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Progressive multifocal leucoencephalopathy and primary hypersplenism

With a note on the association between disease of the reticuloendothelial system and progressive multifocal leucoencephalopathy

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SYNOPSIS A patient with progressive multifocal leucoencephalopathy was found to have primary hypersplenism, a benign disorder of the reticuloendothelial system. He failed to respond to conventional doses of corticosteroids. The clinical and pathological manifestations of his illness are described, and the development of the histopathological changes in the nervous system is discussed.

Consideration of available data on progressive multifocal leucoencephalopathy reveals a striking association with disease of the reticuloendothelial system, the significance of which is discussed in relation to aetiology and treatment.

Progressive multifocal leucoencephalopathy is a demyelinating disease of the brain which may occur terminally in patients with malignant reticuloses and leukaemia. It was first recognized as a pathological entity by Åström, Mancall, and Richardson in 1958, and a fuller description of the syndrome has since been given by Richardson (1961). The clinical manifestations relate directly to the situation and extent of cerebral disease, and their variation in the early stages depends upon this. Later, disorders of speech, vision, and intellect are accompanied by extensive locomotor disturbances to produce the picture of severe diffuse cerebral involvement characteristic of the final stages of the illness. Although usually associated with malignant disease, in several instances the disorder has been found complicating a benign process; thus it cannot be regarded in any sense as belonging to the group of carcinomatous neuropathies, despite the occasional coexistence of both types of neurological disorder in patients with carcinomatosis (Fisher, Williams, and Wing, 1961). Common to many cases of progressive multifocal leucoencephalopathy is involvement of the reticulo-endothelial system by the underlying disease process, which so far has been found on occasion to include sarcoidosis, carcinomatosis, miliary tuberculosis, and, more commonly, leukaemia and the malignant reticuloses (Richardson, 1961).

The purpose of this paper is to describe the co-existence of progressive multifocal leucoencephalopathy with primary hypersplenism, an association not previously reported, and to discuss certain features of the clinical presentation and aetiology which arise from consideration of this case.

CASE REPORT

A right-handed 59-year-old bachelor previously in good health noticed the onset of weakness of the middle three fingers of his right hand in mid-July 1960. Three weeks later the weakness had increased and his thumb was involved; on admission to hospital five weeks after the onset of symptoms he had severe weakness of the right upper limb and shoulder. His upper arm ached after he had been up and about for several hours each day, and the hand became swollen and blue towards evening. There were no other symptoms. For many years he had worked as a coach painter in a factory making railway carriages, and, apart from having smoked 20 cigarettes

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a day for 45 years, he was not exposed to known injurious substances.

The lower pole of the spleen was palpable 2-3 cm. below the left costal margin, and the fingers showed early clubbing. Apart from this, general examination on admission showed no abnormalities. Neurological changes were confined to the right upper limb and shoulder girdle, which were considerably weakened especially distally, with general muscle wasting in the shoulder, arm, and hand. Occasional fasciculation was present. All muscles were flaccid except the biceps brachialis, which was somewhat spastic. The biceps, triceps, and supinator jerks were increased. Position sense was impaired in the fifth digit, and there was blunting of light touch and pin prick along the ulnar border of the hand. Intellect was judged to be unaffected, and there were no disturbances of speech or vision.

Laboratory tests gave the following results:—

BLOOD Haemoglobin 10·1 g./100 ml.; reticulocytes 6%; erythrocyte sedimentation rate 15 mm. in one hour (Westergren); total white cell count 1,400/c.mm. (normal differential); total platelets 200,000/c.mm.; a stained film showed anisocytosis, poikilocytosis, polychromasia, Howell-Jolly bodies, and occasional normoblasts. Red cell osmotic fragility was normal. An acid haemolysin test (Crosby, 1950) was negative. The direct antiglobulin reaction was negative twice, weakly positive once. An L.E. cell test was negative. The serum haptoglobin level was reduced. A ^{51}Cr-red cell survival test by the method of Mollison and Veall (see Mollison, 1961) showed that the half-survival time of Cr was reached at 17 days (normal 25·5 days), indicating an active haemolytic process. Liver and spleen counts (Lewis, Szur, and Dacie, 1960) showed initial high splenic radioactivity but no progressive liver or spleen increment as seen in acquired auto-immune haemolytic anaemia. Tests for cold agglutinins, haemolysins, and cryoglobulins were negative. Wassermann and Kahn reactions were negative. 'Liver function' tests were normal. Serum proteins were normal by paper electrophoresis. Blood urea was 42 mg./100 ml.

Bone marrow (sternal aspiration) was of normal cellularity and composition with normoblastic erythropoiesis and no diagnostic infiltration was seen.

LUMBAR PUNCTURE Clear cerebrospinal fluid was under normal pressure and the cell count was normal (less than 1 lymphocyte/c.mm.); protein 46 mg./100 ml.; sugar 63 mg./100 ml.; the Wassermann reaction was negative; the colloidal gold curve 1,1,1,1,0,0.

ELECTROENCEPHALOGRAM On 5 September 1960 a low amplitude slow wave disturbance was shown in the left fronto-temporal region.

ELECTROMYOGRAPHY (RIGHT HYPOTHENAR EMINENCE) On 20 September 1960 spontaneous positive potentials and a few very low voltage potentials on volition were recorded. The conduction time from the ulnar nerve at the elbow to the hypothenar eminence was within normal limits.

RADIOLOGICAL INVESTIGATIONS The chest was normal apart from thoracic scoliosis. The skull was normal. The pineal was calcified and in the sagittal plane. There was lower cervical scoliosis and spondylosis with considerable narrowing of the intervertebral foramina for the sixth and seventh cervical nerve roots on the right side. A myelogram showed that the sixth and seventh cervical nerve root sheaths on the right side failed to fill but it was otherwise normal. Left carotid angiograms (August and December 1960) showed no definite abnormality. An intravenous pyelogram and barium meal examination of the intestine were normal apart from displacement of the stomach, colon, and left kidney by the enlarged spleen.

BIOPSIES Liver and inguinal lymph node biopsies were normal.

A muscle biopsy (right palmaris longus) was taken on 20 September 1960. A haematoxylin-and-eosin preparation showed slight atrophy of muscle fibres with increase in sarcolemmal nuclei. Cholinesterase preparations showed palely stained and poorly defined subneural apparatuses of the end plates with a tendency to form two or three groups of elements in the long axis of the muscle fibres. Vital staining with methylene blue showed a preservation of nerve fibres at variance with the muscular weakness if this were indeed due to a lower motor neurone lesion. There did, however, appear to be an excess of fine beaded axonal fibres (sprouts) in the intramuscular nerve bundles. There was no obvious loss of myelinated nerve fibres from a small cutaneous nerve fixed and stained with osmic acid.

PROGRESS Between August and October there was a slight increase in sensory and motor impairment in the right arm. A short course of deep *x*-ray therapy was given to the right side of the neck in the hope of relieving pressure on nerve roots from a possible locally invasive process such as a reticulosis, but without any change. From October the patient began to develop signs of a pyramidal lesion affecting both the right leg and the right face, and within a month there had been further marked deterioration. Prednisone, 30 mg. daily, was given for a month in October, but this exerted no observable beneficial influence either on the neurological or haematological disorder and so it was withdrawn. The visual fields remained normal when tested (by confrontation) in December, but by now the signs of left parietal lobe disease were unmistakeable. The optic fundi remained normal. A month later he was admitted to hospital for terminal nursing care with marked intellectual deterioration and hemiplegia. Detailed examination shortly before death showed that there was no change in his haematological status; the degree of splenic enlargement was unchanged. He died on 25 February 1961 with bronchopneumonia.

