there are two sphincters at this level, an internal one, containing smooth muscles and a second, external, composed of striated muscle. The parasympathetic NS only influences the internal sphincter.) In this way, it plays an important role in the coordination of the urinary function. Also the genital organs are largely influenced by the parasympathetic innervation. Together with a massive sympathetic activation during the orgasm also the parasympathetic NS is involved.

In the upper **respiratory tract**, acetylcholine leads to an increase in the tracheobronchial secretion and it triggers bronchoconstriction.

6.24.4 Non-adrenergic and non-cholinergic autonomic nerves

Besides the sympathetic and parasympathetic NS there are also efferent fibers using neither norepinephrine nor acetylcholine. If we try to block pharmacologically the conduction at the mentioned synapses of these fibers with norepinephrine and acetylcholine antagonists, they still remain active, indicating their special role in the ANS. These nerve fibers are included into a system called nonadrenergic non-cholinergic. We recognize 2 possible candidates for the neurotransmitter role in this system: dopamine and NO.

6.24.4.1 The peripheral dopaminergic system

The role of dopamine is usually an inhibitory one in the CNS. Additionally, it seems that dopamine also plays a role of a transmitter in the sympathetic ganglia. Finally, there is evidence that except for this classical roles, dopamine serves a transmitter function on the periphery. Actually, we suspect the existence of a peripheral dopaminergic system as there are effects induced by dopamine that can not be explained by the mechanism of activation of the re-

ceptors of any other type (adrenergic, cholinergic, histaminic, etc.). The mentioned system probably participates in the relaxation of the lower esophageal sphincter, it slows down the gastric evacuation, leads to a dilation of the renal and mesenteric arteries, decreases the secretion of aldosterone, directly stimulates the sodium excretion in the renal tubules and inhibits the elimination of norepinephrine on the peripheral sympathetic nerve endings. How precisely these effects are brought on has not been thoroughly explained yet. We do not think dopamine could act as a classical hormone through its presence in blood. Most often it is evoked that the dopaminergic system could be primarily located in the kidneys, as it has been demonstrated that the urine contains more dopamine than can be explained by its clearance from the blood circulation.

6.24.4.2 NO and the ANS

It has been shown that the endothelium derived relaxing factor of vessels (the last link-molecule in the regulatory cascade of vasodilation) was identical with nitric oxide. A large spectrum of functions of this chemically very simple substance (until then only considered as an air pollution factor) have been discovered since.

The NO-synthetase, a constitutive enzyme (constantly present) in a number of neurons, produces the NO from the aminoacid L-arginine. It is not only to be found in the CNS, where it is thought to contribute to the existence of memory (long-term potentiation of synaptic efficacies) mainly in the hippocampus and the cortex, but it also can be found in the peripheral nerve endings of the ANS. The participation of this, still imprecisely characterized system inside the ANS, can be documented on the case of hypertophic pylorostenosis and achalasia. This system also intervenes in intestinal relaxation.

A recently acquired knowledge about NO is that it can induce vasodilation in corpora cavernosa (relaxation of the smooth muscle of the vessel wall), so that it is an agent participating on erection (its failure plays a role in pathogenesis of impotence). More, NO probably has a transmitter function in retina and adrenal medulla. The relation between the NO system and the dopaminergic system is not clear, however an important physiologic role of the NO in the ANS seems rather probable.

6.24.4.3 The intestinal ANS

The intestinal ANS has a particular position inside the ANS. It is autonomous in the true sense of the word. It is well known that the intestine will continue working after a total liquidation of its innervating fibers. In addition to a conserved motoricity, some secretory functions will remain conserved as well. This is possible because of its proper "nervous system" inside the intestinal wall. This nervous system is composed of the s.c. myenteric and submucose plexus that are sometimes designed by a popular common term "intestinal brain". This web of neurons includes a subgroup of sensory neurons excited by a tension or contraction of the intestinal wall, interneurons and efferent neurons, innervating the smooth muscles of the intestinal wall.

