ANNUATION

THE PATHOLOGY OF MULTIPLE SCLEROSIS—FACT, FICTION AND HYPOTHESIS

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Accepted for publication 21 November 1980


Annotation. The pathology of multiple sclerosis—fact, fiction and hypothesis

The present state of our pathological knowledge of multiple sclerosis is reviewed emphasizing the 'hard facts' while highlighting subjects of disputed interpretation and of ignorance.

Introduction

Pathological observations in multiple sclerosis (MS) fall historically into two periods. The first spans the years 1829–1916 when workers such as Cruveilhier (1829–1842), Carswell (1838), Charcot (1868) and Dawson (1916) recognized the disease, made many of the cardinal pathological observations and advanced arguments as to the significance of these observations. As a result of these and later observations, there is general agreement that the pathological reaction which accounts for most of the clinical symptomatology in MS is that of periaxial demyelination (Dawson, 1916; Lumsden, 1970). The mechanism of this reaction, whereby there is focal destruction of myelin in the central nervous system (CNS) with relative preservation of axis cylinders in demyelinated lesions, is unknown. Moreover while most workers consider the associated abnormalities of oligodendrocytic loss, astrocytic proliferation, inflammatory reaction and vascular sclerosis to be secondary phenomena, the exact significance of these reactions is debated and evolution of the very early lesion is unknown.

During the second period of observation, from 1916 to the present day, investigation of the disease has been intensive and the use of immunology, biochemistry and electronmicroscopy has produced much new information. During this time important advances in our knowledge of the epidemiology of the disease have also been made and various epiphenomena, for example the cellular and biochemical abnormalities in the cerebrospinal fluid (CSF), have been recognized. It must be said however that, while none of this scientific effort has been misdirected, much of it has been based on speculation rather than on observation and many reports have been based on small numbers of chronic cases, inadequately controlled. MS, moreover, has become a subject of interest to the news media and unfortunately, many premature reports of its cause and cure have appeared. Many aetiological hypotheses have been advanced, none entirely satisfactory, and although contributions in the biochemical and immunological fields have
been numerous, in many of these studies the desirable degree of histological control has been lacking. It seems opportune therefore to review the present state of our pathological knowledge with the aim of emphasizing the 'hard facts' and of highlighting subjects of disputed interpretation and of ignorance.

The essential lesion: its evolution

ANATOMICAL DISTRIBUTION

Pathologists are agreed that the characteristic pathological abnormality in the CNS in cases of classical MS is the presence of scattered, demarcated lesions in which periaxial demyelination can be demonstrated. Old lesions are grey in colour and firm in consistency (hence Charcot's description 'sclérose en plaques'): more recent lesions have an oedematous edge, are yellow or pink and of soft consistency. Cases usually come to necropsy in the chronic stage of the illness, death occurring because of secondary infection either in the lungs or in the renal tract. In such cases plaques of varying age may be observed throughout the cerebrum and spinal cord, often on the surface of the brainstem or in the periventricular white matter, particularly around the occipital horns of the lateral ventricles where these lesions are often symmetrical. Other lesions appear to be scattered haphazardly throughout the white matter, including that of the usually severely affected optic nerves. Plaques vary in size and shape and are often apparently related to small blood vessels: in the grey matter they may not be seen with the naked eye, but histologically it is apparent that the myelinated axons in the grey matter are not exempt and numerous foci of demyelination may be apparent. Several studies have confirmed the peculiar vulnerability of myelin in the optic nerves, periventricular region (Brownell & Hughes, 1961) and spinal cord (Oppenheimer, 1978) and it is not surprising that 90% of definite cases of MS have electrophysiological evidence of past optic neuritis (Tallis, 1980). The significance of the distribution of plaques is unknown. It has been suggested that the vulnerability of the periventricular white matter suggests a toxin circulating in the CSF. Against this view, however, is the fact that certain specific areas around the lateral ventricles, e.g. the suprolateral angles of the anterior horns, are severely affected, while much of the periventricular white matter is not especially vulnerable, e.g. the third ventricle wall is no more commonly affected than white matter generally. A vascular basis for plaque formation was proposed in some of the original descriptions of the disease and, although it is now accepted that there is no evidence of vascular thrombosis as the basis of plaque formation, it has been suggested that local susceptibility may be particularly great in regions situated in the boundary zone between territory of supply of major cerebral arteries (Brownell & Hughes, 1961). Fog (1965) in a detailed analysis of forty-three plaques concluded that thirty-nine were related to one or two veins while four were related to several veins, and the striking relationship of plaques to the terminal veins in the wall of the lateral ventricle is seen in Figure 1. Oppenheimer (1978) in a study of the spinal cord in 18 cases of MS found that lesions in the cervical cord are about twice as common as at lower levels of the cord and that fan-shaped lesions in the lateral columns predominate. He has suggested that mechanical stresses may be a factor in determining the site of the lesions and that, in the cervical cord, the denticulate ligaments may, during neck flexion, produce stress resulting in vascular leakage. In assessing the significance of the predominant anatomical pattern of the lesions in MS it is possible that certain chemical differences exist between myelin from the cerebral hemispheres and from the spinal cord (Waehneldt, 1978). If one favours the auto-allergic hypothesis of the disease, such chemical differences might be
significant. In summary, it may be said that all CNS white matter is susceptible in MS, the cause of the increased vulnerability of certain anatomical sites is unknown; a relationship of plaques to veins seems to be significant and the possibility that these are the site of both cellular and chemical leakage at an early stage in the disease needs further study.