FINDINGS AT NECROPSY

There was extensive bilateral bronchopneumonia. The spleen was diffusely enlarged (990 g.) but its cut surface appeared normal. The liver (1,520 g.), heart (260 g.), kidneys (each 110 g.), ureters,

bladder, and alimentary tract showed no gross abnormalities. The aorta was moderately atheromatous, but there was no sign of thrombosis either there or in the carotid arteries, which appeared healthy. The sternum and vertebrae contained red marrow. There were no enlarged lymph nodes and no tumours.

MICROSCOPY There was no evidence of any neoplastic process in the spleen. The normal splenic architecture was preserved but somewhat altered. The sinuses were prominent, with large lumens, and contained numerous red cells and many mononuclear cells. In some of the mononuclear cells erythrocytes were to be seen, and in others there was iron pigment. Scattered through the pulp were numbers of small focal collections of cells including plasma cells and larger cells, possibly immature plasma cells. Malpighian follicles were normal.

The lobular architecture of the liver was normal. Small foci of parenchymal cells showing fairly marked fatty change were irregularly distributed in the lobules. The Kupffer cells contained small amounts of iron pigment.

Moderate post-mortem autolysis, but no significant change, was found in the kidneys.

The myocardium was normal.

The brain, which was fixed undissected, showed no external abnormality except possibly for a very slight increase in fullness of the left frontal lobe. There was no uncal or subfalcine herniation. The vessels at the base of the brain were free from atheroma. Coronal section at a level just anterior to the head of the caudate nucleus showed a linear softening extending from the cortex around the left inferior frontal sulcus into the centrum semi-ovale for 1 cm. There was also a very slightly yellowish softening embracing the cortex in the depths of the left superior frontal convolution. Further posteriorly the softening around the left superior frontal sulcus became more marked and had a spongy appearance (Fig. 1). At the level of the dorso-medial nucleus of the thalamus the softening was almost liquefied, its edges were poorly defined, and it occupied a cross-sectional area of 2·5 × 1·5 cm. There was also in the lateral nucleus of the left thalamus a translucent area 0·3 cm. in diameter. At the splenium of the corpus callosum the white matter in the parasagittal region also showed a commencing spongy softening; at this level the upper bank of the Sylvian fissure on both sides showed small, pinhead-sized, grey, translucent, well-demarcated areas. The softened areas became still more distinct in the occipital region, occupying the whole of the dorsal half of the left occipital lobe and about half this area on the right side where the most dorsal part of the lobe was spared.

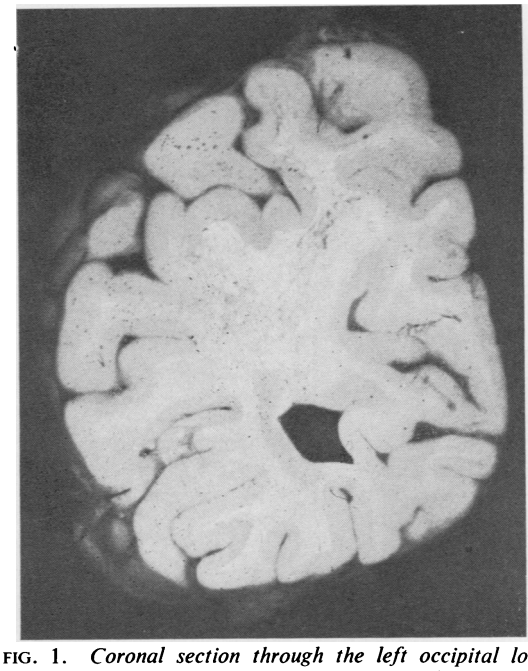


FIG. 1. *Coronal section through the left occipital lobe showing multifocal spongy degeneration of the white matter.*

HISTOLOGICAL EXAMINATION OF THE BRAIN AND SPINAL CORD

Blocks were taken for embedding in low viscosity nitrocellulose from the right and left frontal lobes, on either side of the fissure of Rolando on both sides, and from the right and left temporal and occipital lobes. The sections through the temporal lobes included the basal ganglia at the level of the thalamus and lentiform nuclei. Blocks were also taken from the right and left lateral lobes of the cerebellum, from the pons and medulla, and from the cervical, thoracic, and lumbar spinal cord. Sections from each block were stained with cresyl violet, Van Gieson, phosphotungstic acid- haematoxylin, and Woelcke for myelin.

Myelin sections confirmed the naked-eye impression of severe degeneration in the parasagittal white matter extending from the posterior frontal region back to the occipital lobes where the degeneration was most extensive (Fig. 2). The degeneration on the right side reached its greatest intensity in the region of the fissure of Rolando where over an area reaching 1·5 cm. in breadth the myelin had completely disappeared, though sections stained with Van

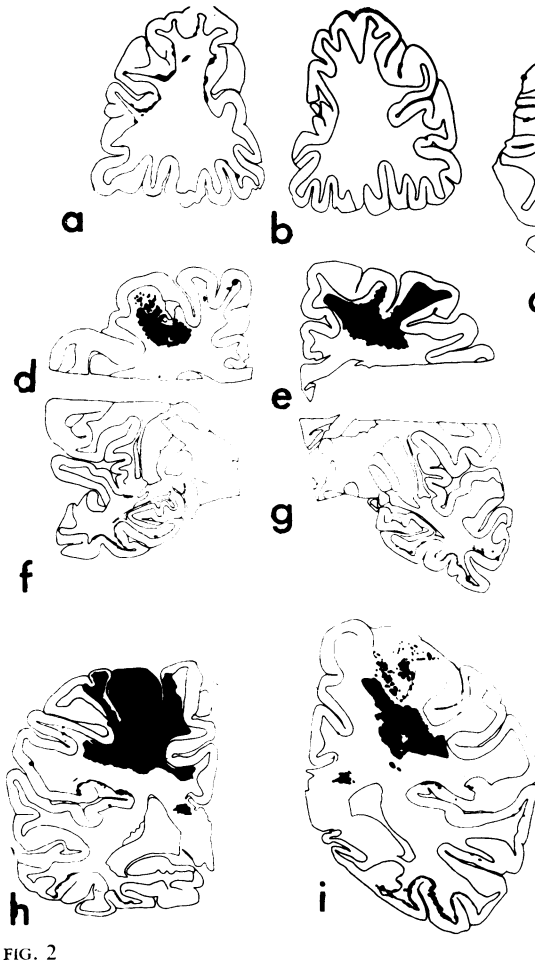


FIG. 2

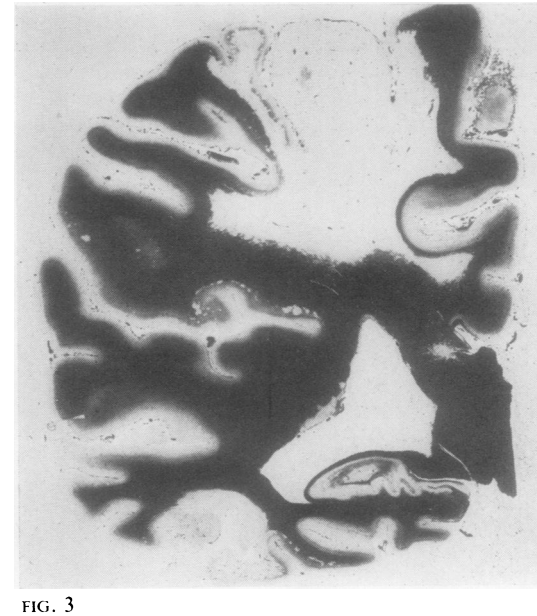


FIG. 3

FIG. 2. *Drawing showing the distribution of degeneration. Note parasagittal situation of largest foci and small foci at junction of cortex and white matter in left frontal and ventral aspects of temporal and occipital lobes:* (a) *Left frontal,* (b) *right frontal,* (c) *left posterior frontal,* (d) *left Rolandic,* (e) *right Rolandic,* (f) *left temporal,* (g) *right temporal,* (h) *left occipital,* (i) *right occiptal.*

