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Chronic relapsing experimental allergic encephalomyelitis: its value as an experimental model for multiple sclerosis

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Summary. Comparison of the pathohistology of chronic relapsing experimental allergic encephalomyelitis (CR-EAE) and multiple sclerosis (MS) reveals a close similarity. Thus, CR-EAE appears to be a valuable model for the study of pathogenetic factors leading to the formation of MS lesions, although the induction of the disease may be different (active sensitization with CNS antigens and adjuvant in CR-EAE versus unknown etiology in MS). CR-EAE furthermore mimicks the pathohistological patterns of other related human inflammatory demyelinating diseases (i.e., acute perivenous leukoencephalomyelitis and acute hemorrhagic leukoencephalomyelitis). The expression of an acute, predominantly inflammatory versus chronic inflammatory demyelinating disease in this model depends upon the time interval between sensitization and sampling of the animals. Recent evidence is discussed that a cooperation between cellular and humoral immune mechanisms, directed against multiple CNS antigens, is responsible for the formation of large demyelinated plaques in EAE and MS.

Key words: Multiple sclerosis – Experimental allergic encephalomyelitis

Zusammenfassung. Die neuropathologischen Veränderungen in Gehirn und Rückenmark von Tieren mit chronisch rezidivierender experimenteller allergischer Enzephalomyelitis (CR-EAE) entsprechen weitgehend denen der Multiplen Sklerose (MS). Obwohl Unterschiede in der Ätiologie beider Erkrankungen wahrscheinlich sind, erscheint die CR-EAE als geeignetes Modell zum Studium der Pathogenese der entzündlichen Entmarkungsherde der MS. Weiters können im Modell der CR-EAE auch die pathohistologischen Veränderungen anderer, akuter, entzündlicher Entmarkungserkrankungen, der akuten perivenösen Leukoenzephalomyelitis und der akuten hämorrhagischen Leukoenzephalomyelitis gefunden werden. Das Auftreten einer akuten Leukoenzephalomyelitis einerseits oder einer chronischen Entmarkungsenzephalitis andererseits hängt vom Zeitintervall zwischen Immunisation und

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der pathohistologischen Untersuchung der Tiere ab. Neuere Befunde weisen darauf hin, daß bei der CR-EAE sowohl zelluläre als auch humorale Immunmechanismen, gegen multiple ZNS-Antigene gerichtet, an der Pathogenese großer Entmarkungsherde beteiligt sind.

More than 100 years ago the first detailed description of the pathology of multiple sclerosis (MS) was published by Charcot [10]. This date can be regarded as the starting point of an intense and systematic research effort to clarify the pathogenesis of this disease and determine possible therapeutic approaches. These studies provided an enormous number of detailed results regarding clinical course, epidemiology, pathohistology, ultrastructure, immunology, neurochemistry, and virology, which are summarized in a large number of original articles, reviews, monographs, and symposia proceedings [3, 5, 62, 64, 75].

The major breakthrough in our understanding of MS pathogenesis is, however, still missing. This is at least partly due to the lack of a suitable animal model, which allows individual findings in this disease to be related to their pathogenetic significance.

Experimental allergic encephalomyelitis (EAE) has been regarded as a model for MS since the earliest description by Rivers et al. [57]. In these experiments, which were confirmed later by others [13, 14, 56], a chronic inflammatory demyelinating disease was induced by repeated challenge of susceptible animals with brain homogenate. The necessity for repeated sensitization was later overcome by the introduction of Freunds's adjuvant [22, 44]. EAE was further simplified by the discovery that myelin basic protein (MBP) is the factor responsible for induction of the disease [25, 58]. These two modifications of the sensitization procedure, however, produced an acute monophasic disease of the central nervous system (CNS) with only sparse demyelination, a disease more comparable to acute disseminated leukoencephalomyelitis than to MS [1].

A reproducible model of chronic, sometimes relapsing EAE was first induced by Stone and Lerner [66] in guinea pigs by single sensitization with CNS tissue. In the following years, it became evident that in addition to the inflammatory changes, demyelination and gliafibrillary sclerosis were pronounced in this model [53, 65]. By modification of the sensitization procedure Wisniewski and Keith [78] were able to induce a model of chronic EAE with regular and predictable remissions and relapses. This model will be compared with clinical, pathohistological, and immunological findings in MS.

