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The Neuropathology of Myelin Diseases

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I. INTRODUCTION

The following terminology (Section II) and classification (Table 1) form the scaffold of both this chapter on neuropathology and the closely integrated chapter (Chapter 9) on the clinical aspects of the myelin diseases. Appropriate naturally occurring and experimental conditions of animals are covered briefly. Naturally occurring disorders of myelin in animals are covered in greater detail in Chapter 14.

II. TERMINOLOGY

Before embarking on a detailed classification of the primary myelin diseases, it might be pertinent to point out that loss of myelin is a common sequela of a multitude of conditions, many of which initially affect other components of white matter, in particular blood vessels, glia, and axons. Myelin, therefore, although the major element, is not the only component of white matter and is secondarily damaged by neoplasia, trauma, infarct necrosis, abscess, edema, anoxia, and hemorrhage and may also be altered after degeneration of the overlying cortex, e.g., in the case of the diffuse atrophy of white matter seen subsequent to neuronal loss in Alzheimer's disease (see Blackwood *et al.*, 1971; Adams and Sidman, 1968; Brain and Walton, 1969; Baker and Baker, 1974). It is possible, however, to segregate a significant number of central nervous system (CNS) and peripheral nervous system (PNS) diseases in which myelin *per se* appears to be primarily and selectively affected. This chapter deals with the varied neuropathology of these conditions in which the myelin loss is related to a host of different factors.

The reader should further realize that in the past, some authors have referred to *all* diseases that affect myelin as *demyelinating* diseases. While this seems reasonable on a strictly semantic basis, the majority of neuropathologists and neurologists now reserve the term *demyelinating* to embrace only the acquired inflammatory demyelinating diseases such as multiple sclerosis (see Adams and Sidman, 1968) in which there is loss of myelin with relative sparing of axons. *Secondary demyelination*, an archaic term applied frequently to

P. Morell (ed.), *Myelin*

the myelin loss associated with Wallerian degeneration, is a misnomer, since in this situation both axon and myelin are lost simultaneously. The process is not secondary to any preceding insult, since nothing happened to the tissue, and is not demyelinative, since the axon is not spared.

In this chapter, the various diseases in which myelin is considered the primary target will be discussed according to etiology and neuropathology. In some cases, evidence is accumulating that suggests that a nosology based on biochemical data might soon become feasible, and such diseases may in future classifications be moved out of the myelin disease group into the neurological storage disorders. Where available, such evidence will be mentioned briefly in the present schema.

III. CLASSIFICATION

It is probably impossible to classify the myelin diseases to the satisfaction of all neuropathologists and neurologists (Table I). A major problem is the subgrouping of diseases in which some of the diseases may not completely fulfill all the criteria of a particular subgroup. For instance, progressive multifocal leukoencephalopathy, a usually noninflammatory demyelinating disease, is included among the acquired inflammatory conditions. A classification similar to that outlined in Table I has been presented elsewhere (Raine, 1977; Morell *et al.*, 1981).

IV. CLASS I: ACQUIRED ALLERGIC (INFLAMMATORY) AND INFECTIOUS DISEASES OF MYELIN (DEMYELINATING DISEASES)

A. Diagnostic Criteria

With only two exceptions, progressive multifocal leukoencephalopathy (PML) and diphtheric neuropathy, the cardinal features of lesions that typify the acquired allergic (inflammatory) and infectious diseases of myelin are perivascular demyelination and cuffs of inflammatory cells. A potentially more significant unifying feature, emanating from recent work from a number of disciplines, is the possibility that most of these conditions may be related to a viral infection.

In the various CNS conditions in this group, brains on gross examination invariably show distinct white matter lesions that microscopically are devoid of myelin. The chronically demyelinated, gray-colored, gelatinous, sclerotic plaques in cases of multiple sclerosis (MS), the most common example of this family, are widely believed to be the end product of the fusion of myriads of small perivascular cuffs around each of which local demyelination had occurred. In the beginning, therefore, demyelination appears to be perivascular. In most cases, older CNS lesions in this group contain fewer inflammatory cells. Oligodendroglia appear to be lost relatively early in the disease process. In the case of the relapsing demyelinating diseases, it is commonly believed that the fluctuating clinical picture may be related to a reactivation of the inflammatory components within and around plaques. Chronically demyelinated plaques in all cases show a marked reduction in the number of intact, naked axons, and it is not uncommon in chronic MS to find old lesions almost completely devoid of axons. Macrophage activity, as judged by oil-red-O and periodic acid-Schiff (PAS)-positive staining material, is common in acute or subacute lesions. Meningeal inflammation and subpial demyelination occur in the more acute members of the group, particularly those linked to a viral infection. In all cases, an intense, fibrous, astroglial response is a sequela of the demyelinative process.

It is interesting to note that the inflammatory demyelinating diseases are not restricted to the CNS and also involve the PNS. This occurrence has been held to be strong evidence that

TABLE I. Classification of Myelin Diseases

Class I: Acquired allergic (inflammatory) and infectious diseases of myelin (demyelinating diseases)
- Human examples
  1. Multiple sclerosis (MS)
  2. Variants of MS
  3. Acute disseminated encephalomyelitis (ADE)
  4. Acute hemorrhagic leukoencephalopathy (Weston Hurst disease)
  5. Progressive multifocal leukoencephalopathy (PML)
  6. Idiopathic polyneuritis
  7. Diphtheric neuropathy
- Animal examples
  1. Canine distemper encephalomyelitis
  2. Visna
  3. Coonhound paralysis
  4. Marek's disease
  5. Mouse hepatitis virus encephalomyelitis
  6. Experimental allergic encephalomyelitis (EAE)
  7. Experimental allergic neuritis (EAN)

Class II: Hereditary metabolic diseases of myelin
- Human examples
  1. Metachromatic leukodystrophy (MLD)—sulfatide lipidosis
  2. Krabbe's disease (globoid-cell leukodystrophy)
  3. Adrenoleukodystropy (ALD)
  4. Refsum's disease
  5. Pelizaeus-Merzbacher disease (sudanophilic leukodystrophy)
  6. Alexander's disease (dysmyelinogenetic leukodystrophy)
  7. Spongy degeneration of white matter (Canavan's disease)
  8. Phenylketonuria (PKU)
- Animal examples
  1. Globoid-cell leukodystrophy (canine Krabbe's disease)
  2. Jimpy mice
  3. Quaking mice
  4. Murine muscular dystrophy
  5. Border disease (hypomyelinogenesis congenita)

Class III: Acquired toxic-metabolic diseases of myelin
- Human examples
  1. Hexachlorophene neuropathy
  2. Hypoxic encephalopathy—anoxic anoxia and anemic anoxia (carbon monoxide poisoning)
- Animal examples
  1. Diphtheric neuropathy
  2. Hexachlorophene intoxication
  3. Triethyl tin intoxication
  4. AY9944 intoxication

Class IV: Nutritional diseases of myelin
- Human examples
  1. Vitamin B_{12} deficiency
  2. Central pontine myelinolysis
  3. Marchiafava-Bignami disease
- Animal examples
  1. Malnutrition

Class V: Traumatic diseases of myelin
- Human and animal examples
  1. Edema
  2. Compression
  3. Barbotage
  4. Pressure release

these diseases result from an autoimmune process related to the different basic proteins of CNS and PNS myelin.

B. Human Examples

1. Multiple Sclerosis

Despite its early recognition as a distinct disease entity by Charcot toward the end of the 19th century, the extensive neuropathological investigations of Dawson (1916), and the numerous analyses by contemporary neuropathologists (see Adams and Kubik, 1952), the underlying disease process in MS remains an enigma. The varied topography of plaques and the chronicity of the changes are consistent with the protracted clinical course of the disease, discussed in detail in Chapter 9. In general, two variants of MS can be recognized on the basis of both neuropathology and clinical course—chronic MS, by far the most common, with a clinical course often extending more than 30 years, and acute MS, a rare condition ranging from weeks to months from onset to death (see Chapter 9). While chronic and acute MS are classified here as variants of the same disease, it is possible that they represent distinct disease entities, and indeed many investigators consider them as such.

a. Gross Pathology. Externally, the brain from a patient who has died with chronic MS is covered with a cortical gray mantle and appears relatively unremarkable. The optic nerves, chiasma, and spinal cord may possess grossly visible plaques (areas of myelin loss) superficially, since such areas have myelinated fibers on their surfaces. Since plaques lack myelin and are sometimes gliotic and shrunken, when seen on the surface of the CNS they may have a pitted appearance. Coronal section of the brain invariably reveals multiple, disseminated plaques, grossly visible throughout the white matter, ranging in size from about 1.0 mm to several centimeters (Fig. 1). The lesions can be differentiated from the surrounding normal CNS tissue on the basis of color and texture, which can also be used as an index of lesion age. Recent (acute) lesions have a pinkish hue; subacute lesions [containing, by light microscopy (LM), an abundance of fat-filled macrophages] appear whitish; chronic, "burnt-out" plaques are gray due to the proliferation of glial scar tissue and depletion of myelin. Serial reconstruction of plaques demonstrates that some are interconnected and anastomose throughout the CNS, much like the branches of a tree. There is a strong tendency for plaques to be associated with paraventricular regions, one of the most common features in MS. In those MS cases in which a relentless chronic progressive course has persisted (see Chapter 9 for clinical variations of this disease), white-matter destruction is usually more widespread and might approach dimensions more commonly seen in the metabolic disorders of myelin. The lesions are not always restricted to the white matter and may encroach on myelinated areas of gray matter (Fig. 1). In such regions, there is remarkable sparing of nerve-cell bodies. The PNS is usually spared, but a few reports exist that describe changes in the spinal nerve roots. Such PNS changes are most likely secondary and either related to the close proximity of a large chronic plaque in the spinal cord or due to avitaminosis or other nutritional or metabolic complications.

b. Histology. In any case of MS (acute or chronic), a spectrum of disease activity may obtain, irrespective of clinical history. In general, CNS involvement is greater than the clinical history would suggest. Completely silent (burnt-out) lesions may display small areas of florid activity along the margins. Chronic MS lesions can be categorized into silent chronic or active chronic, each of which is further divisible on the basis of degree.

Myelin stains of typical silent chronic MS plaques reveal a near-total lack of myelin from affected areas (Figs. 2 and 3). Demyelinated axons are by and large preserved (Figs. 4 and 5), although in older lesions, axons may be reduced in number. An intense astroglial response is common, and the usually heterogeneous parenchyma is replaced by fibrous astroglial

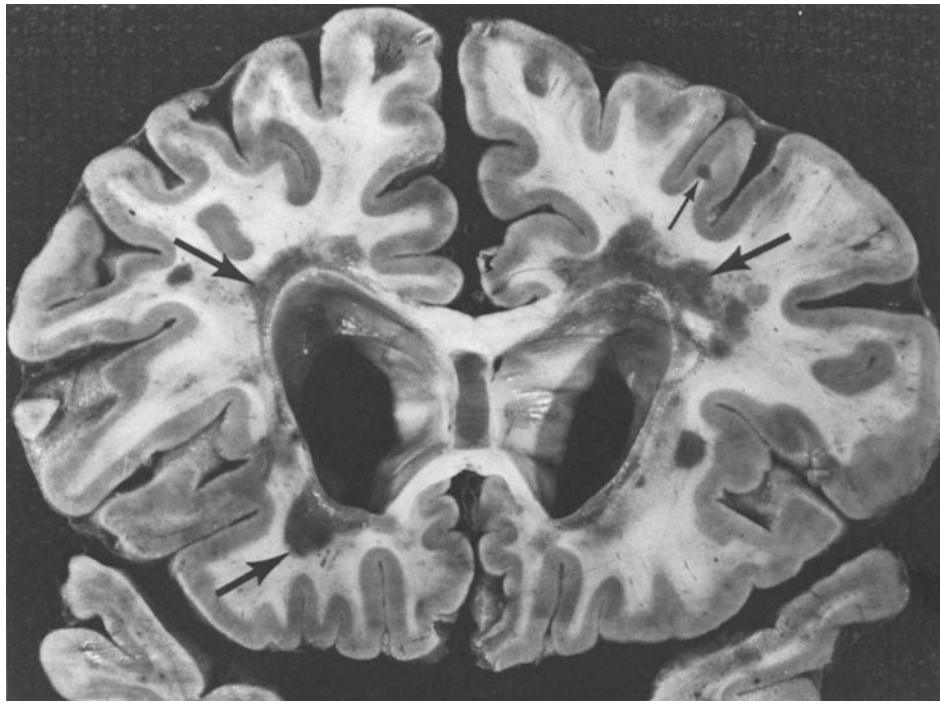


FIGURE 1. Chronic MS—coronal slice. The demyelinated plaques are clearly visible in this gross specimen (large arrow). Note their predilection for white matter and their greatest development in the paraventricular areas. Some small plaques (small arrow) may involve both gray and white matter.

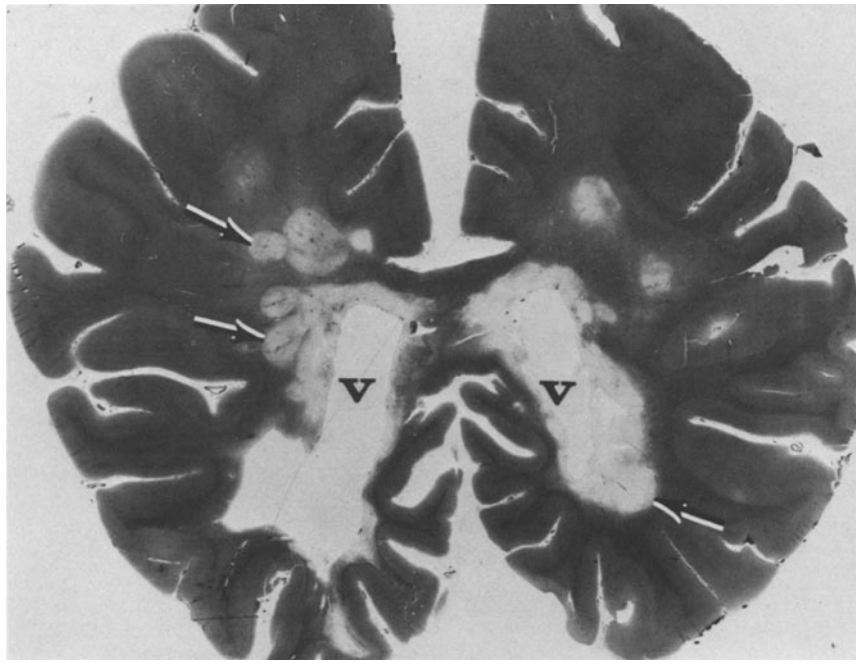


FIGURE 2. Chronic MS—myelin stain, whole mount. In this section taken vertically through the cerebral hemispheres, demyelinated plaques stand out as unstained, pale areas of white matter (arrow). Note that some plaques have gray edges and others are entirely gray; these may be "shadow plaques" (remyelination). (V) Ventricle.

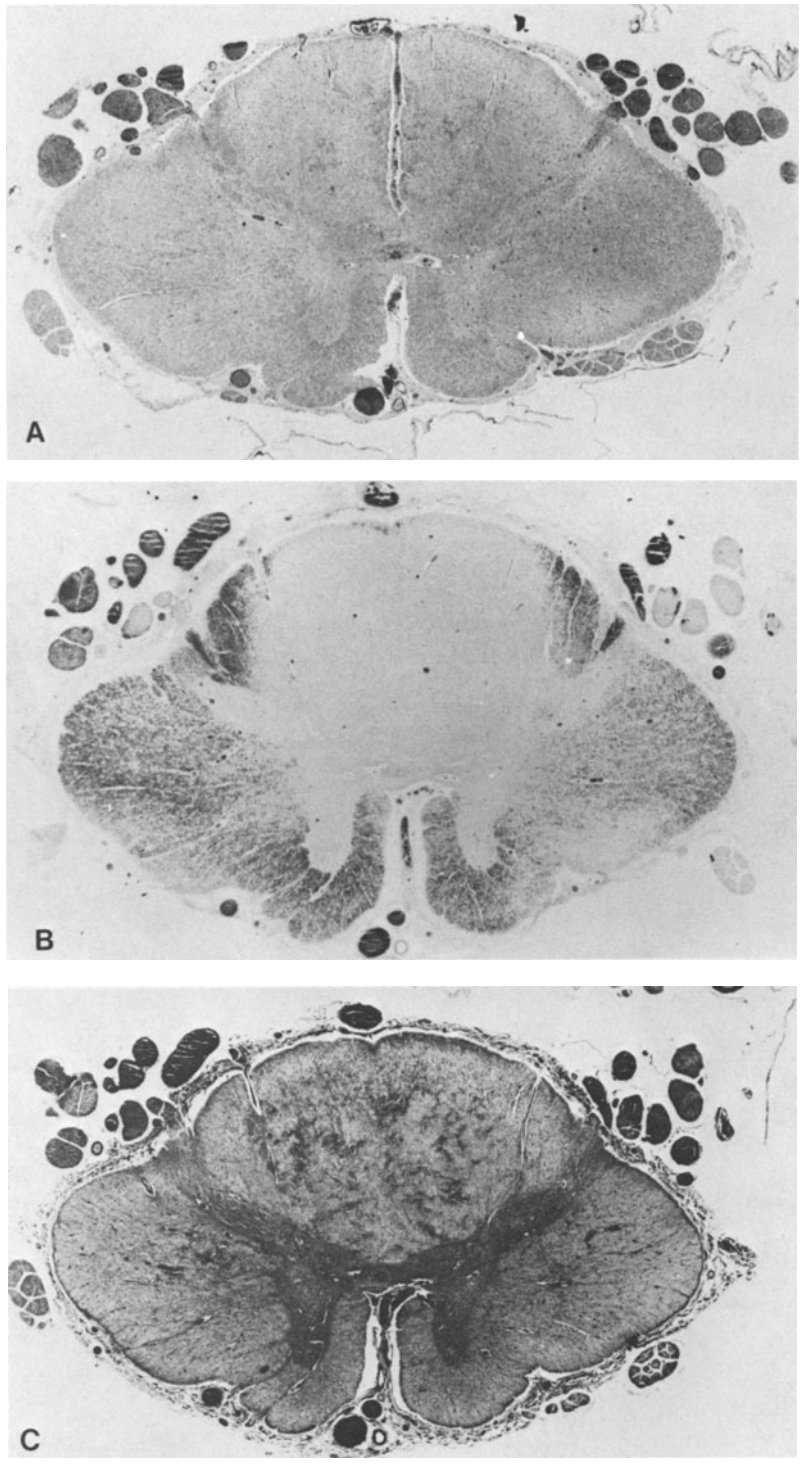


FIGURE 3. MS—histological sections. Spinal-cord sections from a typical case of MS are stained for routine histology (A) by hematoxylin-eosin (HE), for myelin (B) by the Heidenhain technique, and for axons (C) by the Bodian technique. Note the good preservation of most elements in the HE preparation, the severe loss of myelin from the dorsal columns and diffuse loss elsewhere in the myelin preparation, and the preservation of axons in the Bodian preparation. The spinal nerve roots appear unaffected. ×10.

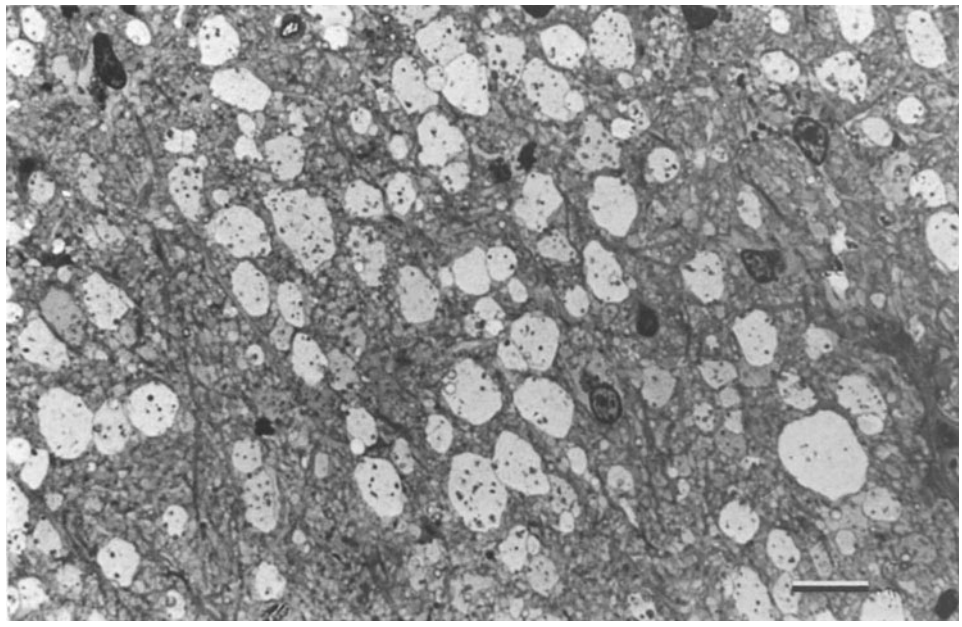


FIGURE 4. Chronic MS—toluidine-blue-stained 1-μm Epon section. A chronically demyelinated plaque from the spinal cord displays naked axons (note mitochondira in the axoplasm) and an intense astroglial fibrosis. Scale bar: 10 μm. ×1000.

processes emanating from large cell bodies, frequently demonstrating multiple or multilobate nuclei. Oligodendroglia are apparently lost early in the disease and are absent from the centers of chronic silent plaques. The edge of many chronic silent lesions will display a narrow rim of CNS remyelination (Fig. 6), manifested by the presence of axons with disproportionately thin myelin sheaths (Prineas and Connell, 1979; Raine, 1982). Sometimes these areas of remyelination extend for some distance from the edge of a chronic lesion toward more normal white matter, so that in a myelin stained section, a gray zone appears between the lesion and the myelinated parenchyma. This type of lesion, traditionally referred to as a "shadow plaque" in most classic texts, is now regarded as remyelinative, while older descriptions classed it as indicative of incomplete demyelination. Electron-microscope (EM) descriptions of shadow plaques have confirmed appearances typical of myelin repair and do not support ongoing myelin breakdown. At the edges of active chronic lesions or silent chronic lesions where myelin repair is encountered, oligodendroglial hyperplasia is not uncommon and a broad band of proliferated oligodendroglia, recognizable by the small round cell bodies and nuclei, extends for a distance into the demyelinated lesion.

