

Multiple sclerosis

Edited by

Jürg Kesselring

*Head of the Department of Neurorehabilitation
Rehabilitation Center
Valens, Switzerland*

Foreword by Professor W. I. McDonald

National Hospital for Neurology and Neurosurgery, London



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Historical perspective

The past is always with us, never to be escaped; it alone is enduring; but amidst the changes and chances which succeed one another so rapidly in this life, we are apt to live too much for the present and too much for the future.

Sir William Osler, *Aequanimitas*, 1889

Multiple sclerosis is a very conspicuous disease which, when full blown, has signs which no experienced clinician should fail to recognize. Nevertheless, until the Middle Ages, there are no descriptions in medical texts of any disease which we would recognize and diagnose as MS today. A possible exception to this may be the history of Saint Lidwina von Schiedham (1380–1422), a nun from the Netherlands (Medaer 1979). Over the course of 37 years, she showed waxing and waning clinical manifestations of symptoms which could be attributed to disorders of various parts of the nervous system.

The diary and letters of Augustus Frederick d'Este (1794–1848), an illegitimate grandson of the English King George III and cousin to Queen Victoria, do provide a record of a case of MS. In 1822, at the age of 28, he suffered from sudden visual disturbances after having attended the funeral of a close relative: "Soon after . . . and without anything having been done to my eyes, they completely recovered their strength and distinctness of vision." Five years later, while in Florence, both his legs became paralyzed: "I remained in this extreme state of weakness for about 21 days, during which period I fell down about five times (never fainting) from my legs not being strong enough to carry my body." In the following years he writes of "very violent pains" and that "my making water is attend with difficulty." Two years later: "whilst in the act of getting out of bed a considerable portion of stool flowed from me, without my having been made aware of wanting to go to the closed stool." In a note made in 1830, we

can detect a hint of impotence: "I formed a liaison with a young woman – I find my acts of connection a deficiency of a wholesome vigour . . ." Some 13 years later, during which time he had been searching for cures in various spas and with various physicians, he noticed some sensory disturbances: "Sitting produces a numbness all down the back part of my thighs and legs, and gives me a curious numb sensation in the lower region of the belly. When standing or walking I cannot keep my balance without a stick." Three months after this, he records a feeling of vertigo for the first time: "For the first time in my life I was attacked by giddiness in the head, sickness, and total abruption of strength in my limbs." In 1844 Sir Augustus needed a wheelchair, "with which a 'wind-cushion', price 10 shillings, was used." The last entry in his diary was written in 1846, 2 years before his death. His writing is clearly affected by ataxia, the previously fluent, orderly script disintegrating into single letters. He describes the use of an orthopedic aid and ends full of hope: ". . . and I walk without my left foot, which some time ago always turned over outwards at the ankle joint unless supported by a steel upright, showing any disposition so to do. Surely this is a decided improvement! Thanks be to the Almighty!" (Firth 1948; McDonald 1983).

There can be found in several biographies of poets of that time, for example Heinrich Heine (1797–1856) (Jellinek 1990), and Eduard Mörike (1804–1875) (H.J. Grüsser, personal communication 1987), various signs and symptoms of disease which, in retrospect, suggest a diagnosis of MS.

Despite the paucity of historical examples, we may assume that the disease did not exist with the same signs, and certainly not with the same frequency, as it does today.

Jean Cruveilhier (1791–1873) is usually assumed to be the first to have described MS. This assumption (discussed by de Jong 1970, and S. Poser 1986) is based on the first monograph on the disease, which was edited by Charcot's pupil Bourneville in 1869 (Bourneville and Guérard 1869). Cruveilhier was professor of pathological anatomy in Paris and, between the years 1829 and 1842, he published a beautiful atlas with the title *Anatomie pathologique du corps human* (Cruveilhier 1829–1842). In the second volume there is a description of four disease protocols and an illustration of "Maladies de la moelle épinière." The disease is described as "paraplégie par dégénération grise des cordons de la moelle," and Cruveilhier uses expressions such as "en tâches" and "en îles" to describe the pathological processes. He draws attention to the firm consistency of these spots, and was not able to compare them to any tissue in the body known to him. In his opinion, this disease was, like rheumatism, the sequel to suppressed sweating.

At about the same time, Robert Carswell (1793–1857), later to become professor of pathology in London, was working as a student in Paris when he produced nearly 2000 watercolors and drawings of normal and pathological tissues which later formed the basis of his work *Pathological anatomy: illustrations of elementary forms of disease* which appeared in 1838. He describes what we would today call MS as "a peculiar disease state of the cord and pons Varolii, accompanied by atrophy of the discoloured portions." One of his figures mirrors one from Cruveilhier's atlas so closely that it is tempting to assume both authors had used the same preparation as a model.

However, careful research into the years of these publications shows that the relevant figures in Cruveilhier's atlas, which was produced in 40 "livraisons," cannot have appeared before 1841, whereas Carswell's work was finished and published in 1838. Thus, the first patient whose disease was diagnosed as MS was French, but the lesions which formed the basis of the disease were depicted for the first time by a Scotsman (Compston 1988).

The dispute as to who was the first to describe MS – Cruveilhier or Carswell – might be resolved by the atlas *The morbid anatomy of the human brain, illustrated by coloured engravings of the most frequent and important organic diseases to which that viscus is subject*, by Robert Hooper

(1773–1835), which was published in 1828 in London by Longman, Rees, Orme, Brown and Green (Hooper 1828). Hooper was a pathologist and practicing physician in London and he based his atlas on his experiences, gained over 30 years, of more than 4000 autopsies which he had performed at the St Mary-le-bone Infirmary (McHenry 1969). He describes "Diseased structures, and unnatural appearances without tumefaction: Morbid firmness, hardness, or induration . . . is not uncommon in the substance of the brain . . . It is mostly accompanied by a dark hue . . . With this preternaturally great cohesion of its particles, the brains feels not merely firm, but morbidly hard, and the cut surface does not show the natural number of blood-vessels in the medullary substance, nor does it receive the impression of the finger readily: and when the finger is removed, it quickly rises to its level . . ." and later: "The delicate colour of the medullary substance frequently undergoes a change. I have seen it of palestone or albine colour . . ."

The first clinical descriptions of MS were by Frerichs in Göttingen, Germany, and appeared in the middle of the last century (Frerichs 1849). Frerichs' clinical diagnosis of "Hirnsclerose" was challenged until, in 1856, his pupil Valentin reported pathological findings from patients who had died and pronounced his master's clinical diagnosis to be "so brilliantly confirmed by postmortem examination." He highlighted a symptom which was later often neglected: "Psychological disturbances of higher degrees accompany the degeneration of the brain almost regularly." Treatment was very limited: "Without sanguinic hope of success he ordered the use of iodine potassium."