THE ESTABLISHED PLAQUE AND THE 'EARLY LESION'

The classical histological view of the established plaque is summarized in Figure 2 together with some of the observed biochemical abnormalities: the only controversial observation represented is the apparent increase in oligodendrocytes in the plaque edge (Ibrahim & Adams, 1965). As yet there is no evidence that the oligodendrocytes in the adult human can respond in this way (Cavanagh, 1970) though in other species this is certainly possible (Lampert, 1978). In an histochemical study of the plaque in MS using combined enzyme and conventional staining, the results suggested that the majority of cells at the edge of active plaques are either astrocytes or microglial cells: in particular the cells often seen in short 'chains' at the edge of plaques have the morphology of astrocytes (Allen et al., 1979). The discrepancy between these results and that of Ibrahim & Adams (1965) needs resolution and techniques presently available are adequate to solve this important problem of the reactive potential of the human oligodendrocyte.

Despite several publications referring to the 'early lesion' in MS nothing is known of the initial stages of plaque evolution. This lack of knowledge is a result of the chronic nature of the disease in most patients and of the lack of biopsy material taken at the onset (i.e., within a few hours) of a clinical relapse. These
difficulties have forced pathologists to speculate on the pathogenesis of the condition and to approach the problem either by study of the edge of the plaque (the most common approach) or by the study of the supposedly unaffected white matter (very few detailed histological studies are available). Both approaches, while perhaps the best available at the moment, are scientifically suspect. By analogy with other diseases we know that the 'edge of a lesion' is its reactive border where the diseased tissue promotes a response in the surrounding healthy tissue; therefore observations are consequently difficult to interpret. Equally the apparently normal white matter may show abnormalities of a secondary nature, consequent on extensive plaque formation.

With this variation in approach different workers have emphasized different factors and in general three contrasting descriptive views of the early lesion are held: these are that it is characterized by: a increased cellularity in which microglial hyperplasia is predominant; b physical disintegration of myelin (swelling and fragmentation) preceding increased cellularity; c perivascular lymphocytic reaction preceding demyelination.

Dawson (1916) emphasized the hypercellularity of the early lesion and recognized the microglial component. Prineas (1975), because of clinical evidence that lesions may progressively enlarge, based his studies of the early lesion on the edge of plaques known to be recently active. He concluded that a characteristic 'inclusion bearing cell', possibly oligodendrocyte, has a key role in the early breakdown of myelin. Zimmerman & Netsky (1950) and Seitelberger (1965) considered the first stage to be that of a physical disintegration of myelin, followed by chemical breakdown. In their view the disintegrated myelin sheath is composed of 'myelin balls' (Lumsden, 1970) which have the histochimical characteristics of normal myelin. Seitelberger (1973) also emphasized the inflammatory cell component in the MS plaque but accepted that demyelination, particularly in the early stages may be observed without an immune cellular response. Adams (1977) suggested that perivascular lymphocytic cuffs in near-normal myelin may represent the initial
lesion and this view is often accepted by other workers favouring an 'auto-allergic hypothesis'.