At the peripheries of many MS lesions, it is not uncommon to find evidence of low-grade macrophage activity (Fig. 7), and even in the adjacent normal white matter, scattered lipid-filled macrophages (foamy cells, gitter cells, compound granular corpuscles) are seen. In one recent EM study (Raine *et al.*, 1981), an active chronic MS lesion was found to display ongoing myelin breakdown in the presence of apparently surviving and proliferating oligodendroglia (Fig. 8). This led the authors to conclude that oligodendroglial cell damage in MS was an event secondary to myelin degradation. Immunocytochemcal study on the characterization of invading cell types in the brain in MS (Traugott *et al.*, 1983) has revealed that macrophages play a major role in lesion development. In active or subacute lesions, macrophages stain positively with Sudan black, oil-red-O, and PAS. More active lesions (particularly those with a pinkish hue on gross examination or those associated with acute MS) contain varying numbers of inflammatory cuffs around blood vessels, many macrophages, and diffuse collections of invading hematogenous cells throughout the

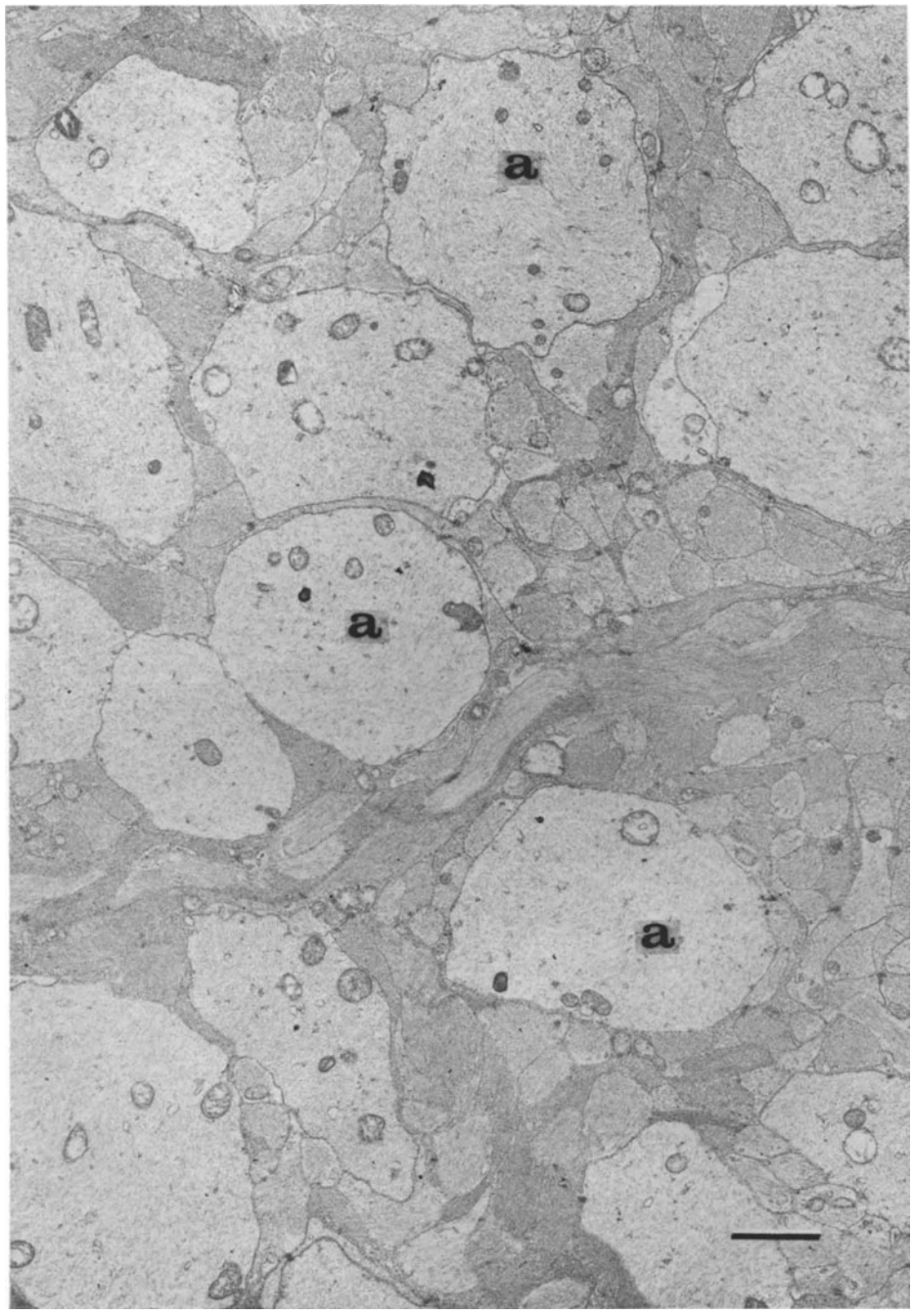


FIGURE 5. Chronic MS—electron micrograph. Large demyelinated axons (a) are seen in transverse section lying in a matrix of dense fibrous astrogliosis. Scale bar: 2 μm. ×6000.

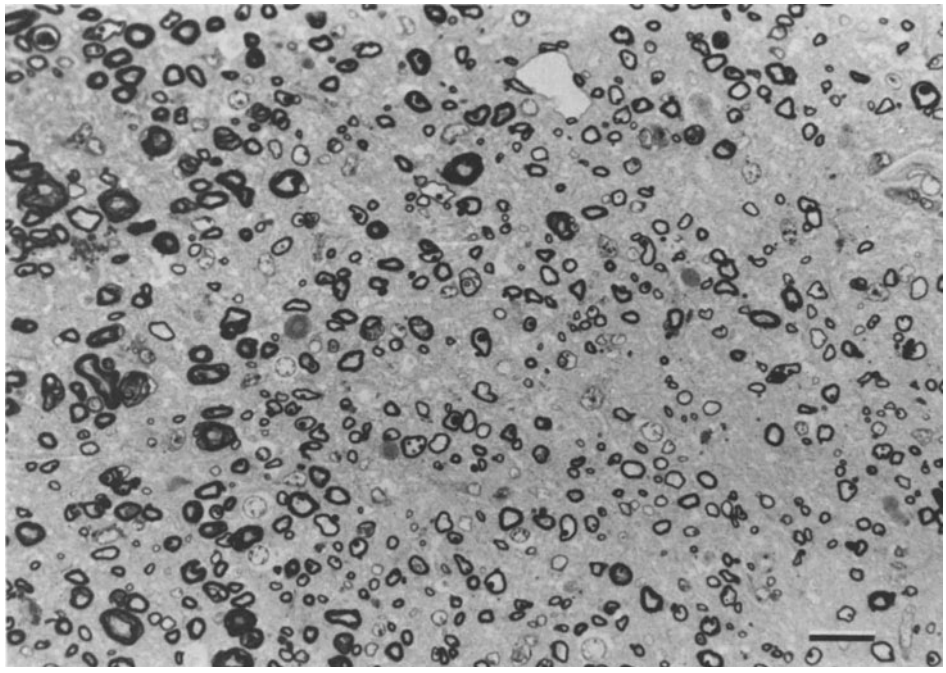


FIGURE 6. Chronic MS—toluidine-blue-stained 1-μm Epon section. At the edge of a silent plaque (center of lesion to the right), a zone of thinly myelinated (remyelinated) fibers is shown, which slowly gives way to normal thickly myelinated fibers on the left. Scale bar: 20 μm. ×400.

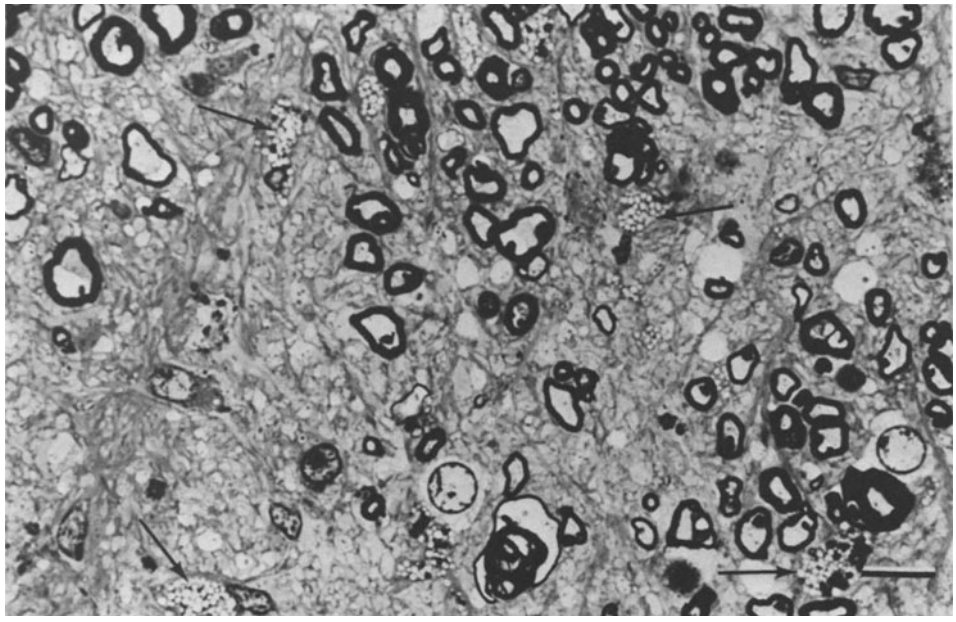


FIGURE 7. Chronic MS—toluidine-blue-stained 1-μm Epon section. At the perimeter of a chronic, established lesion in the spinal cord, macrophages [foamy cells (arrows)] can be seen among the apparently normally myelinated fibers. Background glial fibrosis is also evident. Scale bar: 10 μm. ×1000.

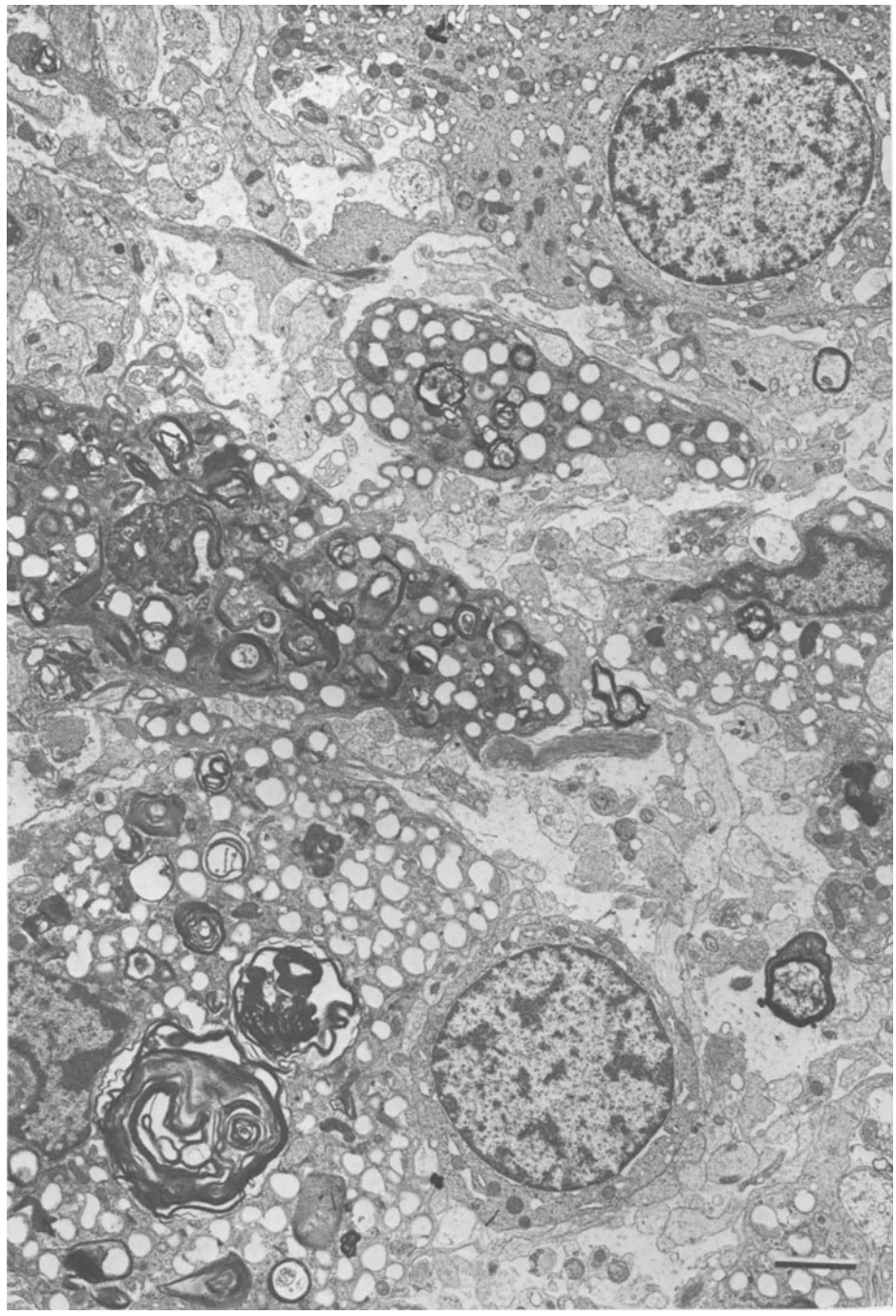


FIGURE 8. Chronic MS—electron micrograph. A collection of macrophages contain lipid droplets and myelin debris lies at the edge of a chronic, active lesion. Note the two surviving oligodendrocytes recognized by their rounded nuclei and narrow rims of cytoplasm. Scale bar: 2 μm × 5600.

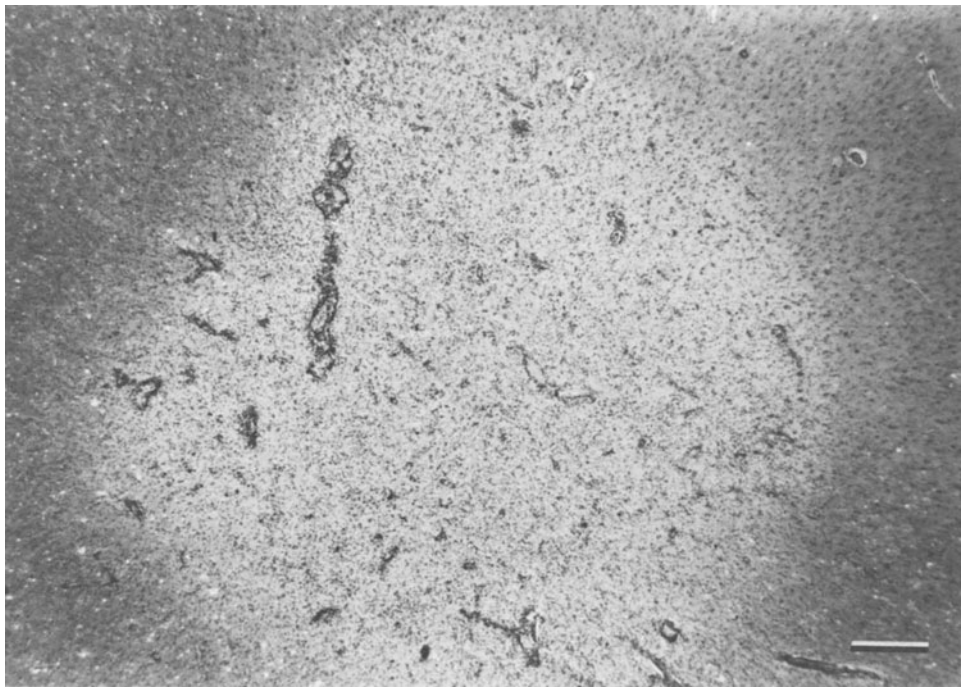


FIGURE 9. Acute MS—HE-stained section. A small, very active lesion is shown. Note the blurred edge and the intense perivascular and parenchymal inflammatory infiltrates. Scale bar: 100 μm. ×100.

parenchyma (Fig. 9). The inflammatory cells are comprised of small lymphocytes, large mononuclear cells, plasma cells, and macrophages (Prineas and Wright, 1978; Raine, 1982). Routine morphology is incapable of designating functional characteristics to the invading cells, but immunocytochemical analyses of MS lesions with monoclonal antibodies to human T-cell subpopulations and I-region-associated (Ia)-antigen-bearing cells (macrophages and B cells) have afforded new data on lymphocyte dynamics *in situ* in MS (Traugott *et al.*, 1982b). These latter studies have shown that active lesion growth is associated with an accumulation of Ia-bearing cells and $T4^+$ (helper, inducer) T cells. $T8^+$ (suppressor/cytotoxic) T cells appear to congregate perivascularly at the lesion edge. Contrary to some opinions, cross-reactivity between oligodendrocytes and certain T-cell subsets is not demonstrable, even after double-staining procedures (Traugott *et al.*, 1982a). Previous attempts to demonstrate an immunological role for oligodendrocytes by way of antibody or cell-mediated immunity have failed to demonstrate a specific response to oligodendroglia in MS (Traugott *et al.*, 1979, 1981).

Fine-structural analyses of MS plaques (Périer and Grégoire, 1965; Suzuki *et al.*, 1969; Prineas, 1975; Raine *et al.*, 1975, 1981; Prineas and Raine, 1976; Prineas and Wright, 1978; Raine, 1978, 1982; Kirk, 1979; Prineas and Graham, 1981) have clarified many of the questions raised by histologists, although a causal agent has not yet been identified. At the lesion perimeter, fibers abruptly lose their myelin sheaths and demyelination is effected by macrophages that become closely apposed to the myelin sheath and lyse the myelin from the axon (Figs. 10 and 11). The process of myelin phagocytosis involves uptake of myelin into membranous crypts at the surface of the macrophage. At the base of each crypt, an association has been noted between the phagocytosed myelin droplet and a coated pit (Prineas and Connell, 1978), a phenomenon also described in animal models of autoimmune demyelination (Raine *et al.*, 1980; Epstein *et al.*, 1983).

Small or early lesions appear to be centered on blood vessels and perivascular cuffs, and in

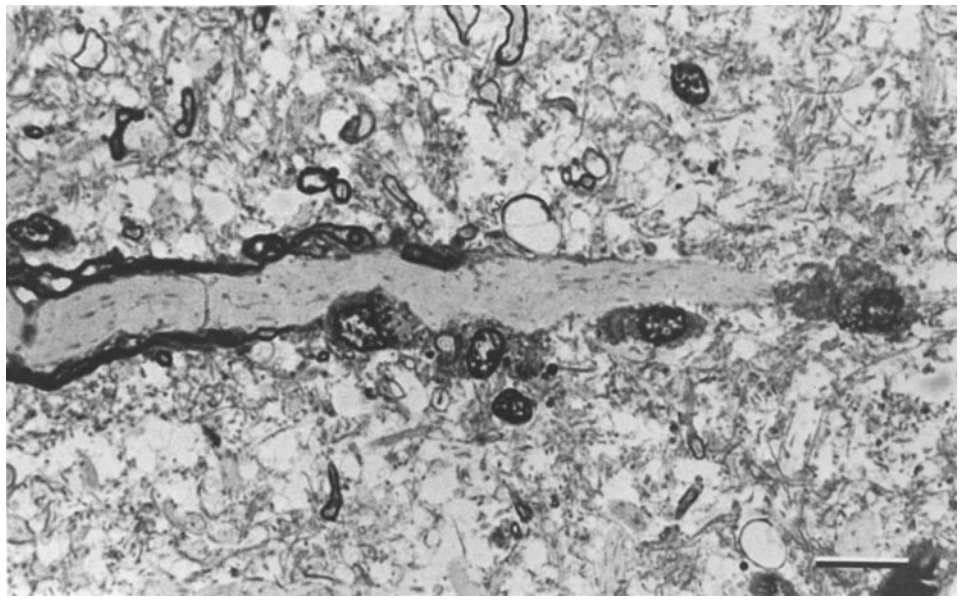


FIGURE 10. Chronic MS—toluidine-blue-stained 1-μm Epon section. At the edge of a chronic lesion, a longitudinally sectioned fiber shows attentuation and loss of its myelin sheath and several closely applied macrophages. Scale bar: 10 μm. ×1250.

chronic plaques, recent activity is manifested by dense perivascular infiltrates containing lymphocytes at the plaque edge (Fig. 12). In acute MS, intense cuffing by small lymphocytes and CNS parenchymal infiltrates is seen (see Fig. 9), and around cuffs, rims of demyelination are observed (Fig. 13). In regions of active demyelination, macrophages and small lymphocytes are the predominant infiltrating cells. Plasma cells are associated more with older, quiescent lesion areas. Totally demyelinated lesions contain naked axons maintained in a matrix of dense fibrous astrogliosis (Figs. 4 and 5), lacking in oligodendroglia and infiltrating cells except for occasional foamy macrophages that sometimes accumulate around blood vessels (Fig. 14). Ultrastructurally, these naked axons have been shown to form membrane specializations with adjacent fibrous astroglial elements (Raine, 1978), structures that may have functional significance.

c. Etiology. Since the earliest descriptions of MS, many agents and predisposing factors have been considered to be causal of MS. Dawson (1916) raised the possibility of a "latent organism or an autotoxin" to explain the remarkable association of lesion with brain vasculature. In more recent years, a number of organisms have been ascribed as possibly being etiologically significant in MS, including certain bacteria, a rabies-like virus, and rod-shaped structures (later identified as centrioles) in glial cells within lesions.