Rindfleisch, in Zurich in 1863, first identified the pathological changes of the blood vessels: "their wall is enormously thickened by the aggregation of nuclei and cells in the adventitia." He considered "often recurrent or persistent irritations of the entire central organs" to be a primary event, and changes in the parenchyma to be secondary phenomena: "The neuroglia undergoes a series of metamorphoses in continuation of the formative irritations from the vessel walls to the neighbourhood. This process carries throughout the mark of scantiness."

A vascular theory of MS was adhered to for several decades (Putnam 1933). It was based on the observation that plaques develop mainly in the neighborhood of small veins in which, from

time to time, organized thrombi can be found. This theory led to several therapeutic trials with vasoactive substances and anticoagulants, but with no success.

Leyden (1863) summarized the state of knowledge of that time as follows:

1. women are affected much more often than men (25:1).
2. the onset of the disease is usually between the 20th and 25th year,
3. there had been only a single hereditary case,
4. there are two main etiological factors: exposure to cold and wet, and trauma,
5. psychological events are important in triggering the disease.

Jean Marie Charcot (1825–1893) gave the first comprehensive description of MS, describing its clinical peculiarities in his famous lectures at the Salpêtrière in Paris (Charcot 1872–1873; McDonald 1993). He distinguished myotrophic lateral sclerosis from MS, and evaluated tremor not as a disease but as a symptom. He clearly distinguished intention tremor from tremor with Parkinson's disease. The "classical symptom triad" of nystagmus, intention tremor, and scanning speech which is named after him was not considered important by Charcot himself, and he stressed repeatedly that the lack of one, or even of all three, of these symptoms could not preclude the diagnosis. He also drew attention to benign cases of the disease (Charcot 1879). As a successor to Vulpian to the chair of pathology, and possibly in collaboration with him, he elaborated the histology of MS and produced drawings of myelin loss and preservation of axon cylinders, proliferation of glia, and perivascular phagocytes containing fatty deposits (Charcot 1868).

Charcot maintained that the cause of the disease was unknown. He assumed it to have some connection with acute infection, and described cases in which it had been preceded by infections such as typhus, smallpox, or cholera. He also mentioned an association with exposure to cold, and with emotional factors such as grief, shock or trauma.

In 1906, Marburg described an acute form of MS which is still named after him. He postulated a myelinolytic toxin as a causal factor. This toxin theory was supported for several decades and received particular attention in the work of Baasch (1966), who thought the disease was caused by a chronic mercury infection from

amalgam fillings in the teeth. Despite his elegant arguments, his conclusions were not confirmed.

The theory that MS is an infectious disease has had its supporters for more than a century, since Charcot and Pierre Marie (1884) (Larner 1986). In the 1930s, it gained new impetus following the observation that the histological picture of perivenous demyelination in postinfectious and postvaccination encephalomyelitis could not be distinguished from that seen in MS (Brain 1930).

On many occasions, specific organisms were isolated and considered as etiological factors. The search for viruses which could be responsible for MS is always accompanied by the same hope and confidence which, in the case of poliomyelitis, were rewarded by vaccination against poliomyelitis viruses. Various viral diseases in humans and animals may lead to changes in the central nervous system (CNS) which, histologically and otherwise, resemble MS. In viral disease, there may be focal inflammation as well as primary demyelination. The recognition of virus persistence in the CNS gave an important impetus to the search for a viral etiology for MS. Several chronic CNS diseases in animals (visna, scrapie, mink encephalopathy) and in humans (Creutzfeldt–Jakob disease, kuru) may be associated with transmissible agents. However, conventional viruses such as measles are also able to persist within the CNS under certain immunological conditions, such as in the case of subacute sclerosing panencephalitis (SSPE). Since the early 1960s, the measles virus has often been implicated in MS (Adams and Imagawa 1962) following the discovery on several occasions of elevated antibody titers against measles in some MS patients, and the detection of the measles viral genome in the brains of some people suffering from this disease (Haase et al. 1981). The fact that positive findings have not been found in all brains and body fluids examined does not exclude the possibility of an etiological connection. However, in the case of the measles hypothesis, definitive proof is lacking. If there were a causal relationship, vaccination against measles, which has been practiced for over 20 years in the U.S., should lead to a significant reduction in the incidence of MS in the near future. An association between MS and other viruses, such as rabies, parainfluenza, cytomegalovirus, corona, herpes simplex etc., has

Pathology and experimental models

INTRODUCTION

Multiple sclerosis is one of the neurological diseases which were defined relatively early in the history of medicine. Descriptions of its macroscopic pathology first appeared during the 18th century, and a detailed summary of histological findings was given by Charcot (1868), whose basic study of MS can be regarded as the starting point for the intensive research into its clinical features, pathology, and pathogenesis which followed.

The clinical definition of MS includes a chronic relapsing or progressive disease course, and signs and symptoms which suggest the presence of multifocal lesions in the CNS. Neuroimaging, electrophysiology, and laboratory tests on the cerebrospinal fluid (CSF) may also help to establish the clinical diagnosis. In neuropathological terms, MS is defined as an inflammatory demyelinating disease of the CNS, which is characterized by chronic perivenous inflammation, multifocal plaquelike demyelination, and reactive glial scar formation. It is obvious that this neuropathological definition not only includes the typical cases of chronic MS, but also atypical cases of acute or monophasic manifestations of this disease. In addition, on the basis of neuropathology, MS is only one member of a larger family of diseases, the so-called inflammatory demyelinating disorders (Hallervorden 1940; Adams and Kubik 1952). These diseases may have an acute or chronic course, they may affect both the central and the peripheral nervous systems, and they may also present as transitional forms between the more clearly defined disease entities (Marburg 1906; Hallervorden 1940; Adams and Kubik 1952; Krücke 1973). For example, combined forms of

acute disseminated or hemorrhagic encephalomyelitis with MS have been described (Krücke 1973). In some MS patients, the peripheral nervous system may be affected with inflammatory demyelination similar to that found in the lesions of the CNS (Marburg 1906; Jellinger 1969; Lassmann et al. 1981a; Lassmann 1983a).

Although such acute and transitional cases are somewhat atypical, and represent only a small minority of all MS cases, their rapid progression and disease activity make them especially suitable for studies on the mechanisms of inflammation and demyelination of this disease. Thus, most of the data presently available on the pathogenesis of MS are, in fact, derived from studies of these atypical cases. In time, it should become apparent to what extent pathogenic concepts derived from the study of acute MS cases are truly applicable to chronic manifestations of the disease.