FIG. 3. *Left cerebral hemisphere showing massive and small foci of degeneration involving cortex as well as white matter. Note small focus in corpus callosum. An identically placed focus was present on the other side. Woelcke stain for myelin.*

Gieson showed that there was no actual cavitation. Isolated foci of myelin degeneration were present in the corpus callosum where there was a focus 0·3 cm. in breadth of spongy degeneration and in the fusiform and inferior temporal convolutions on the right side where a series of confluent circular or oval foci of complete pallor of myelin staining occupied the junction of the cortex and white matter (Fig. 2). On the left side the parasagittal myelin degeneration was even more extensive, occupying at the level of the posterior border of the hippocampus a cross-sectional area of 1·5 cm. × 2·8 cm. (Fig. 3). The pallor did not respect the cortex but extended across it so that no myelin staining could be seen with the naked eye in the cortex of one complete and part of a second convolution. On this side the parasagittal area of degeneration also extended further forward and was still very marked at the level of the head of the caudate nucleus. Where the cortex was spared sometimes the subsulcine fibres were preserved. The strings of small confluent, circular or oval foci of myelin pallor could again be seen in the fusiform gyrus but the inferior temporal gyrus was almost completely demyelinated. The corpus callosum appeared to be remarkably symmetrically affected, because at the level of the posterior end of the

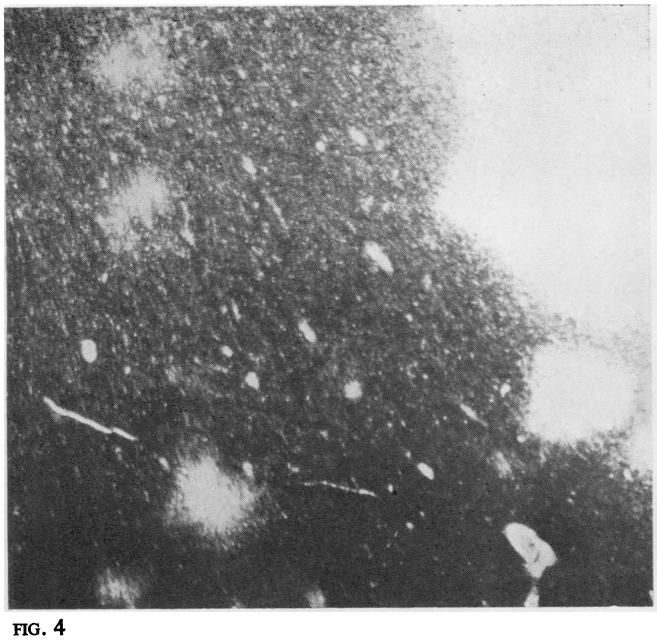


FIG. 4

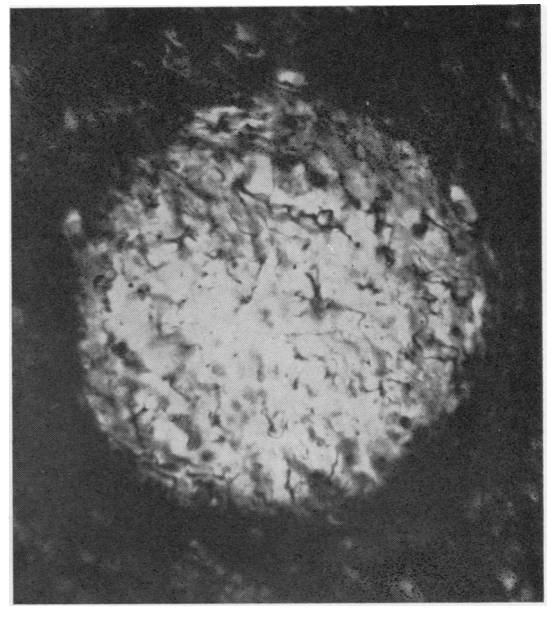


FIG. 5

FIG. 4. *Small foci of demyelination adjacent to a large parasagittal focus. Woelcke* × *20.*

FIG. 5. *More sharply defined round focus of demyelination in the corpus-callosum, showing surviving attenuated myelin sheaths. Woelcke* × *350.*

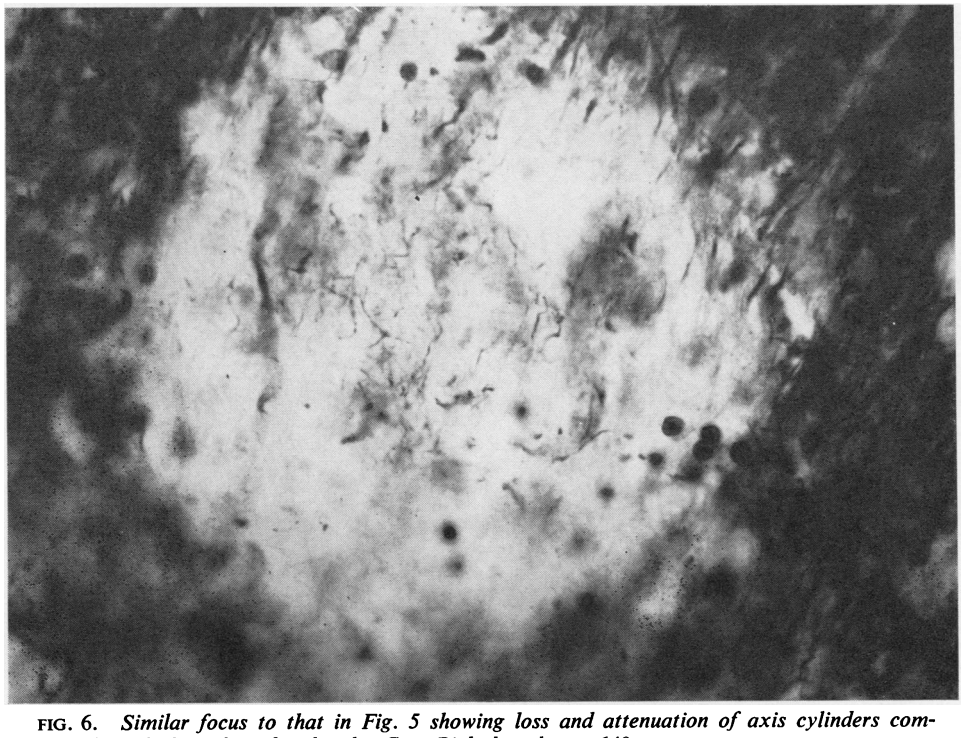


FIG. 6. *Similar focus to that in Fig. 5 showing loss and attenuation of axis cylinders comparable with that of myelin sheaths. Gros-Bielschowsky* × *640.*

