

quite rare. It occurs in two occasions, always as a part of a systemic infection (in cases of congenital toxoplasmosis and opportunistic infections of the adults).

The primary infection in the gravid women appears as a mild fever, and enlargement of the lymphatic nodes, as well as some other clinical manifestation. *T. gondii* can affect the intrauterine developing foetus. According to the stage of foetal development the disease might cause discoloration, heavy brain destruction as well as the destruction of other tissues with the consequent foetal death, or foetal brain destruction and chorioretinitis, that are compatible with life, but with a permanent physical affection of the child.

The opportunistic infection of the adults is not always manifested after the contact with the infectious agent. *Toxoplasma gondii* for example survives inside the cyst till the flare up of the disease. This reactivation can occur in cases of disturbed immunity, immunosuppressive treatment, Hodgkin disease, etc. Systemic infections here always lead to a localized meningoencephalitis.

6.17.4.3 Amoebiasis

Amoeba only rarely cause CNS diseases. Practically we know only two types of diseases:

1. **Brain abscess** – often complicates the course of colitis or hepatitis caused by *Entamoeba histolytica*.
2. **Meningoencephalitis** caused by free living amoebas, that are not usual pathogens for man (*Naegleria* and *Hartmannella*). They reach the CNS from the water, where they could be in high concentrations, e.g. when swimming, diving, these microorganisms enter the body via the nasal cavity and the cribriform lamina. The intracranial infection is usually fatal.

6.17.5 Metazoal infections

The important agent of this group is **cysticercosis**. Larvae of *Taenia solium*, that can reach CNS, form cysts and made some complications (intracranial hypertension, edema) or even epilepsy.

6.18 Nutritional, toxic, and metabolic dysfunctions of the brain (encephalopathies)

In the end consequence most of these diseases are caused by abnormal neuronal metabolism, so it is difficult to make an accurate classification. Despite that we might divide those diseases into three groups:

1. Diseases caused by nutritional disturbances.
2. Diseases caused by the effect of extrinsic (exogenous) toxic substances.
3. Metabolic injury of the nervous system that is secondary to other diseases.

6.18.1 Diseases caused by nutritional disturbances

Vitamins of the B group are well known coenzymes of many intracellular oxidative events. Their deficiency, that might result from a primary malnutrition (usually related to alcoholism), is the main cause of degenerative changes of the brain tissue, spinal cord, and peripheral nerves.

Wernicke encephalopathy belongs to this group. It is clinically manifested by disturbances of attention, ataxia, and visual disturbances, without an immediate and effective treatment it will progress fast and cause death in coma. **Alcoholism** and mainly its chronic form is a serious problem of many countries – similar to the case in Slovakia. Chronic alcoholism is related to the disturbance of normal nutrition that by itself leads to vitamin B deficiency, and mainly thiamin. The nutritional disturbances are accentuated by alcoholic vomiting. The pyruvate level in the blood raises. Lesions such as glial proliferation and neuronal absence appear in some typical localities – along the 3rd ventricular wall, along the aqueducts and on the base of 4 ventricle. We might find some small haemorrhages.

The prevention of further progression is done by thiamin intake. Yet if the treatment is inadequate

or late, it is not possible to prevent the permanent brain injury.

6.18.2 Diseases caused by exogenous toxic substances

The nervous system is very sensitive to a number of different substances, poisons, heavy metals, and pharmaceuticals that are commonly used in medicine (e.g. hypnotics, and narcotics).

In many acute situations the metabolism of neurones is prominently blocked and can lead to cellular death. The most common is cerebral hypoxia, and hence metabolic disturbances of the brain cells caused by the injury of other organs, which function is necessary for the provision of adequate function of the brain tissue. So from this point of view it seems that it is very hard to determine the primary cause of many types of brain tissue injury.

The end results of the primary effect are mainly biochemical changes and only minimal or no morphological changes. During autopsy we might find non specific edematous and hypoxic changes. Specific changes are usually not present. In some cases there will be changes in the peripheral nerves – neuropathies. In alcoholism it is hard to document the direct toxic neuronal destruction, but it is probable that the brain is suffering from a nutritional deficiency due to liver dysfunction.

This group includes the metabolic diseases, that are discussed elsewhere. A group of congenital metabolic abnormalities (dysfunction and disturbance of lysosomal enzymes:

1. **Demyelination diseases (leukodystrophy)** in which there is an abnormal metabolism of the central nervous system cells, that form an abnormal myelin.
2. **Diseases that deposit substances in the neurones**, this group is manifested in the first decade of life. Due to the deficit or disturbed lysosomal enzymes there will be accumulation of metabolites or metabolic products in the neurones. The diagnosis depends on the histochemical determination of the accumulated product.
3. **Metabolic diseases** that affects the nervous system together with other organs:
 - (a) **aminoacidopathies** – a wide scale of abnormalities, that mostly affect the hepatic

function (hepatic enzyme defect of many types). The nervous system injury is not always primary, and this is a non specific disease of the nervous system.