**PRIMARY AND SECONDARY SIGNIFICANCE OF HISTOLOGICAL ABNORMALITIES IN THE PLAQUE**

In view of controversy and ignorance relating to the early lesion, it seems worthwhile to review the various histological structures affected in plaque formation and to attempt to assess their primary or secondary involvement (Table 1).

**Mechanisms of demyelination and remyelination**

Nothing is known of the exact mechanism of demyelination in MS and its relationship to death of the oligodendrocyte. While it is conceded that both myelin sheaths and oligodendrocytic cell bodies are absent from the established plaque, it is argued by some (vide infra) that the primary attack in MS is on the 'extended oligodendrocyte', i.e., the myelin sheath, but by others that the cell body itself may be primarily affected. Certainly in recently formed plaques, cell structures suggestive of degenerating oligodendrocytes may be seen; in such lesions however degenerating myelin is also apparent.

Only relatively few systematic studies of the ultrastructure of MS have been made (see reviews by Andrews, 1972; Lampert, 1978; Prineas & Connell, 1978; Kirk, 1979a) and ultrastructural studies on the apparently normal white matter can best be described as preliminary. Varying patterns of demyelination have been observed (Table 2). This variation may indicate that different primary mechanisms operate in MS or, as seems more likely, that observations to date have often been at a late stage of the disease when secondary effects are also apparent.

While the ability of the interfascicular oligodendrocyte in the human to regenerate is debated, most workers believe that remyelination, albeit incomplete, is possible. Remyelination with peripheral type myelin apparently due to Schwann cell activity has been demonstrated histochemically and by electron-microscopy in MS (Ghata et al., 1973; Ogata & Feigl, 1975; Schoene et al., 1977). Most of these observations have been in relationship to the brain stem or spinal cord where the proximity of Schwann cells in nerve roots may be a

<table>
<thead>
<tr>
<th>Structure</th>
<th>Pathological reaction</th>
<th>Primary (P) or secondary (S)</th>
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</thead>
<tbody>
<tr>
<td>Myelin sheath</td>
<td>'Necrosis' or disorganization</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>Incomplete healing</td>
<td>S</td>
</tr>
<tr>
<td>Oligodendrocyte</td>
<td>Necrosis</td>
<td>?</td>
</tr>
<tr>
<td>Astrocyte</td>
<td>Hypertrophy and hyperplasia</td>
<td>?</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Hyperplasia and phagocytosis</td>
<td>S</td>
</tr>
<tr>
<td>Immune competent cells</td>
<td>Infiltration perivascular space</td>
<td>?</td>
</tr>
<tr>
<td>N-ural neuronal perikaryon Axons</td>
<td>Unaffected</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Unaffected initially. Some late degeneration</td>
<td>?</td>
</tr>
<tr>
<td>Blood vessel wall</td>
<td>Hyalinization</td>
<td>S</td>
</tr>
<tr>
<td>Blood-brain barrier</td>
<td>Increased permeability</td>
<td>?</td>
</tr>
<tr>
<td>Meninges</td>
<td>Mild inflammation</td>
<td>S</td>
</tr>
</tbody>
</table>
Table 2. Ultrastructural patterns of myelin disorganization reported in MS

1. Increased myelin inter-lamellar spacing
2. Splitting and vacuolation of sheath
3. Sheath fragmentation, ball and ovoid formation
4. Granular-lamellar degeneration within sheath
5. Filamentous accumulations in sheath
6. Irregularly thin myelin sheaths
7. Cell associated myelin thinning (microglial)
8. Micropinocytosis Vermiformis
9. Vesicular demyelination

Sample references: Suzuki et al. (1969) 2, 4, 6; Gonatas (1970) 1, 3, 4, 6; Lumsden (1970) 3, 4, 9; Prineas (1975) 2, 3, 4, 5, 6, 7; Prineas & Raine (1976) 7; Prineas & Conell (1978) 8; Kirk (1979a) 9.

factor. Other workers have interpreted abnormally thin myelin sheaths in the CNS in MS as representing possible incomplete remyelination and the presence of short intermodes as definite evidence of remyelination (Andrews, 1972). Shadow plaques, i.e., lesions where myelin is not absent but is reduced in amount, have been variously explained as areas of partial demyelination (Lumsden, 1970) or of partial remyelination (Suzuki et al., 1969). The presence of oedema and of astrocytic proliferation may be additional factors in the faint histological staining of myelin in these lesions.