Epidemiological data have more or less established that high- and low-risk geographic areas exist and that persons moving from high- to low-risk areas after the age of 15 years carry with them the same high risk of acquiring the disease, which has a mean frequency in the United States of about 40 per 100,000. It has been suggested that exposure to the putative MS agent(s) occurs before the age of 15 (see Chapter 9).

From the virological standpoint, it has been known since 1962 that elevated titers of antibody to measles virus are present in the sera of a significant number of MS patients in comparison to normal subjects, and since that time, this finding has been confirmed on numerous occasions in tests on sera and cerebrospinal fluid (CSF) samples from MS cases (see reviews by Norrby *et al.*, 1974; Iivanainen, 1981). Such immunological data raise the

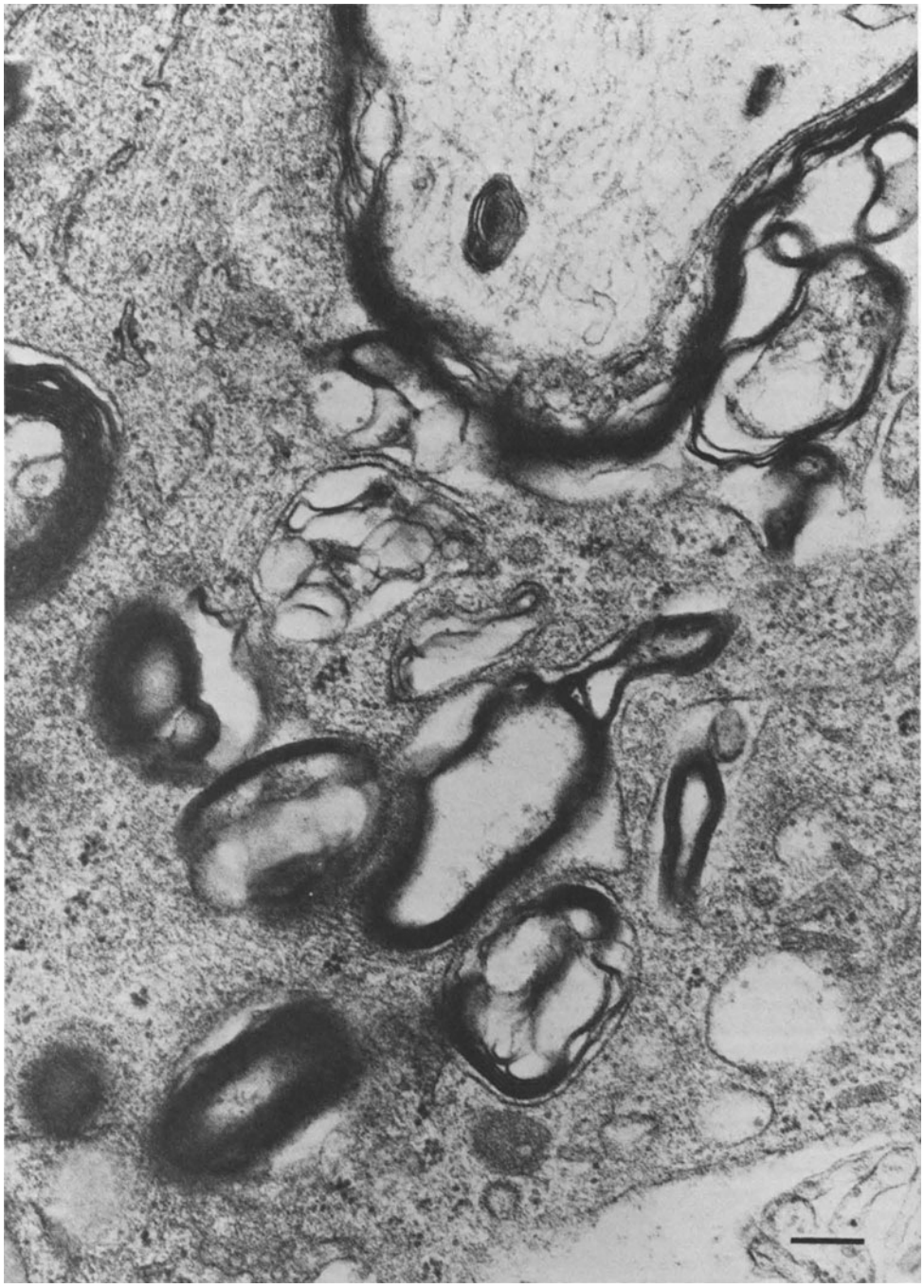


FIGURE 11. Chronic MS—electron micrograph. A nerve fiber (above) is under attack by a macrophage (below). Note the droplets of myelin leaving the myelin sheath to be taken up into chambers within the macrophage. Scale bar: 0.2 μm. ×49,000.

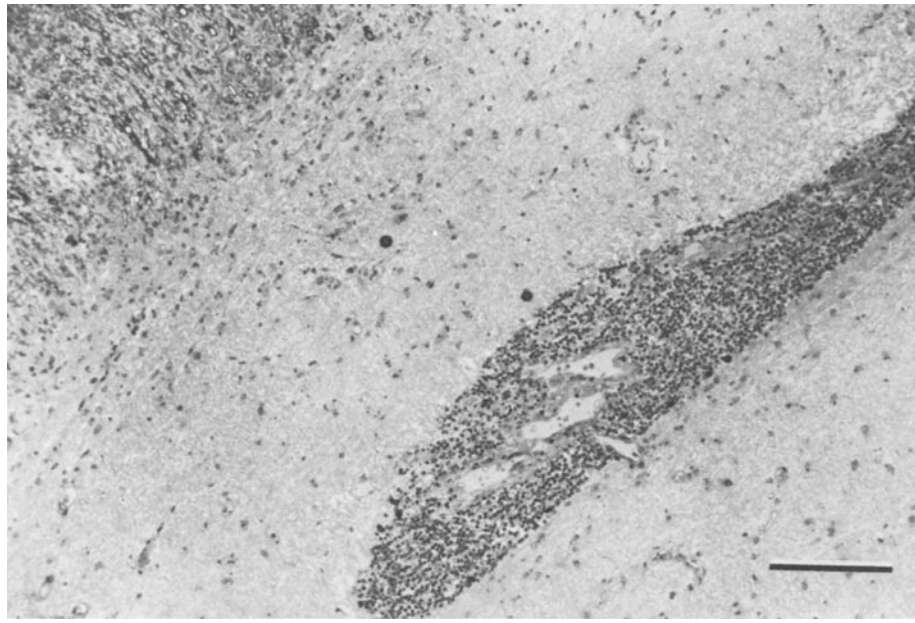


FIGURE 12. Chronic MS—toluidine-blue-stained 1-μm Epon section. At the edge of an otherwise silent chronic lesion (myelinated white matter, upper left), intense inflammation is seen around a blood vessel, a feature indicative of recent activity. Scale bar: 100 μm. ×160.

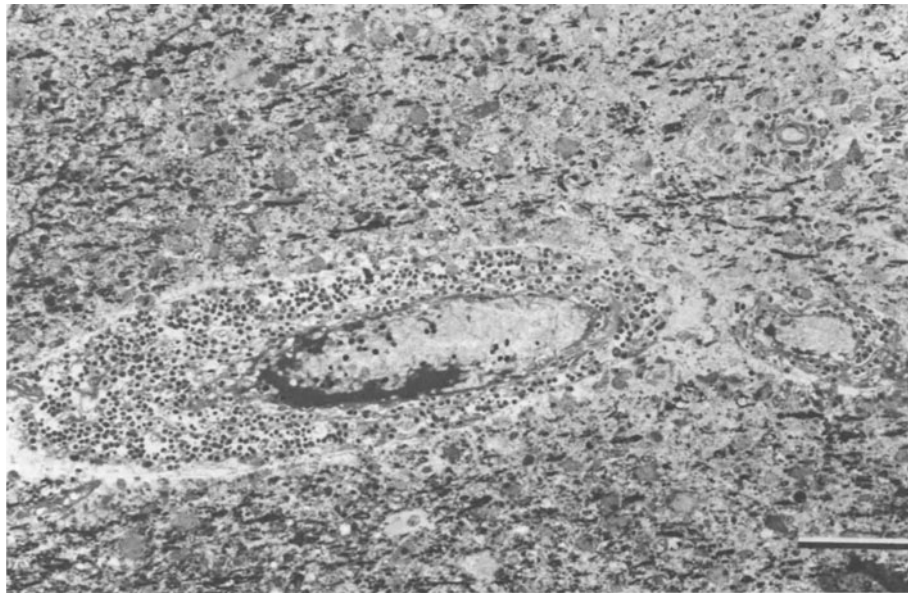


FIGURE 13. Acute MS—toluidine-blue-stained 1-μm Epon section. A typical perivascular cuff of hematogenous cells (mainly small lymphocytes) is seen rimmed by a narrow zone of recent demyelination. Scale bar: 50 μm. ×300.

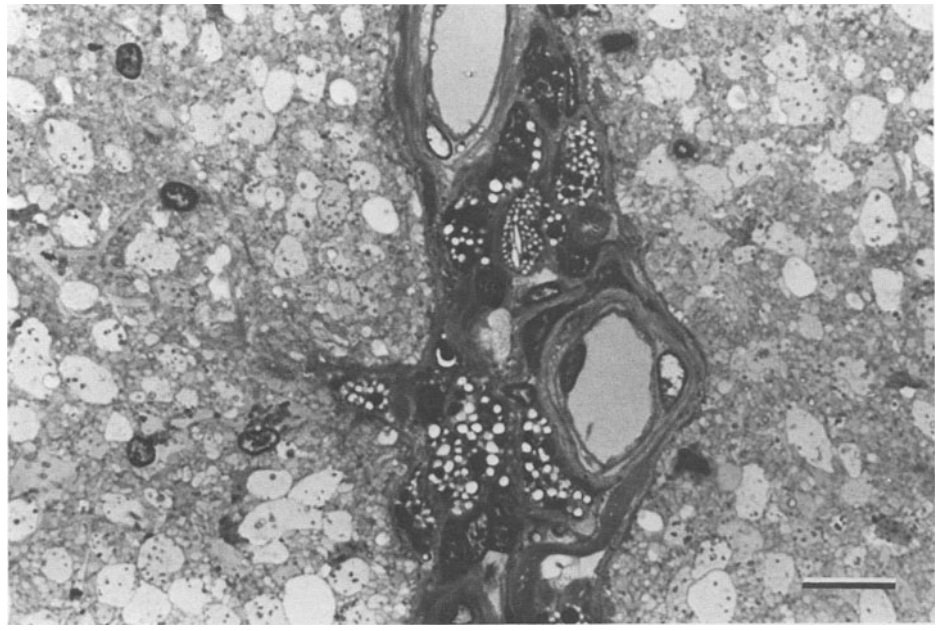


FIGURE 14. Chronic MS—toluidine-blue-stained 1-μm Epon section. Deep within a chronic lesion (note the many demyelinated axons), the Virchow-Robin space around two vessels contains a prominent cuff of foamy macrophages. Scale bar: 10 μm. ×1250.

possibility that measles may be causally related to the disease. Antibody titers to a wide variety of viruses have now been tested in MS and control cases, but only measles antibodies remain consistently elevated in significant numbers. Ter Meulen *et al.* (1972a), using cell-fusion techniques, reported on the isolation of a parainfluenza type I agent from brain cells grown out from two MS biopsy specimens. To date, this has not been confirmed, and there might exist some question as to whether or not the agent was a contaminant. Also in 1972, Prineas (1972) described "paramyxoviruslike" material in acute lesions from a patient with chronic relapsing MS. This observation has been confirmed by several groups who have prepared MS tissue for EM by a variety of techniques. On the basis of comparative studies with autopsy tissue from a number of unrelated diseases, it has now been established that this "paramyxoviruslike" material is not specific for MS and may be a by-product of cellular degeneration (Raine *et al.*, 1975). Measles virus has also been claimed to have been found in the jejunum and measles genome has supposedly been localized in the brain (Haase *et al.*, 1981) in MS subjects, and other reports have suggested that a coronavirus or distemper virus might be involved. In all these latter cases, reports to the contrary have appeared. Apart from the indirect immunological data implicating a measleslike infection, there is no direct evidence that a virus is involved in MS, although additional circumstantial evidence from a number of conditions related to MS and a number of naturally occurring and experimental viral diseases suggest that a virus is the most likely candidate (for a recent review on this subject, see McFarlin and MacFarland, 1982a,b).

Secondary to the putative infection in MS, it is hypothesized that an autoimmune (autoallergic) response to myelin antigens develops, akin to that produced in animals following sensitization to CNS myelin antigens [experimental allergic encephalomyelitis (EAE), (Raine 1976a, 1982)], thus accounting for the perivenular cuffing and demyelination The latter are constant features in EAE, in which a delayed hypersensitivity response to myelin is well established. One form, chronic relapsing EAE in guinea pigs (Raine and Stone, 1977), has proven particularly useful in the analysis of immunological events of

relevance to MS (e.g., Raine, 1978; Raine *et al.*, 1982; Traugott *et al.*, 1982a). Lesions in this disease approach dimensions and appearances highly reminiscent of those seen in MS [see Figs. 1-3, pp. 263-264.]. The comparative pathology of MS and this condition has been presented elsewhere (Raine, 1982). Attempts to demonstrate sensitization to myelin in MS have not yet been conclusive. Skin tests to myelin basic protein (MBP) are negative in MS, unlike EAE, but as in EAE, although to a lesser degree, positive results have been obtained from *in vitro* tests for lymphokines and serum and CSF demyelinating factors (see Paterson, 1973; Raine, 1976a). Based on animal experiments on the causation and treatment of autoimmune demyelination, it has recently been suggested that in MS, an immune response against combinations of myelin components might be operative (Raine and Traugott, 1982). Finally, there is growing interest in the possibility that histocompatibility antigen (*HLA*) types may influence susceptibility to MS [e.g., DRW_2 (see Chapter 9)], and some cases display a tendency for certain types to be linked (e.g., HLA-A3 and HLA-A7).

2. *Variants of Multiple Sclerosis*

Although considered by some to represent separate disease entities, a small number of chronic demyelinating conditions of the CNS exist that are most conveniently grouped together with MS. Such a condition is Devic's disease, in which plaques are located in the optic tracts associated with necrotizing lesions in the spinal cord. Balo's concentric sclerosis is another, exceedingly rare, condition with some similarities to MS; in some inexplicable way, lesions develop concentrically with zones of apparently normal white matter alternating with grossly visible bands of demyelination. The latter condition can only be diagnosed post mortem.

3. *Acute Disseminated Encephalomyelitis*

a. Pathology. Acute disseminated encephalomyelitis (ADE) is a broad disease category embracing a number of relatively short-term, frequently fatal, fulminant inflammatory CNS conditions of varied etiology. The members may be spontaneous or iatrogenic. The most common disease in this group follows an exanthematous infection by a virus, e.g., measles, vaccinia, varicella, or influenza. These examples are also known as the postinfectious encephalomyelitides. Another form with identical lesions is seen after rabies immunization, in which case the patient develops an autoallergic, EAE-type of response within the white matter, now known to be related to CNS tissue incorporated within the inoculum.

The neuropathology of these conditions, despite the variation in causal factors, is remarkably uniform. The lesions are often not visible grossly, but show well after myelin staining (Fig. 15). By LM, the white matter contains cuffs of lymphocytes, mononuclear cells, plasma cells, and occasional macrophages in relationship to the Virchow-Robin spaces of venules and small veins. Associated with the latter are perivascular rims of demyelination and macrophages consisting of pleomorphic microgliocytes, histiocytes, and monocytes. In contrast to acute and chronic MS, this group of diseases displays inflammatory changes in the pia-arachnoid covering the brain stem, spinal cord, and optic nerves. This inflammation invariably overlies rims of subpial demyelination. EM reports on these conditions are rare and add little to the histopathological picture.

b. Etiology. Examination of the clinical chart in most of the cases described above will invariably reveal a recent exposure to a viral infection affecting either the patient or a close family member. However, specific viral-isolation techniques have not been performed in most cases. Successful demonstration and isolation of virus material from cases of postinfectious encephalomyelitis are rare, examples being the observation or viral inclusions by Adams *et al.* (1966) and the rescue of a defective measles agent from one case by Ter Meulen *et al.* (1972b). Because the pathology in these conditions does not conform to that

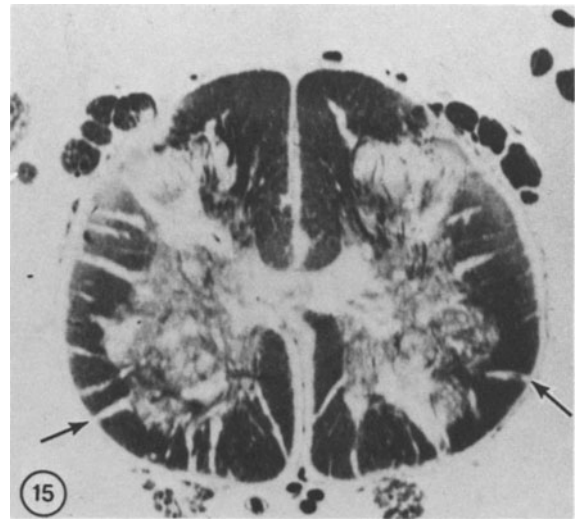


FIGURE 15. ADE—myelin stain. This paraffin-embedded section of spinal cord displays linear radiating zones of demyelination (arrows) related to blood vessels penetrating from the meninges. ×10.

usually associated with demyelination, it has been hypothesized that the disease is an immunological reaction to the virus or to brain constituents possibly altered during the infection course. Such a phenomenon would strengthen the significance of EAE to the study of ADE.

Indeed, *in vitro* tests for lymphokines produced in response to MBP as tested on lymphocytes or by blast-cell transformation have been positive in one case of post-infectious encephalomyelitis (Behan *et al.*, 1968). Post-rabies-immunization encephalomyelitis today is a rare condition but was relatively common toward the end of the 19th century, during the early trials with the Pasteur antirabies vaccine. The disease is analogous to a human form of EAE and was shown to be causally related to CNS tissue incorporated into the vaccine during the culture of the virus in embryonic tissue.

4. Acute Hemorrhagic Leukoencephalopathy (Weston Hurst Disease)

a. Pathology. Acute hemorrhagic leukoencephalopathy (Weston Hurst disease) is rare, and the presence of hemorrhage and necrosis sometimes makes it difficult to recognize an inflammatory demyelinating state. Despite these differences, however, it is generally regarded as a more severe form of postinfectious encephalomyelitis.

The lesions are large and grossly visible due to extravasation of red cells and infarction (Figs. 16-18). Microscopically, one sees that this disease differs from postinfectious encephalomyelitis by the presence of vascular injury and fibrin thrombosis with infarction and abundant neutrophils in the vessel walls, lesions, and meninges. The major lesions are also accompanied by inflammatory foci, and all changes are of the same age.

b. Etiology. Acute hemorrhagic leukoencephalopathy is usually preceded by an upper respiratory tract infection, but can also follow an exanthem or vaccination (Johnson and Weiner, 1972). Also implicated in the disease process is an autoallergic response to myelin antigen, and work by Behan *et al.* (1968) has shown positive blast-cell formation in the presence of MBP by lymphocytes from patients with this disease.

5. Progressive Multifocal Leukoencephalopathy

a. Pathology. A rare CNS condition, PML usually occurs in individuals with long-standing diseases of the reticuloendothelial system or neoplasms or in those receiving immunosuppressive therapy. Typically, death follows about 3-12 months after onset of CNS

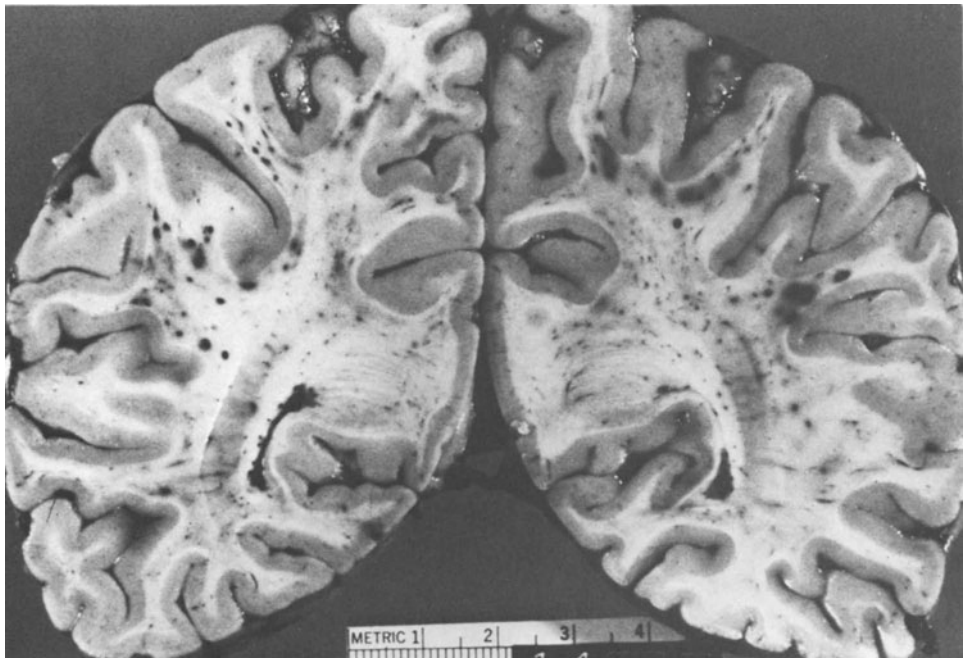


FIGURE 16. Acute hemorrhagic leukoencephalopathy—gross specimen. In this coronal section, note the many punctate, hemorrhagic lesions within the white matter. Gray matter is uninvolved. Specimen provided by Dr. Julio Garcia, University of Alabama.