Requirements for the induction of CR-EAE

Several models of chronic relapsing experimental allergic encephalomyelitis (CR-EAE) have been described. The detailed sensitization procedures are contained in the original publications [24, 42, 47, 66, 78]. There are several requirements for the induction of CR-EAE which differ from those necessary for the induction of acute EAE. One of the most important factors is the use of very high doses of antigen and adjuvant in the sensitization medium [66, 78]. Both the antigen and the adjuvant

doses are, depending upon the model, 10–100 times higher than that necessary for the induction of acute EAE. The high antigen dose is apparently necessary to obtain some kind of tolerance during the first months of the disease [82]. Furthermore, when different CR-EAE models are compared with each other, it becomes evident that the higher antigen dose, the milder and more chronic is the disease course [29]. This appears to be one of the major differences between the model described by Stone and Lerner [66] and that described by Wisniewski and Keith [78].

Another important factor for the expression of CR-EAE is the persistence of antigen at the inoculation site [82]. Removal or loss of the sensitizing material from the site of sensitization results in an arrest of the chronic disease [70, 82].

The genetic background of the animals is also of critical importance. In guinea pigs, Strain 13 and Hartley animals are highly susceptible, whereas Strain 2 and Magnum guinea pigs are relatively resistant [32, 40, 66, 67]. Little is known yet about the immunogenetic background of guinea pigs, which is responsible for these differences. CR-EAE may also be induced in rats [33], mice [9], and monkeys [55] when appropriate animal strains are used.

The age of the animals at the time of sensitization is also a factor influencing the clinical and pathohistological expression of CR-EAE [32, 67]. However, the young age of animals at the time of sensitization is not strictly required for the induction of CR-EAE. Adult guinea pigs may develop a chronic demyelinating type of EAE when a much higher dose of antigen is injected than necessary to induce CR-EAE in juvenile guinea pigs (Wisniewski, personal communication).

Neuropathology of CR-EAE

An important aspect of the neuropathology of CR-EAE is that the alterations in the central and peripheral nervous system vary from animal to animal. A detailed and complete comparative neuropathology between CR-EAE and MS would thus by far exceed the volume of this short review; readers interested in more detailed information are referred to a recently published monograph [29]. The present report will thus be confined to the basic principles of neuropathology found in all models of CR-EAE.

One important factor in the pathohistological expression of CR-EAE is the time interval between sensitization and the formation of a lesion in the CNS [34]. This is best studied at present in the model of CR-EAE in Hartley guinea pigs, but is similar, with minor variations, in all other chronic EAE models in guinea pigs and rats. When active disease is present during the acute stage of the disease (10–20 days after sensitization—dps) a predominantly inflammatory disease of the CNS is noted. Perivenous inflammatory infiltrates are found in the meninges and throughout the white matter. Some inflammatory cuffs may also be present in the grey matter. Demyelination is generally absent or restricted to few perivascular nerve fibers. The most severely affected animals during this stage of the disease may show extensive perivenous necrosis and hemorrhage with massive infiltration of the tissue by polymorphonuclear leukocytes [30, 32].

In animals with active disease during the subacute stage of the disease, perivenous inflammation is still the leading event in pathohistology. However, in

