THE DEMYELINATING DISEASES
AND RECENT ADVANCES IN THIS FIELD

By Jack Colover, M.D., M.R.C.P.*

From the Canadian Red Cross Memorial Hospital, Taplow, Bucks., England; the Department of Neurology, The Brook Hospital, London, S.E.18; and the South-East Metropolitan Regional Neurosurgical Unit

The term 'demyelinating diseases' is applied to a group of disorders of the central nervous system which show loss of the normal myelination of the white matter and in which this loss is regarded as being of especial importance. This paper is a short review of such conditions and it will also include a brief survey of recent research work which it is believed may throw light on them, particularly with regard to aetiology and pathogenesis.

Loss of the myelin in the white matter of the brain or spinal cord frequently can be recognized by the naked eye, but it may require demonstration by special histological methods based upon specific staining of myelin and its absence in areas of demyelination. In addition, special histological techniques are employed to show the presence of abnormal substances, some derived from breaking down myelin, in the pathological areas. Apart from such changes there may be reactions in the mesodermal elements and abnormal accumulations of cells derived from the blood, as well as hypertrophy and proliferation of the astrocytic cells and fibres giving rise to the sclerotic changes seen in some of the subacute and chronic diseases.

Numerous conditions may cause loss of myelin, such as infarction and cerebral softening, invasion or compression by neoplasms, Wallerian degeneration due to loss or damage of the neurones or their processes, and ascending or descending tract degeneration. Strich (1955) has described an extensive degeneration of the cerebral white matter following head injuries. However, these conditions are not usually included in the group of diseases under discussion.

An attempt will be made to provide a classification of the demyelinating diseases, but it should be remembered that there is much overlapping between the different types described. However, such a classification may be of value in identifying or labelling a particular case. Clinically the mode of onset, acute, subacute or chronic, and the duration of the active phase of the illness is important. However, even chronic multiple sclerosis may start with an acute attack. The age of onset, the total duration of symptoms and the tendency to relapse or improve over a long period are also points of diagnostic value. The presence of a family history is a feature of some types of diffuse sclerosis, although it is also met with in a small percentage of cases of disseminated sclerosis. Finally, the nature of the pathological changes found at autopsy is of great value in identifying the type of disease.

Acute Types

Acute haemorrhagic leucoencephalitis is not frequently diagnosed during life. It is an unusual condition often following in the wake of an acute respiratory infection and associated with the rapid onset of cerebral symptoms such as drowsiness, hemiplegia and coma. There is usually pleocytosis of the cerebro-spinal fluid and there may be neck rigidity. At autopsy numerous haemorrhages are found in the white matter associated with extensive areas of demyelination (see Fig. 1).

Acute disseminated encephalomyelitis, which some think is closely related to the previous disorder nosologically (Russell, 1955), may arise either spontaneously or in association with an acute virus infection such as measles, varicella, rubella, variola or influenza, when it is referred to as post-infectious encephalitis. It may also follow vaccination with cowpox (post-vaccinal encephalitis) or vaccination with attenuated rabies virus. There is always an interval of ten days at least between the infection with the virus and the onset of the neurological complications. These may be either cerebral or spinal. Fever is common in both types. The cerebral forms of the disease are characterized by headache, vomiting, neck stiffness, confusion, drowsiness, coma, convulsions and hemiplegia; cerebellar signs such as nystagmus and cerebellar ataxia and signs indica-

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FIG. 1.—Acute haemorrhagic leucoencephalitis. Section of pons. Shows perivascular demyelination with haemorrhages occurring more peripherally, the red cells staining black. Some ballooning of the myelin can be seen (× 175 Loyez stain).

tive of damage to the brain stem also occur. The predominantly spinal cases develop paralysis of the lower limbs and acute retention. The prognosis is variable, but many cases after measles do quite well, although there is quite a definite mortality and permanent sequelae are seen in cases which recover. Extensive cellular infiltrations are found in and around the vessel walls as well as extensive perivenous demyelination histologically.

