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FUNDAMENTAL PROBLEMS IN THE PATHOLOGY OF MULTIPLE SCLEROSIS AND ALLIED DEMYELINATING DISEASES*

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[WITH PHOTOGRAVURE PLATE]

In 1868 appeared Charcot's original description of the histology of multiple sclerosis. Out of the 82 years of unrelenting research since then has emerged a conviction that this disease is not caused by any single infective or single extrinsic toxic agent but that, along with the other primary demyelinating diseases, it has its causation in some more complex intrinsic biological disturbance within the highly specialized myelin sheaths which insulate most of the conducting apparatus of the brain and spinal cord. It is not my intention to deal with the research, which has been entirely unsuccessful after several false trails had been followed, done in the attempt to show transmissibility of multiple sclerosis ; this has been fully reviewed elsewhere, notably by Brain (1930) and by Schaltenbrand (1943).

With regard to the other theories of their causation, the 660-page volume, *Multiple Sclerosis and the Allied Demyelinating Diseases*, published this year by the Multiple Sclerosis Commission of the American Association for Research in Nervous and Mental Diseases, provides a fairly comprehensive bibliography. In addition to this volume, and to Schaltenbrand's monograph, there have in recent years been several interesting shorter papers of a review character such as those of Moreau (1932), McAlpine (1946), van Bogaert (1947), and, on experimental aspects, that of Hurst (1944). No such review is therefore necessary here, and it is my purpose simply to deal with some of the problems that appear to me from the standpoint of experimental pathology to be fundamental.

The term "demyelinating disease" applies to those conditions in which myelin sheaths are primarily destroyed but the axons and neurone bodies are largely spared, although to a variable degree in the individual disease. By common usage, in this group, in man, are multiple sclerosis and the diffuse demyelinating diseases, including neuromyelitis optica and the concentric sclerosis of von Baló, of which latter disease Hallervorden and Spatz (1933) have given a most interesting account, with special regard to the physical and chemical factors thought to be concerned in the spread of this process. On debatable frontiers lie three groups of conditions in which myelin is also, but to a much more limited extent, specifically involved—namely, in (a) acute disseminated leucoencephalopathies occasion-

ally complicating the exanthematous and certain other fevers ; (b) subacute combined degeneration of the cord ; and (c) certain metabolic disorders such as the lipodystrophies and phenylpyruvic oligophrenia.

In animals, also, several demyelinating disorders, possibly of different nutritional deficiency origins, occur notably amongst apes (Schroeder, 1908), monkeys (Levaditi *et al.*, 1933 ; van Bogaert, 1939), dogs (Perdrau and Pugh, 1930 ; Scherer and Collet, 1939), lambs (Bennetts and Chapman, 1937 ; Innes and Shearer, 1940), and horses (Hurst). While working in the Institut Bunge, Antwerp, I was able to study material on these conditions reported by van Bogaert and by Scherer, and I am also indebted to Dr. J. R. M. Innes and Dr. E. W. Hurst for the opportunity to examine some further material. Similar conditions, it should be added, have been reported also in foxes, moose, and goats (King and Meehan, 1948). By comparison with human material it is quite evident, however, that whatever their causes none of these animal diseases is exactly similar to multiple sclerosis. It may therefore be important to consider whether multiple sclerosis is a specific form of reaction on the part of the human brain. For this reason it might be that even if, for the sake of argument, we found the cause of multiple sclerosis to be a specific transmissible agent, animate or inanimate, it might not be capable of evoking the lesions of multiple sclerosis in animals. Even negative experimental results will therefore have to be scrutinized with care.

Encephalitis Periaxialis Diffusa

In man "encephalitis periaxialis diffusa," separated out from the diffuse scleroses by Schilder (1912), is itself a heterogeneous group of conditions. Einarson and Neel have proposed the present classification : (1) glioblastomatous reactive type ; (2) inflammatory reactive type ; (3) sporadic degenerative type : (a) with metachromatic prelipoids, and (b) with both fatty and metachromatic lipoids ; and (4) familial heredo-degenerative type, subdivided into : (a) acute infantile form (Krabbe, 1916), (b) subacute juvenile form (Scholz, 1925), (c) adult form (Ferraro, 1927), and (d) chronic "Pelizaeus-Merzbacher" form.

In the main this classification is approved by Greenfield (1950), except for the glioblastomatous type, which most neuropathologists agree should be excluded, for

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the reason that, with the modern improved identification of the gliomata, it has become evident that the glioblastomatous form of demyelinating disease is simply an expression of a diffusely infiltrating glioma with secondary demyelination such as can occur from associated oedema (Greenfield, 1939).

Of the other varieties in the present list I have examined material altogether from 23 cases: three were original, and the others, studied at the Salpêtrière and at the Institut Bunge, were mainly from among cases already reported from these laboratories.

The most striking impression one gains is that of the wide range of histochemical differences from case to case amongst the "degenerative" type, whether of familial or of sporadic nature. In this degenerative group of cases, including those with different grades of "prelipoid" substances, those with true metachromatic substances, those with mucinoid change in the oligodendroglia, and other variants such as Collier and Greenfield's (1924) type with "globoid" cells, there is a wide spectrum indeed.

Continental workers call these "heredo-degenerative" types *leucodystrophy*, a strictly accurate and certainly useful term to distinguish them from the classical type of Schilder's own Case 1. It does not always seem to be clearly appreciated in the literature that Schilder himself described under the name "encephalitis periaxialis diffusa" three quite different types of cases:

1. The 1912 case, in a girl aged 14, was the now classical form with a giant plaque of demyelination and sclerosis with sharply punched-out contours, occupying asymmetrically a large part only of each hemisphere. There were a few other discrete demyelinating lesions elsewhere in the brain and brain-stem, and Schilder thought that the condition might be a childhood variant of multiple sclerosis.