6.24.5 Involvement of the ANS in the pathophysiology of disease states

The very complex structure of the ANS is in constant interaction with other regulatory systems. Such interactions can be revealed at the level of spinal autonomous neurons, but also at higher levels, understanding structures such as medulla oblongata or hypothalamus. The open character of the ANS makes it difficult to determine its role in the pathophysiology. There is also the problem that changes in the ANS activities accompany practically every disease that leads to a dysbalance of homeostasis. It is therefore not easy to decide, whether in concrete cases the ANS plays a primitive or just a secondary role. We shall thus mention only a small number of diseases concerning the ANS. We shall namely give examples of such diseases (chosen from the vast group of disease states with a participation of the ANS), where the vegetative nerves play a key role.

Cardiac insufficiency: Sympathetic NS participates to a high degree in the picture of cardiac insufficiency. In the initial phase the venoconstriction and the positive inotropic, dromotropic and chronotropic effects of catecholamines have a key meaning for the safeguard of basic tissue perfusion. This regulatory mechanism has, however, also a negative side - an elevated tonus of sympathetic NS increases the oxygen consumption by the myocardium, impairing the state of this organ. In the particular case when cardiac insufficiency occurs as a complication of **myocar-**

dial infarction, it is of extreme importance that the sympathetic NS is activated. **Shock** and **trauma** are other examples of situations with an elevated sympathetic activity. The main sympathetic effect consists of a mobilization of the energetic sources and of favorization of the circulation in these situations. **Physical effort** also leads to an activation of the sympathetic NS. Due to it, a better perfusion of the skeleton muscles is achieved, together with an increased output volume of the heart, an adequate circulation and liberation of energetic substances. This situation is at the same time an example of anticipatory regulation. Physical training will lead to a diminished activation not only during the resting state but also during effort, thereby increasing the compensatory ability of cardiovascular system.

If the concentration of blood **glucose** falls under the physiological limit, the CNS neurons sensitive to glucose will be activated, the information will pass to the ANS, which in turn stimulates the adrenals to secrete adrenaline. As a consequence, glucose will be mobilized from liver and fatty acids from fat tissue, the insulin secretion will decrease (hindering the blood glucose to leave circulation) and the insulin-regulated consumption of glucose in the skeleton muscle will be inhibited. If we examine the symptoms at the beginning of a hypoglycemic complication in a diabetic patient (palpitations, agitation, tremor and others) we realize that they can be attributed to adrenaline. In a long-lasting diabetes, however, the answer of the sympathetic NS becomes less important and the mentioned symptoms less expressed.

Cold: The skin and the CNS thermoreceptors can react to a decrease in body temperature by sympathetic activation. The training to cold probably increases the quantity of heat generated as an answer to the sympathetic activation. The regulating center of the body temperature finds itself in the posterior part of the hypothalamus while a warm receptor is being localized in the anterior part of hypothalamus. The latter registers the temperature of the body core - **core temperature**. The skin cold receptors register the temperature on the periphery and send the information on it to the thermoregulation center **(body shell temperature)**. The skin warm receptors seem to be of no importance for thermoregulation. The organism can get rid of the heat by peripheral vasodilation and by sweating. As far as heat generation is concerned, the organism possesses several mechanism. First, by peripheral vasoconstriction heat loss will be limited, second, the heat production will increase through a physical effort, by tremor or due to the caloric effect of an elevated production of thyroxin. The main heat producent in the organism is the Na/K pump.

Another important factor participating in the regulation of the sympathetic activity is **food intake**. Fasting inhibits and excessive food intake stimulates the sympathetic NS. During fasting the activity of the sympathetic NS is inhibited, consequently the basal metabolism is diminished and bradycardia and hypotension appear. Like this organism chooses a lower turnover, regulating its energy consumption towards a more economic way. The influence on the ANS is in this case probably exerted from the center of hunger in the hypothalamus.

Hypoxia also activates the sympathetic NS, probably by activating first the corresponding CNS structures.

The ANS is, to an important degree, involved in the development of **angina pectoris**. We have already mentioned that the sympathetic NS increases the consumption of oxygen by the myocardium through the positive inotropic, chronotropic and dromotropic effects resulting from its excitation. Let us have a look at the symptoms of angina pectoris from this point of view. We known that constant angina pectoris manifests itself in some charge situations. If the blood supply of the myocardium becomes progressively insufficient, it first manifests only in stress situations requiring an optimal perfusion of the myocardium. In such situations the sympathetic NS will be excited and, as a consequence, in agreement with what we have previously mentioned, the productivity of the heart will be increased.