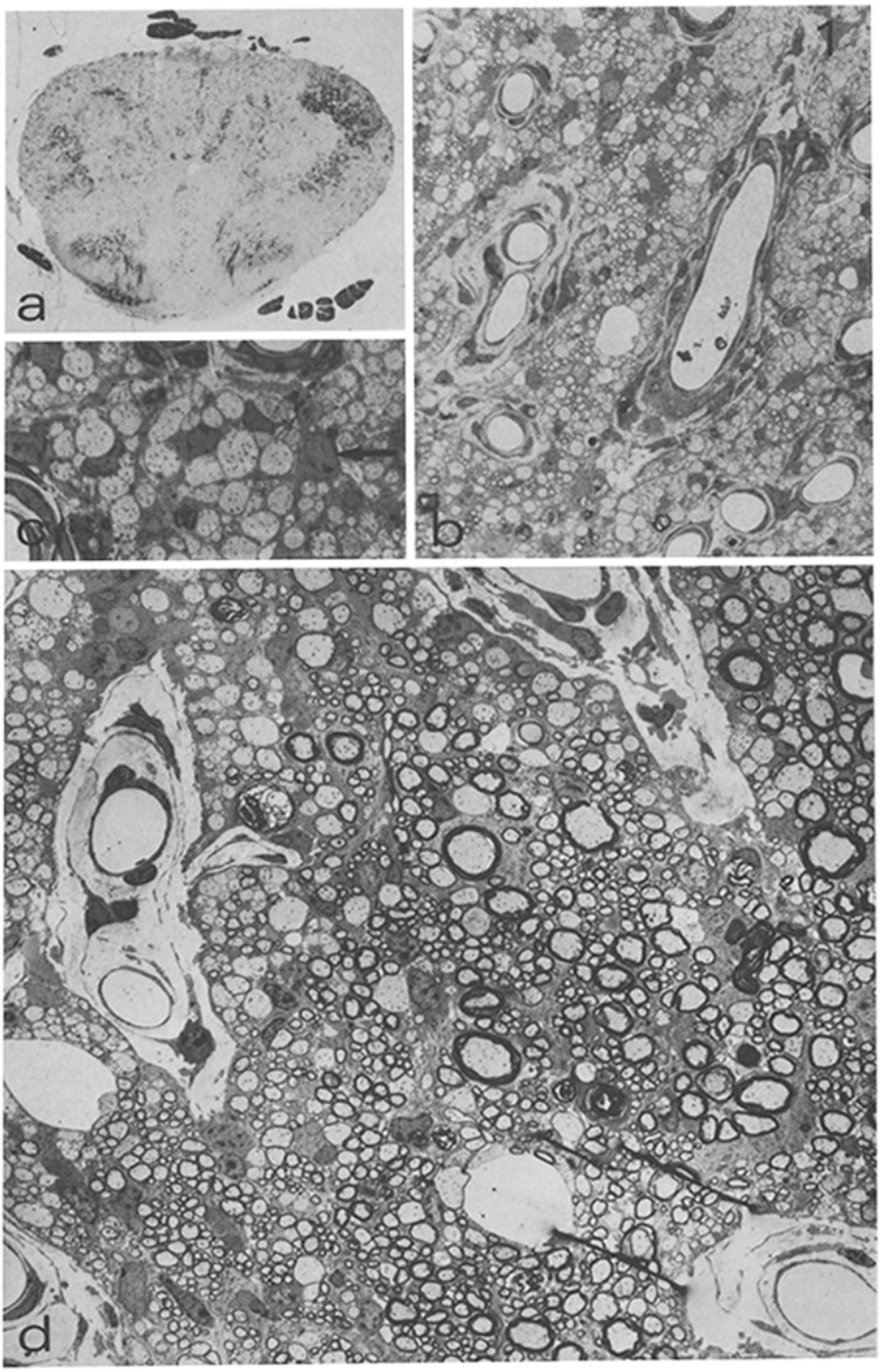

Fig. 1 a–d

addition to the inflammatory response perivenous sleeves of demyelination appear. Comparing the pathohistology of animals in this acute-subacute stage of the disease with that found in human diseases, the described alterations in the CNS closely resemble those found in the acute forms of inflammatory demyelinating diseases, i.e., acute disseminated (perivenous) leukoencephalomyelitis and acute hemorrhagic leukoencephalomyelitis.

In animals with active disease during the early chronic stage (40–100 dps) large confluent demyelinated plaques are the most prominent alteration in the CNS and the majority of the lesions show evidence for ongoing demyelinating activity [31, 53]. Axons are generally spared. Astrocytes are increased in number in the lesions and gliafibrillary sclerosis is present [31, 53, 65]. Oligodendrocytes are relatively spared, although frequently reduced in number. Remyelination, predominantly of central type is frequent, although varying from animal to animal, and may start as early as 10–14 days after plaque formation (Fig. 1a–d). The intensity of perivenous inflammatory reaction is comparable to that found during the acute-subacute stage of the disease and blood-brain barrier permeability is increased as in the acute-subacute stage of the disease [26, 29]. The pathohistological pattern in this stage in all essential respects resembles that found in Marburg's type of acute MS [41].

