and there will be intracerebral haemorrhage. When bleeding into the subarachnoid space the intracranial pressure increases and the perfusion worsens. Some regulatory mechanisms are activated and these will provide the adequate amount of oxygen supply to the brain. In the area of haemorrhage vascular spasm might occur and this might lead into a secondary brain infarction. In this case the infarction is a complication of the original disease. Examination of the cerebrospinal fluid reveals blood and pink supernatant that remains after centrifugation due to erythrocyte haemolysis. After 24 hr. xanthochromia appears (yellow discoloration of the CSF due to degeneration products of the blood).

6.16 Aging changes and brain tissue atrophy

We know that brain tissue atrophy begins in the 3rd decade and the morphological changes of the brain tissue are associated with aging. The brain volume decreases by 2–3% for every 10 or 20 years and by about 100 g wt from the 30th year of age. Its necessary to mention that these results were collected from many studies and still they don’t contain a wide scale of variability in relation to individual characteristics, life style, geographical and other conditions.

Macroscopically the brain of older people is smaller (the normal weight is about 1380 g in men and 1204 g in women), the arachnoid mater is thicker with a higher number of granulations, the subarachnoid space is thickened, the gyri are narrow and on the contrary the sulci are wide (normally it’s the opposite). The most important microscopic aspect is the reduction of neocortical neurones, as well as the reduction of the number of Purkinje cells layers of the cerebellum and the motor cells of the spinal cord. In cases of senile dementia (as well as in cases of senile Alzheimer dementia) these signs are very marcable. Yet if the dementia occurs in any age, its always accompanied with degenerative or atrophic changes of the brain.

Dementia is clinically manifested with disturbance of memory, new memory and disturbance of the intellectual functions. This gradual disorientation worsens progressively and relatively fast and hence the stage of complete dementia can develop within few years. The wide variability of manifestations of the clinical picture points to the fact, that these changes are not merely related to age. There is probably some multifactorial process. We suppose that a common incidence is related to a high incidence of cardiovascular diseases. Even in those diseases many hereditary factors as well as factors of the external environment could be more accurately specified.

6.17 Infections

CNS infections are in comparison with infections of other localities very rare diseases. The course of CNS infection can be asymptomatic with some minimal pathological changes (e.g. viral infections), yet the course of the infection might be very difficult and may lead to a permanent dysfunction and death.

Generally we devide the infectious diseases of the CNS according to their localization into two groups, those which can cross the barrier formed by pia mater, such as diseases of the meninges (meningitis, empyema and abscess), and those diseases affecting the brain tissue (encephalitis and abscess). The etiopathological agents are usually bacteria, viruses and mixed infections.

6.17.1 Bacterial infections

1. Infections that usually spread via blood. Very common infections to occur this way are infections in the area of subarachnoid space (meningitis) that can be pyogenic (e.g. meningococci, pneumococci and haemophilus), and granulomatous (e.g. tbc, treponema pallidum). If the bacteria sett directly in the brain tissue a brain abscess will form, that could be of two types (pyogenic – mixed infection, staphylococcal infection, or granulomatous – tuberculotic).

2. Infections that cross the blood brain barrier due to the distruction of the protective tissues (dis-
6.17. Infections

In this case we usually have a pyogenic infection. According to the existence of distraction and the entrance of infectious agents to the wound there might be the following results:

(a) extradural abscess
(b) subdural abscess (empyema)
(c) meningitis.

The spread of infection to the cranial cavity can be a very grave complication in cases of untreated pyogenic infection of the middle ear (otitis media), or the cavity system involvement of the mastoid bone. The infection spreads to the bone, and penetrates into the dural spaces (meningitis, infectious thrombosis of the lateral sinus) and hence to the whole brain tissue with consequent abscess formation. In cases of purulent meningitis, the whole subarachnoid space is filled with purulent exudate, that is concentrated in the brain base and fills the gyri. This inflammation in its early stages does not injure the brain tissue itself, and an early effective treatment usually leads to complete healing (primam intentionem). When untreated or upon a non effective treatment some serious complications might appear, that might be some cranial nerve injury, hydrocephalus, and brain tissue injury. The inflammation is diagnosed by examining the cerebrospinal fluid.

Pyogenic brain abscess is the result of direct spread of the infectious agents into the brain tissue (haematogenous spread, bronchiactesis, and a direct entry). The abscess that results from a wound, has usually got less marked clinical symptomatology. The original wound might heal together with the local inflammation far before the abscess is manifested. The abscess is usually covered with a pyogenic membrane. Further development might be towards healing (scar formation) with the possible resulting functional changes and dysfunction (including epilepsy), or towards a gradual development of the disease stage, that is manifested with the developing local edema around the abscess that might increase the intracranial pressure and the abscess rupture into the ventricular system of the brain or the subarachnoid space that leads to the development of meningitis. Other complications of the staphylococcal infection might be microabscesses of the brain, or bacterial endocarditis. The brain pathology in this case is only a part of the general systemic infection.