Subacute Types

In neuromyelitis optica or Devic's syndrome the brunt of the disease falls on the optic nerves and spinal cord, producing bilateral loss of vision and paraplegia. Either event can precede the other. Complete functional recovery, permanent disability or rapid death may ensue.

Inclusion body encephalitis (Dawson, 1934) and the closely related subacute sclerosing encephalitis (van Bogaert, 1945) show a variable amount of demyelination. These conditions usually develop in children when rapid mental deterioration associated with epileptiform attacks, tonic fits, myoclonic jerks, aphasia, apraxia or agnosia occur. Marked trembling movements or signs suggestive of extra-pyramidal disturbance such as choreiform movements, are also features. These diseases are fatal and run their course in about six months. The cerebro-spinal fluid often shows a paretic Lange curve.

A subacute course is occasionally run by multiple sclerosis.

Chronic Types

The commonest of these is disseminated or multiple sclerosis. The incidence of this condition is sporadic and seems to be partly influenced by geographical factors. A family history is unusual, but does occur in a small percentage of cases. The onset is commonest in young adults and it tends to be sudden. Often there are a series of episodes separated by intervals of months or years. Each episode may be followed by a remission but with some extra residual disability. The total disability thus increases with the duration of the illness. The symptoms are protean depending on the sites of the lesions, which are usually multiple in the later stages. Amongst the commoner sites of damage are the optic nerves, causing blurring of vision and defects in the visual fields of a scotomatous type, an important cause of retrobulbar neuritis.

Frequently transient sensory disturbances occur lasting only a few weeks, such as parasthesiae, numbness and pins and needles. Disorders of eye movements such as nystagmus, diplopia, and
Fig. 2a.—Disseminated sclerosis. Section through the lateral ventricle, showing perivascular and periventricular demyelination, the lesions being confluent. The normal myelin and filled blood vessels stain black (× 10 Loyez stain).

Fig. 2b.—Experimental allergic encephalitis. Section through guinea-pig brain adjacent to the lateral ventricle, showing perivascular demyelination and some periventricular demyelination on the right. Note the close similarity in the location of the lesions in this section with those occurring in the section of disseminated sclerosis in Fig. 2a (× 95 Loyez stain).
combined nystagmus and defects of ocular movement may be observed. Cerebellar disturbances such as scanning speech, intention tremor of the limbs and head nodding are common. Paraplegia in extension or flexion associated with painful flexor spasm often occur. Urinary disturbances such as precipitancy or retention are usual. Other spinal symptoms, such as constipation and impotence, also occur. Unusual symptoms are epilepsy, prolonged vertigo and even deafness. On examination the tendon reflexes are usually exaggerated, the abdominal reflexes absent, and the plantar reflexes extensor. Commonly, the only permanent sensory disturbance is loss of vibration sensibility at the ankles, but more extensive sensory loss is found in the last stages which are often associated with bedsores. The presence of euphoria has been over-emphasized and seems to be of less consequence now than formerly. The cerebro-spinal fluid is abnormal in many cases, showing a pleocytosis, an increase in protein and a paretic Lange curve, but the latter is often the only abnormality.

The acute lesions at autopsy are pink, but in the later stages the plaques are grey, firm and shrunken, particularly noticeable where they impinge on a surface. They are often periventricular (Fig. 2A) or perivascular. They are less obvious when they occur in the grey matter. In addition to the loss of the myelin staining, sudanophil droplets both free and ingested by fat granule cells are seen in the lesions, especially in the early stages. The older plaques tend to be gliosed and lose the oligodendrocytes. Many of the lesions show sharp margins.

The aetiology of this most disabling disease is unknown, but occasionally cases are seen, apparently precipitated by infections.

Balo's disease may be regarded as a variant of multiple sclerosis in which the demyelination occurs in concentric bands alternating with normal zones. Marchiafava's disease is a demyelinating condition of the corpus callosum which occurs in individuals who consume large quantities of red wine. The symptoms are predominantly mental in nature.