Significance of astrocytic response

From the earliest observations in MS it has been suggested that gliosis, i.e., astrocytic hypertrophy and hyperplasia, may be a primary event in plaque formation. This suggestion comes from the observation of the marked astrocytic hypertrophy and hyperplasia in active plaques (Dawson, 1916) and from the finding of diffuse astrocytosis in the apparently normal white matter in MS (Andrews, 1972; Allen & McKeown, 1979). In the interpretation of these findings various characteristics of the astrocyte must be remembered: it has been shown that this cell can react within hours to any pathogenetic stimulus (Aparicio, Lumsden & Jennings, 1968). It is known that blood-brain barrier breakdown and a release of a variety of molecules will stimulate the astrocyte and recently it has been shown that lymphocytes can release an astrocytic stimulating factor (Fontana et al., 1980). These general properties of astrocytes mean that astrocytosis within the plaque is to be expected and may not necessarily be of primary significance. Moreover, the diffuse astrocytosis of the normal white matter in severe cases of MS which has been studied in one relatively large series (Allen & McKeown, 1979) could be explained as secondary to plaque formation and Wallerian degeneration, or as secondary to blood-brain barrier damage in MS (vide infra). There is, of course, the possibility that the diffuse astrocytosis is a primary event in the disease: a preliminary study of a series of mild or predominantly spinal MS cases (Allen, Glover & Anderson, 1981) suggests that diffuse astrocytosis also occurs in these cases in which one would not expect this response if it were not an essential component of the disease. Biochemical and further histological studies are necessary to confirm this finding.

The association of gliomatous transformation with MS is rare; some 19 cases of varying histological types having been reported in the literature. This incidence
might well represent chance association and there is no evidence of a carcinogenic agent operating in MS.

Significance of the inflammatory response

It is generally agreed that in the established plaque a secondary inflammatory response in which macrophages and mononuclear cells (lymphocytic in type) predominate is common. There is no doubt that a percentage of the cells present in this reaction are immunologically competent (Esiri, 1980) and plasma cells can be demonstrated not only in the perivascular region but also within the brain substance (Prineas & Wright, 1978). Of fundamental importance is whether or not this immune reaction is directed against a specific antigen and may therefore give an indication as to the pathogen in MS. Nothing is known of the exact relationship of these antibody producing cells in the CNS in MS to the immunoglobulins in the CSF (Cuzner, 1980) and to the multiple sclerosis specific antigens described in MS brains by Rastogi, Clausen & Fog (1978). There is undoubtedly an abnormality of the blood–brain barrier in a proportion of chronic established cases of MS (Tourtelotte & Ma, 1978) and part of the immunoglobulin present in the CSF is presumably haematogenous. The evidence for immunoglobulin synthesis in 'perivascular spaces' within and around plaques is strong (Ryberg, 1980), but there has been no direct immunohistochemical attempt to relate the proteins in the CSF to the cells in the CNS. Efforts to demonstrate the ability of the CSF globulins to react with normal brain have failed (Kennedy & Lisak, 1979), as have attempts to absorb them out with measles antigen or with various components of CNS tissue (Sever, 1975). There have been several reports of astrocytes within plaques containing immunoglobulin (Prineas & Raine, 1976) but this is probably a non-specific phenomenon reflecting the ability of these cells to absorb macromolecules.

Significance of vascular abnormalities

Hyalinization of small blood vessels with perivascular deposition of collagen is a feature of the established plaque and is thought by most workers to represent a secondary response. Attempts to demonstrate early abnormalities in blood vessels have been few: Brown (1978) in a biopsy from a patient with MS showed a marked increase in pinocytic vesicles within endothelial cells in the region of an acute plaque but could detect no other abnormality. Perivascular deposition of lipofuscin is found extensively outside the plaque (Allen & McKeown, 1979), but there is no increased incidence of vascular hyalinization in the apparently normal white matter. The vascular hyalinization within plaques possibly accounts for the blood–barrier abnormality in MS though further study of this aspect of the disease is needed.