The late chronic stage of the disease starts approximately 100 dps [34]. In Hartley or Strain 13 guinea pigs sensitized according to the method of Wisniewski and Keith [78] this stage lasts 12–15 months after sensitization. In other models, especially when higher anitgen doses are used for sensitization, the clinical course may be more prolonged, lasting 24–30 months. In animals with active disease during the late chronic stage some actively demyelinating plaques are found in the CNS besides many other inactive or remyelinating lesions. Inflammation in these animals is less pronounced than in earlier stages after sensitization and blood-brain barrier damage is mild [29]. Plaque-like demyelination and gliafibrillary sclerosis are the leading pathohistological alterations. Reduction of oligodendroglia cells in these lesions is generally more pronounced and central remyelination is less efficient. Peripheral (Schwann cell) remyelination is frequently encountered in plaques, reaching the meningeal surface. The presence of large confluent demyelinated plaques in similar topographical distribution, the preservation of axons in the lesions, the extensive gliafibrillary sclerosis, the patterns of plaque growth, and the patterns of inflammation closely resemble the pathohistological changes present in chronic MS. As will be discussed later, there seem to be some differences in the extent of oligodendroglia destruction and remyelination between CR-EAE and MS [29, 31].

Fig. 1a–d. a Hartley guinea pig, chronic relapsing experimental allergic encephalomyelitis (EAE), 90 days after sensitization. Myelin stain of a cross section of thoracic spinal cord. With exception of few focal areas all central myelin is destroyed. Normal myelination in the peripheral nerve roots. Klüver/PAS × 15. **b** Hartley guinea pig, chronic relapsing EAE, 80 days after sensitization. Demyelinated plaque in the spinal cord with beginning remyelination in the center and vascular fibrosis. Toluidine blue × 500. **c** Detail from Fig. 1b. Complete demyelination with preservation of axons and reactive astrocytes *(arrow)*. Toluidine blue × 950. **d** Hartley guinea pig, chronic relapsing EAE, 80 days after sensitization. Central remyelination in a spinal cord plaque; note the disproportionately thin myelin sheaths. EM × 750

When a large number of guinea pigs are sensitized for CR-EAE, not all animals pass through all the above-mentioned stages of the disease. A varying percentage of animals die during the acute phase and thus never reach the chronic stage. Other animals do not develop disease during the acute-subacute stage (especially when high doses of antigen are used for sensitization) and thus clinically as well as pathohistologically the disease may start with alterations typical of the early or even late chronic stage of the disease. Furthermore, owing to the relapsing course of the disease, stages may not be expressed when animals do not have active disease at this point in time after sensitization. Thus, following an acute disease episode animals may have their next relapse later than 100 days after sensitization with pathohistological alterations of the late chronic stage of the disease.

Myelin or oligodendroglia: the target of the immune response

There is little doubt that in EAE the primary target of the immune response is the myelin sheath [27, 28, 80]. Oligodendrocytes, as far as they can be identified on pure light and electron microscopic morphology, are relatively spared in acute and chronic EAE lesions in comparison to myelin sheaths. Central (oligodendroglia) remyelination is present in nearly all CR-EAE lesions, although the extent varies from animal to animal. Remyelination may start very early after demyelination—at the earliest 10–14 days after plaque formation [27, 34]. However, it has to be kept in mind that the degree of oligodendroglia reduction and remyelination is different in various stages of the disease and that there is a high variability in this respect both from animal to animal and within a single animal from lesion to lesion.

In MS evidence for primary myelin versus oligodendroglia destruction is controversial. There is good agreement that in chronic MS lesions myelin is totally lost and oligodendrocytes are reduced in number, although never completely destroyed. With special silver impregnation techniques as well as with electron microscopy, lesions have been identified with total demyelination but normal or even increased content of oligodendrocytes [18, 19, 54], especially in cases of acute MS. However, the cell counts performed by Ibrahim and Adams [18, 19] also suggest that oligodendroglia reduction in MS plaques varies greatly from case to case. Initial myelin changes, similar to those found in EAE (myelin stripping and vesicular disruption of myelin) may also be found in MS plaques when highly active lesions are studied [29]. Central (oligodendroglia) remyelination is present in MS plaques, although in classical chronic cases it is restricted to the borders of lesions [52, 69]. However, there are also numerous cases where shadow plaques are the dominant type of lesions, which apparently represent remyelination [29, 41, 69].

All these observations suggest that myelin is the primary target in MS lesions and oligodendrocytes may additionally be damaged to a degree that varies from case to case.