It is interesting to note that chest discomfort more easily appears in a cold environment or as an direct answer to cold, like, e.g., during a walk against cold wind and during angina decubitus, even when the skin enters into contact with cold bed cloth. The cold as such (as we have mentioned above) stimulates sympathetic NS. In addition, as an answer to cold, thyroxin is secreted, further potentiating the effect of sympathetic NS. All this increases the myocardium requirements of oxygen.

Hyperthyroidism comprises symptoms that are without any doubt mediated by the sympathetic NS.

The accentuation of the sympathetic effects is here probably achieved through the beta receptors. On one hand, as an answer to thyroxin, the number of receptors is increased, on the other hand the association of the receptor with adenylatecyclase is favorized. Both of these effects lead to an accentuated reaction to an adrenergic stimulus in the corresponding tissue. As in hyperthyroidism the plasmatic levels of catecholamines rest unchanged (i.e. the activity of the ANS is not directly influenced by thyroxin) we consider the mentioned effects of thyroxin as causal in the relation to the signs of sympathetic hyperactivity in hyperthyroidism.

The ANS activity is also affected in **Parkinsons disease**. The pathophysiology of this disease has not been thoroughly explained yet. In order to approach this problem we must first touch, at least for a very basic reference, the neurophysiology of basal ganglia. It is important to know that the human motor system can be devided into pyramidal and extrapyramidal. However, this division is very artificial. In reality the two parts are very tightly interconnected on several levels and work as a functional unit.

The planning of movements takes place in the basal ganglia. The neurophysiological cascade of voluntary movements starts with the s.c. readiness potential, a diffuse activity on the cortex of both hemispheres, which later concentrates on the associative cortex of the corresponding hemisphere (areas 5, 6 and 7 after Brodmann). The activity then spreads to the cerebellum and to basal ganglia. These pathways then converge in the ventrolateral nuclei of thalamus and continue from there by means of the thalamocortical fibers into the primary motor cortex (precentral gyrus). There the pyramidal pathway is activated. The collaterals of this pathway reach the cerebellum, where fine adjustments of movements take place. (Except the pyramidal tract there are tracts originating in red nucleus - cerebellum, superior colliculus, vestibular nuclei and reticular formation.) This description clearly reveals the key role of basal ganglia in movement preparation. As for every basal ganglion, however, their individual functions remain unclear. The neural signal at this level is processed in 4 pathways. The **main striatum circuit** represents one of them. The excitation of the corresponding cortical region (area 5,6,7) passes through the corticostriate tract to reach the striatum (caudate nucleus and putamen). Both components of the striatum contain precisely described areas, corresponding to precise cortical areas. This underlines the importance of striatum in the architecture of CNS. A projection from striatum to the pale globe (striatopallidal tract) entertains, by means of fascicullus thalamicus, a close relationship to the ventrolateral thalamus. Ventrolateral thalamus provides fibers to the area 4 of the cerebral cortex. The activity of this neural network is modified by 3 circuits:

1. striatum – pale globe – thalamus – striatum
2. pale globe – subthalamic nucleus – pale globe
3. striatum – substantia nigra – striatum

It is namely this third accessory circuit that plays a decisive role in the pathophysiology of Parkinsons disease. Tremor and rigidity are the main symptoms in parkinsonism. The rigidity of parkinsonian type is a consequence of malfunction in the control mechanisms of muscle tonus (the gamma system plays the important role here). Experiments on animals show that a lesion of the substantia nigra evokes **rigidity**. There are still obscure points in our understanding of the pathomechanisms of rigidity in Parkinson's disease as well as of the clinical manifestations of the disease as such. A deficient nigrostriatal pathway seems indeed its most decisive element and the therapy of the disease is oriented to a correction of such deficit. (The locus coeruleus changes in parkinsonism are of unclear consequence on the pathomechanism of the disease.) The substantia nigra is, additionally to the system described, associated by its efferent fibers with superior colliculus and reticular formation (nigrotectal fibers). **Tremor** is explained by a lesion of those structures near the black substance, where its afferent fibers from the cerebellum and the red nucleus pass.

