3. **Atresia of foramen Magendie and Luschke** that leads to the dilitation of the IVth ventricle, the IIIrd ventricle, and the lateral ventricles.

Acquired hydrocephalus can be caused by many factors. The usual causes are brain tumors (primary or secondary), haemorhage or meningitis, upon which the resorption capacity of the arachnoidea is decreased.

A unique type of hydrocephaly is the so called **secondary hydrocephaly**, that in contrast with the former mentioned types, **is not manifested with high intracranial pressure**. This condition follows an overcommed brain infarction or a generalized brain atrophy, where the ventricular system dilatation comes secondary and this space is then filled with the CSF.

As an outcome of hydrocephally in the newborn and in children with still opened fontanels there will be an expansion of the brainy part of the skull, and a prominent network of cerebral vessels will appear, the childd's eyes will look very much like a sun set, and the percussion of the head will reveal a sound that is similar to the sound of a cracked ceramic pot. The brain is dilated, the CT or sonography reveals a massively dilated ventricular system in the cut sections, the brain tissue and according to the severity of hydrocephaly forms a thicker or a thinner layer on the margins. The brain groves become flattened, and the gray mater might often form only a layer of few mm. Some mental disorders will appear, as well as disturbances of vision, fine motor movements, and other functions. In the adults or in children with closed cranial sutures upon hydrocephaly there will be a raise in the intracranial pressure and the dominant signs and symptoms arise from this syndrom.

6.10 Demyelination disease

The group of demyelination diseases includes diseases, in which there will be a local or a diffused demyelination of the central or the peripheral nervous system. **Demyelination occurs most commonly in the white mater**, and only rarely in the gray mater of the CNS. The loss of myelin sheath can be primary or secondary. Upon myelin sheath destruction the neurons and axons remain intact. The affection of their function is secondary. It is usually not connected to specific neuronal pathways or tracts. There are two types of demyelination disease:

1. **The myelin-classical type** – where the myelin is normal until adulthood, and its degradation occurs later on.

2. **Dysmyelin type** – the myelin is structurally abnormal from the early childhood.

The pathomechanism is yet unknown. We assume that there is **an autoimmune process, viral infection**, or the presence of both processes.

The secondary type might follow a previous injury to the neuron itself, or its axon. This type usually affects certain nerve tracts and hence it is possible to localize the precise anatomical position of the injury. This type of degeneration is typical for more disease groups. As a typical example we may take the degeneration of the neuronal tract as a consequence of a regional infarction.

Demyelination loci create neuritic plaques. The size of these plaques is variable. Histochemically it is a lipid degeneration of the myelin sheaths. The remainder of the degenerated myelin sheaths is removed by macrophages, that together with lymphocytes are geathered around the locus. The older loci are gray and sclerotic (hard). There is no cavitation what so ever. The consequences of the pathoanatomical changes are very similar in both cases (demyelination, the removal of the lipid particles by the phagocytic cells, gliosis).

Not only the covers of the neurons but even the axons themselves are inju red by demyelination. Demyelination causes block of the neuronal conduction of stimuli.

Depending on the recent notes about the pathogenesis some of this disease group are classified under the so known neuroimmunological diseases. A relatively common disease such as multiple sclerosis belongs to this group.

6.10.1 Multiple sclerosis

Multiple sclerosis (MS) is a chronic, primarily **demyelination disease that involves the central nervous system**, and only very rarely the peripheral nervous system. It usually affects the young adults, more women than men (ratio 2:1). The beginning of the

disease is between the 20–40 year of age. As a rule this disease leads fast to a permanent invalidity. The course of the disease can be in bouts, after which the patient's condition always deteriorates, or the disease develops slowly, but continuously. It is interesting to notice the occurance of MS in some geographical areas – almost always to the north of the 40 parallel (the European, and south American zone). According to the geographical position there are some differences in the characteristics of the disease course. Multiple sclerosis in our country affects about 1/1000 citizen (nearly 10 % of all neurological patients). The patients close relatives have the risk of the disease 15 times higher than normal population.

The etiopathogenesis of multiple sclerosis is not clearly understood. There are many theories that attempt to explain the pathomechanism of the occurence and the development of MS, based on **the immuno-genetico-viral etiology**. We expect an interaction between the genetic predisposition and the risk factors of the external and internal environment. Some histocompatibility markers (HLA-A3, B7, Dr2, Bf, DW2) were more often found in patients suffering from MS. According to this theory there was an introduction of a haplotype MS gene marker that has got a low penetration, and it modificates the responce of immune system to the external enviroment antigenes in a wrong direction.