This concept was recently challenged by Itoyama et al. [20] in an immunhistochemical study of the distribution of myelin basic protein and myelin-associated glycoprotein in MS lesions. By comparing MS lesions with those found in progressive multifocal leukoencephalopathy, the authors suggested that oligodendrocytes appear to be the primary target in MS. This study, however, is based

on a low number of MS cases and lesion samples. Furthermore, definite evidence is missing that reduction of myelin-associated glycoprotein invariably reflects oligodendrocyte damage. Thus, future studies with more specific oligodendrocyte markers are necessary to resolve the question of the primary target in MS. In addition, the possibility has to be considered that in some MS cases myelin and in others oligodendrocytes are the major target in the pathogenesis of the lesions.

The variability of inflammatory demyelinating lesions in CR-EAE and MS

It is now well established that the pathology of MS is characterized by the presence of large demyelinated plaques throughout the CNS. Histologically, the triad of perivenous inflammation, widespread (plaque-like) demyelination, and reactive gliosis is present in all MS cases (Fig. 2). In addition, however, structural aspects of MS plaques may vary from case to case, a fact well known in neuropathology since the beginning of this century [29]. The variables include the extent of inflammation, the degree of oligodendroglial reduction [18, 19] and remyelination (shadow plaque formation) [41, 52, 69], astroglial changes [41, 50, 59, 68], the degree of axonal and even nerve cell destruction [15], the extent of peripheral (Schwann cell) remyelination [17], the patterns of vascular pathology [35], and the occurrence and incidence of inflammatory demyelinating lesions in the peripheral nervous system [21, 36, 41, 51]. One case may show throughout the CNS the typical chronic MS lesion with complete demyelination with preservation of axons, heavy gliafibrillary sclerosis, marked reduction of oligodendrocytes, and lack of remyelination. Another case may reveal mainly shadow plaques with disproportionately thin myelin sheaths indicating remyelination and comparatively mild gliafibrillary sclerosis (Fig. 2). Other cases may show acute (active) or chronic demyelination in the peripheral nervous system. Although each of these cases is definitely identified as MS on the basis of neuropathology, it is difficult to find a common pathogenetic target in them all.

As discussed in detail earlier, a similar variability of structural aspects of the lesions is found in CR-EAE [29, 34]. Thus, in its different stages this model not only reflects all types of acute and chronic inflammatory diseases but also the wide spectrum of structural alterations in chronic MS lesions. It may help us to determine the pathogenetic factors responsible for this variability.

The stages of CR-EAE as an expression of a cooperation of cellular and humoral immune mechanisms directed against different antigens

Most studies in EAE pathogenesis suggest that the induction of the disease is due to a cellular immune reaction. This evidence comes from investigations of delayed-type hypersensitivity reactions [76], passive transfer studies [48], analysis of T-cell fluctuations and their subpopulations [71], and immunohistochemical visualization of T cells and their subpopulations in active lesions [73]. Furthermore, the initiation of a relapse in CR-EAE also coincides with fluctuations of T-cell subpopulations in the blood of animals [72]. Myelin basic protein (MBP) seems to be