If we consider that we have a lesion of substantia nigra and that the nigrostriatal tract is composed of dopaminergic neurons, in fact we have a deficit in the dopaminergic system. A dysbalance appears with a prevalent activity of the cholinergic neurons. The situation of parkinsonism is, of course, much more complicated, deficiencies of other transmitters like the noradrenaline, serotonin and GABA are implied. It has been impossible to restitute the exact cascade of events until know. The mentioned prevalence of the cholinergic system leads to a manifestation of parasympathetic hypertonicity. Sometimes the salivation is increased, sometimes it is unchanged, but

the deglutination is impaired, other GIT troubles occur, the blood pressure is instable with a tendency to hypotonia.

There is recent knowledge that the disease could be associated with a disturbance in the serotonin-melatonin system (biorhythms). Other sources claim that the primitive damage might concern the glutamate-producing neurons (what seems to be associated with a disturbed NO production) and the deficiency of the dopaminergic neurons is just secondary.

The ANS is equally involved in the pathogenesis of bronchial asthma, migraine, other cases of cefalea, etc. The ANS represents a sort of neuralgic point in the pathogenesis of **terminal states** as they decide about their reversibility. If, in these states, the ANS is disturbed, the homeostasis regulation fails and death appears.

6.24.5.1 Pathophysiology of the ANS

Diseases in which the ANS is primitively concerned can be inborn (consequences of factors having appeared intrauterinary or intra partum), induced by an invasive intervention into the ANS (inflammations, injuries, etc.) or may even be functional in character (alteration in the interconnection patterns of the ANS centers, e.g. based on pathological afferentation). The cause and the character of the problem is often not clear. This can be explained by the open character of the ANS and by a large convergence and divergence inside the system (ANS is influenced by a multitude of other systems and in turn it influences the activity of several other systems).

A classical example of a disease associated with **primitive** alterations inside the ANS is **essential hypertension**. The organs participating in the regulation of blood pressure are the vessels themselves, the heart, the kidney, the adrenal gland, all of them underlying a regulation by the ANS. We shall not explain the details of this regulation here, as it is described in the chapter dealing with hypertension.

An involvement of the sympathetic NS in the development of an elevated blood pressure is evident. However, the evaluation of the degree of its involvement is very complicated, especially because there is a number of factors impaired in hypertension and the temporal consequence in the pathophysiology is difficult to assess. It seems that in essential hypertension the baroreceptor fails to respond to steping over the upper threshold of blood pressure. Hypertension does not improve easily, as the regulation as such is affected, namely its feedback (the afferentation of the sympathetic NS). The baroreceptor is a sensor monitoring changes in blood pressure, not its absolute value. If (e.g. as a result of repeated stress situations) the pressure repeatedly rises as a physiological response to a nonphysiological stimulus, and if this situation does not rapidly improve (in animals stress is usually followed by physical activity, while in man a stress stimulus is usually not followed by physical activity, so that the elevated blood pressure persists much longer), the baroreceptors stop reacting to the elevated blood pressure (they adapt to it). Like this, a nonphysiological value of blood pressure will be interpreted as a physiological one at the level of baroreceptor. Thus, a tendency to react to physiological values as to values in the hypotensive range will appear. The hypertension becomes fixed. Of course, there can be other reasons for a longer lasting elevation of blood pressure, like increased sodium intake, etc. (see chapter on hypertension), but the pathophysiological mechanisms that appear further are thought to be common for those situations.

If we see the problem from this point of view, the therapy of hypertension by vasodilators and diuretics can seem delicate, as both medicaments show a tendency to further activate the sympathetic NS. We must take into account, however, that if their hypotensive effects are maintained for a longer time, they will have the tendency to reset the baroreceptors back to lower blood pressure values. This also gives the sense of such therapy. Then we also understand that the therapy with antiadrenergic agents will be justified.