2. His second (1913) was a redescription of a case reported previously by Haberfeld and Spieler (1910). This was familial. It corresponded much more to the classical familial variety in which the whole of the neoneuronal myelin is affected even into cortex, and it was characterized by a dense accumulation of "prelipoid" substance.

3. The third case, reported in 1924, presented a different picture altogether, as Schilder recognized. It occurred in a woman aged 37 one month after influenza. A study of his report now suggests that the condition had much more in common with van Bogaert's (1945) subacute sclerosing leucoencephalitis than with either of Schilder's earlier cases.

A Variable Feature

Those cases of diffuse sclerosis of the type similar to Schilder's Case 1 are the preponderating type, and in contrast to the structural and histochemical variations in the leucodystrophies they show a remarkable uniformity in their basic features. Their only variable feature is in the location of the large plaque. The fact that in Bouman's (1934) well-known monograph, *Diffuse Sclerosis*, four out of five cases examined post mortem showed lesions of this plaque-like form served to perpetuate the misapprehension of the unity of Schilder's "encephalitis periaxialis diffusa," when the more logical assumption would now seem to be that this form, like Schilder's Case 1 on the one hand and the heredo-degenerative or leucodystrophic forms on the other, is fundamentally different.

We have seen that in Schilder's own Case 1 the giant plaque was not the only lesion present. Scrutiny of the literature shows that this multiplicity of lesions is often described. Bouman recognized the existence of "poly-sclerotic" forms, and finally Heernu, Martin, and van

LEGENDS TO PLATE

Figs. 1 to 8 illustrate some of the main features discussed of "encephalitis periaxialis diffusa," and Figs. 9 to 13 show some of the main aspects of classical and acute multiple sclerosis. Figs. 15 and 16 allow comparison of the naturally occurring post-vaccinal encephalomyelitis of man and the experimental "allergic" encephalomyelitis of lower mammals. Fig. 14 is from a living oligodendroglial cell.

Figs. 1-3.—Leucodystrophy. Formalin-fixed brain of 4-year-old child. Frontal, central, and parietal levels respectively. Note the transparent moiré appearance of the white matter due to the absence of myelin, except in the lower parts of the pyramidal tracts passing down into the crura of the mid-brain.

Fig. 4.—Same case as in Figs. 1-3. Giant paraffin section at level of Fig. 2. Stained by Loyez's method for myelin (black). This confirms the absence of myelin except in region of thalamus and crura cerebri.

Figs. 5-6.—Another case of leucodystrophy. Fig. 5 is a coronal section taken at level of posterior horn of lateral ventricle. There is residual myelin in the tapetal zone. In this case there is diffuse demyelination also in the cerebellum (Fig. 6). Myelin preparations.

Fig. 7.—"Prelipoids" from a case of familial leucodystrophy. The section is stained for myelin, which has disappeared from the nerve-fibre sheaths and now occurs as coarse masses, up to 50 μ in diameter. On the left some of it has been engulfed by phagocytes (the smaller spherical masses seen in the vicinity of a blood vessel—i.e., towards the left of the picture) ($\times 60$ approx.).

Fig. 8.—"Encephalitis periaxialis diffusa" of the type of Schilder's classical Case 1. The lesion is a giant plaque of demyelination with sharply punched-out contours. The cavity seen in the centre of the gyrus at the bottom right corner is due to loss of the thin friable tissue during technical handling. Spilmeyer's method for myelin.

Fig. 9.—Multiple sclerosis. Two typical plaques in periventricular white matter (ventricle, left middle). Note the sharply cut-out edges of the plaques but without swelling, shrinkage, or tissue loss. Loyez's stain for myelin (black). Slightly enlarged.

Fig. 10.—Early multiple sclerosis. Two "shadow plaques" in the white matter (staining black). The white arcuate zones to the left, top, and right are unstained cortex.

Fig. 11.—Typical multiple sclerosis plaque round a small vein, seen (on the right side) immediately subcortically. Unstained, formalin-fixed, slice of brain ($\times 2$ approx.).

Fig. 12.—Microscopical view of edge of a typical multiple sclerosis plaque showing abrupt delimitation of the process with the absence of breakdown of the ground substance. Loyez's iron-haematoxylin for myelin (black) ($\times 60$ approx.). The small scattered black elements in the demyelinated region are cell nuclei and erythrocytes in the lumina of blood capillaries.

Fig. 13.—Acute multiple sclerosis. Dr. van Bogaert's case (see text). Numerous sharply defined shadow plaques (grey) seen in the white matter (stained black). The small oval white lumina are spaces left where the thin-walled veins, cut in cross-section, have fallen out of the preparation.

Fig. 14.—Living oligodendroglial cell in tissue culture. Photographed under phase-contrast ($\times 400$). For description, see text.

Fig. 15.—Post-vaccinal encephalomyelitis in man. Loyez's stain for myelin ($\times 60$). Showing the halo of cellularity and "myelinoclasia" around small vein, seen cut across four times in this plane. The lumen of the vein is black owing to staining of the contained erythrocytes by the method.

Fig. 16.—Experimental "allergic" encephalomyelitis in guinea-pig brain. Same stain and same magnification as Fig. 15. See text.

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Bogaert (1945) produced conclusive evidence that there is no real anatomical distinction between Schilder's disease of his classical Case 1 type and multiple sclerosis. Amongst the intermediate forms are Devic's neuromyelitis optica, von Baló's concentric sclerosis, and another variety which Greenfield (1950) has added—namely, a demyelinating myelopathy with a coincident diffuse demyelination of one occipital lobe.