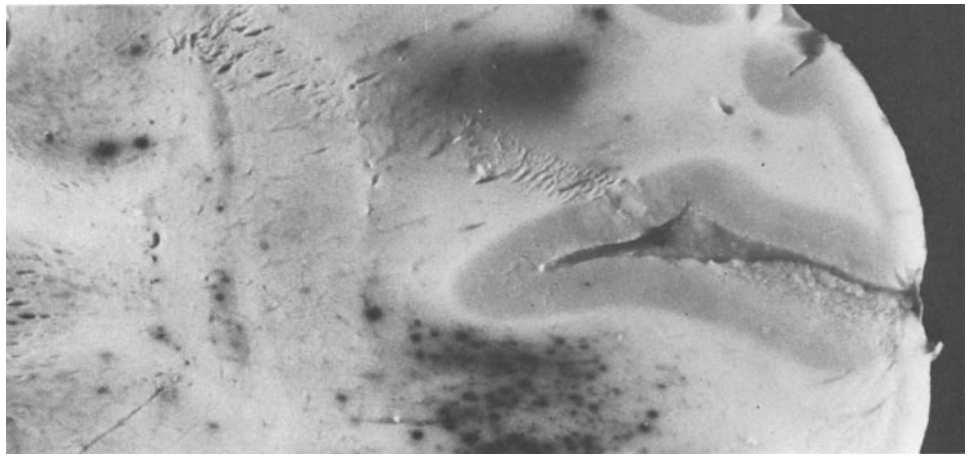


FIGURE 17. Acute hemorrhagic leukoencephalopathy—gross specimen. Within two gyri, note how the punctate hemorrhagic lesions are localized to white matter. Specimen provided by Dr. Wayne Moore, Memorial University of Newfoundland.

symptoms. Coronal sections of the fresh brain disclose multifocal, grossly visible lesions that by LM are rimmed by bizarre astrocytes containing abnormal mitotic figures (Figs. 19 and 20). Large oligodendroglia lie toward the peripheries of the lesions, and many of these cells contain intranuclear inclusion bodies (Fig. 21). Myelin and oligodendroglia are absent within the lesions, and it is not unusual to find a significant amount of axonal dropout.

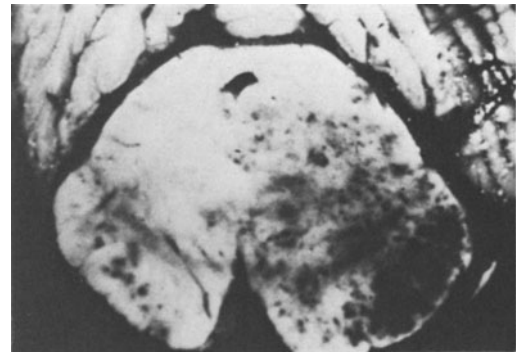


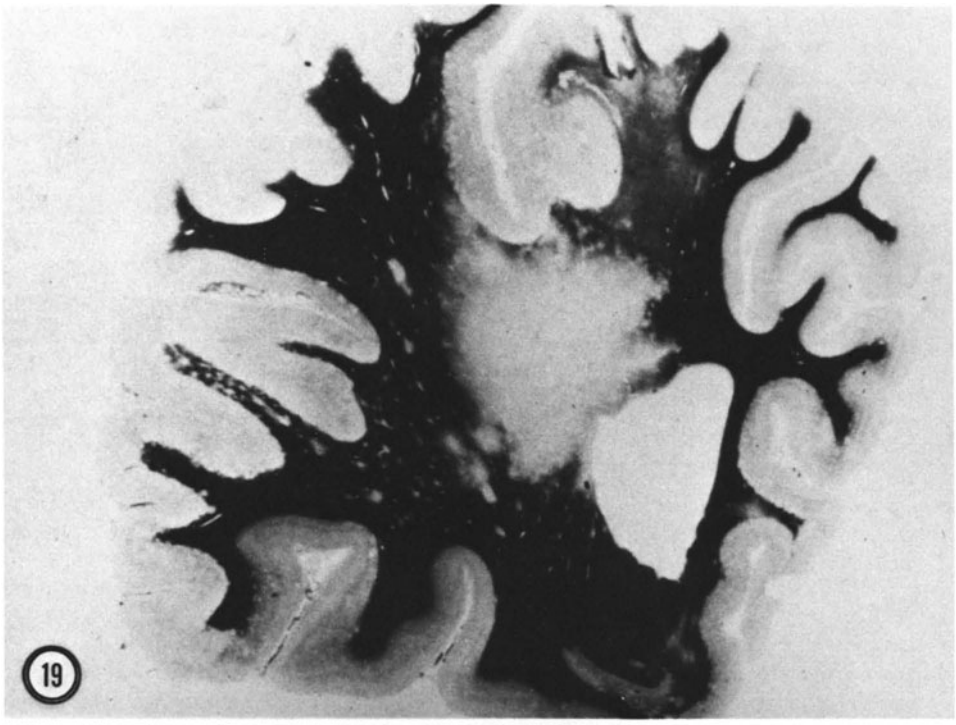
FIGURE 18. Acute hemorrhagic leukoencephalopathy—gross specimen. The discoloration of white matter in this region of mesencephalon is due to severe hemorrhage, inflammation, and probably necrosis.

Variation in the topography and neuropathology of PML lesions has been surveyed by Brun *et al.* (1973). In contrast to other acquired demyelinating conditions, PML lesions are essentially noninflammatory. The mechanism of myelin degeneration is not known, but it is speculated that the demyelination is a consequence of selective damage to oligodendroglia.

b. Etiology. A virus has been implicated in PML (for a review, see Johnson and Weiner, 1972). EM of PML lesions by Zu Rhein and Chou (1965) uncovered the presence of unequivocal viral particles within oligodendroglial nuclei, and the suggestion was made that these particles resembled a papovavirus. This finding was later confirmed by Zu Rhein (1969) in a study of more than 20 cases. Prompted by these EM observations, successful isolation of papovaviruses from autopsy and biopsy PML brain tissues was achieved (Padgett *et al.*, 1971; for a review, see Johnson and Weiner, 1972). The results form the serological and virological studies of Weiner *et al.* (1972) and Johnson and Weiner (1972) are consistent with there being more than one papovavirus with the ability to produce PML. The specificity of the infection for oligodendroglia supports the theory that myelin breakdown occurs subsequent to their death, and the failure of subjects to mount an efficient inflammatory response is in accord with an immunological deficit and the absence of immune-mediated demyelination.

6. *Idiopathic Polyneuritis*

a. Pathology. The term *idiopathic polyneuritis*, which embraces the various forms of Landry-Guillain-Barré syndrome (LGBS) and postinfectious polyneuritis, represents a group of inflammatory demyelinating conditions that specifically affect the PNS. Lesions are not visible grossly, but LM examination reveals a multifocal intense inflammation associated with primary demyelination (Figs. 22 and 23). The disease is most evident in radicular zones and ganglia, with the extremities being less affected. While the majority display an acute, monophasic course, sometimes with a fatal outcome, some are chronic progressive or relapsing and display evidence of remyelination (Prineas and MacLeod, 1976). The fine structure of LGBS and other idiopathic neuritides has been investigated extensively (see Prineas, 1971), and a process of demyelination akin to that seen in the animal models of autoimmune demyelination—EAE and experimental allergic neuritis (EAN)—was the common pattern. As a general rule, there is little or no axonal degeneration in these diseases. Sometimes, in more severe cases in which inflammation of the spinal nerve roots persists for several weeks after onset, there is secondary degeneration in the posterior columns of the spinal cord. Minor inflammatory changes are sometimes localized within the meninges. Even in cases with clinical recovery, there may be long-standing foci of inflammation within peripheral nerves (Asbury *et al.*, 1969).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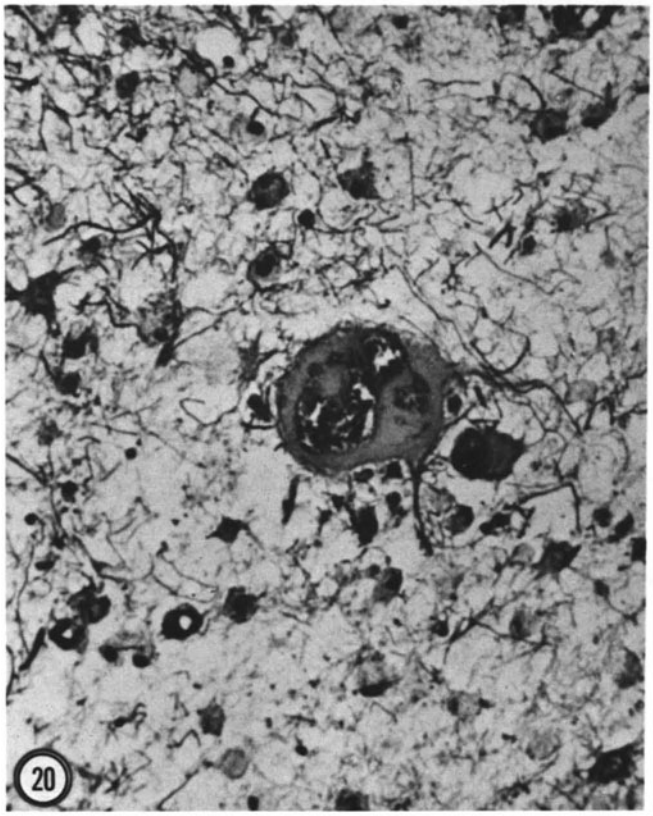
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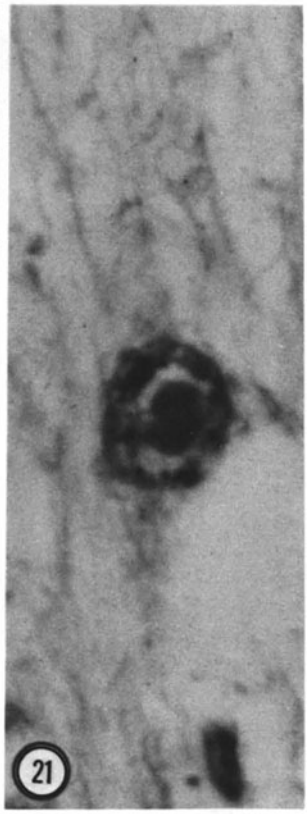
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b. Etiology. While an autoallergic phenomenon has been accepted as the underlying cause of the PNS demyelination in these conditions, a conclusion heavily influenced by comparison with the animal model EAN, many workers attribute the primary insult to an antecedent viral infection. Reports exist, for example, in which idiopathic polyneuritis developed after a bout of measles, infectious hepatitis, respiratory tract infections, rabies infection, or infectious mononucleosis, although direct demonstration or isolation of a virus is lacking. Serological tests on some cases of LGBS have shown significantly higher titers of antibody against Epstein-Barr virus, a cell-associated herpesvirus, and cytomegalovirus. See Chapter 12 for further discussion of relevant immunology.

7. *Diphtheric Neuropathy: Pathology and Etiology*

Diphtheric neuropathy in man is the direct sequela of a bacterial infection, i.e., *Corynebacterium diphtheriae*. The myelin breakdown is caused by an exotoxin secreted by the organism and not by the bacterial invasion itself. Frequently, the disease is fatal and related to respiratory paralysis or disordered cardiac function. Primary demyelination occurs in the PNS and shows a predilection for the spinal nerve roots and proximal regions of nerves. There is remarkable preservation of axons and neurons. Myelin becomes fragmented and might be taken up locally by Schwann cells. A few mononuclear cells are also seen. The brain and spinal cord usually remain normal. The manner in which the toxin effects this demyelination has been attributed to its specific affinity toward membrane systems (Webster *et al.*, 1961). Biochemical data have shown the exotoxin to be a potent inhibitor of protein synthesis.

C. Animal Examples

There exist a number of naturally occurring and experimental diseases that have marked similarities to the previous group of human diseases. In most of the spontaneous animal conditions, a viral etiology is either proven or highly likely. The experimental situations are induced by infection with a known virus or sensitization with nervous system antigen, the latter effecting a delayed-hypersensitivity-type response within the CNS or PNS.

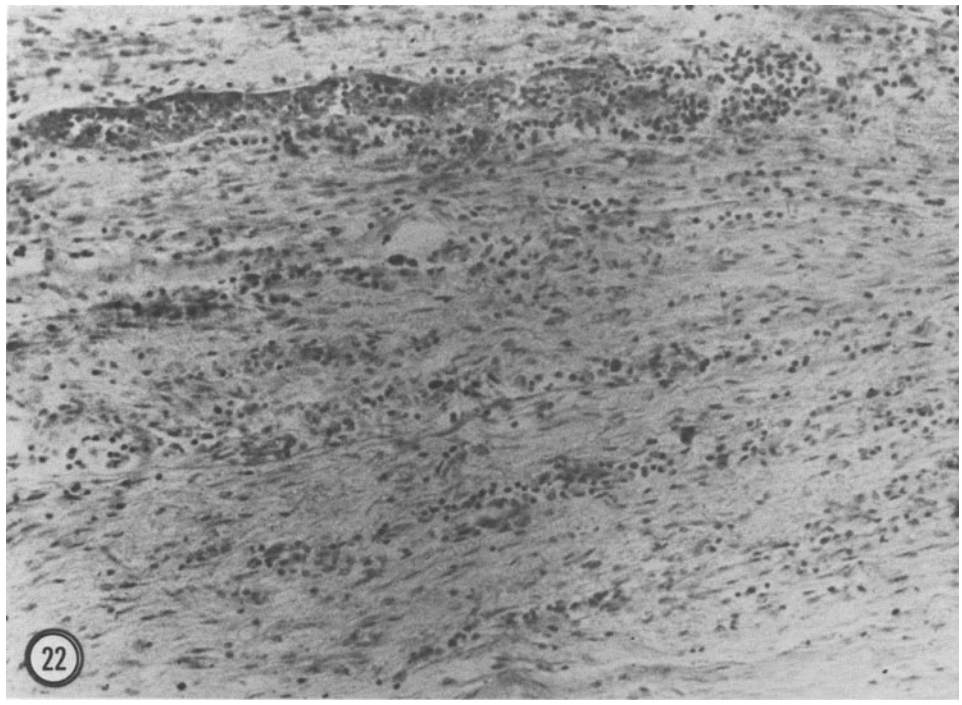
1. *Canine Distemper Encephalomyelitis: Pathology and Etiology*

Canine distemper encephalomyelitis, a usually fatal condition, occurs naturally in dogs and may be induced experimentally in a number of species, in particular dogs and ferrets. Canine distemper virus, a paramyxovirus closely related to measles, usually produces a systemic infection and exanthem that precede the nervous system syndrome by 1-2 weeks. The disease has a number of forms—acute, chronic and relapsing—and the pathology varies according to the persistence of the agent. At autopsy, the CNS of a distemper dog might display large visible plaques throughout, although it is not unusual to detect no abnormalities on gross examination. Microscopically, lesions are inflammatory, demyelinative and destructive. Some burnt-out or severe plaques might show considerable axonal loss. Viral inclusions can be detected in a number of cell types. Ultrastructurally, the process of demyelination is associated with macrophages (Raine, 1972, 1976b; Wisniewski *et al.*, 1972) and proceeds in

FIGURE 19. PML—myelin stain, whole mount. This section of occipital lobe shows a large white-matter lesion with a puffball appearance, surrounded by several small lesions.

FIGURE 20. PML—HE-stained paraffin section. A bizarre astrocyte is located within an area of demyelination. ×500.

FIGURE 21. PML—HE preparation. An oligodendroglial cell nucleus contains a viral inclusion. ×1200.



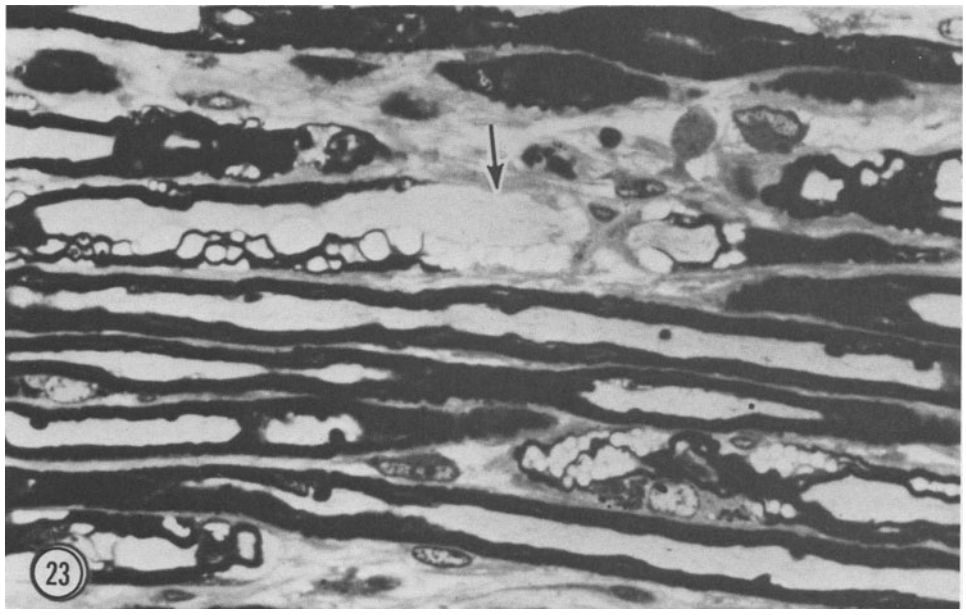


FIGURE 22. LGBS—HE section. This longitudinal section of a spinal nerve root demonstrates an increased cellularity due to inflammatory cells between the nerve fibers and related to blood vessels. ×200.

FIGURE 23. LGBS—toluidine-blue-stained 1-μm Epon section. Several longitudinally sectioned fibers demonstrate vacuolar changes in the myelin and foamy macrophages within the Schwann tube. A short segment of one fiber (↓) is completely naked. ×600.

the presence of local viral material. Whether there is active sensitization to myelin components or whether the demyelination is a sequela of specific infection of oligodendroglia, cross-reactivity between viral and myelin proteins, or accidental damage occurring in the midst of regions where lymphokines and hydrolytic enzymes might be produced against the virus, is not known. The infectious agent has been well characterized by a number of workers (see Appel and Gillespie, 1972), and *in vitro* tests have suggested depression of T cells and the possibility of specific myelinotoxic factors in the serum of infected animals.

2. *Visna: Pathology and Etiology*

Visna, a naturally occurring disease among Icelandic sheep until eradicated by an intensive killing program, exists today as an *in vitro* virus that is used to transmit the disease experimentally. CNS lesions are often grossly visible, and many display nonspecific necrosis. This necrotic feature may invalidate the inclusion of visna in the inflammatory group. However, some inflammatory demyelinating lesions can be found in the white matter. There is a predilection for lesions to affect subependymal regions. Since the disease progresses in the presence of an increase in spinal fluid protein and serum antibody and the observation that viral release *in vitro* is by a process of budding, it has been suggested that antigen-antibody reactions might occur on infected glial cell membranes, leading to cellular destruction and demyelination (for a review, see Johnson and Weiner, 1972). However, definitive proof of the latter is lacking. Studies on the characterization of the agent suggest that visna is related to the C-type tumor RNA viruses (Retroviridae). The neuropathology of this condition has been extensively studied (Petursson *et al.*, 1976; Georgsson *et al.*, 1977).

3. *Coonhound Paralysis: Pathology and Etiology*

In coonhound paralysis, a naturally occurring condition of dogs, the PNS is specifically affected by an inflammatory disease process that renders the model highly suited for the study of the LGBS in man. Also, there are many similarities to EAN (see p. 282). After the onset of limb weakness, the nerve roots and peripheral nerves display diffuse inflammation and concomitant segmental demyelination (Cummings and Haas, 1967). The disease is probably related to a viral infection, as yet not characterized, that occurs after a coonhound (other breeds of dogs are also susceptible) is bitten by a racoon. The present consensus is that the disease might result from a combination of viral and autoimmune factors.

4. *Marek's Disease: Pathology and Etiology*

Among poultry breeders, Marek's disease provides a severe economic threat, since it accounts for more deaths among chickens than any other condition. Marek's disease is predominantly a malignant lymphomatous state related to infection by a herpesvirus. As a secondary complication, the PNS may become involved. This neurological complication is typified morphologically by the invasion of the PNS by inflammatory cells that destroy myelin in a manner similar to that seen in LGBS and EAN (Prineas and Wright, 1972). This suggests that autoimmune factors might play a role. Although it is assumed that the demyelination follows the viral infection, it is usually difficult to visualize virus particles in affected nerves.