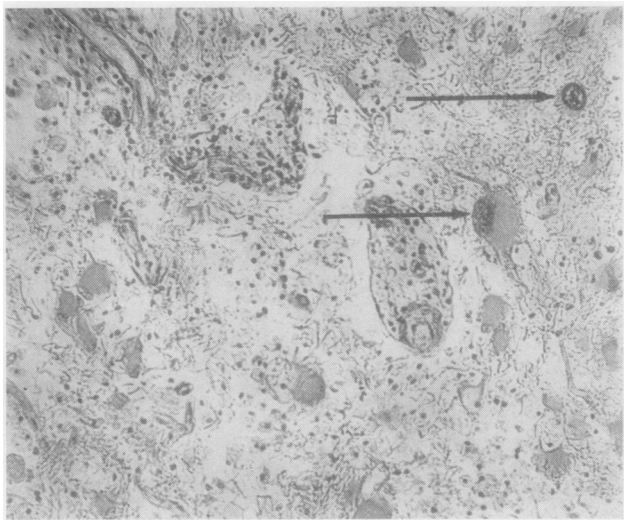


FIG. 7a

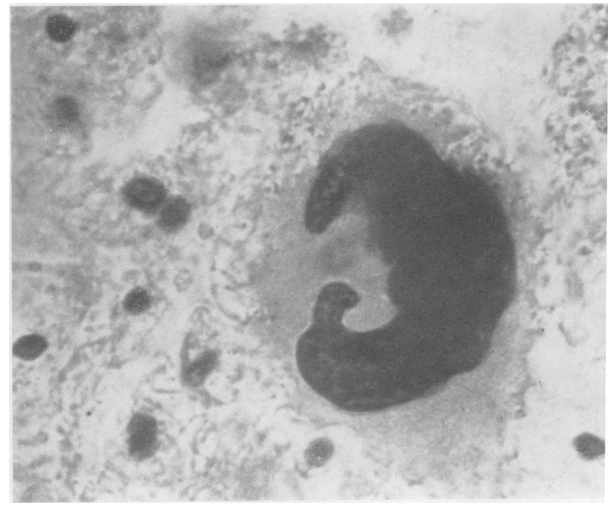


FIG. 7b

FIG. 7a. *Left occipital lobe white matter from parasagittal softening showing giant cells with nuclei (arrows) up to 10 times as large as those of the other glial cells. Haematoxylin-Van Gieson* × *160.*

FIG. 7b. *A giant cell with single large hyperchromatic nucleus. Compare size of hyperchromatic nucleus with that of the surrounding microglia. Haematoxylin-Van Gieson* × *925.*

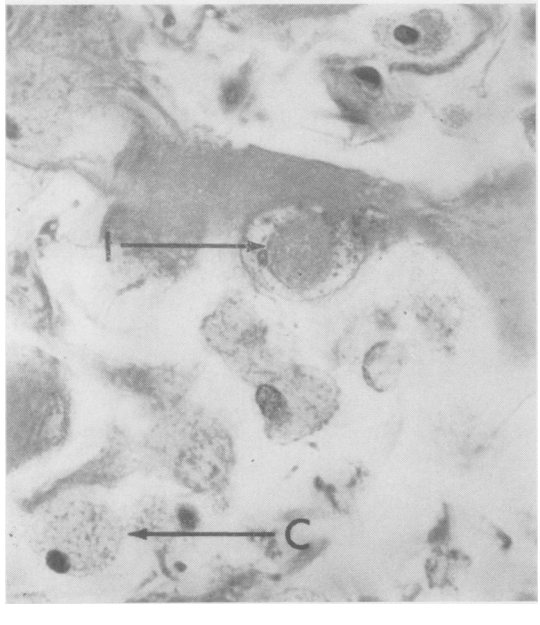


FIG. 7c. *As Fig. 7a showing intranuclear inclusion (I) staining amber and compound granular corpuscle (C). Haematoxylin-Van Gieson* × *740.*

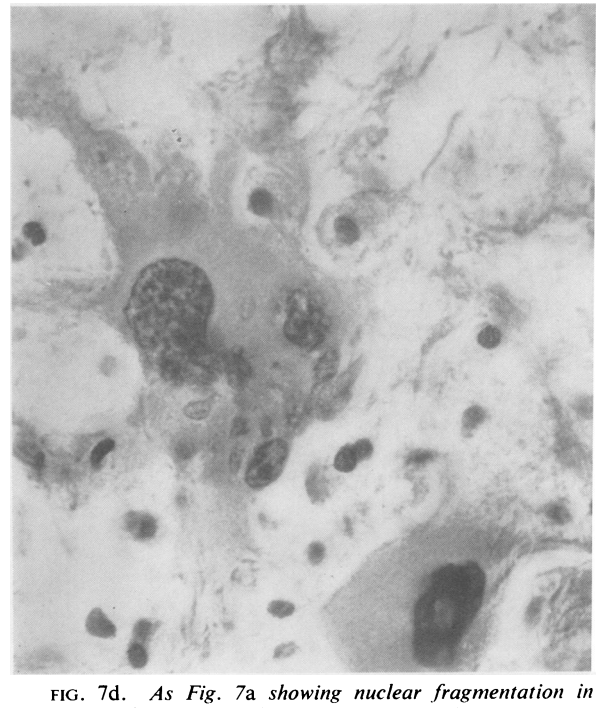


FIG. 7d. *As Fig. 7a showing nuclear fragmentation in giant cell. Haematoxylin-Van Gieson* × *740.*

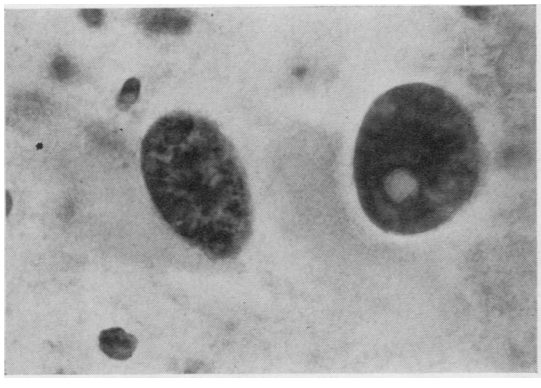


FIG. 8a

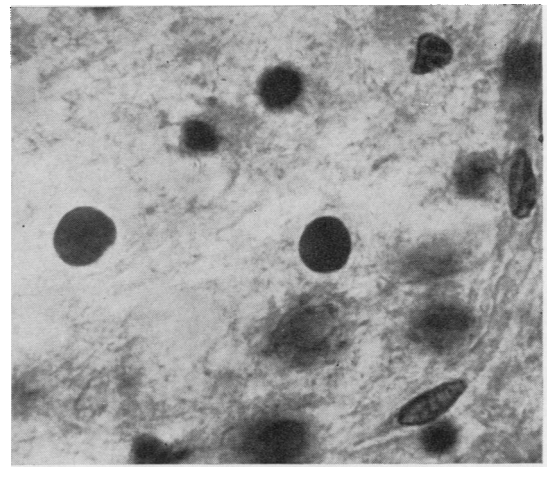


FIG. 8b

FIG. 8a. *Giant cell showing degenerative changes in the nuclei which are about to be extruded. Haematoxylin-Van Gieson* × *540.*

FIG. 8b. *Two extruded homogenous giant cell nuclei easily mistaken for oligodendroglial nuclei. Haematoxylin-Van Gieson* × *540.*