In summary, then, there are in fact really only two varieties of true primary demyelinating disease in man: (1) the leucodystrophies, and (2) multiple sclerosis, with, as a variant, diffuse sclerosis of the type of Schilder's Case 1.

The Leucodystrophies

The most remarkable structural feature of the leucodystrophies is the high frequency with which "prelipoid" substances, and products staining metachromatically with basic aniline dyes, are present. The "metachromatic leucoencephalopathies" have been the subject of several interesting papers recently by van Bogaert and Dewulf (1939), Einarson and Neel (1938, 1940, 1942), Einarson *et al.* (1944), Norman (1947), and Greenfield (1950); but the relationship to those of older cases in the literature which were characterized by masses of tinctorially abnormal prelipoids, such as the cases of van Bogaert and Scholz (1932), of Scholz (1933), and of van Bogaert and Bertrand (1933), has never been formulated.

It is now evident, however, that, since attention has been drawn to this feature of metachromasia, more and more, and perhaps all, of the familial cases show this abnormal accumulation of higher lipoids in variable degree, as well as the "sporadic" forms of leucodystrophy. It is well to remember that cases classified under the "sporadic" group undoubtedly include many cases of only children, so the distinction between "familial" and "sporadic" forms is just not valid. Further, metachromatic prelipoids are not necessarily limited to diffuse forms of leucoencephalopathy. For instance, Guillain, Bertrand, and Gruner (1941) have described under the title "leucoencéphalite à nodules morulés gliogènes" a most interesting case in which clusters of cells like Greenfield's "globoid" cells containing metachromatic prelipoid were present in two discrete symmetrical foci in the white matter of the putamina.

That the oligodendroglia is especially affected was first suspected by Collier and Greenfield in 1924 in a case which later proved to be familial. They proposed that the primary attack in diffuse demyelinating disease is "upon those cells that have to do with the nutrition of myelin." This view was also expressed by del Rio Hortega in 1928. Since that time Greenfield (1933) has separated out as a special variety those forms in which the affection of the oligodendroglia seemed particularly marked. The occurrence of metachromatic substances in the so-called "mucinoid degeneration of the oligodendrocyte" as well as the freely occurring prelipoid in the leucodystrophies suggest a close relationship in the metabolism of myelin and of the cytoplasmic constituents of the oligodendrocyte. As metachromasia seems to be due to polysaccharide constituents within cells it may be postulated for the moment that the metachromatic substances present in the leucodystrophies are, or are related to, galactosphingosides or cerebroside, and that the oligodendrocyte is intimately concerned with the metabolism of these substances,

which indeed may be the main energy source of this cell. We shall see the possible importance of this when discussing the physiology of this cell later.

Meanwhile it should be noted that Norman (1947) has emphasized that in these leucoencephalopathies the metachromatic substances are not limited to the central nervous system but have been found also in renal tubular epithelium, in liver, gall-bladder, pituitary, and testis—evidence indicating that these diseases are not limited to brain myelin but that they bear kinship with the general lipoidoses. In support of this, attention has been drawn to the widespread arrest of myelination in early cases of Tay-Sachs's disease (Norman), in Niemann-Pick's disease (Bertrand and van Bogaert, 1934), in Gaucher's disease, and in xanthomatosis both of the Schüller-Christian type (Davison, 1942; Globus, 1942), and of the curious type described as "cerebral cholesterolinosis" by van Bogaert, Scherer, and Epstein (1937).

Throughout all of these general lipoidoses there is the same individual variation from case to case in the distribution of the stored lipoid within the various organs as we have seen occurs in different elements of the nervous system as well as in other organs in the instance of the leucodystrophies. Yet the sphingomyelin in Niemann-Pick's disease, the kerosin in Gaucher's disease, and the cholesterol in xanthomatosis appear from such analytical studies as have been made (Sobotka, 1942; Sperry, 1942) to show no qualitative difference from those normally metabolized. Nor has any increase of these lipoids been found in the blood stream in cases of Gaucher's, Niemann-Pick's, and Tay-Sachs's disease (Thannhauser and Schmidt, 1946).

It is apparent that it is not so much with abnormal lipid or with an excessive supply in the blood plasma that we are dealing, but that it is *the rate of their metabolism* within the affected cells which is impaired. And the wide range of difference in the histological distribution of the lipoids from case to case indicates, further, that this defect resides in individual cells and not in any general chemical disturbance within the circulating fluids. In other words, the "metabolic abnormality" which is commonly taken to be present is not an abnormality of the lipid substrates but of the intracellular mechanisms—that is, enzymes—concerned in the utilization of these substrates for the immediate purposes of the cell and its processes. In this regard it should be noted that studies with the stable isotope deuterium (Sperry and Waelsch, 1950) have confirmed that these brain lipids, even in the adult, are in a state of constant metabolic turnover or "dynamic equilibrium."

Multiple Sclerosis

It is important to note that, although the disease is only of sparsely scattered incidence anywhere in the world (up to about 50 cases per 100,000 of population), there seems to be a significantly great geographical variation, as McAlpine (1946), Limburg (1950), and Kolb (1950) have severally indicated. Mortality statistics show no selective association between multiple sclerosis and population density, however. Nor are seasonal variations in onset and recurrence of and death from the disease statistically significant, so that there is no real support here for an infective theory. There is no evidence of any racial factor. It would appear, therefore, that the variation is in some way due to a geological or climatological factor, including, of course, a nutritional element.

In the histopathology of the disease my own experience is based on the examination, in various centres, of some 60 cases, 15 of which have been reported in some detail elsewhere (Lumsden, 1948).