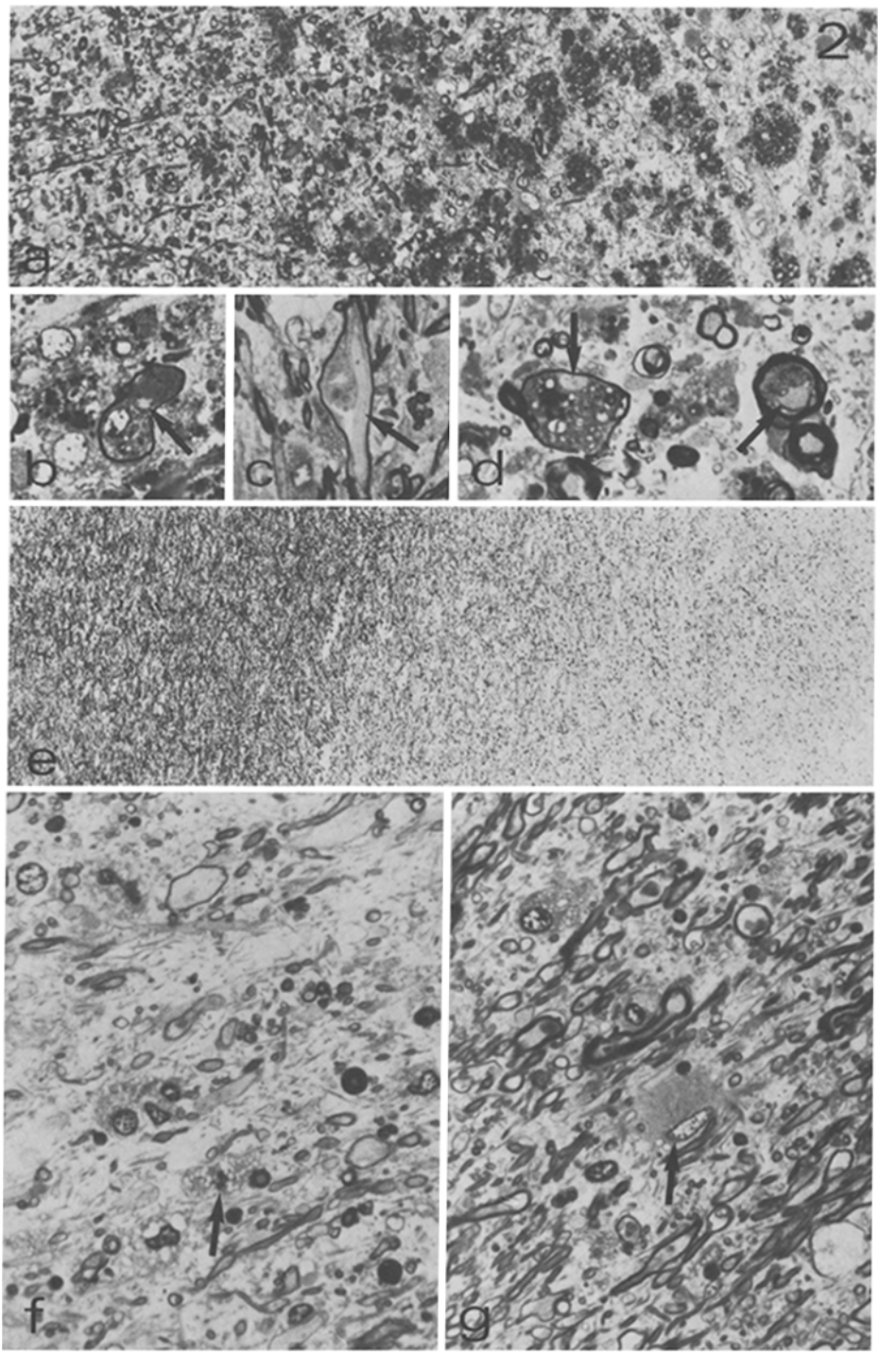

Fig. 2 a–g

the major, if not the only antigen responsible for the induction of this cell-mediated immune response [25, 58]. Antibodies do not influence the induction and the clinicopathological expression of MBP-induced acute EAE [4, 46]. The induction of CR-EAE with MBP is difficult and, when successful, produces a chronic, mainly inflammatory disease of the CNS with little demyelination [47, 82]. These studies strongly suggest that a cell-mediated immune response directed against MBP is responsible for the induction of the acute or chronic (relapsing) inflammatory disease in the CNS of EAE animals. However, additional factors appear to be necessary for the formation of large demyelinated plaques in CR-EAE.

There are several indications that humoral immune reactions against antigens other than MBP may play a role in the pathogenesis of demyelination. The formation of antibodies against various surface antigens of myelin in EAE has been described by many authors [11, 16, 38, 45, 49, 61]. In addition, sera from animals with EAE may induce demyelination in vitro when applied to myelinated CNS tissue cultures [6]. Furthermore, CR-EAE sera injected into the CSF of normal recipient animals induce demyelination in the central and (or) peripheral nervous system [37]. In vivo demyelination induced by application of CR-EAE sera to the CNS appears to be mediated by a cooperation of antibodies and activated effector cells [8, 39, 81].

In CR-EAE there is some correlation between the morphology in different stages of the disease and the humoral immune response against myelin antigens. In the acute-subacute stage of the disease, which shows a predominantly inflammatory type of pathology, the humoral immune response is mild or absent [23, 38; also, Schwerer et al., unpublished work] and demyelinating activity of the sera is rare and mild [37]. On the other hand, during the chronic stage of the disease, when plaque-like demyelination in the CNS is the leading type of pathology, increased immunoglobulins may be noted in the serum, CSF, and brain extracts [23, 43], high antibody titers against myelin surface antigens are found [38; also, Schwerer et al., unpublished work] and the incidence and extent of in vivo demyelinating activity of the sera is high. Similarily, the presence of a humoral immune response directed against myelin antigens and demyelinating activity has been described in MS sera and CSF [2, 7, 12, 60].