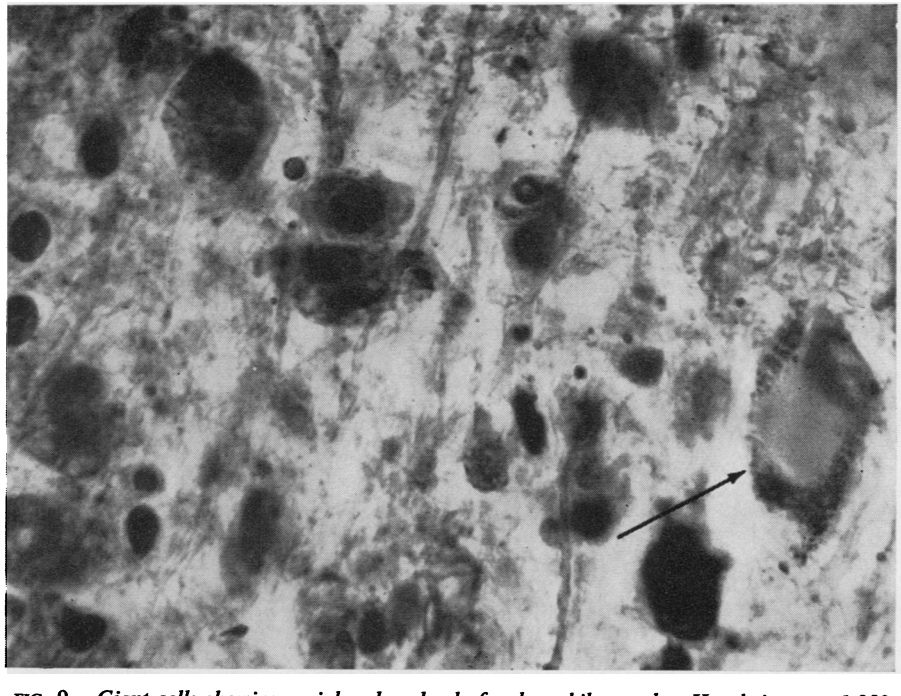
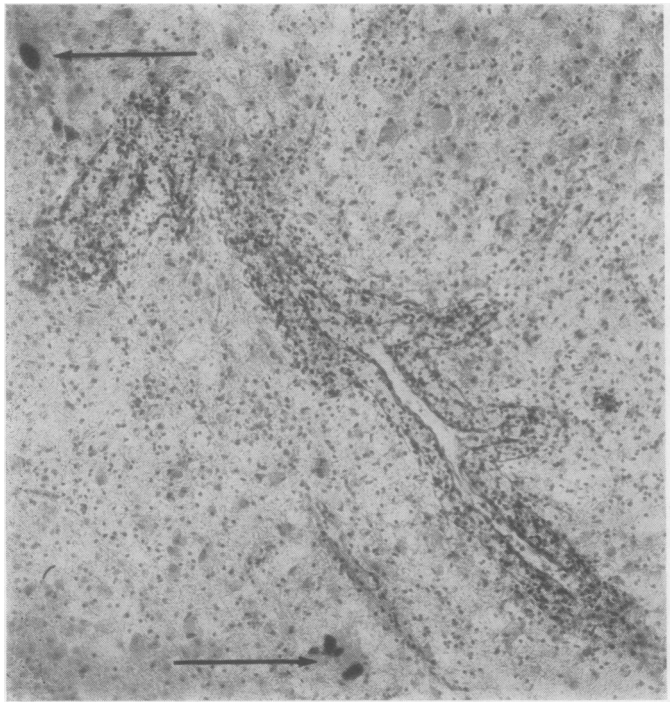


FIG. 9. *Giant cells showing peripheral garland of sudanophil granules. Herxheimer* × *1,250.*



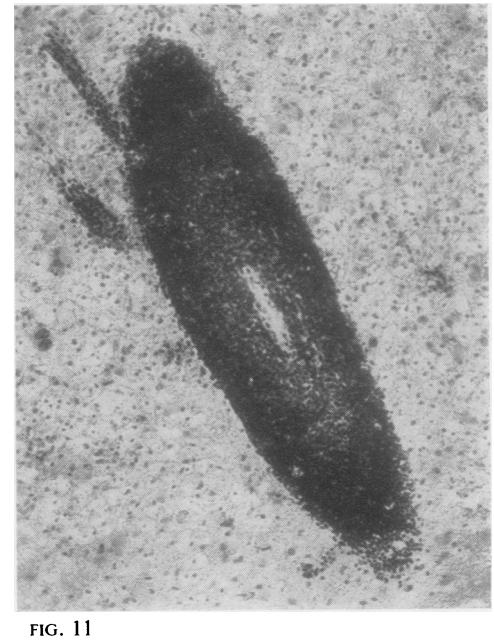


FIG. 11

FIG. 10

FIG. 10. *Parasagittal softening showing perivascular accumulation of compound granular corpuscles and giant cells (arrowed). Haematoxylin-Van Gieson* × *290.*

FIG. 11. *As Fig. 10 but showing severe perivascular lymphocytic cuffing. Haematoxylin-Van Gieson* × *130.*

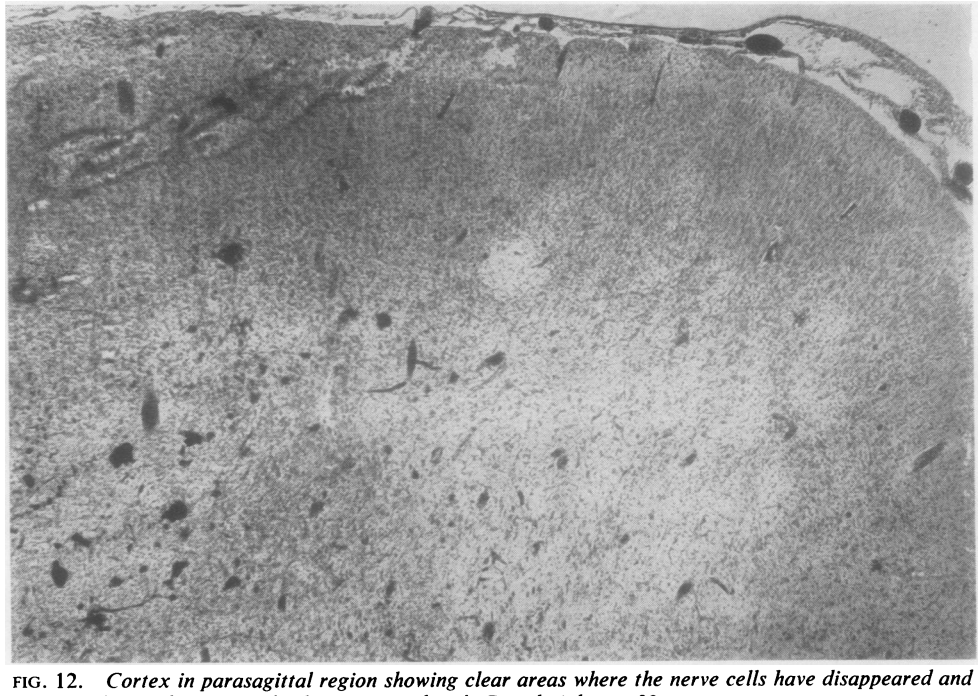


FIG. 12. *Cortex in parasagittal region showing clear areas where the nerve cells have disappeared and compound granular corpuscles have accumulated. Cresyl violet* × *29.*

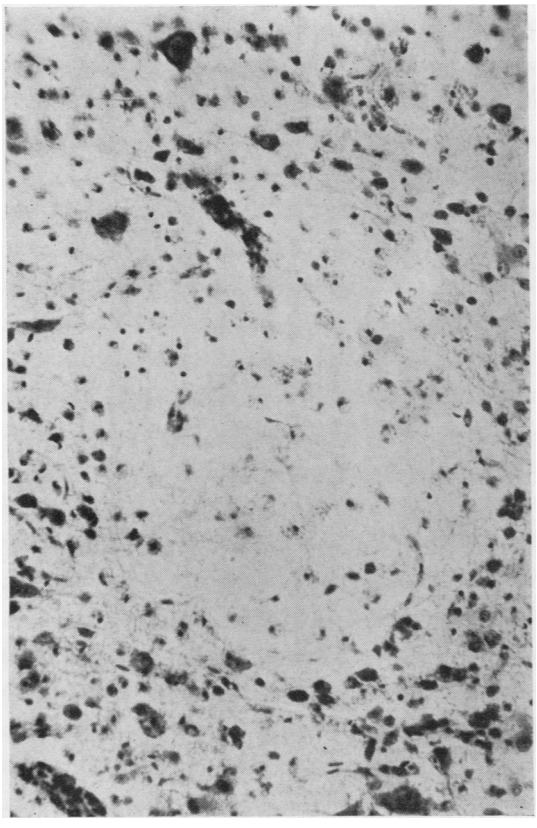


FIG. 13. *Circumscribed area in cortex just visible in Fig. 12 showing replacement of all pre-existing elements by compound granular corpuscles containing granules insoluble in lipid solvents. Cresyl violet × 176.*