5. *Mouse Hepatitis Virus Encephalomyelitis: Pathology and Etiology*

In mice, an experimental viral encephalomyelitis with some features reminiscent of ADE and PML can be induced. The disease is caused by infection with a virus (JHM strain) isolated originally from the brain of a mouse (Cheever *et al.*, 1949). The agent has been since classified

with the mouse hepatitis viruses among the Coronaviruses. An affinity for myelin to be damaged was observed, and this was later confirmed by Waksman and Adams (1962). Ultrastructural study by Lampert *et al.* (1973b) has reported on the presence of virus in lesions and the occurrence of nonspecific demyelination related to mononuclear cells. The loss of myelin has been proposed to result from a specific infection of myelinating cells and not from an immune mechanism, a thesis supported by experiments on infected immunosuppressed animals that displayed myelin loss yet lacked inflammatory changes (see Johnson and Weiner, 1972). More recent work has demonstrated that even though the infection is widespread in the CNS, its effect is most marked in myelinated areas (Fleury *et al.*, 1980).

6. *Experimental Allergic Encephalomyelitis: Pathology and Etiology*

As the name suggests, EAE is an experimental disease. It is inducible in most laboratory species and generally involves the sensitization of animals with a single inoculation of white matter or MBP emulsified with complete Freund's adjuvant (CFA), although other protocols (viz., the omission of CFA from the inoculum or the substitution for this component by other adjuvants) are capable of causing the disease. About 2–3 weeks following the subcutanous administration of the encephalitogenic emulsion, animals become paralyzed. This acute, monophasic disease is typified microscopically by foci of perivascular and meningeal inflammation that are almost invariably related to local demyelination (see Waksman and Adams, 1956). Acute lesions bear some morphological resemblances to those of ADE and acute MS. The fine structure of the mechanism of demyelination has been shown to involve active stripping of myelin from axons by invading mononuclear cells (Lampert, 1967) and vesicular disruption of the myelin sheath (Raine *et al.*, 1974). In some species, the PNS is also affected. Manipulation of the induction protocol can cause a hyperacute disease that mimics acute hemorrhagic leukoencephalopathy. The amino acids of MBP have been sequenced, and encephalitogenic sites on the molecule are now recognized for a number of species. The disease is T-cell-mediated (Gonatas and Howard, 1974), and evidence for sensitization against myelin components is well known (see Paterson, 1973). Chronic forms of EAE also exist, some with relapsing disease courses (Raine, 1976a). The latter have clinical and pathological stigmata resembling the human condition MS (Raine, 1982), for which EAE is a possible experimental analogue (Figs. 24 and 25).

7. *Experimental Allergic Neuritis: Pathology and Etiology*

EAN, the PNS counterpart of EAE, was originally described by Waksman and Adams (1956). Animals are sensitized against whole PNS tissue or PNS MBP in CFA and develop leg weakness in 2–3 weeks. Histologically, the PNS contains ongoing demyelination in the presence of inflammation, shown by Lampert (1969) to be effected by an active stripping process by invading mononuclear cells, analogous to the pattern described in EAE (Figs. 26 and 27). Chronic and recurrent forms of EAN are also known. The disease is the standard laboratory model for the study of the LGBS. The major neuritogen in EAN is a PNS myelin-specific basic protein, P_2 (Eylar *et al.*, 1982) (also see Chapter 12).

V. CLASS II: HEREDITARY METABOLIC DISEASES OF MYELIN

A. Diagnostic Criteria

The group of hereditary metabolic diseases of myelin covers a large number of conditions, each of which might have several variants, usually determined by age at onset. There are distinctive clinical and morphological features that unify the various diseases in this group. Clinically, these diseases are reflections of inborn errors of metabolism that often become manifest in the first decade of life. Morphologically, the diseases (known collectively in most cases as the leukodystrophies) demonstrate a diffuse loss of both myelin and axons

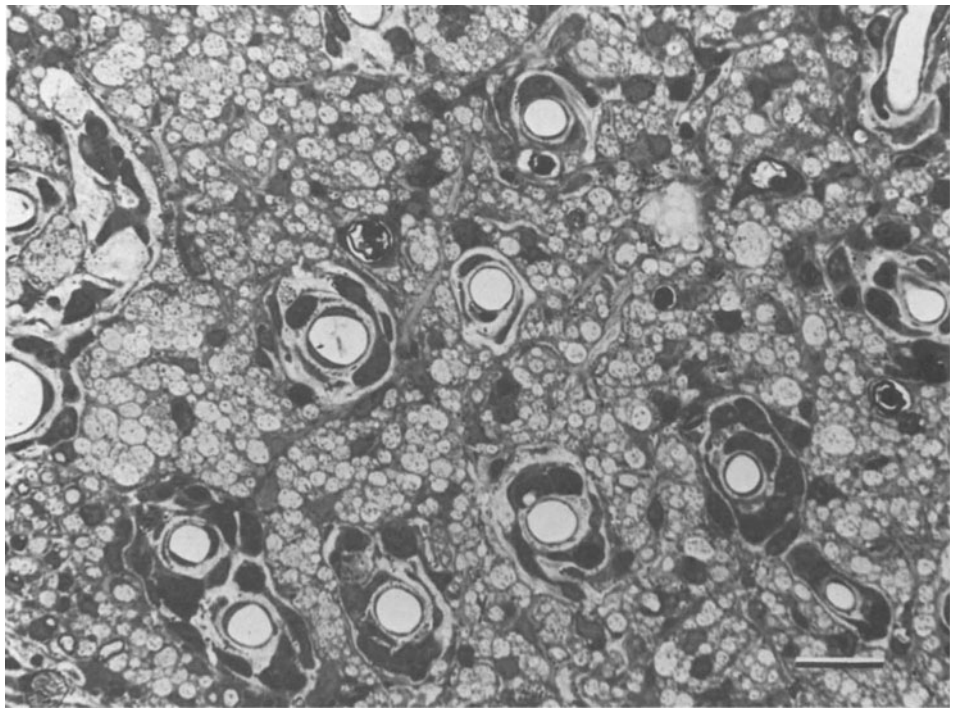


FIGURE 24. Chronic relapsing EAE in the guinea pig—toluidine-blue-stained 1-μm Epon section. From the center of a plaque, an area of naked axons and fibrotic blood vessels is shown. Scale bar: 10 μm. ×1250.

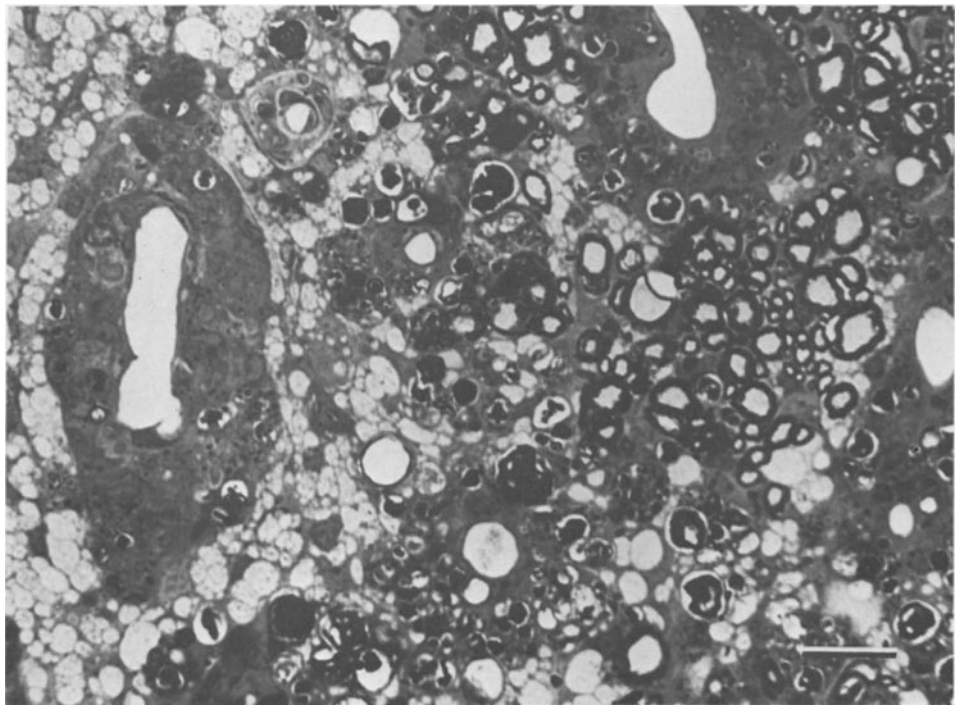


FIGURE 25. Chronic relapsing EAE in the guinea pig—toluidine-blue-stained 1-μm Epon section. At the edge of an established lesion, a recent bout of clinical activity is matched by recent inflammation and ongoing myelin breakdown. The plaque center containing mainly naked axons is located below. Scale bar: 10 μm. ×1250.

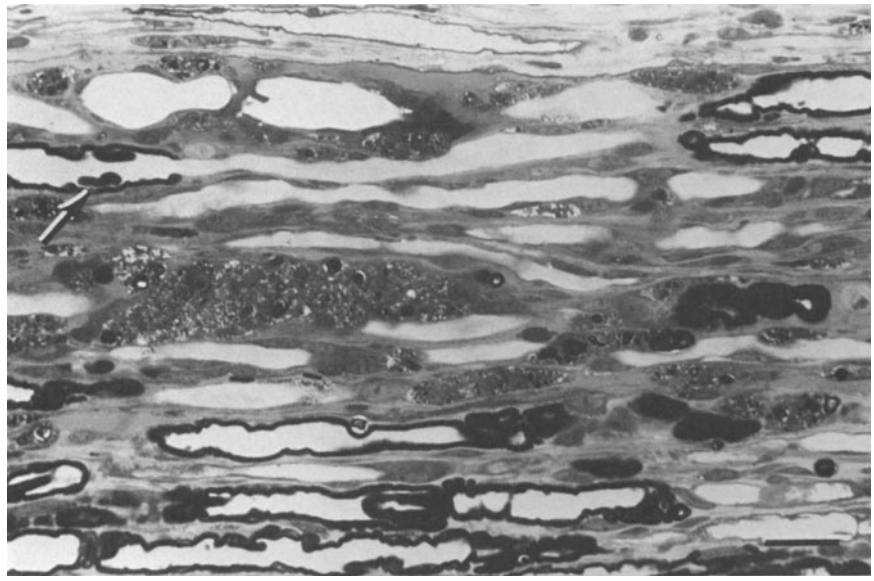


FIGURE 26. EAN in the rabbit—toluidine-blue-stained 1-μm Epon section. A longitudinal section shows many demyelinated axons, some with preserved internodes of myelin (⟶), perivascular cuffing, and many endoneurial macrophages containing myelin debris. Scale bar: 25 μm. ×480.

from large areas of white matter. Since the nervous-system damage is more widespread than in the Class I diseases, the term *leukodystrophy* is general and ignores the involvement of neurons and other organs in some instances and serves only to emphasize the severe destruction of white matter common to all members. It is becoming apparent that most leukodystrophies represent disorders of lipid metabolism, and some are already classified among the lipidoses. With the exception of adrenoleukodystrophy (ALD), the conditions are noninflammatory. Viral, and immunological factors have not been implicated. All are extremely rare. See Lyon and Goffinet (1980) for a recent review.

B. Human Examples

1. Metachromatic Leukodystrophy—Sulfatide Lipidosis

a. Pathology. Metachromatic leukodystrophy (MLD), a rare familial disease, has its onset in most cases between the ages of 1 and 5 years, and has a duration of 3-6 years. Adult forms exist, but are rarer. The condition derives its name from the abnormal, metachromatically staining myelin degradation products (cerebroside sulfatide). Coronal section of the brain reveals extensive involvement of the entire white matter (Fig. 28), often in a symmetrical fashion, so that lesions have a butterfly configuration. Sometimes, in cases of long duration, the white matter is reduced to a narrow strip 1-2 cm in diameter, and the shrinkage of the white matter can lead to enlargement of the ventricles. The disease primarily affects myelin, but the subsequent breakdown process invariably affects neurons and their axons. It is therefore not classed as a "demyelinating" disease, but rather as a disorder of myelin. Early in the disease, myelin is completely lost from lesion areas, and this loss is followed by axonal degeneration. At the edge of affected areas and scattered throughout lesions are macrophages that contain the specific degradation product (Fig. 29). Nerve cells throughout the brain show ballooning and swelling and presence of cytoplasmic inclusions

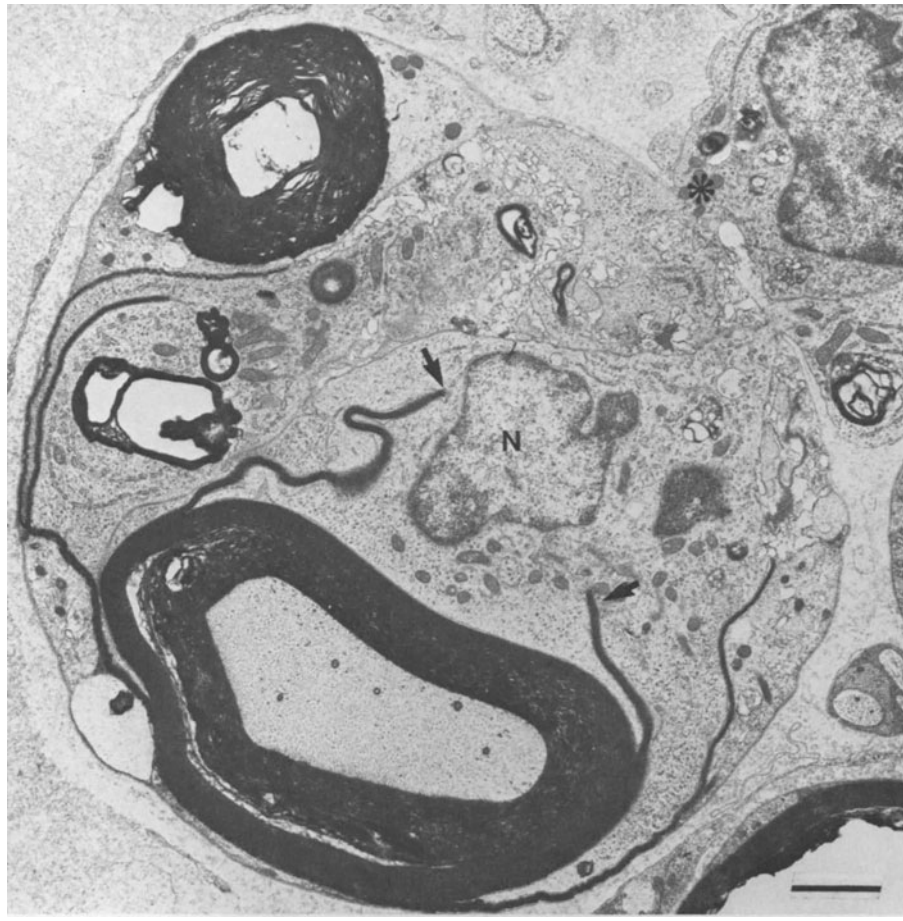
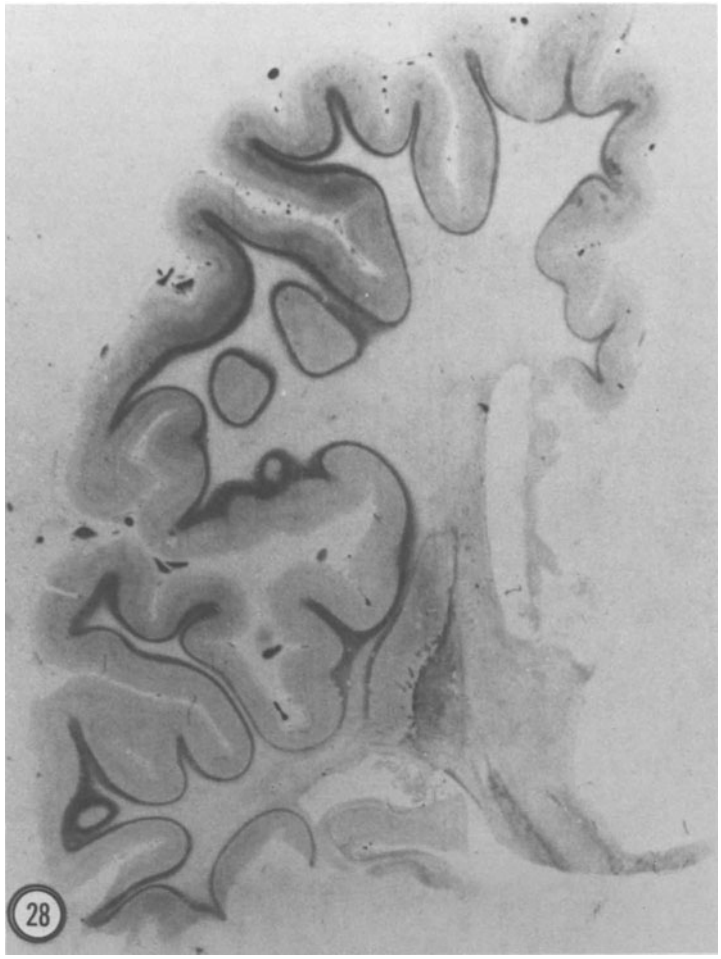


FIGURE 27. EAN in the rabbit—electron micrograph. A PNS nerve fiber is sectioned transversally and shows macrophage (nucleus at N) within the Schwann-cell tube and one still entering (*). Processes of the macrophage in the center have penetrated between layers of myelin, lifting it away in layers from the rest of the sheath (⟶). Scale bar: 2 μm. ×6000.

containing cerebroside sulfatide. The most severe nerve-cell changes occur in the mesencephalon, pons, medulla oblongata, and spinal cord. Similarly, certain areas of white matter are more severely affected, mainly those that are myelinated late in ontogenesis. By LM, oligodendroglia are absent from lesions. The specific inclusions (Fig. 30), which have a characteristic lamellated morphology (see Terry, 1970), are not only found in neurons and macrophages in the brain but also occur in Schwann cells of the PNS and in a variety of other organ systems, e.g., viscera (Wolfe and Pietra, 1964).

b. Etiology. Biochemical assays have determined that the myelin breakdown in MLD is due to a genetically determined deficiency of the enzyme cerebroside-3-sulfatase (arylsulfatase A) detectable in a number of tissues both pre- and postnatally (Pfeiffer, 1970; Moser, 1970) (see Chapter 11 for details). Normal-appearing myelin from unaffected areas of white matter also shows biochemical abnormalities. It is hypothesized that myelination at first is normal despite the enzyme defect, but gradually sulfatide accumulates and the myelin becomes abnormal.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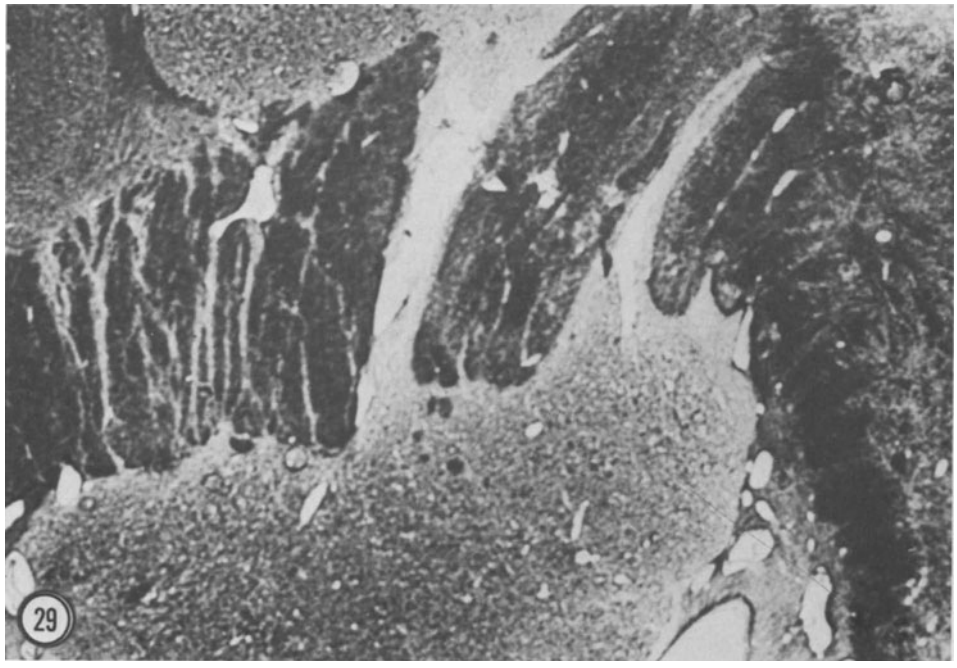
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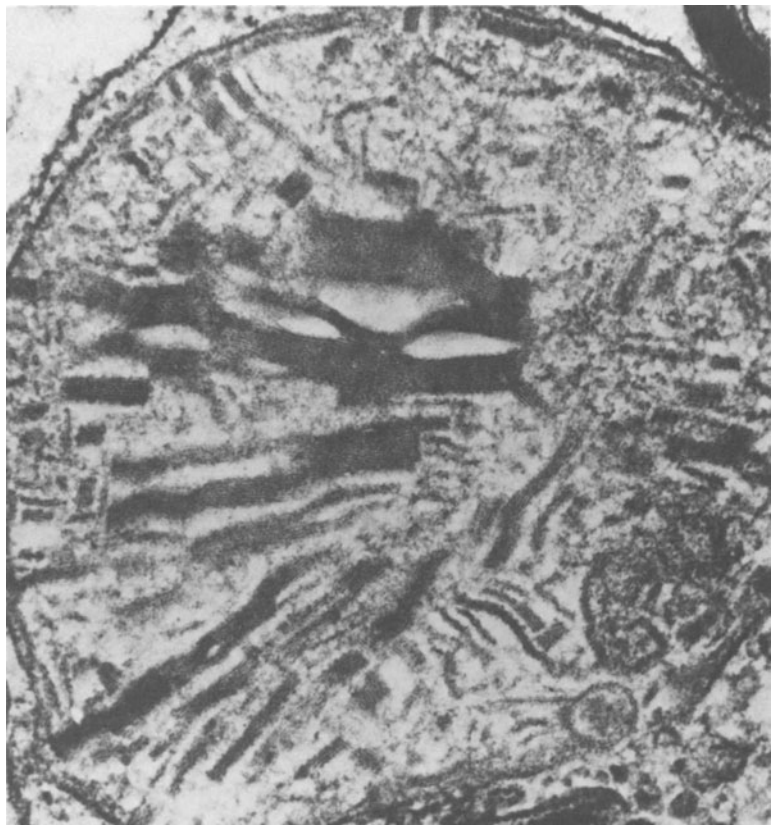