Dysautonomia (autonomic neuropathy) is a disease englobing the classical neuropathies, with regard to autonomic nerves. It is characterized by structural modifications occurring on the preganglionic as well as on postganglionic neurons. It appears usually as a part of a picture of an overall polyneuropathy (e.g. in diabetes mellitus, alcoholism, to name two most mentioned), or, seldom, as symptoms of an isolated autonomous neuropathy. Among the symptoms we can find orthostatic hypotension (will be explained in detail below), syncopes, anhidrosis, hypothermia, vesical atonia, dry mouth, impotence, etc. Rarely hyperfunc-

tional symptoms are seen: hypertension, diarrhea, hyperhidrosis, sometimes tachycardia.

Orthostatic hypotension is most frequently mentioned as a nosological entity. Principally, we must be aware of the fact that here again (similarly to hypertension) the autonomous system must be affected. Otherwise it would be able to compensate the disorder to a large degree in activating the sympathetic NS. Behind a significant postural hypotension either a deficient intravascular volume can be found (that can no longer be compensated by the ANS) or disturbed circulatory reflexes. Its picture illustrates diseases of the neural system as tabes dorsalis, syringomyelia or diabetes mellitus. But also receptor blockers, given for a therapeutical purpose, can lead to orthostatic hypotension.

In the case of **idiopathic orthostatic hypotension (Shy-Drager syndrome)** the pre- and postganglionic sympathetic neurons are affected. The term "idiopathic" is for its unknown cause. The described neuropathologic changes are located in the brainstem, basal ganglia and intermediolateral column of the thoracic spinal cord. Abnormalities are also found in the peripheral autonomic ganglia. The changes include cell loss and an accompanying gliosis, which are widespread and symmetric, affecting the caudate nucleus, substantia nigra, locus coeruleus, olivary nuclei, dorsal vagal nuclei and sometimes the cerebellum. The s.c. Lewy bodies typical of Parkinsons disease are present in some cases. The disease can manifest all symptoms of dysautonomia. The hypotension does not improve sufficiently after norepinephrine.

We very often hear about the disease state of the ANS designed as **neurovegetative dystonia**. Its etiology is unknown, according to some authors it could be a congenital condition, marked by functional modifications in the integrative parts of the ANS leading to a dysbalance of efferent autonomous pathways. The whole system is destabilized and this becomes apparent when reactions to deviations of regulated variables are required (reaction to the perturbations in the controlled variables) – they are not adequate. Such dysregulation can even impair the symptomatology in question. In psychiatry, for an equivalent dysbalance the term neurasthenia is applied. The instability of the ANS activity can manifest itself as heart rate lability, blood pressure instability, GIT disturbances, troubles of the sweating and of body temperature regulation.

In the **Babinski-Froment syndrome** reflex trophicity disturbances appear, most often following injuries. It is supposed that if there is a predisposition to excessive vegetative reactions then even a small, traumatic or other pathologic process can make such troubles apparent. A modified somesthesia seems to be an important element of the disease. Sometimes osteoporotic changes are found **(Sudeck's atrophy)** accompanied by modified tonus and other symptoms. It is interesting that this disease state does not touch any typical area of innervation of a nerve or nerve root. A similar syndrome is the **algodystrophic syndrome**, with pain being the main symptom.

The sympathetic ganglia of the neck can be involved in pathological processes touching the neck area. Here the **Claude-Bernard-Horner syndrome** (ptosis, miosis and enophthalmus) is associated with a disturbed sympathetic innervation of the eye. If a disturbance in trophicity of a delimited skin area appears (corresponding to the innervated area of the lesioned ganglion) associated with a cervicobrachial or cervicocranial syndrome, it will be designed as **quadrant syndrome**.

Causalgias represent another interesting problem. They are perceived as intense pain, accompanied by trophicity and vasomotor disturbance. They are most often induced by a partial lesion of the peripheral mixed nerve. The manifestation of such lesion is a consequence of interruption of some nerve fibers. In addition, a short circuit of electric activity arises between the vegetative, sensitive and motor fibers on one side and nociceptive fibers on the other. This gives rise to an intensive pain whenever an irritation of the (e.g.) sensitive nerve in the given area takes place. It is a problem very difficult to treat.