A large group of demyelinating diseases are included under the term 'diffuse sclerosis,' which includes the types described by Schilder. These diseases for the most part tend to occur in children and young adults, and in some there is a family history. In them the white matter of the cerebral hemispheres is affected and the transition from the normal to the demyelinated areas in most types is more gradual than seen in such diseases as disseminated sclerosis (Fig. 2A). However, the subcortical arcuate fibres are usually spared as may be the tracts which myelinate before the third month of life. The neuropathological distinction between different types of diffuse sclerosis is largely based on recognition of various abnormal deposits or substances present in the affected areas. Sudanophil droplets, or less commonly, substances staining metachromatically with toluidin blue (Norman, 1947; Brain and Greenfield, 1950) are found. These metachromatic substances have also been discovered in the liver and kidney. Mucinoid bodies staining with mucicarmine and associated with loss of the interfascicular oligodendroglial cells have been described in the type of diffuse sclerosis (Fig. 3), first recognized by Greenfield (1933). In this type, which is closely related to the metachromatic type, the child affected usually dies before the age of three. In the disease described by Krabbe (1916) large multinucleate globoid cells are a feature. The course of diffuse sclerosis tends to be steadily downhill and disturbances of cerebral function, such as progressive dementia, cortical blindness and fits, are frequently the leading symptoms. Occasionally there may be signs suggestive of raised intracranial pressure. In the type associated with mucinoid bodies, weakness of the arms and ataxia are important clinical features.

The essential lesion of subacute combined degeneration of the cord is also considered to be a form of demyelination of the nerve fibres. The myelin sheaths in the spinal cord show marked ballooning. One rare form of demyelinating disease occurs in association with cerebral arteriosclerosis in the elderly, Binswanger's disease. In a number of other diseases, such as cerebral-macular degeneration and xanthomatosis, demyelination has occasionally been described.

Pathogenesis

Although there is as yet no general agreement about the essential pathological nature of processes which lead to demyelination, numerous theories have been put forward and various micro-organisms have even been described. On the other hand, it has been shown that a number of chemical poisons such as carbon monoxide, potassium cyanide, and sodium azide (Hurst, 1942) produce demyelination, although all these agents also produce necrosis. Various toxins, such as ergot, saponin, bee venom and tetanus toxin, can also cause demyelination (Hurst, 1944). From the field of veterinary medicine has come the knowledge that a demyelinating disease of newborn lambs, swayback, is caused by a deficiency of copper in the maternal diet.

Organic phosphorus compounds, e.g. tri-ortho-cresyl phosphate, will cause tract degeneration in the spinal cord in hens and it was suggested that the effect is due to inhibition of the enzyme
pseudo-cholinesterase, although Barnes and Denz (1953) were not able to show a direct relationship. However, such long tract degenerations are not a feature of human demyelinating diseases. Organic compounds of tin produce a diffuse degeneration of the spinal cord of rats (Magee, Stoner and Barnes, 1955).

Christie, Judah and Rees (1953) have studied the metabolic processes of isolated brain mitochondria in vitro, described their essential metabolic requirements which include cobalt and a new co-factor, and have suggested that some diseases may be due to deficiency of micro-nutrients essential to the metabolism of these mitochondria, which contain batteries of enzymes, and have suggested that the demyelinating diseases might be investigated from this point of view. It would seem possible that the cage paralysis of monkeys which is a demyelinating disease occurring spontaneously in monkeys kept in captivity may come into this category, and also the demyelination of subacute combined degeneration which is prevented by vitamin B12, which contains cobalt, may also fit into this class.

Cumings (1953) has investigated the chemistry of some lipids in cases of disseminated sclerosis and described not only loss of phospholipids in the demyelinated areas but also slight loss of phospholipids in the apparently normal areas.