Although the present data are still incomplete, they indicate that plaque-like inflammatory demyelinating lesions at least in CR-EAE may be due to a

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Fig. 2a–g. a–d Active demyelination in multiple sclerosis. **a** Border of an active lesion from a patient with severe chronic relapsing multiple sclerosis with 4 years clinical duration. Complete demyelination and numerous phagocytes with earliest stages of myelin debris in the plaque *(right side),* only mild reactive gliosis. Some edema but otherwise normal white matter in the periplaque area *(left side).* Toluidine blue × 500. **b, c, d** Earliest myelin changes in active plaques in acute-subacute multiple sclerosis. Invasion of phagocytes between axon *(arrow)* and myelin sheath or between myelin lamellae. Toluidine blue × 1000. **e–g** Remyelination in multiple sclerosis plaques. **e** Shadow plaque in the same patient as described in Fig. 2a; *left side:* normal white matter; *right side:* shadow plaque with disproportionately thin myelin sheaths. Toluidine blue × 150.**f** Early remyelination in multiple sclerosis; same case as in Fig. 2a. Clusters of nerve fibers with very thin myelin sheaths in a plaque with sudanophilic myelin degradation products *(arrow).* Toluidine blue × 800. **g** Typical shadow plaque in the same case with relatively thin myelin sheaths and reactive astrocytes. Toluidine blue × 800

cooperation of cellular and humoral immune responses, directed against different antigens.

The structural variability of inflammatory demyelinating lesions as an expression of multiple, variable targets

When structural features of many inflammatory demyelinating lesions in CR-EAE and MS are compared, it is impossible to imply that identical pathogenetic factors are responsible for the formation of the plaques; as an example, in an MS case with little oligodendroglia loss, massive shadow plaque formation (remyelination) and extensive inflammatory demyelinating lesions in the peripheral nerve system (PNS) [21, 36]. This has especially to be considered in acute MS, which shows inflammatory demyelinating plaques in the PNS in more than 50% of cases [41, 51]. Similarly, the variable extent of damage to axons, neurons, astroglia, and blood vessels may be an expression of an immune response directed not only against myelin, but also against other CNS antigens. In this connection it is interesting that in sera of MS patients as well as EAE animals antibodies were detected not only against pure myelin surface antigens, but also against antigens shared by myelin, neurons, and astroglia [2, 38]. Furthermore, the incidence and titers of antibodies against various CNS antigens vary from individual to individual. These results indicate that multiple different antigens on the surface of myelin and other CNS structures may be the target in inflammatory demyelinating lesions. Thus, the structural expression of a given lesion may be the expression of the sum of immune responses directed against multiple target antigens, located not only on the surface of myelin sheaths, but also on other CNS components.

CR-EAE as a model of multiple sclerosis

Using CR-EAE as a model of MS we have especially to keep in mind the differences between these two disease entities. CR-EAE is induced by active sensitization with CNS tissue and adjuvant, and the disease activity correlates with the persistence of antigenic material at the sensitization site [70, 82]. Although similar active sensitization by accident may also lead to a disease closely resembling acute MS in humans [63, 74], most cases are probably brought about by other still unknown etiologic factors. CR-EAE will thus contribute little to the question of etiology of MS. The close similarity in the pathology of the lesions in CR-EAE and MS, however, renders this model especially valuable for the study of pathogenetic factors involved in the formation of the lesions. Furthermore, it indicates that immunological mechanisms play a key role in the pathogenesis of the lesions. Nevertheless, in this regard it has to be kept in mind that the antigens involved in the formation of the lesions do not necessarily have to be the same in EAE and MS. In EAE present evidence indicates that MBP is the antigen responsible for the induction of the disease and of the inflammatory component of the lesions. In MS, however, in spite of extensive research efforts in this field the involvement of MBP in the pathogenesis of the disease is controversial [77]. This may partly be due to the difficulties in measuring a cellular immune response against MBP in the chronic

stage of the disease, a difficulty also encountered in CR-EAE [79]. On the other hand, the induction of an immune response against MBP in MS patients during therapeutic desensitization trials with the antigen indicates that, at least in some patients, the antigen responsible for the induction of the inflammatory disease is not MBP [77].

Nevertheless, understanding the pathogenesis of CR-EAE lesions will be very valuable in the interpretation of immunological findings in MS patients.

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