The pathophysiological mechanisms in the development of MS are:

1. **The interaction** between the immune system and the CNS
2. **Demyelination** of the CNS nerve fibers – and the formation of neuritic plaques.
3. **Affecting the CNS** function.

How does the interaction occur is yet unknown. Chronic **viral infection** probably the so called slow viruses – results in a mild inflamatory reaction in the small vesseles of the central nervous system (**vasculitis**). The injury to the vascular wall causes an intermittent local **disturbance of the blood brain barrier**. There is a chance for **the B-lymphocytes** to be in contact with the CNS tissues. As a responce to an antigen the stimulated B-lymphocytes form plasma cells. That start to produce **immunoglobulins G-antibodies** against the provoking antigenic structure. The production of IgG continues during the whole course of the disease, and it increases with the disease exacerbation. It is manifested with a high IgG titer in the liquor, but not in the serum. The number of **T-supressor cells** in the peripheral blood and in the initial stages of MS or its exacerbation prominantly decreases.

There is another theory that claims that the slow **viruses release basic proteins** form the neuronal membranes and hence the myelin sheath cells that are potent **antigenes**. The lymphocytes in the affeted areas initiate the formation of **antibodies against those basic proteins** and they transfer this information about this antigen type to the lymphatic tissues. Here this information is transferred to other generations of lymphocytes. Upon a repeated lymphocyte diffusion into the injured locus in the CNS an immune reaction will occur with the consequent myelin sheath injury (demyelination, plaques, neurological symptomatology).

Together with the previous theory in the past they also mentioned some **metabolic abnormalities of the oligodendroglia**, that have got a direct effect on the myelin sheath metabolism. Probably they tried to find the relationship between small vessel thrombosis in the cerebral field and the demyelination process, or the disturbance of some heavy metal or lipid metabolism in the CNS.

There are some famous experimental work, where the transport of lymphocytes from animals with experimental alergic encephalitis to other animals led to the transport of this disease to these animals. It was proved experimentally that there is **an immunological reaction activated by basic proteins of the myelin sheath**.

The cell mediated immunity leads to the destruction of the normal myelin and oligodendroglia. **This mechanism will then act as a triggering factor for the occurence of demyelination** in the already injured myelin. In this relation the question of vascular injury (**the vascular component of the disease**) remains unsolved. Some studies show that the myelin of patients with MS has got a different composition and mainly in the content of non saturated fatty acids (less). It is not clear wheather it is a congential predisposition or an acquired defect.

Upon evaluating the present information we might say that most of the facts point to **the neuroimmuno-autoagressive mechanism** for the occurance and development of the MS.

From the clinical course: MS most commonly occurs in attacks, among which there are some long or short-lasting remissions, with a basic yet never complete dissapearance of clinical signs and symptoms. The flare up of the disease is usually associated with common cold, another infectious disease, physical or psychological tension (stress, gravidity, lactation, etc.). Patients with M.S. can not tolerate an increased body temperature. The flare up of the disease might raise the plasma calcium level.

The manifestation of the disease depend on the type of CNS affection:

1. **The cerebrospinal form** (the most common, affects the wole body).
2. **The spinal form** (rare, mixed symptomatology).
3. **Cerebello-brain stem form** (relatively rare).
4. **Diencephalic form** (rare, endocrinal disorders).
5. **Polyneuritic form** (rare, demyelination of the peripheral nerves).

MS can be generally devided into 3 forms according to the course of the disease: (1) an acute complicated disease, that leads fast to death, (2) a chronic disease without remissions and (3) a chronic disease with some gradual small changes. A benign process of MS is more common in patients with late manifested disease, on the contrary the young patients usually suffer a malignant course of the disease with prominant immobility.

6.10.2 Acute disseminated encephalomyelitis

Acute encephalitis, in which the dominant and characteristic sign is **demyelination**, it is a very rare complication of some viral infections and post vaccination complications (e.g. chicken pox, rabies etc.). The clinical manifestations of the disease are fever, headache, vomiting, disturbances of consciousness that might end with coma. There might be some neurological signs of focal brain lesion. The pathological changes include the whole brain (mainly in the deep structures of the white mater and pons) and the medulla and their progression is fast. There will be a perivascular cellular infiltration (lymphocytes, plasma cells, macrophages) and demyelination. We might notice cellular infiltration even in the meninges.