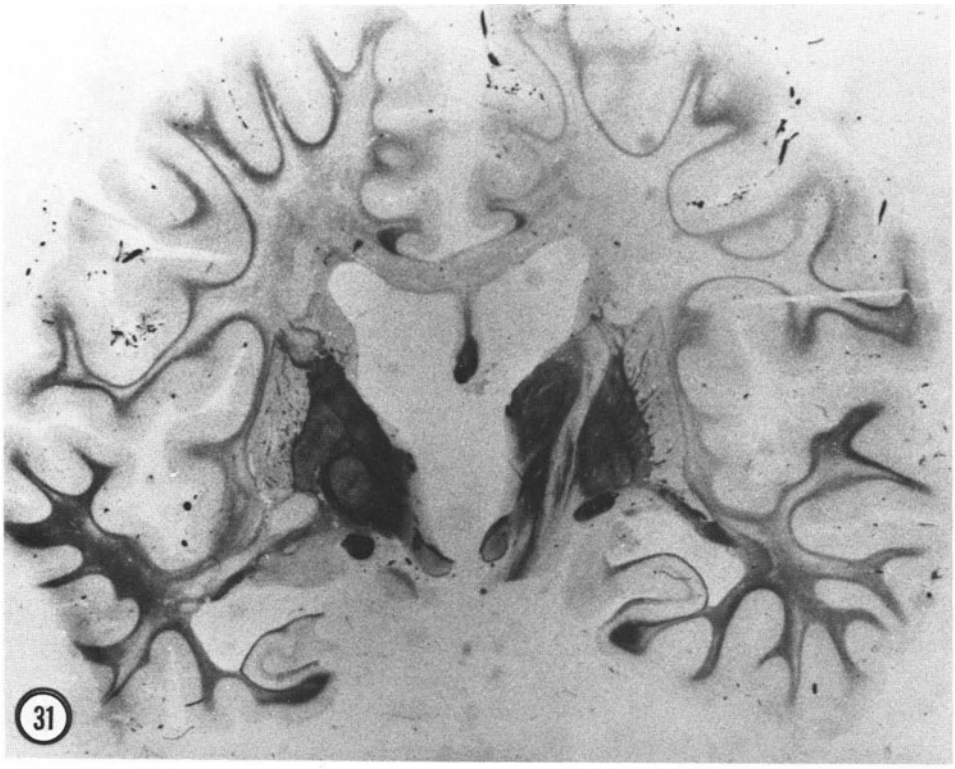
FIGURE 30. MLD—electron micrograph. The macrophages that contain the lipid storage product possess inclusions with a specific lamellated substructure. ×100,000.

2. Krabbe's Disease (Globoid-Cell Leukodystrophy)

a. Pathology. Krabbe's disease (globoid cell leukodystrophy) generally develops during the first 6 months of life, and the patients succumb in about 14 months. Examination of the gross brain reveals that it may be somewhat reduced in size. On coronal section (Fig. 31), it is seen that the cortex is relatively spared (except for occasional areas in the temporal and occipital lobes), but there is marked reduction in the amount of white matter, which shows a brown discoloration, more pronounced posteriorly. In the cerebral hemispheres, there is a tendency for arcuate fibers to be spared. Although loss of myelin occurs throughout the white matter, it is less pronounced in certain areas, e.g., frontal lobes. In grossly visible lesions, myelin and most axons are lost. Globoid cells, the pathognomonic feature of the disease, are apparent microscopically (Fig. 32). They are most common in less advanced

FIGURE 28. MLD—myelin stain, whole mount. This cerebral hemisphere demonstrates the severe involvement of white matter, the widespread loss of myelin, and the preservation of subcortical arcuate fibers.

FIGURE 29. MLD—acid cresyl violet stain. The degenerating fibers in the internal capsule have been stained darkly blue due to the presence of metachromatic material in contrast to the pale-staining, adjacent basal ganglia. ×100.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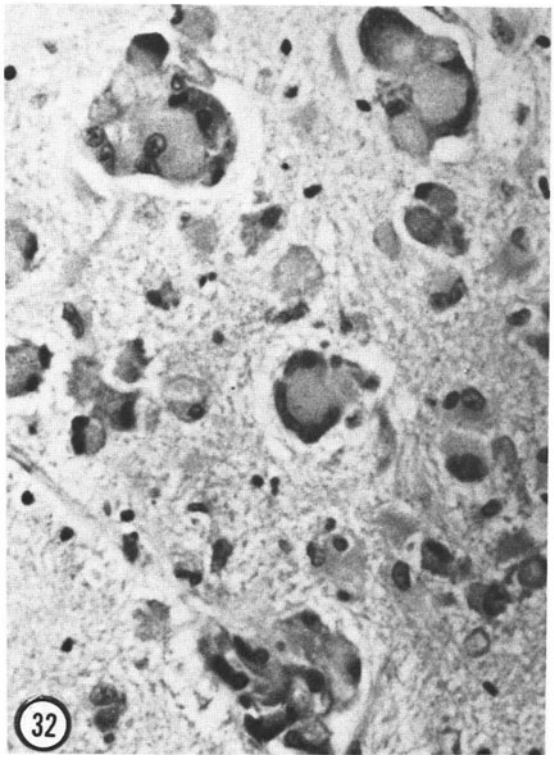
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lesions and may show a tendency to accumulate around blood vessels. These cells are multinucleated and contain specific crystalloid cytoplasmic inclusions (Yunis and Lee, 1969) (Fig. 33). Large rounded cells with single nuclei and a finely granular cytoplasm also occur and may be precursors of globoid cells, since transitional forms between the two have been described (see Volk and Adachi, 1970). Neurons are relatively unaffected in this disease.

b. Etiology. It is well established that there is a familial trait in this disease. The defect has been found to be related to the deficient activity of galactocerebroside β-galactosidase detectable in a variety of tissues including white cells and fibroblasts (Y. Suzuki and K. Suzuki, 1971; K. Suzuki *et al.*, 1971) (see Chapter 11).

3. Adrenoleukodystrophy

a. Pathology. ALD, which typically affects males during late infancy, has a clinical course of about 2–4 years, although a few cases in older males (40–60 years) are known. CNS lesions are large and grossly visible. The lesions are often symmetrical and involve massive areas of white matter of the cerebral hemispheres with preservation of the subcortical arcuate fibers (Blaw, 1970). There is usually severe involvement of both occipital poles (Fig. 34). There is widespread loss of myelin with subsequent loss of most axons. Unlike other metabolic disorders of myelin, there is an intense inflammatory response within lesions (Fig. 35), which has prompted some workers previously to classify this condition among the acquired inflammatory demyelinating diseases. This inflammatory response appears to herald a secondary immunological problem. The changes in the adrenal glands are pathognomonic (Schaumburg *et al.*, 1972, 1982).

b. Etiology. On the basis of sex-linked familial traits and white-matter involvement, this genetic leukodystropy is thought to be due to an enzyme deficiency, as yet unknown. The presence of similar specific intracytoplasmic inclusions (Fig. 36) in the adrenal glands, CNS, PNS, and testis (Schaumburg *et al.*, 1975) indicates that the disease has a pathogenesis related to abnormal lipid storage. This hypothesis is further supported by the finding of a hitherto unrecognized long-chain fatty acid in the CNS and adrenal glands (Igarashi *et al.*, 1976; K. Suzuki, 1972).

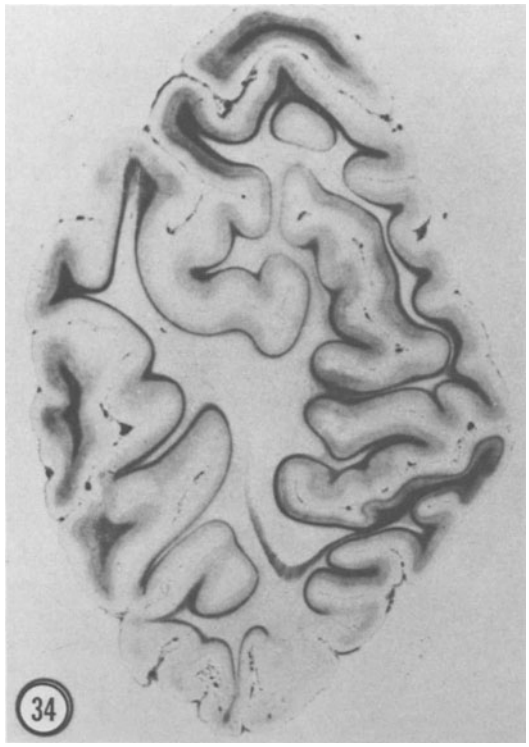
4. Refsum's Disease

a. Pathology. In Refsum's disease, a genetically determined condition, the PNS is a major site of involvement. The clinical course is long, frequently with remissions, and the disease usually develops during adolescence, although adult cases have been reported. Pathologically, the nerves are hypertrophied due to an increase in Schwann cells and interstitial tissue. The aberrant Schwann cells form characteristic onion-bulb formations (Fardeau and Engel, 1969). This hypertrophy is brought about by repeated damage to nerve fibers. Loss of myelin and axons occurs, and there is some remyelination. There is sometimes involvement in the CNS (Solcher, 1973).

FIGURE 31. Krabbe's disease—myelin stain, whole mount. Note the widespread involvement of myelin, the preservation of subcortical fibers, and the enlargement of the ventricles.

FIGURE 32. Krabbe's disease—HE preparation. Multinucleated globoid cells are located within the affected white matter. ×400.

FIGURE 33. Krabbe's disease—electron micrograph. The specific crystalloid inclusions of the globoid cells are shown. ×40,000.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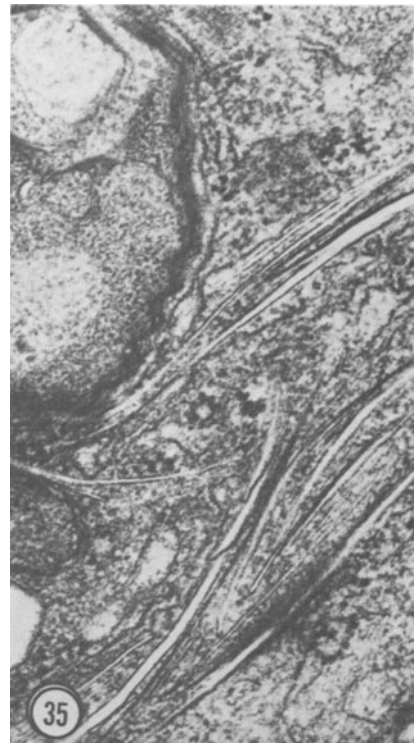
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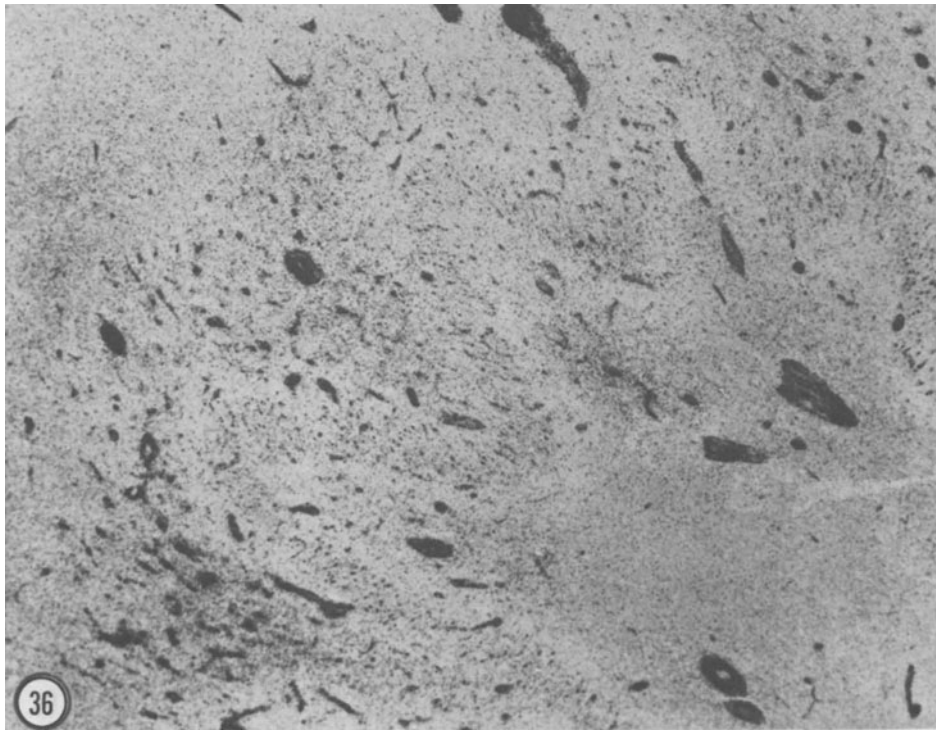
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b. Etiology. The disease is related to a specific deficit of lipid metabolism with high levels of blood and tissue phytanic acid. This inability to degrade phytanic acid is due to a deficiency in phytanic acid α-oxidase (Steinberg, 1972).

Comment on Classification of the Leukodystrophies. The four conditions discussed in Sections V.B.1-4 are believed to reflect an enzyme deficiency that expresses itself *after* the period of myelination. The three conditions discussed in Sections V.B.5-7, on the other hand, are considered to represent an inborn metabolic disorder that manifests itself during or *before* the myelination period and consequently leads to a paucity of myelin formation. This "hypomyelination" might in future be used as a pathological feature to subdivide the leukodystrophies.

5. Pelizaeus-Merzbacher Disease (Sudanophilic Leukodystrophy)

a. Pathology. Pelizaeus-Merzbacher disease (sudanophilic leukodystrophy), which can develop congenitally or during the first 6 months of life, is characterized by a slow, progressive clinical course lasting for up to 30 years. Lesions in the congenital form show an almost total depletion of myelin with relative sparing of axons. In the later-onset form, the process of myelin loss is sometimes patchy, giving a "tigroid" appearance (see Seitelberger, 1970) (Fig. 37). Ultrastructural examination has revealed a lack of compaction of CNS myelin around axons and nonspecific crystalloid inclusions in a few hypertrophied astrocytes (Watanabe *et al.*, 1969, 1973). Other varieties of this disease exist (see Lyon and Goffinet, 1980).

b. Etiology. The precise biochemical lesions that correspond to the two forms of the disorders have not been clarified. Studies using induced AY9944 intoxication in animals (see Section VI.C.4) may contribute to their elucidation.

6. Alexander's Disease (Dysmyelinogenetic Leukodystrophy)

a. Pathology. Alexander's disease usually manifests itself during the first year of life and has a variable course. Megalencephaly and hydrocephalus are not uncommon gross features (Fig. 38). Lesions are characterized by a lack of myelin, with widespread formation of Rosenthal fibers within astrocytes (Fig. 39), the pathological hallmark of this disease (see Herndon *et al.*, 1970; van Bogaert, 1970). Axons are relatively spared, and there is an intense proliferation of astrocytes. EM examination has shown that the Rosenthal fibers are ill-defined, rodlike structures with an amorphous, granular matrix.

b. Etiology. The underlying biochemical defect is not known. Some workers consider that on the basis of a lack of macrophage activity and the paucity of myelin, the disease might represent a genetically determined error in myelinogenesis, although precise evidence is lacking.

FIGURE 34. ALD—myelin stain, whole mount, occipital pole. Note the total loss of myelin from the deeper white matter and the preservation of subcortical fibers in this section.

FIGURE 35. ALD—HE section. The centers of ALD lesions are totally devoid of myelin and invariably contain perivascular cuffs of lymphocytes and other hematogenous elements, seen here at low magnification. ×150.

FIGURE 36. ALD—electron micrograph. Macrophages within demyelinated areas contain crystalloid, spicular inclusions. ×53,000.

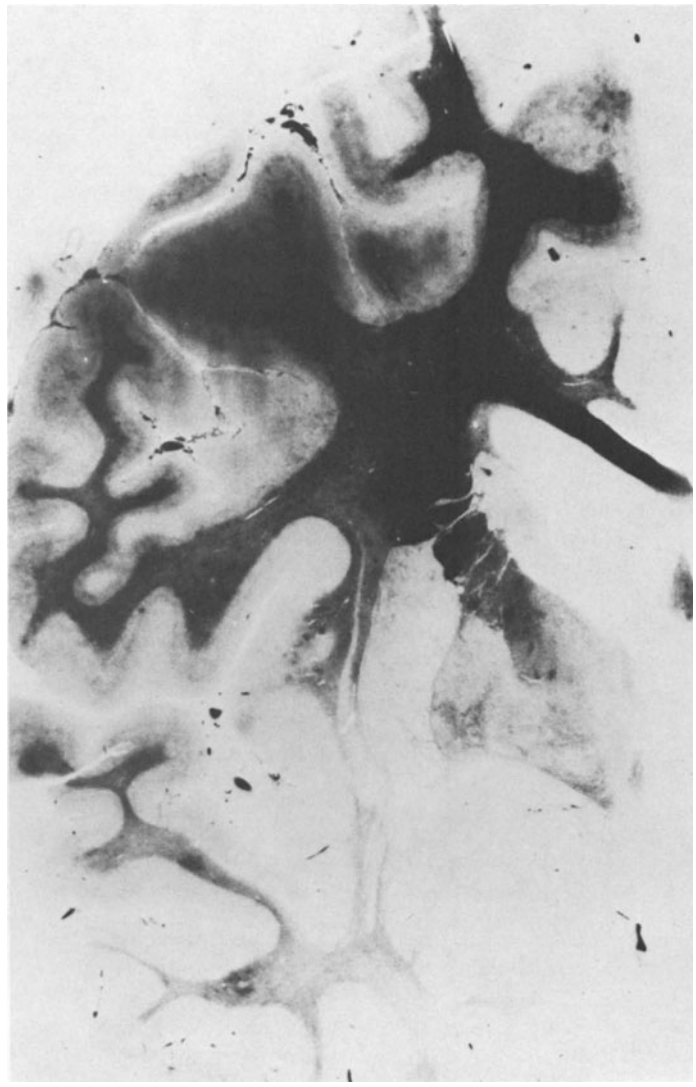


FIGURE 37. Pelizaeus-Merzbacher disease—myelin stain, whole mount. This section shows the widespread depletion of myelin, particularly in the temporal lobe (below).

7. Spongy Degeneration of White Matter (Canavan's Disease)

a. Pathology. Canavan's disease usually appears between 3 and 6 months after birth and is fatal in less than 2 years. Megalencephaly is typical, apparently due to increased intracellular water content, principally in the subcortical white matter (Fig. 40). There is marked vacuolation of myelin sheaths, with secondary degeneration of some fibers (Figs. 41 and 42). Alzheimer type II astrocytes are present in great numbers. There is a generalized hypertrophy of protoplasmic astrocytes (Figs. 43 and 44), which have been shown to contain bizarre, abnormally large mitochondria that have a crystalline substructure (Fig. 45).

b. Etiology. Although chemical investigations relevant to this disorder have been carried out, the metabolic defect is not known.

8. Phenylketonuria: Pathology and Etiology

Phenylketonuria (PKU) which occurs as both early- and late-onset forms, is known to have a familial pattern (Malamud, 1966). Clinically, the patients are mentally retarded. Repeated testing of the urine usually confirms the diagnosis of PKU, but in some instances it can be made on the phenylalanine content of the blood. Grossly, the brain is microcephalic. Spongy changes and a diffuse pallor in myelinated areas are common. Frank demyelination with sudanophilia is present in older patients (Jervis, 1963; Malamud, 1966). The disease is believed to be the result of a block in the oxidation of phenylalanine to tyrosine in the liver due to an inactive form of phenylalanine hydroxylase (Knox, 1972). Biochemical studies have also demonstrated an increased cholesterol content and a rise in cholesterol esters, the latter in accord with a process of demyelination (Crome *et al.*, 1962).

C. Animal Examples

The genetically determined metabolic diseases of myelin in man possess a number of animal analogues, both naturally occurring and experimental. Because of their ready availability and the rarity of the human conditions, these animal models have contributed considerably to our knowledge of genetic myelin disorders, particularly from the morphological and biochemical standpoints. See Chapter 14 for additional biochemical data on these models.