THE PLAQUES

The essential lesions of MS are the confluent demyelinated plaques scattered throughout the brain and spinal cord (Fig. 2.1). The macroscopic and histological appearances of these lesions were described in detail at the beginning of this century (Marburg 1906; Siemerling and Raecke 1914; Dawson 1916; Hallervorden 1940). In chronic, inactive MS, the plaques appear macroscopically as pale-gray, sharply demarcated, round to polygonal, frequently confluent lesions. On the lesional border, fingerlike extensions which follow the distribution of small venules can be seen entering the plaque (Dawson 1916; Fig. 2.1). Due to the astroglial scar tissue formation, the tissue texture is more dense

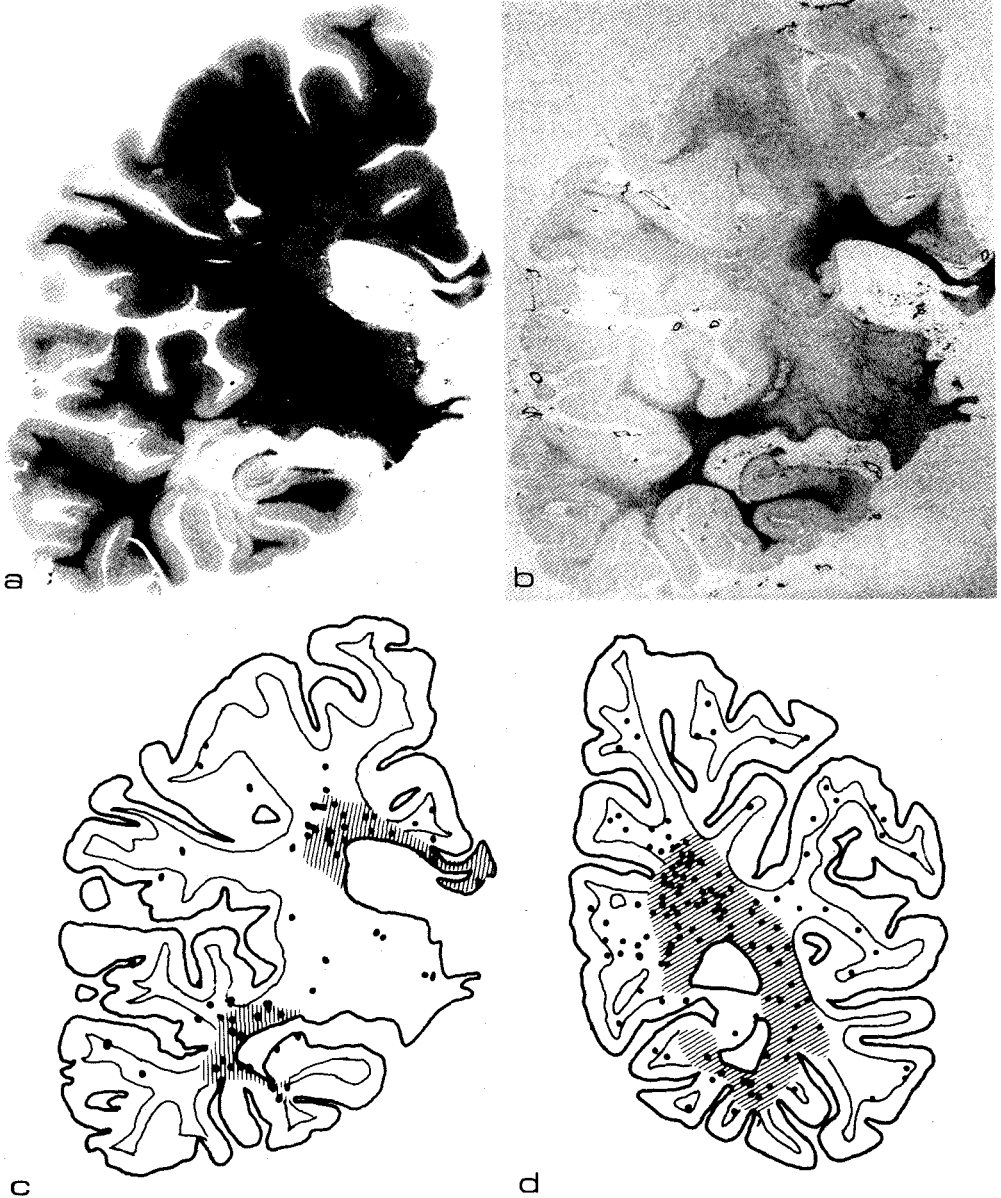


Fig. 2.1. Distribution of plaques in the CNS in active MS: large confluent demyelinated plaques with reactive gliosis in periventricular sites. (a) Luxol-fast blue myelin stain; (b) Kanzler stain for glia scar formation. $\times 1$. (c) Diagram of inflammation (points) and demyelinated areas (shaded) in the areas shown in (a). (d) A similar

diagram of inflammation and demyelination in the occipital lobe of the same patient. Inflammatory infiltrates are not restricted to areas of demyelination, but are also present in high density in the surrounding "normal" white and gray matter.

in the plaques than in the surrounding tissue. Although plaques are located in both the white and gray matter of the brain, the color difference between myelinated and demyelinated tissue means that they are more clearly visible

without the aid of a microscope in the white matter.

Histologically, the plaques are characterized by complete loss of myelin. In most of the lesions, oligodendrocytes are also lost, or are at

least greatly reduced in number. In comparison to the myelin sheaths, axons are relatively well preserved in the lesions, although there is frequently some reduction of axonal density within the plaques. A typical feature of chronic inactive lesions is an intense glial scar formation (Fig. 2.1), characterized by an increased number of astrocytes and their cell processes, which are densely packed with glial filaments. These cells and their processes represent the majority of the cellular matrix between the demyelinated axons of the plaques. The myelin sheaths of nerve fibers which enter a plaque from the normal white matter terminate at a node of Ranvier, whereas the demyelinated axon can be traced into the demyelinated plaque, in what is known as segmental demyelination. Nerve fibers with atypically thin myelin sheaths and short internodal myelin segments are frequently found at the borders of inactive chronic plaques. These thin myelin sheaths seem to be the result of a limited degree of remyelination (see Fig. 2.5).

Besides demyelination, characteristic alterations of medium-sized or larger vessels are typical in inactive MS plaques. Light microscopy shows an intense perivascular fibrosis (Spielmeyer 1922). Under the electron microscope, the perivascular spaces appear to be dilated, and the perivascular glial limitans is separated from the vessel wall by septated connective tissue spaces which in many respects resemble small lymphatic vessels (Prineas 1979). It has not yet been determined whether these structures represent true lymphatic drainage sites (Prineas 1979), or simply connective tissue proliferation due to the chronic inflammatory process (Lassmann et al. 1981b).