- (b) **hepatolenticular degeneration (Willson disease)** in this relatively rare disease there will be accumulation of Cu, that has got some serious toxic effects. This is an autosomal recessive disease, in which there is a primary lysosomal defect in the hepatic cells. Most patients have low levels of ceruloplasmin. The proper relationship between the deficit of ceruloplasmin and the primary deficit of the liver enzymes is yet unknown. We suppose that there might be some abnormalities of the feedback inhibition with the ceruloplasmin deficit that will cause a deficiency in Cu absorption (low Cu: ceruloplasmin ratio).

6.18.3 Secondary conditioned metabolic injury to the nervous system

First of all we have to mention that, the CNS metabolism can be affected by a disease in any other system of the organism.

Acute hypoxia and hypoglycaemia cause disturbances in the basal metabolism of the neurones and a serious disturbance might continue even after the removal of the main cause. In many other diseases, the neuronal injury is commonly reversible, apart from cases that were long lasting. In the last cases there will be a permanent affection of the nervous system in the chronic stage of the original disease. The mechanism in these cases is usually not well understood or defined – it is usually indirect and it contains:

1. Disturbances of water and electrolyte balance (mainly Na^+ and K^+) as well as changes in the pH, that have a prominent effect on the neuronal environment.
2. The effect of abnormal (toxic) metabolites, e.g. ketones, organic acids (including amino acids), directly disturb the neuronal metabolism.
3. The changes mentioned above as point 1. and 2. have a negative effect on the chemical transmis-

sion of stimuli in the synaptic junction of the nervous system.

The mentioned disturbances might occur in those cases for example:

1. Cases of diabetes mellitus, where the most serious disturbances are usually worsened by the effect of other disturbances, these are hypovolemia (due to dehydration), hyperosmolarity (due to hyperglycemia), Na^+ , and K^+ depletion, ketoacidosis, and lactoacidosis.
2. In cases of hepatic failure – and mainly due to disturbances of NH_3 and amino acid metabolism (see hepatic failure) .
3. In cases of renal failure (uremia) – there will be a whole complex of disturbances that lead to water balance disturbances, electrolyte balance disturbance and disturbances of metabolite excretion (see renal failure). Moreover renal failure is usually accompanied by malignant hypertension, that leads to some neurological dysfunctions.

6.18.4 Ethanol

6.18.4.1 The mechanism of action of ethanol metabolites

Ethanol molecule is weakly ionized, and can easily pass via the biological membranes. Ethanol can very quickly reach a state of balance between blood and organs. The effect of alcohol depend on the quantity used. The level of ethanol in the blood is expressed in centiles (promile). Ethanol in higher doses depresses the CNS functions, where as in low doses it causes agitation. Its action is similar to other sedatives, e.g. benzodiazepins, barbiturates, yet it differs from the others by that the psychopharmaceuticals bind a special membrane receptors, whereas ethanol acts on all membranes. It increases the fluidity of the phospholipid fraction of the membrane, where transmethylation takes place. In cases of chronic alcoholism the amount of cholesterol in the membrane wall increases and this will equalize the higher fluidity caused by ethanol. This mechanism is most probably responsible for the developing tolerance to ethanol. The effect of ethanol on the membrane structure will change the membrane permeability for Na and K, and this will decrease the stabilization effect of ions

on the membranes. Those ionic changes will disturb the transmembrane action potentials in the active cells, and the transport of nutrients across the membrane is suppressed. When the level of ethanol in blood is high (0.2%) the function of aerobic oxidase is suppressed mainly in the Liver and myocardium, the ATP turnover is lowered, Creb's cycle becomes slower, and this will lead to disturbances of glucose, lipid, and protein metabolism.

The largest portion of alcohol is absorbed in the jejunum, yet it also passes via the oral mucosa, esophagus, stomach, and the large intestine. When the stomach is empty the absorption is much faster. 2–10% alcohol is excreted in an unchanged form from the lungs, the kidneys, and by sweat glands. Alcohol is metabolized into acetaldehyde via three pathways, and this takes place in the liver:

1. Cytosol alcohol dehydrogenase is a non specific enzyme that contains Zn. It needs a coenzyme NAD, that is reduced into NADH^+ . Any change in the hepatic membrane polarization, and this will depress gluconeogenesis.
2. The microsomal ethanol oxygenase system (MEOS) is usually activated when a high level of alcohol is reached in the blood. The reaction requires NADPH that will produce NADP. In alcoholic people the activity of MEOS is increased by induction.
3. Catalase needs H_2O_2 for the reaction to occur, and this is a limiting factor for its activity. It only slightly participates in the metabolism of ethanol.