1. Globoid Cell Leukodystrophy: (Canine Krabbe's Disease): Pathology and Etiology

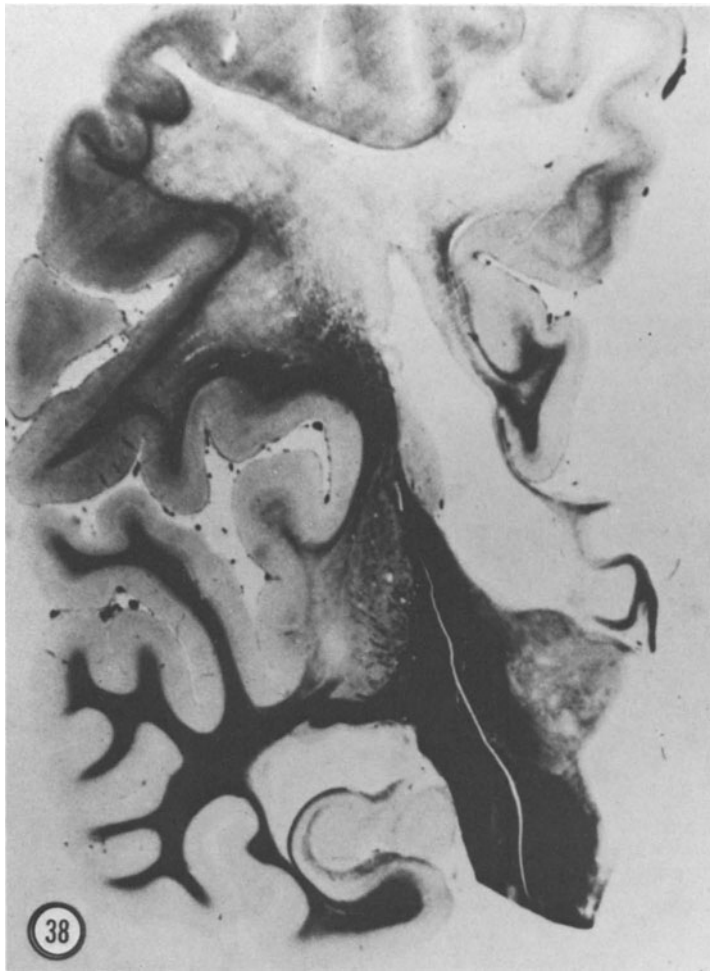
Certain breeds of dogs (e.g., Cairn and West Highland terriers) carry genes for globoid-cell leukodystrophy, a disease that mimics human Krabbe's disease. Morphological similarities between the respective CNS lesions are striking. Multinucleated globoid cells with tubular inclusions and diffuse destruction of cerebral white matter occur. The PNS is also affected and contains myelin changes and globoid macrophages. Experimental production of globoid cells is well known (Austin and Lehfeldt, 1965), and the cytoplasmic inclusions are believed to contain galactocerebroside (K. I. Suzuki, 1970). The inherited deficiency rests in a decrease in the catabolic enzyme galactocerebroside β-galactosidase, detectable in several tissues in addition to brain (Y. Suzuki *et al.*, 1970).

2. Jimpy Mice: Pathology and Etiology

In jimpy mice, which have a genetically determined neurological disorder, recognized at the same time as "quaking" mice (see Section V.C.3) by Sidman *et al.* (1964), there is a marked deficiency of CNS myelin occurring in the presence of sudanophilic deposits. This subsequently prompted Sidman and Hayes (1965) to refer to the disease as a murine form of inherited sudanophilic leukodystrophy. The neuropathology of jimpy mouse brain has been approached using both the LM and the EM (Hirano *et al.*, 1969). The most striking anomaly was an almost total lack of myelination from large areas of the brain and the presence of lipid-laden macrophages. Abnormalities have been noted in oligodendroglia (Meier and Bischoff, 1974; Meier *et al.*, 1974). Axonal changes were also prominent but less specific, being observed in both jimpy mice and their apparently normal littermates.

3. Quaking Mice: Pathology and Etiology

Quaking, another murine mutant first recognized by Sidman *et al.* (1964), is a condition in which CNS myelin formation commences apparently normally but the process is not completed, so that at time points when unaffected littermates display abundant CNS myelin, quaking animals show large numbers of axons with only a few lamellae. This microana-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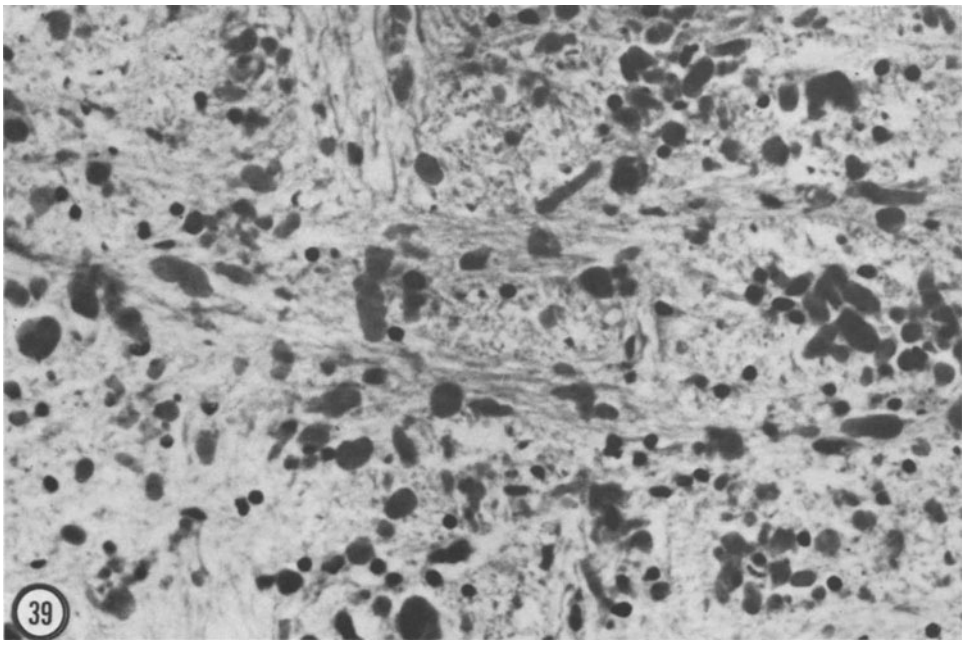
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tomical impediment appears to be related to aberrant oligodendroglial cell activity, since these cells fail to deposit myelin correctly and produce instead immature lamellar arrangements that frequently never become compacted. The fine structure of the myelination problem has been described by several workers (e.g., Berger, 1971; Wisniewski and Morell, 1971). Further clarification may come from studies using AY9944 intoxication (see Section VI.C.4).

4. Murine Muscular Dystrophy: Pathology and Etiology

Among the murine mutants with myelination defects, perhaps one of the most enigmatic occurs in the 129 Re *dy/dy* mouse, and the related mutant dy_2J, of the Bar Harbor strain. This model, utilized for some years as a major tool for research into muscular dystrophy, has been reported to possess profound abnormalities in PNS myelination (Bradley and Jenkison, 1973). The PNS lesion was microscopic, was most marked in the proximal regions (spinal nerve roots), and consisted of a near-total lack of Schwann cells and myelin from nerve fascicles. This amyelination resulted in adult *dy/dy* animals displaying areas of the PNS with organizations reminiscent of the fetal state. Other studies have shown the affected PNS in these animals to contain oligodendroglia and CNS myelin, a feature known in no other neuropathological condition (Weinberg *et al.*, 1975). The myelin defect is genetically determined, and affected animals are double recessives. Biochemical analyses of the PNS of these animals have not yet revealed significant data.

5. Border Disease (Hypomyelinogenesis Congenita): Pathology and Etiology

In border disease, a naturally occurring disease of sheep, the CNS is affected in a manner akin to that encountered in quaking mice. The condition was first recognized in the border counties between England and Wales, hence the name. The anomaly, known also as hypomyelinogenesis congenita, microscopically consists of a retardation of myelination evinced by lack of compaction of oligodendroglial cytoplasm around axons, thin myelin sheaths, and oligodendroglia containing lipid deposits. Large areas of spinal cord white matter can be affected in this way (Barlow and Dickinson, 1965). Genetic factors are implicated in the disease, but some data have also shown that the disease may have an infectious etiology, since inoculation of pregnant ewes with brain suspensions from animals with border disease transmits the disease to the offspring. The nature of this putative agent is as yet uncharacterized.

VI. CLASS III: ACQUIRED TOXIC-METABOLIC DISEASES OF MYELIN

A. Diagnostic Criteria

The third group of primary diseases of myelin, the acquired toxic-metabolic disorders, is represented by a collection of diseases all secondary to the action of exogenous myelinotoxic compounds. Most are exceedingly rare complications but are nevertheless important since they serve to demonstrate the exquisite sensitivity of myelin to certain foreign compounds. The few examples presented here are representative of a much larger collection. Two are chosen since they best illustrate the variation in the action of myelin toxins. These diseases exist both as naturally occurring human diseases and as experimental

FIGURE 38. Alexander's disease—myelin stain, whole mount. This section illustrates the degree of myelin involvement. Some hydrocephalus is also apparent.

FIGURE 39. Alexander's disease—HE section. Darker-staining Rosenthal fibers, a striking feature of this disease, are present in large numbers. ×200.

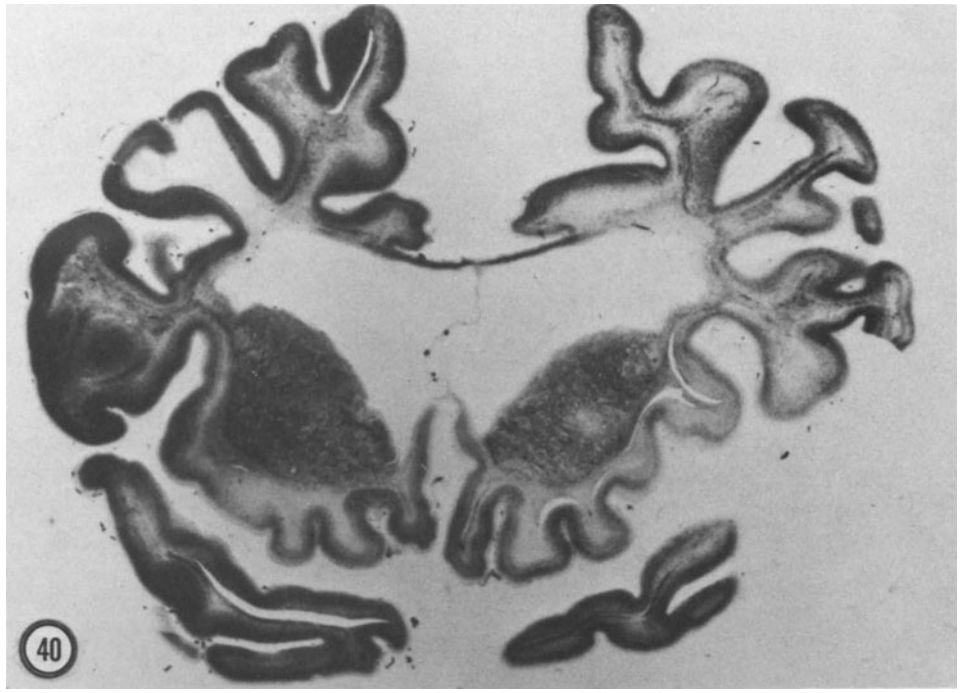


FIGURE 40. Canavan's disease—myelin stain, whole mount. Note the generalized involvement of white matter with a striking accompanying enlargement of the ventricles.

FIGURE 41. Canavan's disease—HE stain. The spongy degeneration of white matter is apparent at the edge of an affected area. ×100.

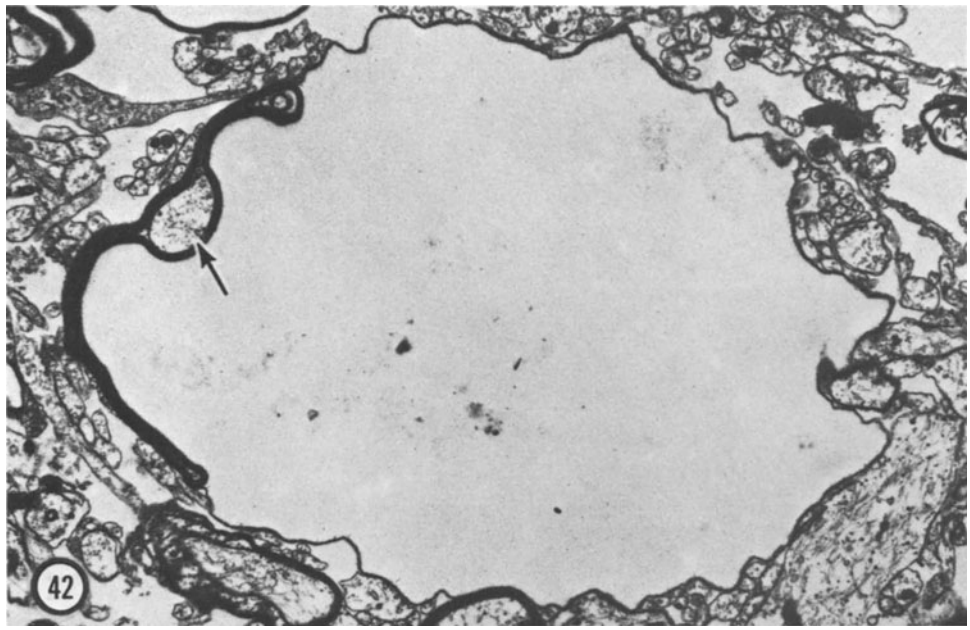


FIGURE 42. Canavan's disease—electron micrograph. The spongy change is due in part to the dilatation of myelin sheaths while the axon (⟵) is located laterally. ×6500.

models. Lesions are noninflammatory, and in cases in which myelin is broken down, phagocytosis is usually accomplished by cells of local origin.

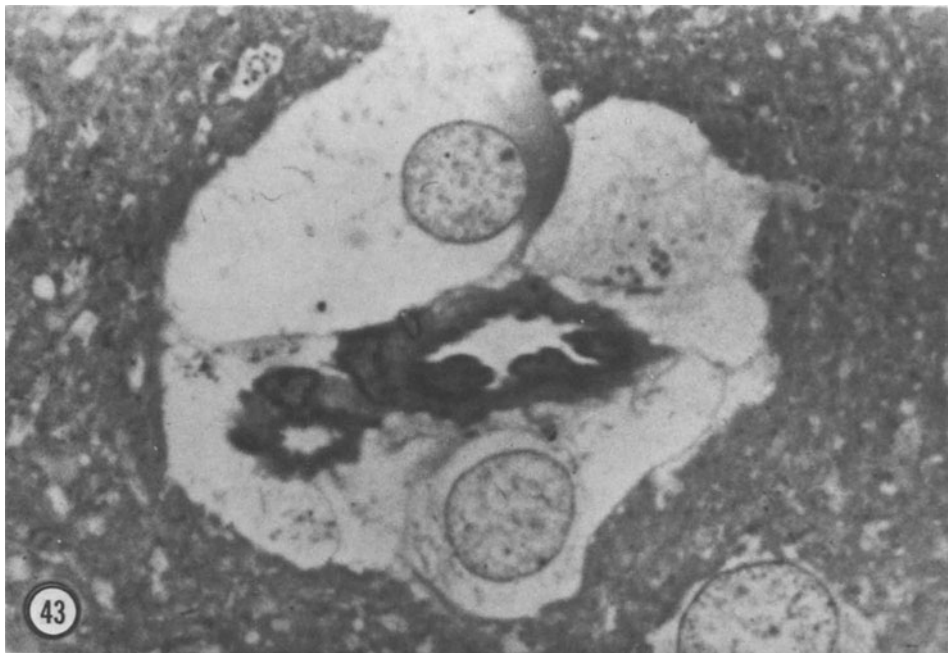
B. Human Examples

1. Hexachlorophene Neuropathy: Pathology and Etiology

Hexachlorophene (HCP) is a compound widely used in hospitals, particularly in newborn nurseries, for the control of bacterial colonization of the skin. Over the past few years, neuropathological examination of the nervous systems of premature infants has uncovered changes believed to be specifically related to HCP exposure. The CNS tissue demonstrates extensive edema of white matter caused by intramyelinic splits and vacuoles (e.g., Powell *et al.*, 1973), akin to triethyl tin sulfate intoxication (Aleu *et al.*, 1963) (see Section VI.C.3). This spongiform encephalopathy has appeared in a number of premature infants with a birth weight below 1400 g who were given topical application of pHisoHex. The number of dermal exposures to the compound is also significant (usually more than four), as is the presence of skin lesions. Dermal absorption has been documented, together with high levels of the drug in the blood. The manner in which HCP causes the CNS changes is not known. It has been speculated that it may be related to its ability to chelate copper, a mechanism believed to effect damage to the bacterial cell walls, or on the basis of laboratory tests, to its being a potent uncoupler of phosphorylation.

2. Hypoxic Encephalopathy—Anoxic Anoxia and Anemic Anoxia (Carbon Monoxide Poisoning)

The CNS complications of anoxic anoxia fall heavily on neurons as well as on myelin. The tissue destruction occurs when insufficient oxygen reaches the blood so that both the arterial oxygen content and tension are low. The selective neuronal loss following anoxic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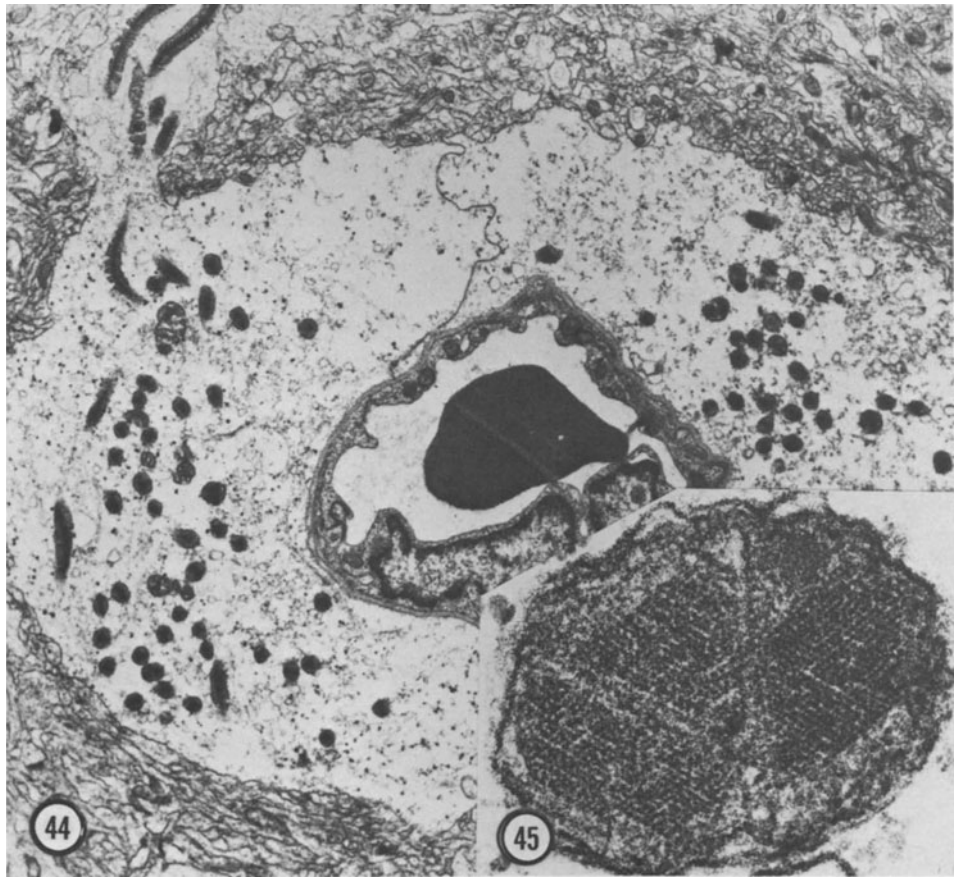
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anoxia (e.g., Purkinje cells, hippocampal neurons, and cortical neurons) represents a common and classic finding in neuropathology. Less appreciated are the neuropathological findings that accompany the clinical syndrome of delayed postanoxic encephalopathy (Plum *et al.*, 1962). In these rare cases, there is relatively little neuronal damage. However, there is massive destruction of myelin. This appears as a diffuse, severe, and bilateral myelin destruction in both cerebral hemispheres with sparing of the immediate subcortical nerve fibers and the brainstem.

In anemic anoxia, the amount of available hemoglobin is insufficient to transport enough oxygen to tissues. In carbon monoxide poisoning, a classic example of anemic anoxia, the hemoglobin is bound as carboxyhemoglobin and is not available for oxygenation of tissues. In addition to the well-known neuronal involvement associated with anoxic anoxia, carbon monoxide poisoning may produce selective necrosis of the globus pallidus. In rare cases, there may be a delayed, widespread, focally accentuated degeneration of the myelin of the cerebral hemispheres, with relative sparing of axis cylinders (Fig. 46).

The mechanisms of myelin destruction in hypoxic encephalopathy remain obscure.

C. Animal Examples

1. Diphtheric Neuropathy

Experimental diphtheric neuropathy is inducible in a number of species by injection of either crude toxoid or incompletely neutralized toxin from *Corynebacterium diphtheriae*. Although diphtheric neuropathy is considered infectious as a human condition because of its association with a bacterium, the disease is classed as a toxic disease in the laboratory since the toxin alone is sufficient to induce the lesions. About 1 week after injection, animals show limb weakness and usually die due to respiratory involvement. PNS tissue shows marked demyelinative changes (Webster *et al.*, 1961; Weller, 1965) and myelin fragments are apparently taken up by Schwann cells. The CNS is usually not involved, but demyelinating lesions can be induced in the CNS by local infusion (Wisniewski and Raine, 1971). It was also found that the PNS and CNS remyelination occurred in chronic lesions. The toxin is specific for myelin or other membrane systems (Webster *et al.*, 1961). Relevant metabolic studies have been carried out.