Active MS plaques are different from inactive lesions in many respects. Macroscopically, active lesions are pink (salmon red) and less well demarcated than inactive ones. In addition, the active lesions have a soft consistency, possibly even softer than the surrounding normal brain tissue. Under the microscope, the characteristic feature of selective loss of the myelin sheath is visible. Although axons are relatively preserved in comparison to myelin, acute changes of axonal degeneration are frequent. The oligodendrocytes are difficult to evaluate, since in lesions with extensive inflammatory infiltration, differentiation between them and inflammatory cells is only possible with specific markers. However, as discussed below, the numbers

and structural features of oligodendrocytes within the lesions may vary in different MS patients. The tissue in active plaques appears spongy due to massive edema, and is heavily infiltrated by macrophages which are loaded with myelin degradation products (Fig. 2.2). In between, highly activated polymorphic and bizarre-looking astrocytes are present in the lesions, and these may sometimes give rise to diagnostic confusion with brain tumors.

Three main criteria are used to separate active from inactive lesions: the increased cell density, the ill-distinct plaque border, and the presence of macrophages with lipid debris. However, none of these three criteria is really reliable. Both the increased cell density due to inflammation, and the presence of macrophages with lipid debris may be present in lesions for a long time, possibly up to 6 months after the initiation of the lesion (Lumsden 1970). Similarly, the indistinct border of a demyelinated plaque frequently represents remyelination and not active demyelination (Prineas and Connell 1979; Lassmann 1983a). Thus, actively demyelinating lesions should be identified by the presence of initial myelin degradation products in the macrophages (Seitelberger 1969; Figs. 2.2 and 2.3).

Apart from the typical MS plaques described above, other lesions have been described in the literature.

Shadow plaques

Shadow plaques are mainly found in the brains of patients with either acute or chronic progressive MS (Lumsden 1970; Lassmann 1983a; Prineas 1986). They are similar to other chronic MS plaques in that they are sharply demarcated from the surrounding normal white matter. They are either found at the margin of large demyelinated plaques or are present as independent lesions (Fig. 2.4). Shadow plaques show a uniform reduction of myelin density due both to the presence of unusually thin myelin sheaths around the axons and to some reduction in axonal density. Like other chronic MS plaques, shadow plaques are characterized by dense astroglial scar formation. In rare instances, the early stages of shadow plaque formation may be associated with signs of ongoing lesional activity (Lassmann 1983a; Prineas 1986). For many years they were regarded as incompletely demyelinated lesions (Lumsden

Furthermore, the MS brain contains changes which are secondary to the presence of demyelinated plaques. These changes have been categorized as MS encephalopathy, and are mainly present in patients with longstanding severe disease (Jellinger 1969; Seitelberger 1973). They include secondary Wallerian degeneration due to axonal loss in plaques, chronic edema, and brain alterations induced by the poor general health of the patients, for example malnutrition, chronic infections, or uremia.

Wallerian degeneration in MS is due to axonal damage in demyelinated plaques which may be quite variable from case to case. In severe cases, it may lead to degeneration of long ascending and descending tracts as well as to a diffuse reduction in the volume of brain white matter. This may finally result in severe brain atrophy, with dilatation of the ventricles and the subarachnoid space.

An additional factor which may damage the nervous tissue outside the plaques appears to be the chronic inflammatory process itself (see Fig. 2.1). This leads to chronic disturbance of blood-brain barrier function, and to direct toxic effects of inflammatory mediators. Both a direct effect of certain cytokines as well as chronic edema can stimulate astrocytes, and thus result in scar formation.

DISTRIBUTION OF PLAQUES IN THE NERVOUS SYSTEM

A characteristic feature of MS pathology is the disseminated distribution of demyelinated lesions throughout the brain and spinal cord. Although plaques may appear at random in any areas of the CNS, certain predilection sites for plaque formation have been described (Steiner 1931; Hallervorden 1940; Fog 1950; Lumsden 1970; Oppenheimer 1978). In the brain, these sites include the periventricular white matter, especially at the lateral angle of the cerebral ventricles (see Fig. 2.1). Other areas with a high incidence of demyelinated lesions are the optic system (optic nerves and chiasm), the cerebellar peduncles, the cerebellar white matter, and the cortico-subcortical junction, particularly in cortical sulci. Within the spinal cord, the lesions are concentrated in the cervical portions, located mainly in the lateral columns (Fog 1950; Oppenheimer 1978).

The topographical distribution of plaques can be partly explained by the distribution of post-

capillary venules in the CNS. Since MS lesions in general arise around a central vein, the probability of an initial inflammatory focus is greater in areas with a high density of postcapillary drainage veins. In addition, however, the concentration of MS plaques at the inner or outer surfaces of the brain and spinal cord suggests that additional factors derived from the CSF may precipitate the lesions.

An additional indication that blood-brain barrier damage may facilitate the formation of plaques comes from observations that demyelination in MS may occur at sites of brain damage which are unrelated to the disease. Although a combination of MS with other brain diseases is rare (Jellinger 1969), demyelinated plaques can sometimes be found around small infarcts or vascular malformations.

A dogma of clinical neurology is that MS is a disease which is specific to the CNS. When lesions in the peripheral nervous system are found, the diagnosis of MS is questioned. This is justified in typical chronic MS, where pathological changes of the peripheral nervous system are mainly due to secondary axonal degeneration resulting from destructive spinal cord lesions or may reflect neuropathies in the course of metabolic disturbances or malnutrition (Hasson et al. 1958). In rare instances, however, primary demyelination can be found in the peripheral nervous system of chronic MS patients.

The situation is different in Marburg's type of acute MS. In this disease, primary inflammatory demyelination in the peripheral nervous system is common (Marburg 1906; Lassmann et al. 1981a; Lassmann 1983a). Although, due to the small number of cases described, a clear incidence figure cannot be given, it has to be considered that in Marburg's original description, all patients with acute MS showed peripheral nervous system involvement. Thus the presence of inflammatory demyelination in the peripheral nervous system does not rule out a diagnosis of MS.

DEVELOPMENT OF PLAQUES

In spite of many years of research, our understanding of the development of plaques in MS is still incomplete. There are several reasons for this.

Actively demyelinating lesions are rare in autopsy material from patients with chronic MS.

Thus most of the published data are taken from the study of active lesions from patients with acute, subacute, or atypical MS. It is not yet proven whether the pathogenesis of demyelination is the same in acute and chronic MS.

Furthermore, biochemical and immunological studies of active MS lesions are hampered by the difficulty of identifying such lesions macroscopically, and there are no biochemical markers available which allow the identification of the early stages of demyelination. Thus, the interpretation of the immunological findings in MS lesions is to a large extent based on analogy with experimental models of the disease, an approach which has not been proved to be justified.