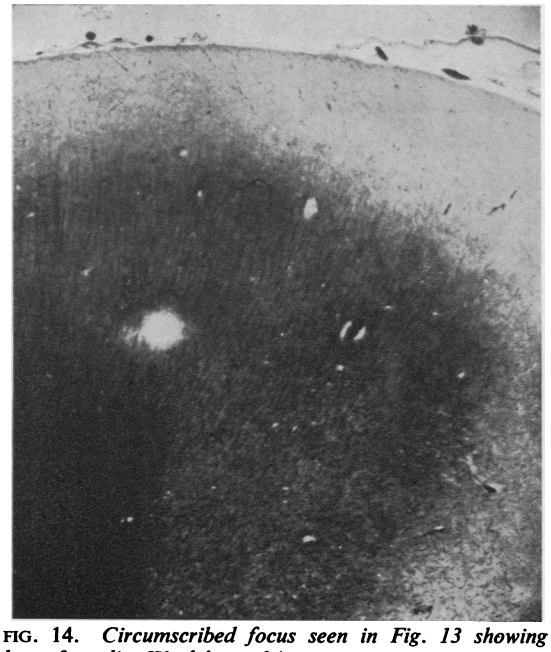


FIG. 14. *Circumscribed focus seen in Fig. 13 showing loss of myelin. Woelcke × 24.*

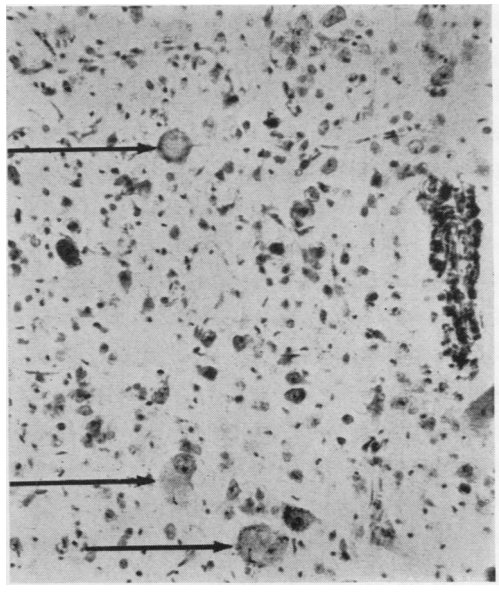


FIG. 15. *Parasagittal cerebral cortex showing nerve cells with retrograde degeneration. Cresyl violet × 176.*

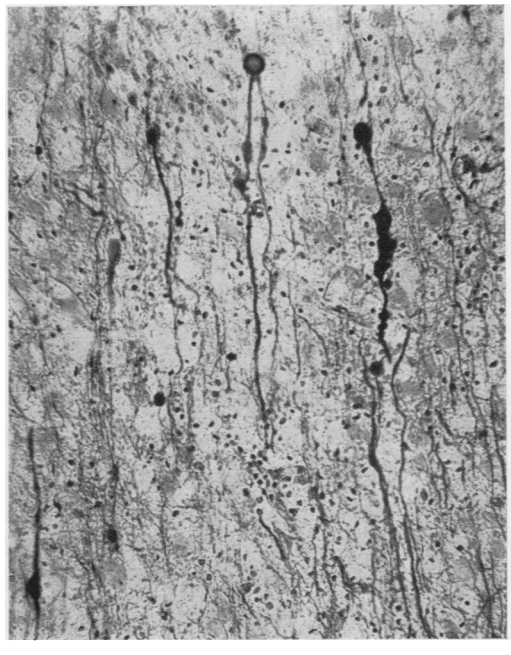


FIG. 16. *White matter from parasagittal softened area showing degenerated axons with irregular and spherical swellings persisting where myelin sheaths have disappeared. Gros-Bielschowsky × 166.*

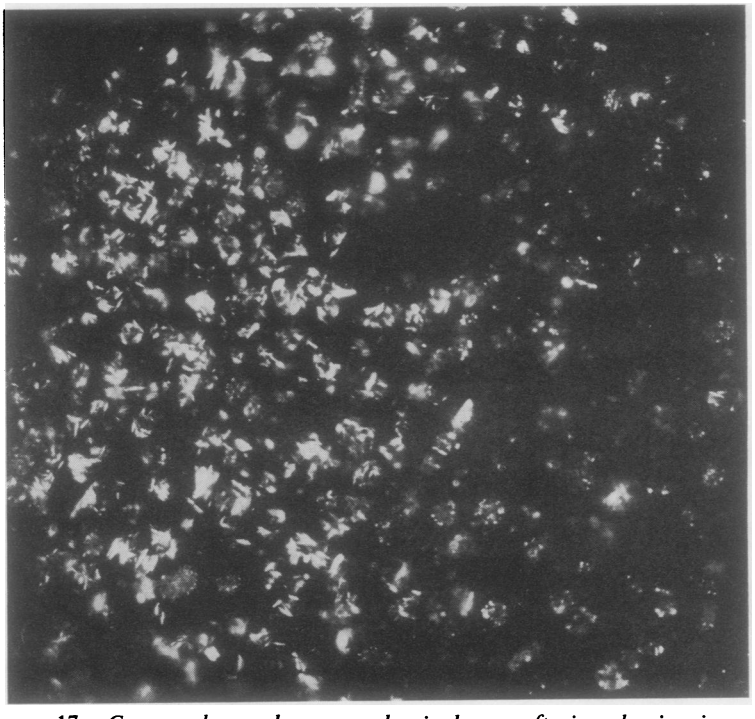


FIG. 17. *Compound granular corpuscles in large softening showing in a preparation photographed with crossed Nicol prisms that most anisotropic material is not sudanophil, thus indicating acuteness of lesion. Herxheimer* × *152.*

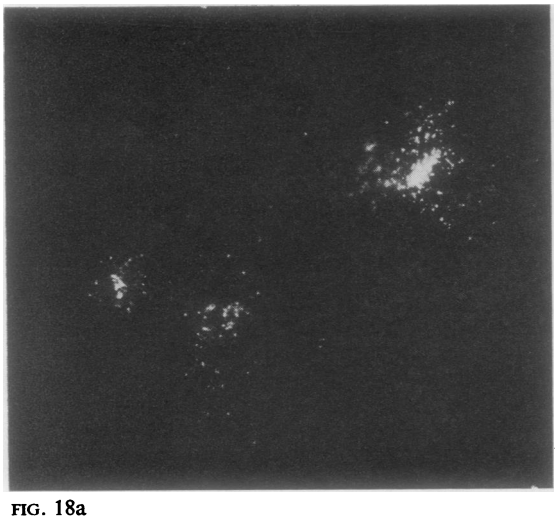


FIG. 18a

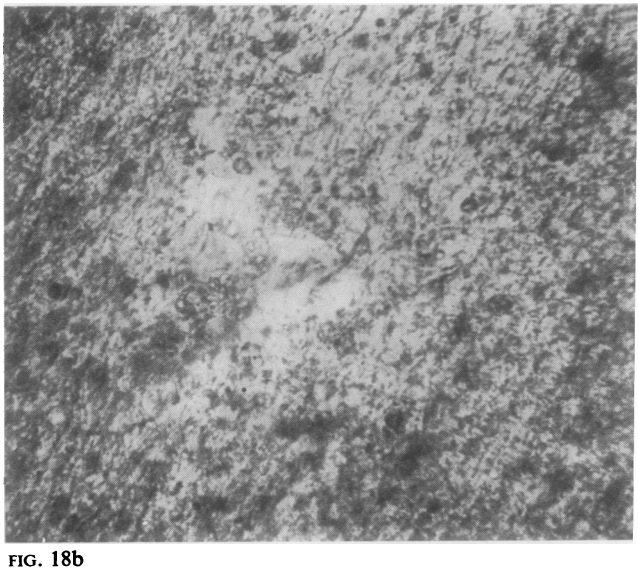


FIG. 18b

FIG. 18a. *Early focus of demyelination photographed with crossed Nicol prisms. The anisotropic material enables the focus to be recognized easily. Herxheimer* × *150.*