2. Hexachlorophene Intoxication

In experiments involving the incorporation of HCP into the diets of laboratory rats, it was found that both an encephalopathy (e.g., Lampert *et al.*, 1973a) and a neuropathy (Pleasure *et al.*, 1974) could be induced. The morphological picture is one indistinguishable in many regards from that produced by triethyl tin sulfate (Aleu *et al.*, 1963) (see Section VI.C.3). A white-matter spongiform encephalopathy was typical, caused by the severe dilatation of myelin sheaths by splits occurring at the intraperiod line and the filling of the vacuoles with fluid. Biochemical assays have shown that HCP inhibits protein and lipid

FIGURE 43. Canavan's disease—toluidine-blue-stained 1-μm Epon section. The spongy change is also related to hypertrophy of protoplasmic astrocytes, a group of which are seen here surrounding a blood vessel. ×1200.

FIGURE 44. Canavan's disease—electron micrograph. The area shown is similar to that in Fig. 43. Note the central blood vessel containing a red blood corpuscle, the surrounding hypertrophied astrocytic endfeet, and the multiple, bizarre, elongated mitochondria, shown in greater detail in Fig. 45. The surrounding neuropil seems relatively normal. ×7000.

FIGURE 45. Canavan's disease—electron micrograph. This shows a single astrocytic mitochondrion that contains paracrystalline arrays of filamentous material commonly associated with the disease. ×70,000.

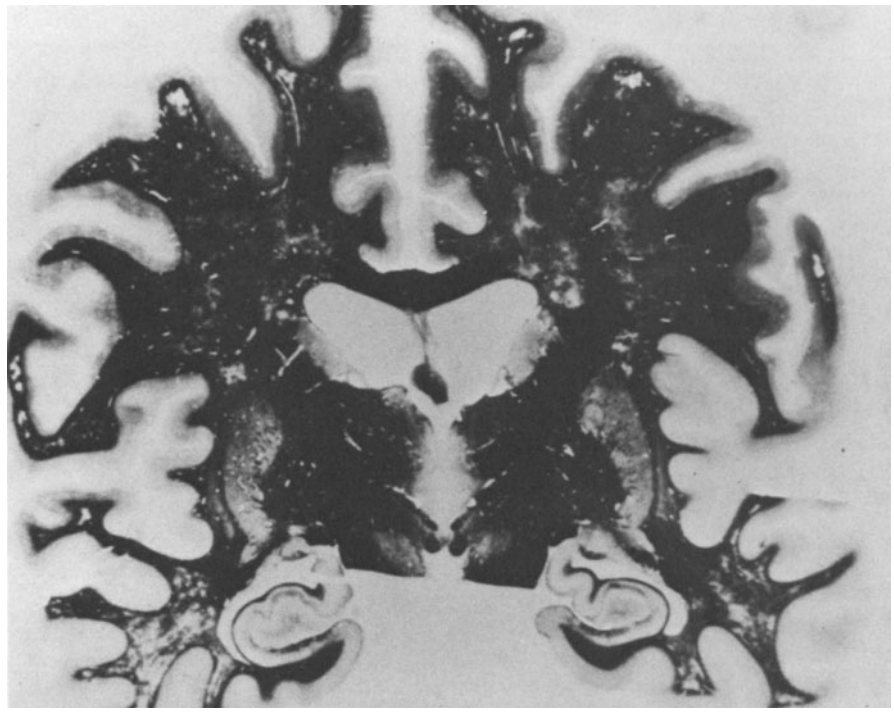


FIGURE 46. Carbon monoxide intoxication—myelin stain, whole mount. Note the widely scattered, small, punctate areas of demyelination.

synthesis in nerves and also that during incubation, the nerve content of ATP decreased, causing a diminution in the rate of activation of 3′-phosphoadenosine 5′-phosphosulfate (Pleasure *et al.*, 1974).

The pattern of myelin breakdown in the aforementioned experiments also bears striking similarities to CNS changes seen after intoxication with other compounds, among them isonicotinic acid hydrazide (INH) (Lampet and Schochet, 1968) and Cuprizone (bicyclohexanone oxalyldihydrazone) (Suzuki and Kikkawa, 1969), which, like HCP, are active chelaters of copper. Unlike HCP and INH, however, Cuprizone has been demonstrated to cause extensive loss of myelin in some areas (Blakemore, 1973), which remyelinate when animals are allowed to recover.

3. Triethyl Tin Intoxication: Pathology and Etiology

Triethyl tin (TET) intoxication as a human condition is now virtually unknown. Today, it exists as an experimentally induced spongy condition of white matter and has been studied in detail at the LM and EM levels by Aleu *et al.* (1963). There is a selective edema of CNS white matter related to the dilatation of myelin sheaths. After intraperitoneal injections of this compound, animals develop generalized muscle weakness, become immobilized within a day of the onset of signs, and frequently die. The edematous change in CNS white matter involves separation of lamellae along intraperiod lines and the formation of large, fluid-filled intramyelinic splits. Other elements appear unaffected. The lesion is specific for CNS myelin, although some workers have demonstrated minor, later changes in PNS myelin. The myelin vacuolation is reversible in animals that recover from the initial intoxication. There is a dramatic increase in water content in TET animals (91% over controls) (Katzman *et al.*, 1963). Using ^{35}S as a marker, it was found that there was no

significant increase in extracellular space, thus correlating with the EM evidence that the edema is intramyelinic.

4. AY9944 Intoxication: Pathology and Etiology

AY9944 [*trans*-1,4-*bis* (2-chlorobenzylaminoethyl)cyclohexane] is a hypocholesterolemic drug with a known affinity to retard both CNS and PNS myelination in developing animals and to cause selective damage to myelinating cells (Rawlins and Uzman, 1970a,b; Suzuki and Zagoren, 1974). The retardation of myelination is manifested morphologically by the formation of thinner-than-normal or uncompacted sheaths. Myelinating cells accumulate abnormal lipid inclusions, describe bizarre configurations around axons, and occasionally undergo frank degeneration. This experimentally induced hypomyelination may be relevant to the study of Pelizaeus-Merzbacher disease (Section V.B.5.b) and some animal mutants, e.g., quaking mouse (Section V.C.3). Biochemical studies on animals treated with AY9944 during the period of rapid myelination have shown that myelin cholesterol is largely replaced by its precursors, and as a consequence, the yield of myelin is reduced.

VII. CLASS IV: NUTRITIONAL DISEASES OF MYELIN

A. Human Examples

1. Vitamin B_{12} Deficiency

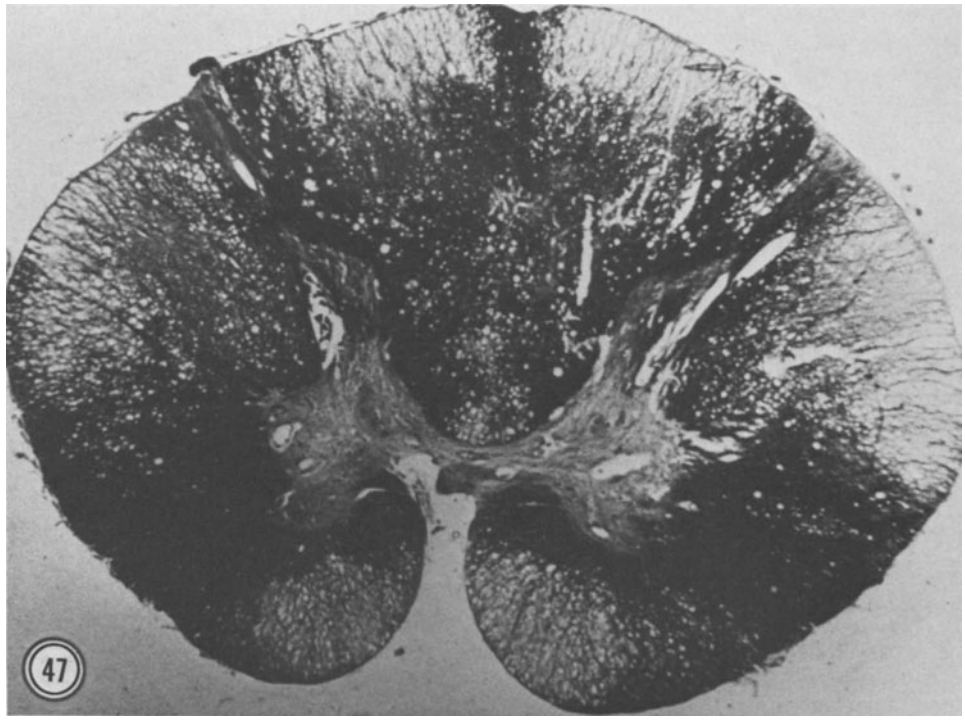
Patients lacking intrinsic factor necessary for the passage of vitamin B_{12} across the gastric mucosa frequently develop CNS and PNS complications. In the CNS, the degeneration is manifested first and largely in the myelin sheath. The major involvement in the spinal cord occurs in the large fiber tracts, i.e., corticospinal pathways and dorsal columns, although in severe cases, all tracts are affected (Pant *et al.*, 1968) (Fig. 47). The thoracic spinal cord appears particularly vulnerable. Rarely, multiple punctate areas of myelin loss are found in the centrum semiovale. A peripheral neuropathy is commonly observed, and optic-nerve degeneration has occasionally been reported.

2. Central Pontine Myelinolysis

Central pontine myelinolysis, first described by Adams (1959) in alcoholics and undernourished individuals, has now been reported in association with a number of other conditions, often with hepatic and other organ disease. Traditionally, most investigators have attributed the condition to nutritional deprivation, although the precise etiology remains obscure. Morphologically, there is a single, symmetrical focus of demyelination in the center of the basis pontis (Fig. 48). Histologically, there is a dissolution of myelin with relative sparing of axons occurring in the absence of inflammation. More recently, Norenberg *et al.* (1981) have speculated that the changes in this condition are related to imbalances in sodium.

3. Marchiafava-Bignami Disease

Marchiafava-Bignami disease, an extremely rare complication of alcoholism, is usually found in Italian males who drink red wine to excess (Merritt and Weisman, 1945). The striking feature of this condition is the symmetrical degeneration of myelin, often restricted to the corpus callosum and the anterior commissure (Figs. 49 and 50). Axons are also involved, but to a lesser degree. There is scant evidence of inflammation, and only moderate capillary endothelial proliferation. Lesions have also been found in the long association bundles and the cerebellar peduncles.



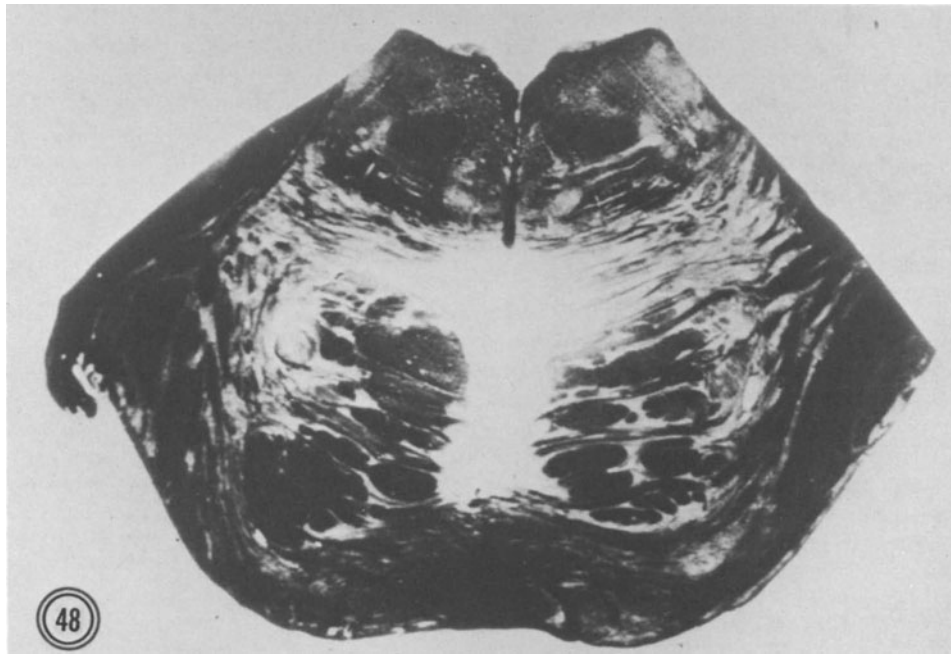


FIGURE 47. Vitamin B_{12} deficiency—thoracic spinal cord, myelin stain. In this combined system disease, note the large-scale involvement of several myelinated tracts. ×15,000.
FIGURE 48. Central pontine myelinolysis—myelin stain. A large zone of myelin loss is seen in the center of the pons. ×3000.

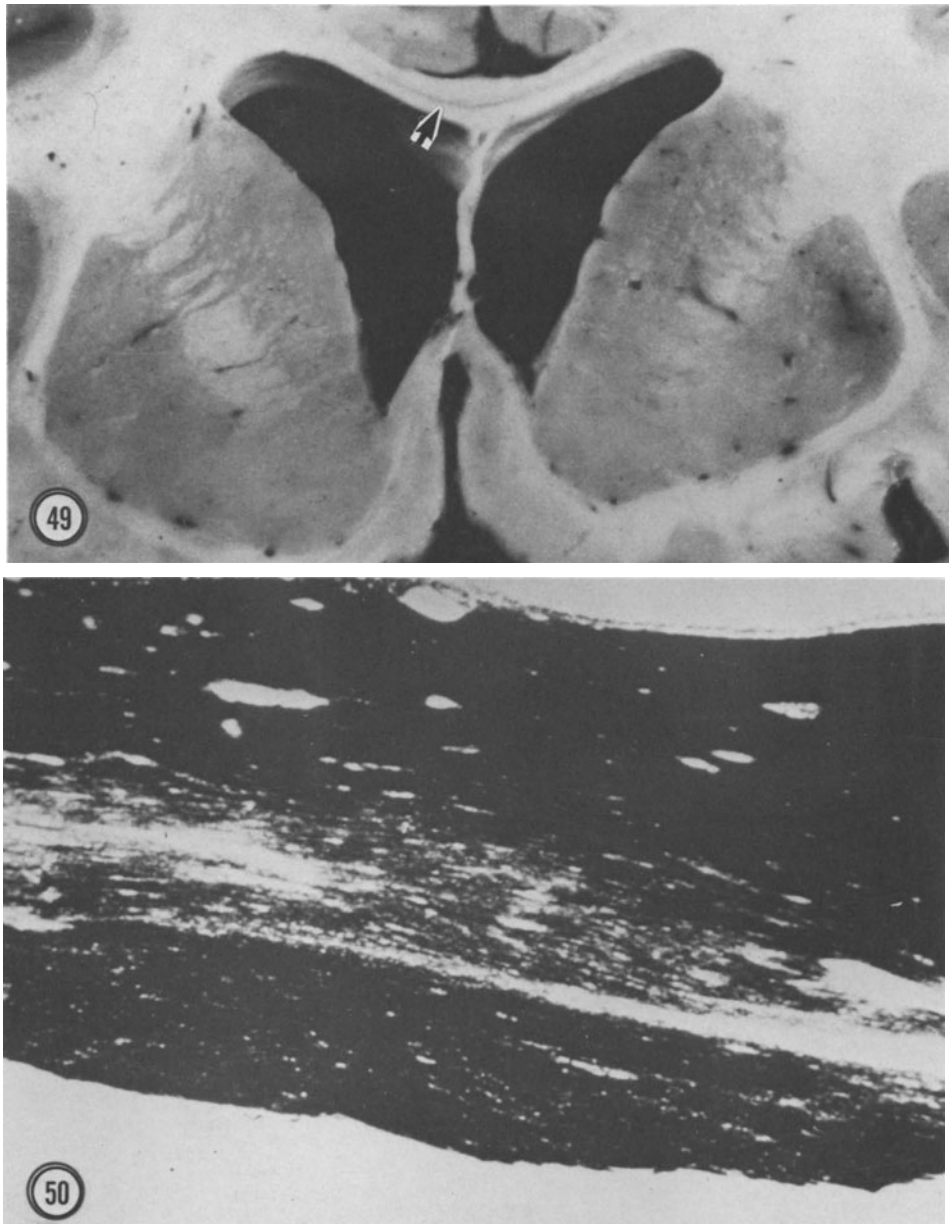


FIGURE 49. Marchiafava-Bignami disease—gross specimen. Note the narrow zone of demyelination in the corpus callosum (arrow).
FIGURE 50. Marchiafava-Bignami disease—myelin stain from Fig. 49. The corpus callosum shows a discrete area of myelin loss. ×15,000.

B. Animal Models

There exist no animal models that precisely mimic the aforedescribed conditions. Studies on undernourished animals, carried out mainly from the biochemical standpoint, have demonstrated that if rats are deprived of food during certain vulnerable periods of CNS development, they show a preferential reduction in the amount of myelin synthesized (Dobbing, 1968). Nutritional deprivation can have a permanent effect if the most proliferative period of myelination is included in the period of starvation, thus suggesting that once myelinating glial cells have passed the time of active division, they are incapable of later extensive proliferation. There is also some evidence indicating that the developmental program for myelinogenesis may be retarded by starvation.

VIII. CLASS V: TRAUMATIC DISEASES OF MYELIN (HUMAN AND ANIMAL EXAMPLES)

1. Edema

It is well known that edema secondary to tumors, trauma, and other causes can cause myelin sheaths to be diffusely affected. The underlying reasons for this degeneration are multiple and usually involve a local disturbance of electrolytes and nonspecific degeneration of the myelinating cells. The pattern of demyelination has received little scrutiny.

2. Compression

If mechanical pressure is applied for prolonged periods to a myelinated peripheral nerve or area of central white matter, a common sequela is the loss of myelin from the affected areas. The myelin becomes fragmented and is taken up by local macrophages. Following the loss of myelin, the surviving axons frequently remyelinate. Examples in man include white matter adjacent to tumors and nerves compressed by tourniquets or in the carpal-tunnel syndrome. Extensive experimental work on pressure effects on myelinated fibers has been done utilizing tourniquet lesions (Ochoa *et al.*, 1972).

3. Barbotage

As a very rare complication of repeated removal and exchange of CSF, there may develop an extensive rim of subpial demyelination that completely encircles the spinal cord. An identical situation can be produced in the spinal cord of animals (e.g., cats) by repeated exchange of CFS. Myelin is rapidly lost, and local macrophages have been shown to participate in myelin removal (Bunge *et al.*, 1960). In animals that survive, remyelination ensues within a month.

4. Pressure Release

It has been known for many years that a local interruption of the perineurium can lead to a herniation of the contents of a nerve, this phenomenon suggesting that nerve fibers exist in an environment that is under a positive pressure. By creating a window in the perineurium of the peroneal nerves of rats, Spencer *et al.* (1975) have reported the occurrence of exquisitely focal demyelination and remyelination of those segments of nerve fibers extruded into the herniated bleb. This implies that the integrity of myelin–axon relationships is in part dependent on the maintenance of a constant endoneurial pressure.

IX. CONCLUSIONS

This chapter has described in detail the varied neuropathology of those conditions in which the myelin sheath is apparently the primary target. A number of types of myelin diseases have been highlighted, viz., myelin degeneration precipitated by a viral infection, an immune response, a genetic defect that manifests itself prior to or after the formation of myelin, a lytic effect of a toxic factor, or a metabolic or mechanical insult to the myelinating cell. That axons frequently degenerate in the examples cited should not detract from the specificity of the disease process, since in most if not all cases, the *primary* lesion is to the myelin sheath. In some cases, biochemical data have permitted precise categorization of diseases. However, in those cases in which *widespread* myelin degeneration occurs, it has been found that degraded myelin is biochemically similar to conditions that show secondary involvement of myelin, e.g., during Wallerian degeneration.

The schema presented above is fairly complete. Further clarification is needed of those acquired inflammatory demyelinating diseases for which the etiology is unknown and of the genetic and metabolic disorders for which a biochemical defect has not been recognized. It is suspected that ultimately the unifying character of the acquired inflammatory group is going to be a viral etiology. That such a putative infection is also governed by immunogenetic factors appears highly likely, although this alone will not explain the geographic distribution of diseases like multiple sclerosis (MS). Another enigmatic issue is the florid inflammatory component in adrenoleukodystrophy (ALD), a disease that belongs to a group in which immunological events are not usually implicated. Retrospectively, it is now easy to understand how ALD, previously called Schilder's disease, was for many years considered to belong to the MS group.

Several positive contributions to the neuropathology of the human disorders of myelin have emanated from the field of experimental neuropathology by the development and exploitation of appropriate animal models. It is possible that no human disease of myelin lacks a valid animal analogue. The major problem in some of the human diseases has rested in their chronicity and fluctuating picture, and in the animal diseases, in the relatively short life-span of the laboratory animals used. Nevertheless, recent experimentation with different species and strains (e.g., in the case of experimental allergic encephalomyelitis) has uncovered some animal models with disease patterns more akin to the human conditions.

Finally, neuropathology is no longer dependent solely on the pathologist, but also depends very heavily on a multidisciplinary approach encompassing clinicians, neuroscientists, virologists, immunologists, geneticists, and biochemists. It is as a direct result of the close collaboration of these diverse disciplines that the present comprehensive classification of the myelin diseases has been possible.

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