Characteristic Lesions

The characteristic lesions of multiple sclerosis are confined to the central nervous system, including the optic pathways. The intrathecal portions of the cranial nerves and of the anterior and posterior spinal roots may occasionally be involved at their origins if in immediate contiguity with plaques within the brain substance, but discrete plaques are never seen. The extravertebral portions of the roots and the peripheral nerves are never involved by plaques, though non-specific varieties of neuritic change have been described sometimes, notably by Hassin (1921) and Schaltenbrand (1943). In two instances only, to my knowledge, have plaques been seen in posterior root ganglia. As these structures contain oligodendroglia, these two instances provide no exception to the general rule that multiple sclerosis plaques are found only where oligodendroglia exists.

The classical lesions within the central nervous system are the widely disseminated discrete plaques of demyelination and gliosis with the characteristically sharply punched-out contours. Such plaques appear to grow by spreading in diameter, preferentially in the white matter, though not infrequently encroaching upon the grey. They may coalesce to form larger lesions, which may, for instance, cover almost the entire cross-sectional area of the spinal cord, with, it is noted, often disproportionately little functional result. Their contours show no evident tendency to be delimited by blood vessels or by pial septa.

Equally peculiar to multiple sclerosis are the true shadow-plaques, or *Markschattenherde*, where demyelination is only partial—but evenly so—throughout the plaque, and where the same sharply punched-out character of the contours is still preserved. With Kultschitsky's haematoxylin they look like an ink-stain blotted while still wet. Their real nature has been a mystery, but the recent studies on the normal myelin that have been made with x-ray diffraction and electron microscopical methods appear to me to suggest an explanation. Schmitt's (Schmitt *et al.*, 1941) work has shown that the lipid molecules in the sheath are arranged with their long hydrocarbon chains extending radially and are laid in concentric layers alternating with neurokeratin. Each lipid-protein layer measures 186 Å and contains 25 Å of water molecules—that is, some 13%. This figure falls short of the chemically realizable water content, which varies from 35 to 50%. To explain the difference it was predicted by Schmitt that there are periodic water channels breaking the myelin into concentric layers. Electron microscopical studies by Fernández-Morán (1950) have confirmed the existence of such myelin lamellae. I believe that the shadow-plaques of multiple sclerosis may be due either to decortication of the outer myelin lamellae or to imbibition of water molecules into the interlamellar channels, and that it should easily enough be possible to elucidate this with one of these two ultraphysical methods.

It is an old controversy, indeed, whether the plaques are centred round blood vessels or related to vascular territories. The failure of Putnam's thrombosis theory of multiple sclerosis to gain acceptance has tended to prejudice some neuropathologists against the view that

any vascular factor is concerned in the genesis of the disease. But in my experience it is indisputable that plaques are *sometimes* centred round veins and venules, particularly in the acute lesions, in such a way as to suggest a more than fortuitous relationship. In most chronic lesions no such perivascular relationship is evident, but the marked tendency to a subependymal distribution of plaques may be due to some relationship with the venous drainage rather than with any intrinsic association with the ventricular fluid. In the same way the distribution of plaques in the spinal cord often suggests a relationship to the venous territories (Fog, 1950).

The microscopical characteristic of the multiple sclerosis plaque is the suddenly delimited demyelination with complete or relative preservation of the axis cylinders—the *dissociation axomyélinique* of the Continental authors—with the laying down of parallel strands of neuroglial fibres alongside the intact axons, a physical structure which is probably the main explanation of the characteristic translucency of plaques.

"Secondary Demyelinations"

Of course, other conditions from time to time mimic plaques of multiple sclerosis. These secondary demyelinations occur in a formidable array of diseases, including the toxic encephalopathies of hepatic disease (Crandall and Weil, 1933; Baker, 1949), uraemia (Hechst, 1932; Hiller and Michalovici, 1941; Knutson and Baker, 1945), eclampsia (Schmorl, 1902; Diamond, 1936), dysentery (Spielmeyer, 1922), and porphyria (Baker and Watson, 1945); in the primarily anoxic encephalopathies associated with chronic cyanotic heart disease, anaemias like pernicious anaemia (Lurie, 1919; Lebensart, 1934), the local anoxic complications of cerebral malaria (Rigdon, 1944), and the cerebral vascular complications of rheumatism (Costero, 1949). In the same category belong the experimental microembolic and microthrombotic lesions which I have reported elsewhere (Lumsden, 1950), as well as the so-called "demyelinating" lesions caused by oedema around tumours such as Greenfield (1939) has reported. In individual lesions there may very occasionally be some difficulty in distinguishing such "*plaques simulatrices*" from plaques of multiple sclerosis, especially when this latter is associated with some axonic damage and secondary Wallerian change, as one must admit can sometimes occur in the necrotizing forms. But the important thing is the overall character of the lesions.

On the basis of the generally accepted histopathological criteria, multiple sclerosis could now be defined as follows: a process affecting nerve fibres within the central nervous system, with the production of focal lesions which are disseminated and which continue to evolve slowly and often intermittently to the formation of sclerotic plaques in which the axis cylinders are largely preserved. The process remains predominantly periaxial and discontinuous, thus producing plaques of demyelination characterized by abrupt contours which extend eccentrically and irregularly through the myelinated parenchyma. Any of the individual criteria in this definition can be fulfilled singly or in groups by other conditions, but, taken together, they delineate a disease process that embraces all cases of classical multiple sclerosis and excludes all other conditions.

I deal later with the more debatable "acute" or initial forms of the disease, but even on the most

generous estimate these have not exceeded 5 or 6% of the total in any large number of cases of multiple sclerosis studied pathologically. It is the entitative character, then, of the 95% of classical multiple sclerosis that has to be explained by any acceptable hypothesis of causation. Far from reproducing this entitative character in 95% of the lesions they cause, the agencies so far blamed for multiple sclerosis—such as spirochaetes and neurotropic viruses (e.g., Bailey *et al.*, 1949), thrombosis (Putnam, 1933, 1935, 1937; Putnam and Alexander, 1939), or lead-poisoning (Campbell *et al.*, 1950)—can only very rarely produce any lesions which even mimic multiple sclerosis.