FIG. 18b. *Same focus as in Fig. 18a showing complete absence of cellular proliferation. Herxheimer* × *150.*

hippocampus and just ventral to the cingulate gyri foci of pallor of myelin staining, 0·5 × 0·3 cm., could be seen on both sides 0·5 cm. from the midline (Figs. 2 and 3). Under the microscope in the most intensely pale areas only occasional small leashes of fibres remained and these appeared to be processes of the giant cells (see below). Towards the borders of the degenerated areas the myelin sheaths showed fusiform and more irregular swellings. In the white matter bordering on the degenerated areas there was a diffuse pallor of staining with focal accentuations. Some of these focal accentuations were rather poorly defined (Fig. 4) but others, which measured only 120μ in cross-sectional diameter, were remarkably circular and contained only fragments of very delicate fibres which were probably myelinated or axonal and not glial fibres, as they failed to stain with phosphotungstic acid-haematoxylin but stained with Woelcke (Fig. 5) and Bielschowsky (Fig. 6) stains. In fact glial fibre increase was virtually absent even in the most severely degenerated areas.

The most interesting findings in the areas of total degeneration were obtained from sections stained with Van Gieson. Here there were large numbers of giant cells reaching a cross-sectional diameter of 90μ, *i.e.*, comparable with a large nerve cell (Fig. 7a). The swollen cell bodies stained amber with Van Gieson and the prominence of their processes indicated that they were also enlarged. The processes did not stain with phosphotungstic acid-haematoxylin or Bielschowsky but were to a considerable extent impregnated with Robb-Smith's stain for reticulin. The nuclei of the giant cells were also enlarged; some of them were poor but others rich in chromatin (Fig. 7b). They were usually rounded in outline although somewhat elongated or even dumb-bell shaped. Only a very occasional giant cell contained an intranuclear inclusion body staining amber with Van Gieson (Fig. 7c). Cells with more than two nuclei were uncommon, though an occasional cell with four or more nuclei or nuclear fragments could be seen (Fig. 7d). Definite mitoses were not seen. Some of the giant cells showed degeneration of their nuclei which became progressively more opaque and appeared finally to be extruded from their cells as circular homogeneous structures staining amber with Van Gieson (Figs. 8 and 8b). In a scharlach R preparation fine sudanophil granules formed a garland at the periphery of the bodies of these giant cells. It is possible that the granules were in fact in microglial cells which had surrounded the giant cells and were closely applied to the cytoplasm (Fig. 9), as one of us has suggested in explanation of the apparently peripheral location of lipid granules in hypertrophic astrocytes in other conditions (Woolf, 1952). In the interstices between the giant cell processes occasional compound granular corpuscles could be seen but most of the cells were surviving oligodendroglia. Larger accumulations of compound granular corpuscles could be seen around some of the vessels (Fig. 10). Some of the vessels in the degenerated areas showed massive cuffing with lymphocytes (Fig. 11) but the vessels outside the degenerated areas appeared normal.

Nissl sections showed the cortex to be little affected but there were small areas, especially in relation to the large parasagittal degenerated areas, where nerve cells had disappeared or showed retrograde degeneration (Figs. 12-15). No other degeneration was seen. In these circumscribed areas there were compound granular corpuscles (Fig. 13). Axis cylinder stains showed that axons were present even in the most severely degenerated areas, but they were very scanty in those areas consisisting only of very slender fibres. In the less severely affected areas the number of axons was less markedly reduced but many of these present showed irregular swelling or bore globular swellings (Fig. 16). Thus the axons were less affected than the myelin sheaths but were not as well preserved as in, for example, disseminated sclerosis.

In a scharlach R preparation about equal numbers of compound granular corpuscles contained scarlet and unstained material respectively (Fig. 17). In cresyl violet preparations the contents of the compound granular corpuscles seemed either to have been dissolved during processing or, in areas apparently at the extending edges of the lesions, *e.g.*, in the deeper layers of the cortex, were visible as bluish granules. The latter material failed to stain even with the sodium hydroxide Herxheimer method. Both materials were strongly anisotropic and an attempt was made to spot the earliest foci of degeneration by scanning the sections under crossed prisms. This showed small pin-head-sized foci containing crystals of doubly refractile material but no compound granular corpuscles or microglial activity (Figs. 18a and b). In these areas the myelin sheaths failed to stain with scharlach R. Microglial impregnation by Penfield's method showed pleomorphism of the microglia in what in these preparations appeared to be similar small areas of demyelination. Such changes were not seen except where the myelin appeared to be degenerated. It was impossible to decide whether the microglial pleomorphism preceded the degeneration of myelin, but this seemed unlikely.

In the lateral lobe of the cerebellum there were degenerative changes confined to the white matter surrounding and in the hila of the dentate nuclei. They consisted of perivascular infiltration with compound granular corpuscles and more diffuse

microglial infiltration. There did not seem to be any marked change in the astrocytes. The spinal cord was examined at C6, C8, and T5 and showed no histological abnormality.

DISCUSSION

The evolution of this illness remains a puzzle. Richardson (1961) has indicated the usual clinical pattern of the syndrome—disorders of movement, sensation, speech, vision, and intellect, central in origin, usually supervening upon a previously-recognized disease entity, often neoplastic—and has emphasized the essentially negative nature of all investigations save the electroencephalogram. This was abnormal, with non-specific slow-wave disturbances replacing or superimposed upon normal activity, in all nine cases so examined and reported (Richardson, 1961; Headington and Umiker, 1962; Loken, Refsum, and Jacobsen, 1962). The cerebrospinal fluid was generally normal, or very nearly so, in most cases. A few showed slight elevation of pressure, or a moderate increase in lymphocyte count, or a slight rise in protein content. In one case there was an abnormally high protein concentration; this occured in a patient with pre-existing carcinomatous neuropathy (Fisher *et al.*, 1961).

Our case once again shows the value of the electroencephalogram as being the only investigation likely to point to the correct neurological diagnosis. If abnormal it assumes particular significance when the accompanying tests are negative, and, since the disease is largely confined to the white matter, which shows little shrinkage, it seems likely that cerebral angiography and pneumoencephalography will usually show no abnormalities in affected subjects. From the information available it appears that only one patient (Headington and Umiker, 1962) out of a total of seven (including the case now reported) has shown ventricular dilatation when examined by these techniques (Bateman, Squires, and Thannhauser, 1945; Christensen and Fog, 1955; Loken *et al.*, 1962; Richardson, 1961; Sibley and Weisberger, 1961).

Because the significance of this investigation pattern was not realized at the time, attention was diverted to the cervical spine when the left carotid angiogram was found to be normal in our patient. At this relatively early stage of the illness the only signs suggestive of disease of the parietal lobe were muscle wasting and increased deep reflexes (Critchley, 1953); the characteristic perceptive changes (astereognosis, right-left disorientation, and loss of two-point discrimination) had not yet appeared. Fasciculation, said not to occur in parietal lobe lesions (Critchley, 1953), was also occasionally noted at this time Under these circumstances, the finding of cervical spondylosis with narrowing of several intervertebral foramina on the right side was perhaps particularly unfortunate, since it diverted attention from the real cause of the trouble and, treatment being limited to a well-fitting collar, served only to aggravate the patient's discomfort. Discussing the neurological manifestations of cervical spondylosis, Brain, Northfield, and Wilkinson (1952) warn against this particular pitfall, stating that when any doubt arises in circumstances such as these, 'cervical spondylosis should not be accepted as responsible for symptoms attributable to lesions of the spinal cord unless myelography demonstrates a protrusion of one or more intervertebral discs sufficient to cause a substantial reduction in the subarachnoid space of the spinal cord in the cervical region'. The myelogram in our case very nearly fulfilled these criteria, and on anatomical grounds (Frykholm, 1951) cord ischaemia secondary to vascular compression was accepted as a possible source of the trouble.