6.17.2 Viral infections

The viral infections of the CNS are rather rare if compared with the general viral infection. Viruses with higher affinity to the CNS, are called neurotrophic viruses. Generally they cause three types of infection:

- **acute** (cellular injury occurs before the end of the viremic phase of the infection. It is the commonest type of infections)
- **persisting** (viruses that apart from the CNS cause tissue injury, and their behaviour in the CNS is atypical, the active affection of the CNS appears later – months or years)
- **slow** (viruses of this group are not yet classified, and after a long period – years – they cause a fatal disease).

The last group mentioned contains the so called latent viral infections (e.g. herpes zoster), to which we relate the occurrence of demyelination diseases. Viral infections have a great role in the oncogenesis of the CNS.

The site of entry of the viruses to the organism is usually the gastrointestinal tract (enteroviruses), the nasopharyngeal mucous (meningococci), and an interrupted skin cover. Viral multiplication usually occurs outside the CNS tissues (e.g. in the lymphatic tissue). The viruses reach the CNS via a haematogenous spread (viremia). Yet in case of rabies the virus reaches the CNS via the peripheral nerves, and the site of entry is a wound (usually where the sick animal bites the person). Factors that potentiate the occurrence of the disease in the CNS are yet unknown.

Some clinical notice about the viral infections of the CNS:

1. The infection is usually mild, affects the meninges (aseptic meningitis), the recovery is complete, with no residuals.
2. When the course of the disease is severe there will be an associated injury of the nervous tissue of variable degrees (encephalitis, meningoencephalitis). Examination of the CSF reveals
mononuclear cellular infiltration (lymphocytes, plasma cells, mononuclears), protein, glucose. The brain tissue shows a perivascular infiltration and some acutely destroyed neurons due to inflammation (neuronal lysis, inflammatory changes). In certain cases we might observe some neuronal inclusions that might be either nuclear or cytoplasmic. Together with the mentioned changes there might be changes of myelin, glia, and small haemorrhages. The viruses cause injury either directly or indirectly. The virus – antibody complexes, cause the vascular inflammatory reaction.

The clinical manifestations in aseptic meningitis are as follows: the disease is mild, mild fever, headache and stiff neck, the healing is always complete.

In case of meningoencephalitis the signs of CNS irritation appear and the neuronal injury manifests itself as some mental dysfunction, disturbances of consciousness, spasms and coma. There might be some signs of local tissue destruction (neurological symptomatology). If the course is mild, a complete recovery might result yet in some severe cases there might be some residual paralysis, or other signs of a permanent injury of the cerebral tissue. In some rare conditions there might be paralysis of the respiratory center and death might occur.

6.17.2.1 Enteroviruses

Enteroviruses are small RNA viruses (picornaviruses, coxackie viruses, and echoviruses). Infection occur after ingesting food that is contaminated with feces of infected individuals. The virus is replicated in the GIT. It is rare for this virus to cross the blood-brain barrier and cause CNS infection. Polioviruses (sometimes even the coxackie and echoviruses) cause the classical paralytic diseases – poliomyelitis. The pathophysiological development of this disease can be devided into three stages:

1. The acute phase (up to 2 weeks)
2. The reversible phase (few weeks or months)
3. The irreversible phase.

In the acute stage the viremia is manifested with fever. The virus has a high affinity towards the motor neurons in the anterior horn of the spinal cord. The destruction is usually unilateral, and it is surrounded by aseptic meningitis. Some serious complications might occur in this phase due to the paralysis of respiratory muscles, upon the involvement of the bulbar motor centers.

Paralysis occur in the reversible stage of the disease and if the course is mild there might be a complete recovery. The neuronal destruction and degeneration will continue together with gliosis and atrophy.

The irreversible stage is the result of some morphological changes, destruction of the anterior horn motor neurons (scar, thinning of the anterior roots), that is manifested as muscular affection (neuropathic muscular atrophy) and some deformities of limbs (the pull of nonaffected muscles is not opposed by the pull of the affected muscles).