Broadly, then, the contribution of structural pathology to the problem of the causation of multiple sclerosis has been to narrow the field to a choice of two views: either (1) if the real cause is a specific transmissible agent it must be a virus or a chemical substance not yet even listed amongst the known pathogenic agents, and one with some extremely uncommon properties; or (2), alternatively, the disease may be only a specific form of reaction on the part of the nervous system peculiar to certain individuals and, within limits, independent of its immediate precipitating cause.

Role of the Oligodendrocyte

On the significance of non-parenchymal reaction in the brain in multiple sclerosis there has been no controversy since the Strümpell-Müller hypothesis of "dysplastic glia development" was dropped and argument subsided on the "degenerative" or "inflammatory" significance of the perivascular round-cell reaction that may be associated with the lesions. In one important respect, however, this field has been completely neglected—namely, concerning the role and fate of the oligodendroglia in multiple sclerosis. A study of my own material showed a complete loss of this cell from the plaques of demyelination both in the acute and in the chronic lesions. The oligodendrocytes disappear as abruptly as the myelin sheaths, but this is equally true in secondary demyelinating conditions. In the grey matter local reactive proliferation of perineuronal oligodendrocytes certainly occurs in syphilitic and other types of polio-encephalitis, but in the white matter the reactive potentialities of the interfascicular oligodendroglia, for instance in rheumatic lesions, is indeed limited and short-lived. This cell undergoes extremely rapid autolysis post mortem, and no cytochemical research has in consequence been so far possible on it in human material.

Perhaps the solution of the whole obscure problem of the demyelinating diseases may prove to be in the biology of the oligodendrocyte. We already know much about the biology of the neurone, its chemistry, its bioelectric phenomena, its mode of growth in culture, and the way it is affected by pathological agencies; and we know something likewise of these aspects of the astrocyte and microglia. Concerning the oligodendrocyte, the most numerous cell within the central nervous system, we know strictly nothing of its role in health and disease apart from the general assumption, attributable mainly to its discoverer, del Rio Hortega (1921, 1928), that it is in some way concerned in the maintenance of the myelin sheaths.

The claim by Canti, Bland, and Russell (1935) to have grown cells from two cases of oligodendroglioma in the human subject suggested to me that it might be

possible likewise to grow the normal oligodendrocyte or at least to maintain it alive in tissue culture for a period of some few days, during which its vital phenomena could be observed. Corpus callosum of the normal healthy adult rat provided explants in which the nucleated cells were almost entirely oligodendroglial. The details of the methods used and observations made are reported elsewhere (Lumsden and Pomerat, 1951).

Briefly, these cells appear in clusters at the margin of the explant, chained together by long filamentous processes, usually four or five per cell, with highly amoeboid terminal expansions. When studied in cinematographic records these oligodendrocytes are seen to exhibit a remarkably strong rhythmic contractility quite unlike the movements of astrocytes and microglia of nervous tissue on the one hand, or fibroblasts, macrophages, and other mesodermal elements on the other. Because of their interconnecting processes these contracting cells engage in a curious and highly characteristic continual tug-of-war. The whole contraction phase of each cell takes about five minutes and consists of a shorter contraction phase, systole-like, lasting one and a half minutes, and a more prolonged expansion phase, diastole-like, lasting about three minutes.

With such preparations it should be possible now to investigate many problems. With the special micro-irrigation chambers (which already exist for this type of work in tissue-culture laboratories) it would be simple to examine the reaction of living oligodendrocytes to various potential "toxins" such as extracts of multiple sclerosis plaques, comparing these with normal brain from the same and also from a healthy subject. Sera from animals with experimental "allergic" encephalomyelitis, and dilute solutions of salts of trace elements like copper or lead such as have been thought to play a part, favourable or adverse to the patient, in the genesis of multiple sclerosis, could be assayed similarly. Furthermore, with these cells, which have such a remarkably rhythmic contractility, electrical phenomena likely to be associated with the contraction can, we hope, soon be studied directly. What effect such electrical changes might have on the normal electroencephalogram offers fascinating material for speculation.

The Initial Lesions

One of the difficulties in understanding the pathology of multiple sclerosis is that, because of the insidious character of the disease, we do not really know what the initial lesions are like. One school of neuropathologists, including Hassin (1921, 1937) and Spielmeyer (1930, 1931), has held that the lesions are always of the classical type from the outset. The opponent school has maintained that they begin as an acute disseminated encephalomyelitis. There are a few cases on record in which death occurred from some incidental cause during the earliest phases of multiple sclerosis. A most valuable case of this type is one reported by Cournand (1930). I had the opportunity of examining the material from this case at the Salpêtrière. Here the lesions, though apparently no more than a few weeks old, even histopathologically, already bear the stamp of indubitable multiple sclerosis.

If, on the other hand, we take a subacute case of post-vaccinal encephalitis for direct comparison—such as a most interesting case (Case XII), with survival for

108 days, as reported in Blackwood's (1944) Edinburgh series—we find that the encephalomyelitis heals by the ordinary processes of glial and mesodermal scarring and shows no resemblance whatsoever to incipient multiple sclerosis. Furthermore, some hundreds of non-fatal cases of acute disseminated encephalomyelitis of the post-exanthematous type have now been followed over a sufficient number of years (Kudelka, 1932; Kaiser and Zappert, 1937) to show that at least this variety never progresses to multiple sclerosis even though it is the commonest form of acute disseminated encephalomyelitis and the one which pathologically, by reason of its "myelinoclasts" or partial softening of the white parenchyma, most nearly imitates multiple sclerosis.