The relationship of biochemical abnormalities to the histopathology

Lipid. The lipid histochemistry of MS is well established. As a result of the chemical degeneration of myelin, cholesterol esters and neutral fat appear and unsaturated lipids can be demonstrated. The sequence of abnormality has been divided into three phases by Seitelberger (1965) who suggests that the lipid changes reflect the normal pathway of myelin degradation rather than any inherent lipid disorder. The histochemical and electron-microscopical evidence as to the exact site of myelin degradation is conflicting. Lumsden (1970) states that the various lipids can be demonstrated both within macrophages and extracellularly. Prineas (1975) suggests that a first stage of myelin degradation occurs within an unusual 'inclusion-bearing cell' while the process is completed by perivascular macrophages.

Lysosomal enzymes. Few workers doubt that the well substantiated lysosomal enzyme abnormalities in the active and chronic plaque in MS are a 'second-
ary phenomenon’ (Cuzner & Davison, 1979), though the suggestion that there could be an inherent abnormality of lysosomal function has been made (McKeown & Allen, 1979). The high lysosomal enzyme levels in chronic lesions indicate that although inflammatory cells are an important source of these enzymes, astrocytes make a significant contribution. It has also been shown that there is a significant increase in lysosomal enzymes in the supposedly normal white matter in MS (Allen & McKeown, 1979) and with histological control it is apparent that this increase, with the exception of β-glucosaminidase, is associated with gliosis. β-glucosaminidase was found to be unusual in that it is elevated not only in a macroscopically normal white matter but also in microscopically normal white matter. Its elevation however may reflect a ‘submicroscopical’ degree of gliosis. The significance of the elevation of lysosomal enzymes is its possible implication in the process of demyelination and in the rendering of non-demyelinated tissue susceptible to a demyelinating influence.

Myelin protein. A third group of important chemical studies has been related to myelin proteins. It has been shown that the basic protein is absent in the plaque and is reduced in the periplaque (Adams, 1972). More recent studies with myelin associated glycoprotein (Itoyama et al., 1979) have shown that loss of this substance is more extensive than loss of myelin or of basic protein. While this is probably not an abnormality specific to demyelination in MS, it is nevertheless the most sensitive immuno-histochemical indicator of demyelination available.

Aetiological hypotheses: support from human and experimental pathology

Over the years suggestions as to the aetiology of MS have followed scientific fashion and numerous hypotheses have been advanced. Current fashion might be summarized thus: 1 The autoallergic hypothesis. 2 The lipid hypothesis. 3 The viral hypothesis. 4 The combined infective-allergic hypothesis.

THE AUTOALLERGIC HYPOTHESIS

The idea that MS develops as an autoallergic response to some component of myelin has received wide attention, particularly as such a response can be evoked in animals. While it is possible to accept a continuing and relapsing autoallergy of this type as the explanation of the disease, it is difficult to visualize what the ‘triggering mechanism’ might be. Various workers have attempted to find support for this hypothesis by the study of the extra-CNS pathology in MS. In a controlled series of 120 necropsy-proven cases of MS there was however no evidence of an increase in autoimmune disorders or of malignancy (Allen, Millar & Hutchinson, 1978). It has long been recognized that in certain cases of acute perivenous encephalomyelitis lesions resembling plaques of acute MS may be found. The most convincing cases of this type are those reported by Uchimura & Shiraki (1957) in whom injections of anti-rabies vaccine prepared from animal spinal cord had been given: these cases could be used as an argument in favour of the auto-allergic hypothesis. In summary, it may be said that a subtle immune abnormality, hitherto undetected, may exist in MS patients and research is now active in this direction.