There is little doubt that in inactive plaques of chronic MS, myelin and the large majority of oligodendrocytes are destroyed, whereas axons and nerve cells are relatively preserved. Such selective damage to the nervous tissue can be induced by several different mechanisms (Wisniewski 1977).

- a. Primary damage of myelin sheaths may be followed by secondary degeneration of oligodendrocytes.
- b. Myelin and oligodendrocytes may be damaged simultaneously in the course of plaque formation.
- c. A primary cytolytic affection of oligodendrocytes may lead to secondary myelin destruction.

The clarification of these points is central to the understanding of the pathogenesis of MS.

Myelin

The alterations in myelin sheaths in active lesions were described in detail during the first decades of this century. In the plaques, myelin sheaths are selectively destroyed, and axons are relatively well preserved (Figs. 2.2 and 2.5). In actively demyelinating lesions, the myelin sheaths appear thin, with irregular pale-staining properties, or they may be transformed into small, granular degradation products (Marburg 1906; see also Figs. 2.2 and 2.3). In the early studies, an irregular destruction of the myelin sheath was described, which starts focally at any point in the internodium and then extends along the entire myelin segment (Marburg 1906). In addition, close contact between macrophages ("gitter cells") and the damaged my-

elin sheath, as well as the uptake of myelin fragments into macrophages were described early in the history of MS research (Babinski 1885). Further details of the patterns of demyelination were discovered using electron microscopic techniques.

Two different patterns of myelin destruction have been described. The first consists of an interaction of phagocytic cells with the myelin sheaths (Prineas and Connell 1978; Prineas 1986). These cells then take up small fragments of myelin. Contact between myelin and macrophages is frequently established through "coated pits," and myelin degradation products can then be found in macrophages in "coated vesicles." A similar pattern of phagocytosis is found in receptor-mediated uptake of macromolecules (Goldstein et al. 1979), and has also been described in the course of the phagocytosis of particulated immune complexes (Montesano et al. 1983; Mellman and Plutner 1984). This sequence of demyelination may thus suggest that myelin, opsonized by specific antibodies, is attacked by macrophages in the course of demyelination (Prineas 1986).

In less common instances, especially in cases where the inflammatory reaction is extensive and severe, an invasion of macrophages into myelin sheaths can be seen (Prineas and Raine 1976; Lassmann 1983a; 1983b), a mechanism which is similar to the "myelin stripping" observed in experimental autoimmune encephalomyelitis (see Fig. 2.2d). In addition, in acute cases with very severe inflammation, myelin sheaths may be transformed completely into vesicular material – "vesicular disruption of myelin" (Lassmann 1983a). It is not clear whether this vesicular transformation is a genuine pattern of demyelination or is mediated by autolysis of predamaged myelin sheaths. Furthermore, in some cases alterations in oligodendrocyte processes, described as "dying back oligodendroglialopathy" have been observed, that indicate a primary affection of oligodendrogenesis in the pathogenesis of demyelination (Rodriguez et al. 1993).

The myelin fragments which are taken up in macrophages are degraded within these cells to cholesterol esters and triglycerides (Seitelberger 1969). The earliest degradation products are small granular cytoplasmic inclusions in macrophages which have the same histochemical and immunocytochemical staining patterns as normal myelin (see Figs. 2.2 and 2.3). Under the

electron microscope, the degradation products can be seen to be built up by lamellated myelinlike inclusions. The initial chemical degradation of these inclusions can be visualized by the positive Marchi or OTAN reaction, which suggests an increase in hydrophobicity of the material compared to normal myelin (Hallpike and Adams 1969). The presence of these early myelin degradation products is at present the safest criterion for the identification of actively demyelinating plaques in MS (Lassmann 1983a; Prineas 1986). In later stages, the myelin degradation products are transformed into neutral lipid droplets (see Fig. 2.3) and some PAS-positive intracytoplasmic granules with a polymorphic ultrastructural appearance (Prineas 1975) which are removed from the tissue very slowly, and can be found within the lesions up to 6 months after plaque formation.

In actively demyelinating lesions, the macrophages are concentrated at sites where myelin sheaths are in the process of destruction (Seitelberger 1969; Prineas and Wright 1978; Hofman et al. 1986). In later stages, debris-containing phagocytes accumulate in the perivascular spaces (see Fig. 2.3). In spinal plaques which are touching the surface of the cord, debris-containing macrophages also drain into the CSF (Marburg 1906).

The vast majority of myelin degradation products are found in macrophages ("gitter cells"). In addition, however, debris may also be present in astrocytes in the form of small osmiophilic inclusions (Marburg 1906). Myelin degradation in astrocytes has been shown in vitro (Raine and Bornstein 1970b), in Wallerian degeneration, and in autoimmune encephalomyelitis (Lassmann 1983a). The conditions which stimulate astrocytes to become phagocytic cells in certain MS lesions are undefined.

Oligodendrocytes

Although in completely demyelinated, inactive plaques of chronic MS the population of oligodendrocytes is greatly reduced, or even completely lost (Prineas 1986), in the periphery of such lesions a variable number of oligodendrocytes is present which are engaged in the remyelination of nerve fibers (Prineas and Connell 1979; see also Fig. 2.5). It is, however, not clear whether these oligodendrocytes were preserved during the demyelinating process or whether they were recruited from a reserve pool of undifferentiated precursor cells.

In early ultrastructural studies, alterations in oligodendrocytes were described which mainly consisted of cellular edema, shrinkage of cytoplasm, condensation of the nuclei, and defects in cell membranes. However, it was difficult to differentiate these cells from the degenerating inflammatory cells which are frequently encountered in active MS lesions. Sometimes oligodendrocytes can be found embedded in the cytoplasm of other cells, in particular of astrocytes (Prineas 1986). However, in spite of complete demyelination, oligodendrocytes may be preserved either at the plaque edge (Raine et al. 1981) or even in the center of the lesions (Brück et al. 1994; see also Figs. 2.2 and 2.4).

Additional evidence which argues against a primary affection of oligodendrocytes comes from the comparison of MS lesions with those formed in disease with primary viral infection of oligodendrocytes. In progressive multifocal leukoencephalopathy (PML), the lesions are formed by the confluence of small demyelinated areas which correspond to the myelin territories of single oligodendrocytes. This gives the lesion a microscopic appearance reminiscent of moth-eaten tissues. Such lesions are fundamentally different from MS plaques, which are sharply demarcated from the normal white matter and are not associated with oligodendrocyte territories.