It would appear, therefore, on the evidence I have outlined, that multiple sclerosis and acute disseminated encephalomyelitis are different diseases from the outset.

Reference must be made here, however, to a unique case in my experience—namely, that reported by van Bogaert from Spielmeyer's laboratory in 1932.

A 12-year-old girl died of an acute febrile cerebral affection 18 days after the appearance of a typical varicellar rash. The brain showed an acute disseminated encephalomyelitis with punched-out foci of demyelination scattered like oil-drops within the white matter. The lesions are uncannily like multiple sclerosis, a fact which Spielmeyer himself admitted, while none the less regarding acute multiple sclerosis and acute disseminated encephalomyelitis as different diseases.

It is untenable that in this case we have two processes fortuitously associated. Is this, then, the unique case upon which, after all, we are to conclude that multiple sclerosis begins as acute disseminated encephalomyelitis? Surely not. If this were so, most multiple sclerotics would have a history suggestive of acute disseminated encephalomyelitis, and most non-fatal cases of acute disseminated encephalomyelitis would evolve to multiple sclerosis. This does not happen. Therefore it seems we must accept this compromise: that, while they are different diseases, in very rare cases multiple sclerosis may arise from acute disseminated encephalomyelitis which is merely *one* of the potential precipitating causes.

Experimental Encephalomyelitis

This problem of the relationship between multiple sclerosis and acute disseminated encephalomyelitis is no longer an academic one, for a form very similar to the latter disease in man can now readily be produced in animals by non-infectious means (Kabat *et al.* 1947; Morgan, 1947; Lumsden, 1949a, 1949b). This, the experimental so-called "allergic" encephalomyelitis, is a curious disorder that can be produced regularly in a high proportion of animals by a single subcutaneous injection, or a short series of injections, of sterile normal brain tissue from either homologous or heterologous species, suspended in an oily "adjuvant" base containing the products of killed tubercle bacilli. The disease can also be produced, though much less frequently or much more slowly, by the brain tissue alone without "adjuvants" (Rivers and Schwentker, 1935; Ferraro and Jervis, 1940).

"Adjuvants" alone and with killed tubercle bacilli will not themselves produce the condition; nor is the toxicity of the dead bacillus of any import, since harmless saprophytic varieties of acid-fast bacteria (Freund, Stern, and Pisani, 1947) serve equally well as a source

of the enhancing substance, suspected to be a lipid. The exact chemical nature of the enhancing agent, however, still remains to be shown, and how it operates—whether by conjugating itself with the active principle in the brain tissue or by evoking some preparatory cellular or humoral change in the body which sensitizes the brain of the injected animal to the brain tissue injected. The animal's own brain tissue removed by frontal lobectomy and injected subcutaneously will produce the lesion (Kabat *et al.*, 1949).

The possibility of a transmissible virus can be excluded, as neither prolonged autoclaving of the inoculum nor prolonged treatment with phenol or with strong formaldehyde solution destroys the encephalitogenic agent (Kabat *et al.*, 1948; Lumsden, 1949b). For these reasons, too, the agent is evidently not a protein. I have also reported that it is extractable with the myelin sheath lipoids sphingomyelin and cerebrosides and not with the axonic lipoids lecithin and cephalin (Lumsden, 1949b). The possibility of activation of a latent virus infection within the injected animals would seem to be excluded on the grounds of the high specificity of the inoculum and on the fact that the phenomenon is shown by a wide range of mammalian species tested—monkeys, guinea-pigs, rabbits, sheep, goats, and dogs—with an incidence rate diminishing in approximately that order from monkeys with a 90–95% susceptibility.

The disease produced in animals so inoculated is remarkably uniform throughout all species. The lesions consist of severe, disseminated, perivascular—essentially perivenular—partial softening in the white matter, with a sharp microglial reaction and a proliferative response of the adventitial histiocytes in the vessel walls. Sometimes this latter element is very marked indeed and there is migration into the parenchymal territory on the part of these mesodermal elements so that a pseudogranulomatous lesion may develop. But, generally, such cellular emigration (including plasma cells and eosinophils) as occurs in some cases always appears subordinate to the general severity of the damage to the parenchyma. There is usually no capillaritis.

The perivenular partial softening appears, of course, in myelin preparations as sleeves of demyelination, and several lesions may become confluent, so that widespread disintegration occurs within the centrum ovale. Even then, however, the neuroglial groundwork remains intact, so that no complete necrosis of the tissue is affected such as occurs, in contrast, in an infarct. Though the central veins and venules may be much engorged, there is no thrombosis. The degree to which the myelin is damaged varies with the animal species, monkeys showing considerably more demyelination than guinea-pigs and other animals. When, in the cases of remission with relapse which sometimes occur, opportunity is given to examine the late results of the lesion, these are seen to be glial and mesodermal scars and there is no evidence of production of any spreading demyelination at all comparable to multiple sclerosis.

If, then, this experimental disease does not reproduce multiple sclerosis, it has at least a remarkable similarity to acute disseminated encephalomyelitis of the post-exanthematous type in man. And somewhere there seems to be a tantalizing link with multiple sclerosis—for instance, in the distribution of the lesions especially in the optic pathways, and in the tendency to spontaneous remissions and relapses. The one thing

the experimental lesion lacks is any evidence of progressive spreading demyelination which is the so far unexplained peculiarity of multiple sclerosis.