6.10.3 The acute haemorhagic leukoencephalopathy

In this condition it is common to notice some tiny petechial hemorhage in the affected vessels mainly in the white mater. This condition is not always the consequence of viral infection. The recent pathophysiology of this process is pointing to the indirect injury of myelin sheath by the viral infection, in other words there is an autoimmune reaction, where the antigen is a part of the myelin and the virus (via yet unknown mechanism) acts as a trigger for this reaction. A very good model for this type of diseases is the so called experimental alergic encephalitis (EAE) in animals. This relatively rare form of encephalitis has got a great value for understanding the pathophysiology of the demyelination diseases, because it forms the transformation from viral infections to chronic demyelination diseases.

6.10.4 Experimental alergic encephalomyelitis

EAE belongs to the group of demyelination diseases (depending on the pathomorphological substrate), and hence to the group of neuroimmunological diseases (depending on the pathophysiological mechanism). It is a disease that is used in **the experimental modeling of the demyelination diseases** in animals. EAE can be brought up (produced) in experimental animals by injecting a homologous or heterologous nerve tissue. First who produced this condition was Rivers in the 1933 in monkies post their 44 or more times innoculation with rabbit brain extract. In the year 1947 Kabat et al. prepared a mycobacteria (Freundd's) adjuvans, that in combination with the nerve tissue antigen might provide surely and in quite a very short time (only upon one or few injections) EAE. It is important to mention that the correlation between the effect of the adjuvans and the human medicine is yet unknown. It was shown shortly after that, the extract from the whole brain contains so many high molecullar weight substances, that we cand't expect the reaction to occur with the

same substance all the time. Many of these antigenically active substances do not have encephalitis generating effect. Finally it was found out that the determinant protein is localized in the myelin.

Injection of the prepared antigen will provoke an imunne reaction, the consequence of which are histological changes in the brain of the experimental animals. The clinical picture is apathy, paresis, paralysis, loss of weight, incontinence, spasms and death. The immunological etiopathogenesis of the EAE is supported by evidences since the 60 yrs:

1. The experimental animals will have signs of sensibilisation after administrating the nervous tissue extract.

2. The disease will appear after 10 days of the day of antigen administration.

3. Upon reimmunisation the latent period is shortened

4. The reaction is very specific. The disease process occurs only after the administration of the antigen that is present in the white mater of the brain and medullary myelin.

The immunological reaction is the delayed hypersensitivity type. This reaction is manifested by the cytotoxic effect of lymphocytes on the antigen containing cells.

We conclude from the mentioned facts that EAE is **an autoimmune disease**, in which the hypersensitivity is experimentally induced by an encephalitogenic component of the nervous tissue (myelin).

The pathogenesis of EAE can hence be the sum of the following:

1. **Lymph node cells sensitization** after the transition of antigen-adjuvans complex via the lyphatic system form the infected site.

2. **Circulation (possibly recirculation) of the immuno competent lymphatic cells** via blood and lymph.

3. **The entrance** of the specifically sensitized cells **into the nerve tissue** via the cerebral circulation.

4. The formation of **contact with the target tissue** (oligodendroglia, and myelin).

5. **The release of chemotactic factors**, that attack other non sensitized leukocytes (a great secondary inflamatory reaction).

EAE can hence occur when antibodies against the administred antigen also react with the same (similar) CNS tissue antigenes.

The possibility to transfer the EAE from an animal with an induced EAE to another healthy animal via a passive transfer of the sensibilized lymphocytes has got a great value in the research of the demyelination diseases.

EAE serves as a model to discover the etiopathogenesis of demyelination diseases. By this way it would be necessary to produce EAE that comes in attacks, similar to the MS for example. Following the formerly explainged method this is not possible yet. EAE also helped in the classification of encephalomyelitis into primary (infectious) and secondary (neuroimmunological).

6.10.5 Dysmyelination diseases

In this group of **leukodystrophies**, the molecular structure of the myelin is disturbed or namely different from the normal. Most of the cases has some genetic basis, that manifest from the childhood and is very progressive. The abnormal or the disturbed enzyme structure leads to the accumulation of different metabolities in the macrophages, glia, or neurons. An example of this might be **metachromic leukodystrophy** with the accumulation of sulfatids, or **Karbbes disease** with the deposition of cerebrosides in the so called globoid cells (polynuclear histiocytes).

We often use the term diffuse cerebral sclerosis in those cases where the abscence of myelin is accompanied with a prominant gliosis.

6.11 Degenerative diseases of the CNS

A large group of diseases belong here. The common sign is the gradual degeneration of neurones and