Another serious problem are vasoneuroses. They exist in two distinct forms: vasoconstrictive and vasodilatative ones. **Raynaud disease**, for example, is a vasoconstrictive alternative. The etiology of this disease is not clear. The existing dysbalance in ANS manifests itself by paroxysmal vasoconstrictions in the limbs. It is characterized by episodic digital ischemia clinically manifested by the sequential development of digital blanching, cyanosis and rubor of the fingers or toes following cold exposure and subsequent rewarming. Emotional stress may also precipitate this phenomenon. The therapy of this condition is very difficult. Among the vasodilative forms

we can name **erythromelalgia**. Its pathogenesis is supposed similar to that of causalgias.

In the category of rare ANS diseases we can mention, e.g. **facial progressive hemiatrophy (Romberg)**. This disease is the consequence of a traumatic or degenerative lesion of the facial nerve. Its association with encephalitis, sclerosis multiplex, tabes dorsalis and certain tumors has been described. It can also appear as a sign of a neck sympathetic lesion. The disease gives rise to facial neuralgias and trophic changes. It often improves spontaneously and is being considered as benign.

Progressive facial hemihypertrophy (Freidrich) is a disease characterized by facial hemihypertrophy. Contrary to Romberg disease it is not associated with pain. Here a hypertrophy of one half of the face appears (usually the right one). Its etiopathogenesis remains largely unknown, a primitive participation of the ANS is supposed. Its progression usually stops spontaneously.

Diencephalopathy is a term that was frequently used in the past, but has been abandoned recently. It was used to design ANS changes induced by pathological processes in the diencephalon. Today, the term **diencephalic syndrome** is still used for some of them. Here, the etiologies are multiple, from tumors through vascular lesions and injuries to encephalitis. Symptomatology appears only if the lesion is bilateral. There are several centers implied in the food intake regulation in the hypothalamus. Food intake (its initiation and its interruption) can be influenced by opioid peptides and by neuropeptide Y. Lesions of the corresponding regions can lead to troubles of food intake. The hypothalamic type of obesity can be associated with lesion of the ventromedial nuclei of the hypothalamus. In the case of diencephalic syndrome due to some tumors loss of weight with no limitation of food income can be found.

In the hypothalamus, as we have already mentioned, there is also the regulatory center for body temperature. Paroxysmal alterations of body temperature in the sense of hyperthermia as well as hypothermia can be observed, for example, during a hemorrhage into the 3rd ventricle. If the posterior parts of the hypothalamus are touched, poikilothermia is diagnosed (in hypothermia other possible diagnoses like renal insufficiency and hypothyreosis should be eliminated).

Lesions of the anterior part of hypothalamus can lead to insomnia (there are several other structures with such importance in the CNS, e.g. nuclei raphe in reticular formation). If lesions are localized in the posterior part of this structure, the water (and also food) intake can be modified. Rarely a primitive polydipsia without the context of diabetes insipidus can be diagnosed.

Rare cases of **diencephalic epilepsy** with paroxysmal states of sympathetic and parasympathetic hyperactivity have been described (while parasympathetic hyperactivity can be achieved by stimulation of anterior parts of hypothalamus, sympathetic hyperactivity can be induced by stimulation of its posterior part). A classical example of an internal disease associated with sympathetic hyperactivity is **pheochromocytoma**. It is a (most often) benign tumor of adrenals or sympathetic ganglia, secreting catecholamines. It manifests itself by sympathetic hyperactivity and by the presence of an elevated level of vanilmandelic acid in the urine.

Computer models indicate that a part of **A-V blocks** could be the expression of a modified ratio of the sympathetic and parasympathetic tonus. The role of the ANS is equally being considered in the **sudden cardiac death syndrome**.

6.24.5.2 Determination of ANS activity

The activity of the ANS can be evaluated by a test called the **sympathetic skin response**. It consists of measuring the resistance changes on the skin following ANS stimulation by e.g. electrical stimuli, noise or profound inspirium. In these cases we are in fact monitoring the activity of the sympathetic fibers that mediate sweating.

Another possibility is to analyze the **R-R interval variability** on the ECG and to perform it in resting conditions as well as during profound respiration.