When, therefore, we consider this experimental disease and its human counterpart, an obvious hypothesis presents itself—namely, that two disease mechanisms are concerned in multiple sclerosis: (1) a preparatory, exogenous mechanism which damages the white matter, and (2) an endogenous mechanism which liberates myelinolytic substance related to the myelin sheaths or the oligodendrocytes. With regard to the preparatory mechanism it may be that several different agencies act in this way. It may be that trauma, visceral tuberculosis, T.A.B. vaccination, diphtheria immunization, and other alleged precipitating causes which have been specifically incriminated in certain cases of plaque-like “Schilder’s disease” in childhood, and that, in multiple sclerosis, lead and other toxic trace elements and the toxins of banal infections, as Pierre Marie maintained, may all be potential “trigger” causes which touch off the intrinsic mechanism which in susceptible individuals will lead to multiple sclerosis. To prevent the disease, our best hope, therefore, will be in some way to jam this exogenous “trigger” mechanism. Rational attempts to arrest the disease once initiated will involve methods designed to block the intrinsic mechanism.

Before concentrating on this latter aspect I would mention that in regard to the precipitating mechanism in the case of the experimental encephalomyelitis it has not yet been settled whether the encephalitogenic agency is really “allergic” or “neurotoxic” in the broadest way. It was only in view of the enhancing action of Freund’s “adjuvants” generally in promoting antibody reactions that the experimental encephalomyelitis was assumed to have a similar antibody, and in consequence “allergic” mechanism. However, for the moment, we should note: (1) that the active agent in brain is apparently non-proteinous; (2) that no counterpart to the lesion is produced in other organs when other organs are used as sources of “antigen”; (3) that it is not possible to transfer the alleged sensitivity to brain in any way like that in which tuberculin sensitivity can be transferred passively; (4) that the histopathological lesions in the brain are not like those of other conditions more generally accepted as “allergic” in character; and (5) that anaphylactic and Arthus reactions can occur in treated animals independently of the encephalomyelitis. Finally, Lumsden *et al.* (1950) found that the antibody responses in the experimental animals, complex in pattern as they were in view of the complex antigenic nature of crude brain used as an inoculum, showed no evident parallelism or relationship with the encephalomyelitis.

Intrinsic Mechanism of Multiple Sclerosis

One possibly important factor is the highly specialized nature of myelin-sheath protoplasm with its uniquely high ratio of lipids to protein, a biochemical peculiarity shared perhaps only with the enveloping membrane of the erythrocyte. This latter analogy is indeed so close that the very active research being conducted just now on the biophysics of haemolysis may prove vital to our understanding also of the nature of demyelination. Exactly what the amounts of protein and lipid are within the sheath is not yet known, but this would seem a problem now amenable to quantitative physical techniques like Caspersson’s (1950) ultra-

violet-light absorption and Engström’s x-ray absorption methods (Engström and Lindström, 1950).

If the protein component of the sheath is so much less than in cytoplasm generally, and in the axoplasm in particular, it may reasonably be predicted that enzyme activity in the sheath will be correspondingly much less than in the axoplasm. Therefore, even though the sheath is structurally part of the nerve fibre it may reasonably be assumed that metabolic processes within the sheath are slower than in the axoplasm by a margin wide enough to permit the phenomenon of axomyelinic dissociation. This low “vitality” on the part of the sheath relative to the axon is indeed illustrated by its characteristic slowness to form *in vivo* as in Speidel’s (1932a, 1932b, 1933) direct observations on the medullating nerves in the tadpole tail, and by recent observations on the development of myelin in tissue cultures of chick embryo dorsal root ganglion reported by Peterson (1950) from Murray’s laboratory at Columbia University.

Possible Role of Enzymes

It might be said that by the tenets of modern biochemistry it is almost axiomatic that, whatever kills the myelin sheath, the final process of lipid degradation will be mediated by enzymes. An examination of the structural formulae of sphingomyelin and of cerebroside, for instance, will give us a clue to the nature of some of the enzymes concerned in the hydrolysis of the more vulnerable linkages. We know, too, that the administration of such enzymes as the lecithinases of *Clostridium welchii* alpha-toxin and of cobra venom can lead to the splitting of crude myelin *in vitro* (Morrison and Zamecnik, 1950), and that *in vivo* the intracerebral injection of purified pancreatic lipase, for instance, can, according to Vogel (1950), cause pools of demyelination resembling plaques of multiple sclerosis. Then, again, there is reason to believe, as I have written elsewhere (Lumsden, 1950), that the brain can be induced by artificial means to liberate myelinolytic substances when certain as yet unidentified enzyme systems are poisoned by cyanides.

If we seek to understand how intrinsically produced myelinolytic ferments could cause multiple sclerosis, as Marburg postulated as long ago as 1906, our real problem is not to find possible sources of such ferments but to explain why in the ordinary processes of myelin degradation in diseases of the nervous system other than multiple sclerosis the action of these ferments is limited to those units already damaged directly by the causative noxa; in other words, why their action does not spread to the myelin of undamaged medullated axons.

In the past, attempts were made by Brickner (1930), Weil *et al.* (1935), Richards and Wolff (1940), and Weil and Heilbrunn (1941) to demonstrate myelinolytic substances in the blood, urine, and cerebrospinal fluid of patients with multiple sclerosis. The methods used, however, have not been sufficiently analytical nor have the results been generally accepted as quantitatively significant. The probability is that even if myelinolytic ferment is liberated within plaques it is utilized, neutralized, absorbed, or otherwise bound locally and does not enter the body fluids in measurable amounts. The logical necessity is therefore to devise a technique for measuring it *in situ*. I personally believe this should now be possible provided suitably fresh material can be

obtained immediately after death, or, preferably, by biopsy sample when for any reason surgical intervention has been undertaken.