These data, taken together, indicate that at least in the majority of MS cases, the myelin sheath is the primary target of the destructive process, whereas oligodendrocytes may simultaneously or secondarily be affected in the course of myelin destruction. This interpretation is challenged by the observation of a disproportionately greater loss of myelin-associated glycoprotein (MAG) in comparison with other myelin proteins in MS lesions. Since MAG is mainly located in peripheral oligodendrocyte processes, these data were interpreted as an indication of primary oligodendrocyte dystrophy in MS lesions (Itoyama et al. 1980). Similar changes were also found in PML, which was taken as a model disease for primary virus-induced damage to oligodendrocytes, but were absent in the demyelinating lesions induced in the course of autoimmune encephalomyelitis. The experimental proof that oligodendroglia damage is a cause of the preferential loss of MAG is still missing. Furthermore, in experimental models of oligodendrocyte infection and virus-induced demyelination, a disproportionate loss of MAG was not found

(Vandeveldel et al. 1983; Dal Canto and Barbano 1985). Similarly, the preferential loss of MAG was not present in MS plaques obtained from early autopsies with excellent tissue preservation (Prineas et al. 1984). Thus the extent to which minor myelin proteins such as MAG may be degraded more quickly than major myelin components in autopsy tissue has to remain unresolved.

With the availability of new markers and the development of new technologies, the fate of oligodendrocytes in MS lesions has again been addressed in recent studies. In some cases, evidence has been provided that oligodendrocytes may be completely destroyed in active lesions, but that new ones may be rapidly recruited from a pool of undifferentiated precursor cells (Prineas et al. 1989). The extent of remyelination appears to be partly determined by the availability of such precursors. In experimental systems, repeated demyelination and oligodendrocyte destruction within the same lesions may deplete this precursor pool and may lead to the establishment of persistently demyelinated plaques without remyelination (Ludwin 1980; Linington et al. 1992a). Other studies, however, led to different conclusions. The preservation of oligodendrocytes was described in early active lesions, and the cells were then lost at later stages in the formation of persistently demyelinated plaques (Selmaj et al. 1991a).

These somewhat conflicting results from different studies into the fate of oligodendrocytes in MS lesions may also be explained by an inherent variability in the development of plaques in different patients. In our own material, we found evidence for oligodendrocyte destruction together with a limited remyelination through precursor cells mainly in cases of chronic MS. In patients with very short disease duration, on the other hand, the majority of oligodendrocytes were preserved in the lesions, and rapid and complete remyelination was found throughout them (Lassmann 1983a; Brück et al. 1994; Ozawa et al. 1994). These data indicate that the mechanisms leading to demyelination may differ in patients with short- and long-standing disease duration (see also Chapter 5).

Astroglia

It is now well established that the alterations of astrocytes in MS lesions represent, at least in part, a secondary reaction to demyelination and

tissue damage. In chronic MS lesions, astrocytes are moderately increased in number, and provide a network of processes which are densely packed with glial fibrils. These cell processes form a dense glial scar, in which demyelinated axons are embedded (see Fig. 2.3).

In active lesions, especially in cases of short disease duration, a protoplasmic glia reaction is mainly encountered (Field et al. 1962). The astrocytes appear as large, polymorphic cells with abundant cytoplasm, and may be multinucleated (see Fig. 2.2d). This pronounced astroglia reaction may sometimes imitate the pathology of a low-grade astrocytoma. However, the incidence of gliomas in MS patients is no higher than in members of a control population (Lumsden 1970).

Since alterations to the astrocytes similar to those described above can be found in a variety of other CNS diseases, they can be interpreted as a secondary reaction to tissue injury. There are, however, some aspects which may indicate an additional affection of astrocytes related to the immunological disease process. At the plaque edges of established lesions, the glia reaction may be found to extend a considerable distance into the surrounding normal white matter (see Fig. 2.3b, c), and may even be found in areas devoid of demyelination or secondary Wallerian degeneration (Allen and McKeown 1979). In addition, the increased activity of proteolytic enzymes found in the normal white matter of MS patients may be associated with increased lysosomal activation in astrocytes (Allen and McKeown 1979; Allen 1983). This general activation of astrocytes may be partly explained by the inflammatory reaction, since certain inflammatory cytokines may activate astrocytes (Fontana et al. 1980).

Another factor which points toward an immunological role of astrocytes in the lesions is the expression of histocompatibility antigens. T-cells recognize their antigens only when they are presented in the context of histocompatibility antigens (MHC antigens). Class I MHC antigens (HLA-A, B and C) are recognized by CD8⁺ cells, whereas Class II MHC (HLA-D) positive cells present antigen to CD4⁺ cells. Thus the presence of MHC antigen expression identifies cells as being capable of activating T-lymphocytes. Whereas Class I MHC antigens may be expressed by virtually all cells of the nervous system after stimulation with certain cytokines such as IFN- γ , the distribu-

be unequivocally identified in MS lesions (Suzuki et al. 1969; Prineas and Connell 1979; Prineas 1986; see also Figs. 2.4 and 2.5). They were found to be present in variable degree in nearly all MS plaques at the border with the normal white matter. In addition, similar changes have been seen throughout entire shadow plaques (Lassmann 1983a; Prineas 1986; see also Fig. 2.4). The first description of shadow plaques came from Hermann Schlesinger (1909), who interpreted these changes as incomplete demyelination. Recent studies, however, suggest that even large confluent demyelinated plaques can eventually become completely remyelinated (Lassmann 1983a; Prineas 1986; Prineas et al. 1993a). Similarly, evidence for remyelination was found in the myelinated areas in a case of Baló's concentric sclerosis (Moore et al. 1985), but this finding was not confirmed in a subsequent study on a larger series of cases (Yao et al. 1994).

Controversy remains concerning the derivation of the oligodendrocytes which are responsible for remyelination in MS. A proportion of oligodendrocytes may survive the active demyelinating episode, and may then be available for remyelination (Lassmann 1983a). A significant proportion of mature oligodendrocytes can be found in MS plaques at the earliest stages of demyelination (Brück et al. 1994). Furthermore, myelin oligodendrocyte glycoprotein is abundantly expressed in oligodendrocytes in such lesions. During development, this antigen appears very late in the course of myelination, and is absent from undifferentiated oligodendrocyte precursors (Brück et al. 1994). Alternatively, oligodendrocytes may be completely destroyed, and remyelinating oligodendrocytes may then be recruited by the proliferation of cells at the lesional border or from undifferentiated precursors (Prineas 1986; Prineas et al. 1989). The recruitment of precursors and the ability of mature oligodendrocytes to proliferate are suggested from experimental models of demyelination (Ludwin 1978; 1980; 1984). Multiple demyelinating episodes in the same lesions, which have recently been shown to occur in MS (Prineas et al. 1993b), may then deplete the pool of precursor cells which are available for remyelination.