The product of all reactions is acetyldehyde, that is a substrate for the enzyme aldehyde dehydrogenase. It is a ubiquitous non specific enzyme. It could be inhibited by disulfiram. An inborn deficiency of the mitochondrial fraction occur in some Chinese and Japanese. This is why manifestation of acetaldehyde intoxication occur in them upon taking a very small amount of alcohol. (And even their habits are formed accordingly, they consume wine in very small amount from a 0.031 glasses). The product of the reaction is acetate, that is metabolized in the Creb's cycle into CO_2 and H_2O .

The behavioral changes upon alcohol abuse are caused by acetaldehyde, and the organic changes upon the parenchymal organs.

6.18.4.2 Changes of behavior, tolerance, dependence

The most important problem of ethanol intake is the problem to determine the maximal daily dose that could not cause dependence nor organic or personality changes. According to Ontario Research Foundation an alcoholic is a person who uses what is equivalent to 150 ml absolute alcohol daily (2.5 dl destilate, or 7.5 dl wine or 5 bottles of beer).

According to specialists "the safe" daily dose ranges between 60 up to 100 g absolute alcohol, reminding that a long term use of such a small amount also causes organic changes. We should not forget that there is an interindividual variability that is very important in the tolerance to alcohol. After 1–2 weeks of regular alcohol use the tolerance increases by 30%. Ethanol has a caloric value of 7.1 kcal (30 kJ)/g. This enables the coverage of the daily caloric need with alcohol drinks. Yet their biological value is minimal, because they do not contain minerals, proteins, nor vitamins. Ethanol lowers vitamin absorption (mainly vitamin B) in the small intestine and hence cause its deficiency. Thiamin deficiency is responsible for Korsakoff's syndrome.

In cases of chronic ethanol abuse (probably due to membrane disturbances) the ionic distribution is changed. The level of K^+ , Mg^{+2} , Ca^{2+} , Zn^{+2} and P in the serum is lower. And the level of Na^+ in the serum is increased because the Na^+ will flow out of cells. The acid base balance might be disturbed as well in term of acidosis. The intake of a higher amount of ethanol might cause a transient hypoglycemia within 6–36 hours. Due to the ethanol effect on gluconeogenesis. The hypoglycemia effect of alcohol is potentiated by poor nutrition. This is why alcoholic patients might develop disturbed glucose tolerance after few days of abstinence.

6.18.4.3 The effect of ethanol on central nervous system

Upon a single use of a high dose there will be some changes in the behavior that depends on the ethanol concentration in the blood and organs. A very low concentration promotes sleep and shortens the REM sleep before midnight, and after midnight the dreams are multiple and nightmares might appear. In some individuals ethanol might cause fragmentation of sleep the so called frequent waking up.

Chronic abuse of alcohol causes peripheral neuropathy in 5 up to 15% alcoholics. The cause is probably thiamin deficiency and acetaldehyde. Patients complain of parasthesia and burning feeling in all limbs, especially the peripheral parts.

A serious complication of alcoholism is Korsakoff's syndrome. It develops in people with an inborn defect of transketolase. Patients with Korsakoff's syndrome show a retrograde and anterograde (disability to learn) amnesia, confabulation (and hence fill the defect in the past events, and they believe their own stories), are emotionally labile. Their intellectual ability is not always affected. Some alcoholics are suffering from cerebellar degeneration. The nervous cells in the cerebellum die due to the toxic effect of ethanol and acetaldehyde. Vitamin deficiency is another co-factor.

Not only cerebellar neurones are affected by ethanol and acetaldehyde. The decreasing brain volume is manifested by an increasing volume of the brain ventricles, and the development of alcoholic dementia. The old doctors used to say that alcohol is the greatest pretender, and in chronic alcohol abusers we might register all forms of psychological diseases e.g. dementia, depression, all forms of psychoses, states of hallucination, and paranoid cases.

6.19 Tumors of the nervous system

Brain tumors can grow directly from the brain tissue, mostly from the microglial cells, from the cranial nerves, or from the brain coverings (meningi). Tumors that arise from the brain tissue usually infiltrate the surroundings, and there are no defined borders between the tumor and the healthy surrounding tissue. Tumors that grow from cranial nerves are called **neurinomes** and those arising from the meningi are called **meningeomes**. They cause pressure on the brain tissue, increase the intracranial pressure and in some localizations they might block the cerebrospinal fluid circulation, and it will accumulate in the brain ventricles. This is how the intracranial pressure is raised and brain edema might