6.17.2.2 The group of herpes viruses

Herpes zoster – is an infection of the adults, that affects one or more unilateral dermatomes (in the course of a certain nerve). There will be a formation of painful vesicles. This is actually a recurrent varicella infection. The virus is in its latent form from the childhood. The virus is usually located in the posterior root ganglia. It might be activated by trauma, radiotherapy, immunological defect etc. After the infection flares up (ganglionitis) the virus slides via the sensory nerve fibers to the skin, and the mucous membrane of the mouth or conjuctiva where it starts its replication. The virus can be isolated from the vesicular content. It should be mentioned that there might be some mild secondary degenerative changes in the spinal cord. In some cases and after the end of the acute stage there will be paraesthesia that lasts for variable period or anaesthesia in the region of injury. When the 5th cranial nerve (trigeminal n.) is affected there might be some serious visual disturbance.

Herpes simplex – even this virus can cause a mild aseptic meningitis in some cases. Only in rare cases it might cause an acute necrotizing encephalitis, and here it mostly affects the temporal lobes. It usually appears in cases where the immunity is deficient, yet in many cases the occurrence of infection could not be explained. Due to the fact that 100% of population is infected by this virus we relate it to a very common vascular disease – atherosclerosis.
6.17.3 Rabies

The rabies virus has got a very strong neurotropic attraction. The disease generally affects mammals. The carriers of the disease are different types of wild carnivorous (wolf, fox, dog, etc). Most of the rabies cases in man are those following a dogs bite. The virus enters the body at the site of bite from the dog’s saliva via the interrupted skin (wound). In the portal of entry there will be local viral replication and the incubation period will start. The incubation period varies from 1–2 months till up to 12 months. The viruses travel along the sensory nerves to the ganglia and spinal roots, and from here they progress to the CNS. Only when the nerve roots are affected and hence the CNS is affected the disease manifestations will appear. Viral encephalitis affects the cerebral gray mater. A diagnostic sign of the disease is the presence of the viral inclusions (negri bodies), that are located in the pyramidal cells of the hippocampus and the Purkinje cells of the cerebellum. Encephalitis is clinically manifested as an extreme excitation of the sensory system. There will be the classical hydrophobia (fear from water) due to spasms of the deglutition muscles and disturbance of swallowing reflexes. Death occurs due to the spasm or paralysis of the respiratory muscles.

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6.17.4 Lethargic encephalitis (post encephalitic Parkinsonism)

Lethargic encephalitis occurred in the form of epidemic in the year 1920. Despite we still do not know the real cause, we suppose it was a viral encephalitis. The unique fact about this disease was that the inflammation affected substantia nigra of the basal ganglia and there were some permanent results – the development of Parkinson disease.

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6.17.2.5 Infections with slow viruses

An example for this type of infection is kuru (subacute spongiform encephalitis). This infection occurs in the eastern parts of New Guinea and it is related to cannibalism. The disease is manifested as a progressive cerebral ataxia and it is always fatal. What is important in the pathological finding is the presence of neuronal degeneration and the absence of astroglial proliferation, that will result in the formation of small cystic areas in the gray mater of the brain (spongiosis). It is very interesting that is no inflammation present. We have to mention that the disease is transmitted by an agent that is resistant against the common physico – chemical factors that usually destroy viruses.

This disease is very similar to Creutzfeld-Jackob disease in men. Some cases of this disease were registered in middle Slovakia, too. The slow viruses were discovered by the american virologist and pediatrition of Slovak origin Charleton Daniel Gajdusek (born in 1923). He received a Nobel price for his discovery in the year 1976.

6.17.3 Infections with yeast and fungi

1. Primary CNS fungal infections are very rare in human being. Some localized infections appear after a long lasting and intensive exposure to a massive infection. In cryptococcal infections (cryptococcus neoformans) the infection shows neurotropism and causes meningitis.

2. Opportunistic infections increase in their frequency of occurrence due to the common use of immunosuppressive treatment. Many fungi including Candida and Aspergillus nocardia can cause a serious brain damage due to abscess formation.

6.17.4 Protozoal infections

6.17.4.1 Cerebral malaria

Brain complication can appear following a heavy acute form of malaria (falciparum), that affects non-immune individuals. This disease progresses very fast to a lethal end. Here there will be a massive affection of the erythrocytes by the parasites, that will cause haemolysis, anemia and a heavy brain hypoxia. This brain hypoxia might also develop as a result of the thickening of the endothelial lining of the brain capillaries with the consequent low cerebral perfusion. During autopsy the brain tissue is edematous with petechie (haemorrhage). Histologically we might see capillary congestion, plasmodium malarial and pigmentation (free or phagocytosed in the macrophages).

6.17.4.2 Toxoplasmosis

Even though infections with Toxoplasma gondii is relatively common, the affection of brain tissue is
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 discouragement, 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. Toxplasma 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.

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**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