THE LIPID HYPOTHESIS

Thompson (1966) has suggested that MS may develop against a background of abnormal lipid metabolism and current work on this hypothesis is reviewed by Cuzner (1980) and Tallis (1980). In relation-ship to the histopathological findings, it may be said that most chemical studies on the apparently normal white matter in MS have been done without sufficient histological control. Lipid stu-
The pathology of multiple sclerosis

A. "The Viral Hypothesis"

Although the finding of abnormal levels of antibody in serum and in CSF against a variety of viral antigens, particularly paramyxoviruses, is well established in MS, its significance in terms of cellular pathology is unknown and viral antigen has not been demonstrated by immunofluorescence in the CNS (Fraser & Haire, 1980, personal communication). Numerous reports of the presence of virus-like particles in the CNS have appeared and are summarized in Table 3 where it can be seen that only that of the corona virus structure is now accepted as almost certainly virus.

It must be remembered that even if virus is convincingly demonstrated in the CNS in MS it does not necessarily mean that the cause is viral. The ability of viruses to persist in normal tissues and to invade diseased tissue is well known and before a viral aetiology based on the finding of virus particles in the CNS could be accepted, Koch’s postulates should be fulfilled. These same arguments however could previously have been used against an infective aetiology in diseases which are now known to be transmissible, e.g. Creutzfeld-Jakob disease, and the viral theory cannot be totally discounted.

B. "The Combined Infective-Allergic Hypothesis"

It is possible that MS is not the result of simple viral infection but rather, represents an abnormal immune response to a common virus or group of viruses. Bloom et al. (1978) have suggested that a virus such as measles may persist in lymphoid cells, occasionally producing a mutant which could induce demyelination, further mutations producing further episodes of demyelination. These same workers have also suggested that the mechanism of demyelination in MS might be a ‘by-stander effect’ with destruction of myelin resulting from cell-mediated antigen-antibody response without any specific antmyelin antibody involved.

C. "The Significance of Laboratory Models of Demyelination for MS"

The number and variety of models of demyelination available is now very

<table>
<thead>
<tr>
<th>Original description</th>
<th>Current interpretation</th>
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<tbody>
<tr>
<td>Paramyxovirus-like nuclear</td>
<td>Artefact (nucleoprotein or chromatin)</td>
</tr>
<tr>
<td>Paramyxovirus-like cytoplasmic I</td>
<td>Artefact (‘spilled’)</td>
</tr>
<tr>
<td>Paramyxovirus-like cytoplasmic II</td>
<td>Artefact (protein)</td>
</tr>
<tr>
<td>Paramyxovirus-like cytoplasmic III</td>
<td>Weibel-Palade bodies</td>
</tr>
<tr>
<td>Panovavirus-like cytoplasmic</td>
<td>Artefact (reticulosomes)</td>
</tr>
<tr>
<td>Virus-like, intracisternal, budding</td>
<td>Nuclear pores or similar</td>
</tr>
<tr>
<td>Virus or mycoplasma-like, dense-cored</td>
<td>?</td>
</tr>
<tr>
<td>Virus-like hollow-cored</td>
<td>Myelin derived vesicles</td>
</tr>
<tr>
<td>Corona virus-like intracisternal</td>
<td>Probable virus</td>
</tr>
</tbody>
</table>
### Table 5. Patterns of demyelination—aetiology known

<table>
<thead>
<tr>
<th>Type of injury</th>
<th>Usual characteristics of myelin loss</th>
<th>Inflammatory reaction</th>
<th>Glial reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Distribution</td>
<td>Pattern</td>
<td>Oligos.</td>
</tr>
<tr>
<td>1. Immune mediated, e.g. EAE, Theiler’s virus</td>
<td>Peri-venular and sub-pial</td>
<td>Lamellar separation, vesiculation, stripping*</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lesion margins ↑</td>
</tr>
<tr>
<td>2. Cytolytic viruses, e.g. mouse hepatitis virus, PML</td>
<td>Patchy</td>
<td>Unusual cytoplasmic connections to oligos. Fragmentation and stripping</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>3. Cytotoxic chemicals, e.g. Cuprizone, 6-aminonicotinamide</td>
<td>Patchy, Dependent on mode of administration</td>
<td>Inner tongue abnormalities, disorganization, dislocation, occasional vesiculation, stripping</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>4. Neuronolytic demyelination, e.g. trauma</td>
<td>Depends on site of neuronal injury</td>
<td>Disruption, occasional vesiculation, stripping</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>5. Myelinotoxic chemicals, e.g. lysolecithin</td>
<td>Site of application</td>
<td>Vesiculation, fragmentation, ? stripping</td>
<td>−</td>
</tr>
</tbody>
</table>