To explore the possible application of the quantitative micro-methods of Linderström-Lang to this special type of problem, working in Glick's laboratory in Minneapolis, I have made a preliminary study of esterase activity in the sciatic nerve of the rabbit at varying intervals after transection. The details of the method and the results will be reported fully elsewhere. Twenty-micron frozen sections of the freshly removed nerves were incubated in micro-reaction tubes along with a suitable buffered substrate, methyl butyrate, and at suitable intervals the reaction was stopped by the addition of phenol and the pH change in the substrate determined by microtitration. Parallel runs were made with tissue without substrate, and others with substrate without tissue. The sections were taken at various levels above and below the line of transection and likewise in the corresponding levels of the contralateral (unsectioned) sciatic nerve. Esterase activity was in this way determined and finally expressed in terms of one milligram of dried tissue. Distal to transection, lipolytic activity falls immediately and progressively till a constant level is attained at about 40% of the normal activity of the normal whole nerve. This irreducible minimum we suspect measures the activity of the endoneurial and perineurial sheath cells, which, far from degenerating in the peripheral stump, undergo a proliferation exceeding in intensity that of the corresponding sheath cells in the central stump.

Meanwhile at the lower end of the portion of the nerve proximal to the transection there is, in the segment of regenerating neurites, a steady rise of lipolytic activity for about 30 days up to 300 to 400% of the normal. Then as reunion occurs the zone of highest activity passes into the upper extremity of the now reunited distal portion. With this method it is possible, too, to take sections adjacent to those used for micro-analysis for ordinary fat and other histological stains, thus permitting qualitative histological and quantitative microchemical studies at the same time. In the same way, given suitable fresh material, it should be possible to make quantitative studies directly, at least of lipase activity to start with, in different regions of a multiple sclerosis plaque.

Conclusion

Until the hypothesis that there is produced within plaques a myelinolytic ferment which diffuses slowly into the surrounding white matter is confirmed or refuted in this way it is perhaps premature to speculate too far upon the possible mechanism of its production. However, when we take account of what is now known chemically of the close relationship, if not identity, of genes and enzymes, and of the role of vitamins and hormones as prosthetic components of enzymes, a whole world of light is shed upon our present problems. In the leucodystrophies and in the myelin lesions of the general lipidoses it may be postulated that the missing enzyme is a gene. In the system demyelinations like subacute combined degeneration of the cord and "swayback" it is probably a deficiency of some prosthetic group. For instance, in subacute combined degeneration it is almost certainly due to a deficiency of the cobalt-containing *crystalline red substance* isolated by Lester Smith (1948) in this country.

In the case of "swayback" the deficient factor is apparently connected with copper, though copper parenterally in inorganic or organic form is useless. It is probable, then, that the copper must be bound in a specific complex before it is presented to the neural tissue and that it forms part of an essential prosthetic group, as for instance does zinc in carbonic anhydrase. But we do not know what precisely is the role of the trace-element copper apart from the fact that it is essential for the formation and maintenance of the enzymes cytochrome oxidase and catalase.

It would seem, then, that insufficiency of essential enzymes would be enough to explain the genetically determined and the nutritional deficiency forms of myelin dyscrasia. But in addition to containing enzymes necessary for the synthesis and maintenance of myelin it seems fairly evident from the experiment I have described on esterase activity in Wallerian degeneration that the *normal* nerve fibre, apparently independently of extrinsic cells, contains the enzymes necessary for myelin catabolism. In other words, the living medullated nerve fibre contains not only myelin lipoids but the specific enzymes which hydrolyse them. One is reminded that this is no remarkable paradox by the classical analogy of Claude Bernard's that the liver cell contains both glycogen and diastase.

In the same way acetylcholine, cholinesterase, and choline acetylase all exist together at the nerve ending, and probably also, as Nachmansohn (1946) has shown, along the whole surface length of the nerve. And again, prothrombin, thrombokinase, and calcium can exist together without clotting, as a result, we say, of the presence here also of a specific antagonistic ferment. In the same way we may postulate that myelin contains not only phospholipases and cerebrosidases but also antiphospholipases and anticerebrosidases. Since on theoretical physical chemical grounds it is thought highly probable that hydrolysing enzymes act at the cell boundary, we may envisage the antiferment molecules arranged as a monomolecular layer immediately outside the lipolytic ferment layers.

Can we then postulate, too, a direct connexion between this layer of antiferment molecules and the peculiar morphology of the oligodendrocyte with its highly tenuous and fragile protoplasm arranged, as the exquisite illustrations of del Rio Hortega have shown us, like a delicate bandage-like membrane just outside the myelin sheath? To destroy selectively the oligodendrocyte and yet to leave a living myelinated axon would then permit the hydrolysing ferment to destroy the myelin. This in turn would permit the diffusion from the *still living axoplasm* of lipolytic ferment, which in turn would damage the oligodendrocytes in the next rank of these cells, so setting in process a chain reaction of myelin disintegration diffusing out slowly like an oil-stain through the white matter.

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ASPHYXIA NEONATORUM TREATED BY ELECTRICAL STIMULATION OF THE PHRENIC NERVE

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Sarnoff and his colleagues (1948, 1950) have recently reintroduced an old method of artificial respiration by the electrical stimulation of the phrenic nerve in the neck through the intact skin. This method was first used as far back as 1783 by Hufeland, who discharged a series of condensers through the patient. The method was again tried after the discovery of electromagnetic induction, when the shocking coil was used. Israel (1927, 1928) reported the use of the shocking coil for the resuscitation of newborn infants, and was most impressed with the results obtained. With modern equipment it is possible to obtain a controlled and smoother contraction of the diaphragm than was previously possible.

Description of Apparatus

The electrical wave-form used to stimulate respiratory movements when applied to the phrenic nerve consists of negative-going rectangular pulses of $\frac{1}{4}$ millisecond