There can be very little doubt that the whole subject of the demyelinating diseases has assumed a new aspect since the work of Rivers, Sprunt and Berry (1933) and Rivers and Schwentker (1935). These workers were able to produce a demyelinating encephalomyelitis in monkeys by means of repeated intramuscular injections of homologous brain suspensions mixed with brain extracts. Following on this important step, Morgan (1946), Kabat, Wolf and Bezer (1946) and Wolf, Kabat and Bezer (1947) produced a demyelinating type of encephalomyelitis in monkeys by means of a few intramuscular injections of homologous brain suspension emulsified with the Freund adjuvants (Freund and MacDermott, 1942). These adjuvants consist of heat-killed acid-fast bacilli suspended in mineral oil and mixed with an emulsifying agent so as finally to produce a water-in-oil emulsion. Either homologous or heterologous brain is effective and success has been achieved even when using a piece of the recipient’s own brain substance. One single injection of such a mixture will produce an encephalomyelitis, although a few repeated injections increase the percentage of positive results. The injection may be given intramuscularly, subcutaneously, intradermally or intraperitoneally, and the condition has been produced in guinea-pigs, rabbits, dogs, mice, rats and other animals.

Fig. 3.—Diffuse sclerosis (mucinoid type). Section through the frontal lobe, showing diffuse demyelination of the central white matter with relative sparing of the subcortical arcuate fibre and some slight sparing of some of the perivascular fibres (× 10 Loyez stain).
Both an acute and a more chronic type of disease have been produced, the latter by smaller doses of the emulsion. The production of the disease requires both the acid-fast bacillus and the brain suspensions in the emulsion, and they must both be present simultaneously at the same site in the body. There is no question of any kind of living micro-organism being present in the injected materials as they may be boiled or autoclaved.

The animals affected by this experimental condition show severe paralyses, tremors, ataxia, nystagmus and sphincter disturbances. Some animals show relapses and remissions over long periods very reminiscent of human multiple sclerosis. Convulsions occur as a terminal feature, and the outcome is usually fatal. The incidence of the condition may exceed 90 per cent. So far it has not been possible to transfer the disease from one animal to another.

Histologically, this disorder is characterized by wide dissemination of lesions in the central nervous system and the white matter is particularly vulnerable. The lesions are usually perivascular (Fig. 4) and show marked inflammatory changes in and around the walls of the veins, with myelin destruction in these latter areas (Fig. 2B). Patchy areas of meningitis occur and the more chronic lesions in monkeys show marked sclerotic changes. Haemorrhages can sometimes be seen in the white matter reminding one of acute haemorrhagic leucoencephalitis, but the general consensus of opinion is that this condition is histologically very much like acute disseminated encephalomyelitis of the post-infectious type.

Kies, Roboz and Alvord (1956) have isolated a glycoprotein from bovine spinal cord which is much more active than the intact cord emulsion in producing this reaction, although Olitsky and Tal (1952) and others have claimed that the active brain factor was a proteolipid. In 1954, Colover showed that heat-killed tubercle bacilli, after they had been subjected to prolonged extraction with boiling fat solvents, were still quite active in producing experimental allergic encephalitis in guinea-pigs, and papers by Colover and Consden (1955, 1956a and b) and Colover (1956) indicated that the bacillary factor was a relatively insoluble substance which was stable and resisted treatment with acids, alkalis at low temperature, and proteolytic and lipolytic enzymes, and they have suggested that it may be a lipoprotein type of compound formed mainly from glutamic acid, alanine, and mycolic acid (C₂₈H₁₇₆O₄). It would appear therefore that substances of this nature have

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Fig. 4.—Experimental allergic encephalitis. Section through the cerebral hemisphere of guinea-pig, showing inflammatory cell and astrocytic reaction around the wall of a vein, with undue prominence of and changes in the surrounding venules (×200 haematoxylin and eosin stain).
arterial stems complicated by cerebral abscess has been described. The right ventricle, which had morphological features of a normal left ventricle and was guarded by a bicuspid valve, gave origin to the aorta. The left ventricle resembled a normal right ventricle, was guarded by a tricuspid valve and gave origin to the pulmonary trunk. There was a large atrial septal defect, and a patent ductus arteriosus. The coronary supply was from a single vessel. The anatomical significance and development of these findings are suggested.

The clinical features and aetiology of cerebral abscess in congenital heart disease are discussed. The good results obtainable by prompt surgery are stressed. It is suggested that the development of even minor signs of focal brain damage in such a patient should arouse suspicions of the diagnosis.

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The Demyelinating Diseases and Recent Advances in this Field
Jack Colover

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