ASSOCIATION OF RETICULO-ENDOTHELIAL DISEASE WITH PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

Richardson's review (1961) shows that a striking characteristic of progressive multifocal leucoencephalopathy is its frequent association with previously recognized chronic diseases of the reticuloendothelial system. Reticuloses and leukaemia were a common accompaniment of the neurological disorder, but there were also cases of systemic diseases (sarcoidosis and miliary tuberculosis) in which reticulo-endothelial involvement is invariable and cases of carcinomatosis in which involvement of groups of lymph nodes was stated to have occurred. More recently, Morningstar (1962) has found it in a patient with pulmonary anthracosilicosis complicated by involvement of thoracic and abdominal lymph nodes and by reactive hyperplasia of the spleen, and Hecker and Reid (1962) have described it in Whipple's disease. Our case of primary hypersplenism[1] and progressive multifocal leucoencephalopathy once again emphasizes this relationship, though in this instance the reticuloendothelial disorder was recognized after the onset of neurological symptoms. It is probable, however, that the reticuloendothelial disorder was the first to develop, since there was no change in the size of the spleen or in the haematological picture during the course of the neurological illness.

[1]The term 'primary hypersplenism' describes the syndrome characterized by simple splenic hyperplasia, active bone marrow, and peripheral leucopenia occurring in the absence of histologically specific disorders of the reticuloendothelial system, cirrhosis of the liver, and metabolic defects of the blood and blood-forming organs.

TABLE

DISORDERS ASSOCIATED WITH 31 CASES OF PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

Source of Data	*Malignant Disorders of Reticulo-endothelial System*	*Benign Disorders of Reticulo-endothelial System*		*Unknown*
Richardson (1961)	17	Sarcoidosis	2	1
		Miliary tuberculosis	1	
		Coronary artery disease	1	
		Congestive cardiac failure		
		Healed apical pulmonary tuberculosis		
		Splenomegaly (marked iron deposition)		
Mancall (see subscript to Richardson, 1961)	1			
Dolman (1962)	2 (one with coexistent oligodendroglioma)			
Headington and Umiker (1962)		Sarcoidosis and miliary tuberculosis	1	
Hecker and Reid (1962)		Whipple's disease	1	
Loken, Refsum, and Jacobsen (1962)		Sarcoidosis	1	
Morningstar (1962)		Anthraco-silicosis	1	
Noble (1962)	1			
Present report		Primary hypersplenism	1	
Totals	21		9	1

Information concerning 31 cases of progressive multifocal leucoencephalopathy is now available (Table). Of these only three (Richardson, 1961) are not stated definitely to have had reticuloendothelial disease. In the first (Hallervorden, case 2, 1930; Richardson, 1961) no further pathological data are available. The second is Richardson's case 7, a man who had coronary artery disease, congestive cardiac failure, and healed apical tuberculosis. In addition to these changes he was found to have an enlarged spleen (400 g.) which on microscopical examination showed sinus congestion and deposition of iron pigment in widely scattered phagocytes and in the capsule and trabeculae (Richardson, 1962). The third case is briefly mentioned by Richardson (1961) in a subscript; here Dolman found progressive multifocal leucoencephalopathy and a previously-undiagnosed cerebral oligodendroglioma. This man, who had suffered from chronic lymphatic leukaemia for several years, underwent splenectomy two and a half years before death. Neurological symptoms referable to leucoencephalopathy occurred terminally and coincided with an aggravation of his leukaemic state (Dolman, 1962).

Thus, progressive multifocal leucoencephalopathy has been associated with disease of the reticulo-endothelial system in every case submitted to full pathological examination.

HISTOPATHOLOGICAL CHANGES The changes in the brain in progressive multifocal leucoencephalopathy are unique. Largely confined, as they are, to the white matter, some resemblance to diffuse sclerosis (sudanophil) is inevitable. In multifocal leuco-encephalopathy, of which our case is a particularly severe example, the large lesions are less sharply demarcated than in diffuse sclerosis and some of them are situated in the cortex, though this was not striking in our case. The process is more rapid than in diffuse sclerosis, as is shown in our case (but not those of Åström *et al.*, 1958) by the high proportion of phagocytes containing non-sudanophil material. The remarkable multinucleate giant cells are larger and their nuclei are more bizarre than the hyperplastic astrocytes seen in any previously described form of diffuse sclerosis. The preservation of axis cylinders was less striking than in diffuse sclerosis.

The curious chain of well-circumscribed small foci along the junction between cortex and white matter (escpecially of the temporal lobe) is also not seen in diffuse sclerosis. Similar small, well-demarcated foci were seen in the cases of Åström and his collaborators (1958) and encouraged them to include 'multifocal' in the name they gave to the disorder. The rounded foci in the corpus callosum are also not seen in diffuse sclerosis.

The tendency for the nuclei of the giant cells to become chromatin-poor and finally escape from the degenerating cells resulted in quite large numbers of uniformly amber-coloured spherical bodies lying free in the white matter where they closely resembled the structures identified as oligodendrocyte nuclei by Åström *et al.* (Fig. 5B, 1958) and by Richardson (Fig. 4, 1961). We did not see any inclusion bodies in phloxine-tartrazine stained L.V.N. sections, but we did see an intranuclear area, possibly a genuine inclusion body. in occasional giant cells in Van Gieson preparations.

Åström *et al.* (1958) considered the smallest discernible lesions to be tiny perivascular collections of pleomorphic microglia without definable alteration of myelin. We would put it the other way round as we saw small foci where myelin staining with scharlach R was diminished and crystalline anisotropic material lay free in the tissues without any cellular response. We failed to find any

significant lesion in the spinal cord despite the clinical presentation with weakness confined to the right upper limb. Nevertheless, as Headington and Umiker (1962) have shown, cord lesions may occur.

On the basis of the nuclear changes observed in oligodendrocytes and astrocytes, Richardson (1961) has suggested that progressive multifocal leucoencephalopathy may well result from a virus infection which follows on a state of immunological hyporeactivity. It has been implied that this state results from 'exhaustion' of the reticuloendothelial system (*Lancet*, 1962). Whilst recognizing the validity of these arguments, we feel certain reservations about accepting the interpretation which Richardson (1961) has placed upon the cytological changes in the disorder. He finds that the only constant abnormality is in the oligodendrocyte nuclei, but eosinophilic nuclear inclusions in these cells (which we failed to observe in the present case) and nuclear changes in the giant cells (which were prominent) are not always seen. As an alternative it seems possible that excess activity of the reticuloendothelial system may be concerned in the aetiology of progressive multifocal leucoencephalopathy; far from being exhausted, it may well be in a highly reactive state, and perhaps therapy should be directed at its suppression. This may well be possible in benign conditions, such as simple splenic hyperplasia, where complete extirpation of abnormal tissue is feasible. The nature of the relationship between the reticuloendothelial disorder and the demyelinating process is, however, at present quite obscure, if it is at all real.

In this connexion one remark must be made in regard to the giant cells. Their astrocytic nature is not absolutely proven. The fact that their processes impregnate with silver in reticulin preparations but not with phosphotungstic acid-haematoxylin makes a mesodermal origin worth considering, especially in view of the association of the brain changes with disease of the reticuloendothelial system. Some of them do indeed recall the very large cells described by Zülch (1956) in the intracranial monster cell sarcoma. In the latter condition, however, the monster cells may reach 1 mm. in diameter, and as the largest cells we saw were less than 100μ in diameter we have referred to them simply as giant cells. The decision as to mesodermal or ectodermal origin for the giant cell is important and further careful impregnation studies are indicated.

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