Recent evidence from our laboratory suggests that both mechanisms may be operating in MS. The extent of oligodendrocyte destruction in the demyelinated plaques was found to

be very similar in different plaques from the same patient, and was independent of lesional activity. However, there was extreme variability in oligodendrocyte loss in different patients, ranging from nearly complete preservation to total loss (Brück et al. 1994; Ozawa et al., 1994). Thus, depending on the patients studied, remyelination may occur either from preserved oligodendrocytes or through the recruitment of undifferentiated precursor cells.

It is thus generally agreed that remyelination may occur in MS, although to what extent it contributes to clinical recovery from the disease remains unresolved. To address this point, several questions have to be answered.

- a. What is the extent of remyelination in MS plaques?
- b. Are there differences in the extent of remyelination in different MS patients?
- c. What is the time course of remyelination?
- d. Does remyelination in MS restore the electrophysiological functions of nerve fibers?

Although we are still far from definite answers to these questions, several interesting aspects have emerged during recent years.

The extent of remyelination in chronic MS plaques in general is small; it is mostly restricted to a zone of less than 1 mm at the plaque edge. As suggested from experimental data, both the oligodendrocytes and their precursors appear to be lost completely in such lesions (Ludwin 1980). In addition, the extensive glial scar formation appears to impede ingrowth of oligodendrocytes from the periphery (Raine and Bornstein 1970a). Intrathecally produced demyelinating and myelination-inhibiting antibodies may further impede the repair process (Lassmann 1983a). In some cases, mostly in acute but sometimes even in chronic MS of long duration, large shadow plaques may be present in high numbers, suggesting that, under as yet undefined conditions, large confluent plaques may be repaired.

Contrary to previous expectations, it turned out that in acute, rapidly progressive MS, remyelination is more abundant than in the typical chronic disease variants (Lassmann 1983a). In such acute cases, signs of remyelination may be found adjacent to areas of active demyelination. Furthermore, shadow plaques are more frequent in acute than in chronic MS (Lassmann 1983a; Prineas 1986).

The speed of remyelination also appears to

In Asia, prevalence rates of MS also appear to follow a North–South gradient. In comparison to similar geographical locations in Europe and America, prevalence rates in Asia (for example, in Japan) are lower by a factor of 10 (McDonald 1983a; 1986).

It is of interest that in Africa, only rare cases of defined MS have been reported. Even if one only considers the reports from hospitals, it seems reasonable to assume that MS is extremely rare in black Africa. Among whites in South Africa, the disease is as frequent as in the Mediterranean region, and corresponds to a medium-risk zone.

According to earlier studies, a zone of high prevalence is defined in Australia and New Zealand between 34° and 44° southern latitude; further toward the equator, MS is found, as in the northern hemisphere, with a medium frequency. More recent studies confirm this North–South gradient (Miller et al. 1990), and point to an average prevalence of 69 per 100,000 inhabitants (Miller et al. 1986). The disease is very rare among indigenous Maoris.

Overall, these data can be summarized as indicating that cases of MS are very rare in regions near the equator, their prevalence increasing toward the poles in both hemispheres.

GEOGRAPHICALLY WELL-DEFINED REGIONS

Because MS is relatively rare, it is recommended that more accurate epidemiological studies be carried out in populations which are not too large (less than 1 million inhabitants), and in geographically circumscribed regions (Dean 1984; Martyn 1991). This allows the examining epidemiologist personally to check the reliability of the diagnosis and the population statistics.

In southern Lower Saxony, a well-defined epidemiological area of about 0.25 million inhabitants has been studied systematically since 1968 with regard to cases of MS. Between 1969 and 1983, the prevalence rate increased from 51 to 89 cases per 100,000 inhabitants, whereas the incidence rate remained constant over the same period. This increase in prevalence rate can be explained in terms of a longer than average disease duration, and a longer life expectancy, which has been confirmed in several other studies concerning the course of the disease (see below). Another factor to explain this

change in prevalence rates may also be the change in the age structure of the normal population (Martyn 1991).

The idea that high prevalence rates over a limited period of time within a defined region may be interpreted as a biologically relevant phenomenon in the sense of a true epidemic (Kurtzke 1983b) has not remained unchallenged (Lauer 1986). An accumulation of cases, such as has been observed on the Faeroe Islands (Kurtzke and Hyllested 1979; 1988) and in Iceland (Kurtzke 1980) since the Second World War, may only be interpreted as an increase in prevalence rate if equally reliable data are available for the time period before and after the apparent "epidemic" (Poser et al. 1992). On the Faeroe Islands, no single case of MS appears to have been identified before the year 1942, whereas in the years up to 1960, 24 definite cases were recorded. In subsequent years, only a single case was diagnosed, in 1970.

In the Orkney and Shetland Islands off the Scottish coast, careful studies revealed the highest prevalence rates (Poskanzer et al. 1980): 309 and 194 cases per 100,000 inhabitants. A more recent statistical analysis on these islands (Cook et al. 1985) demonstrated a reduction in the incidence rate. This reduction is interpreted as due to a diminished efficacy of a putative pathogenic factor from the environment, since it is assumed that the genetic background of the population examined has not changed (Swingler and Compston 1986).

In Great Britain, an overview of all prevalence and incidence studies carried out during this century (Swingler and Compston 1986; Phadke 1987) demonstrates again a North–South gradient of the prevalence of MS. There are, however, some regions which do not follow this rule (Orkneys: 258; North-East Scotland: 155; Wales: 113; East Anglia: 130 (Mumford et al. 1992); Northern England and Northern Ireland: 76–79; Southern England: 63 – all figures per 100,000 inhabitants). As far as comparisons are applicable in terms of variation of methodology, there is a linear relationship between the prevalence of MS and the distribution of the genetic marker DR2. This may be taken as an argument for the role of genetic influences on disease development (Spielman and Nathanson 1982).

The most recent studies from North America concerning MS are based on the registry of the Mayo Clinic in Olmsted County, which is one

typical of MS and was part of Charcot's classical symptom triad: syllables and words are uttered irregularly, rapidly, and loudly, leading to an almost explosive character of speech. This sort of speech disturbance is characteristic of advanced cerebellar involvement.

Trunk ataxia leads to disturbance of equilibrium which renders gait more difficult. It may be little influenced by visual control. In MS, the most frequently occurring gait disturbance is a combination of spasticity and ataxia (spastic atactic gait), which occurs only rarely in other circumstances, such as in combined degeneration of the spinal cord.

Disturbances of ocular movements in MS include symmetrical horizontal directional nystagmus, which depends on lesions in the cerebellum and its efferents. Other forms of nystagmus, such as dissociated nystagmus of the abducting eye as part of internuclear ophthalmoplegia, are discussed elsewhere (see p. 77).