* Removal of disintegrating or damaged myelin sheaths from axons by macrophages. In this the most widely used sense of the word stripping is something which follows myelin damage, i.e. it is a secondary phenomenon. In experimental allergic neuritis, for example, to quote Lampert (1978) 'Demyelination begins when invading cells (lymphocytes and macrophages) have established contact with myelin lamellae. Initially the sheath is dissolved in focal areas, visible by the formation of gaps in the sheath where lamellae terminate abruptly. Subsequently, invading macrophages strip the remnants of the damaged sheaths from the axons.'
great (Lampert, 1978; Martin & Nathanson, 1979) and their study, with a view to understanding the pathogenetic mechanisms involved, is intensive. For the pathologist, the patterns of demyelination are of most interest insofar as they may indicate which particular pathogenetic mechanisms are operating. Tables 4 (below) & 5 (opposite) illustrate this point. It is known, e.g. that the site of damage and pattern of demyelination varies in different diseases depending on the target of the insult (Table 4).

The animal model which bears the closest relationship to MS is the chronic relapsing form of experimental allergic encephalitis (EAE) (Raine et al., 1980). This model has been refined and a lesion bearing clinical and pathological resemblance to MS has been produced by injection of brain extract with adjuvant into juvenile animals from inbred susceptible strains. Points of similarity with MS are the chronic relapsing clinical course, the plaque-like demyelinated lesions with a similar anatomical distribution to that seen in MS, and the evidence of immunoglobulin synthesis within the CNS (Lassmann, Kitz & Wies- niewski, 1980). There are, however, dissimilarities: inflammation is more intense in chronic relapsing EAE, remyelination is extensive and many of the ‘plaques’ look like coalesced foci of perivenous demyelination. Whatever the differences, this model is the best available for the study of possible lines of treatment in MS.

The role of the histopathologist in the further study of MS

The histopathologist is likely to contribute most to the further study of MS not by working to any accepted aetiological hypothesis, but rather by extending pathological observations using classical and new techniques. Many aspects of the histopathology of this disease are not fully understood and Table 6 lists some of the cardinal problems. A simple scheme of histological events may be helpful in planning further observations and a possible pathological sequence of events is given in Figure 3.

In conclusion, it may be said that no better advice could be given to the

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Table 4. Sites of primary damage in experimental models of known aetiology

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1. Oligodendrocytes, e.g. PML, JHM virus encephalomyelitis of mice.</td>
<td></td>
</tr>
<tr>
<td>2. Myelin sheath, e.g. EAE, idiopathic polynuritis, bee and snake venoms.</td>
<td></td>
</tr>
<tr>
<td>3. Oligodendrocytes and myelin, e.g MS and EAE sera on myelinated CNS cultures.</td>
<td></td>
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</tbody>
</table>

Table 6. Some unsolved problems in MS pathology

<p>| |</p>
<table>
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<tbody>
<tr>
<td>The significance of the anatomical distribution of plaques</td>
</tr>
<tr>
<td>The mechanism of demyelination and the early lesion</td>
</tr>
<tr>
<td>The significance of shadow plaques</td>
</tr>
<tr>
<td>The correlation of biochemical and pathological findings</td>
</tr>
<tr>
<td>The significance of the astrocytosis</td>
</tr>
<tr>
<td>The significance of the lymphocytic infiltration and the relation of the CSF abnormalities to the CNS histopathology</td>
</tr>
</tbody>
</table>
Pathogenetic stimulus

Blood vessel (increased pinocytosis, hyalinization) *

Blood-brain barrier defect *

Leakage of macromolecules

Inflammatory cell infiltration

Astrocytic response

? Demyelination *

? Partial remyelination

Figure 3. A schematic view of a possible pathological sequence of events in MS. * Abnormalities already observed.

References


Brownell B. & Hughes J.T. (1962) The


Chacorn J.M. (1868) Histologie de la sclérose en plaques. Gazette Hôpital (Paris) 41, 554-566

Crevello J. (1829–1842) Anatomie pathologique du corps humain, Ballièrè, Paris


Ogata J., & Feigin L. (1975) Schwann cells and regenerated peripheral myelin in...