OPHTHALMOLOGICAL DISTURBANCES

Optic neuritis

It has been known for over a hundred years, since the classical work of Uhthoff (Uhthoff 1890), an ophthalmologist from Berlin, that MS plaques occur within the optic nerves. Assessment of their frequency in MS depends on diagnostic criteria and is variable. A study of more than 1200 MS patients which was specifically designed to address this question (Wikström et al. 1980), found involvement of optic nerves at disease onset in a third of cases (34.7%), and optic neuritis as an isolated initial symptom in 17% of cases. This should not be interpreted as indicating that disease onset should be defined unequivocally by optic neuritis, because in acute isolated optic neuritis prolonged latency in the nonaffected eye is found in a quarter of cases, indicating a subclinical involvement and dissemination of the disease process (Matthews et al. 1991).

Over the course of MS, optic nerve lesions are diagnosed in three quarters of cases (McDonald 1983b; McDonald and Barnes 1992). However, on postmortem examinations of chronic cases after long disease duration, involvement of the optic nerve is almost always found (Ulrich and Groebke-Lorenz 1983).

Clinically (Optic Neuritis Study Group 1991), optic neuritis manifests itself as anything from

diminution of vision of variable degree, to complete visual loss. Normally, however, both eyes are affected with equal frequency. Generally, patients indicate very precisely the point at which they became aware of their visual disturbance. It begins rather suddenly, and is followed by further progressive worsening, usually lasting for 3 to 7 days, and rarely for longer than 14 days. The initial visual disturbance is described as blurring of vision, as a "veil or smokescreen," or as a "haze."

When measured objectively, the degree of visual loss may be very variable. Because of the tendency for improvement to occur spontaneously, this also depends on how long after the onset of symptoms the examination takes place. Most frequently, a reduction from counting fingers to 0.5 on Snellen charts is found within the first week after onset. On average, a linear relationship exists between visual loss and extension of demyelination when demyelination found at post mortem is compared to the last visual capacity measured during life (Ulrich and Groebke-Lorenz 1983). On the other hand, several exceptions to this rule have been reported: marked visual loss with only discrete demyelination, and, particularly interestingly, marked demyelination with normal vision as determined shortly before death (Wisniewski et al. 1976).

Restriction of visual fields usually takes the form of central or paracentral scotomata (Patterson and Heron 1980). The extension also depends on the stimulus used, and may reach far into the periphery of the visual field (Perkin and Rose 1979). In MS patients, subclinical deficits of visual field may be detected frequently by more refined methods of perimetry. This may be important for diagnosing a second lesion when dissemination of the disease process is suspected (Meienberg et al. 1982). Initially, patients can rarely see clearly, even in the periphery of the visual field, and even when objectively only a central deficit is found.

On funduscopy soon after the onset of symptoms, the optic papilla appears normal in only about half of cases. On careful examination, blurred margins of the papilla are found in at least a quarter of cases, and striped hemorrhages close to the papilla are reported with variable frequency (up to 17%). Periphlebitis retinae, which may also be detected on fluorescence angiography (McDonald 1983b), is found in nearly a third of cases. It may be a mark of disease activity since the prevalence of regional

show very marked degeneration of the joints caused by inappropriate loading of the cervical and thoracic spine, leading to complications affecting the peripheral nervous system. Too often, one can observe how wheelchair-bound patients have to adopt painful positions because others fail to communicate with them on eye level.

In chronic MS, painful osteoporosis (insufficient bone formation) may be due to inactivity or to irresponsible long-term prescription of steroid therapy which still occurs occasionally.

Lesions of the peripheral nerves are less dramatic, but are often overlooked and preventable. For example, lesions of the median nerve at the wrist can occur following the long-term use of canes, and of the ulnar nerve at the elbow in someone who uses an armrest on a wheelchair. On several occasions, we have seen lesions of the peroneal nerve below the head of the fibula caused by the belts of foot supports which have been too tightly applied to correct foot deformity.

A general feeling of fatigue and fatiguability is often considered the most disabling symptom in MS (Freal et al. 1984; Krupp et al. 1988). There is no easy pathophysiological explanation for this. It appears to be an organic phenomenon and should be differentiated from loss of energy due to depression (see p. 82). It may be exacerbated by exposure to heat, heavy meals or, according to the spontaneous reports of many patients, by smoking. It is improved at rest, less so by sleep. Fatigue in MS is probably not only due to increased muscular load, for example due to spasticity, bad posture, or increased respiratory exertion (Olgiati et al. 1986), but it is the subjective expression of those processes which form the basis of the disease. It is a symptom which is often misunderstood by partners, companions, and employers at the work place, as well as by physicians and caregivers. Fatigue and increased fatiguability are also the classical excuses of shirkers. The trust of patients must be gained in order to be able to make this important distinction. Although it is difficult to provide measurable clinical data, the similar experiences of many MS patients and the opinions of many experienced clinicians are valuable evidence that fatigue and increased fatiguability are important symptoms of MS which themselves may cause disability.

PAROXYSMAL PHENOMENA AND INVOLUNTARY MOVEMENTS

All manifestations of MS may occur only very briefly. They should be considered to be exacerbations if they last less than 24 to 48 hours (see Chapter 8). Apart from possible psychological stress factors (see p. 83), transient clinical symptoms are mainly due to Uhthoff's phenomenon: rising body temperature leads to amplification of clinical symptoms or the formation of new ones. Apart from such transient changes in the clinical picture in MS, paroxysmal clinical symptoms may occur, lasting only for seconds to minutes. Although they are somewhat rare relative to the whole spectrum of clinical symptoms of MS, they may be of particular importance to those affected, and should be recognized as they are amenable to symptomatic therapy.

Epileptic seizures

In the literature on clinical symptoms and signs of MS, there have been several reports of cerebral seizures since the first description by Leube in 1917. Indications of frequency vary widely: in the epileptological literature, we found up to 10% (Trouillas and Courjon 1972); in some neurological centers the average figure for epilepsy is 0.5%. Summarizing 20 publications since 1905 (Hopf et al. 1970) concerning MS patients, there are 207 cases with cerebral seizures, corresponding to 2.5%. This is in accordance with our own figure of 27 patients with epilepsy among 1016 MS patients (Beer and Kesselring 1988), and with another study from Finland (Kinnunen and Wikström 1986). If the age distribution of both diseases is taken into consideration, the coincidence cannot be by chance, and epileptic seizures appear to occur about 10 times more often than in the general population.

As far as types of epileptic seizures are concerned, two thirds are focal in nature, and in one third of cases, simultaneous central deficits (monopareses and hemipareses of sensory disturbance or sensory loss) are present on the same side.

It would appear that, on the one hand, plaques lying close to the cortex may induce seizures by mechanical and electrical irritation, and, on the other hand, lability of cerebral reg-