SUDANOPHILIC DIFFUSE SCLEROSIS ("SCHILDER'S DISEASE") WITH ICTAL ONSET

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The finding of extensive disease of the white matter in a man who until six weeks before his death was a successful car-rally driver seems worthy of record.

Case Report

A professional racing driver and garage proprietor aged 45 was admitted in deep coma to St. Mary's Hospital, London, on July 19, 1956. The previous evening he had come to London to attend a dinner. He had appeared quite normal, though he had complained that same morning of a headache on waking. At the dinner he had been temperate and apparently well, but at midnight he had telephoned his wife to say that he would not return home until the next day. In the afternoon of that following day he was found lying comatose in his hotel bed.

During the previous year, though he had carried on normally with his business and had driven successfully in several events, he had had four fits, one of grand-mal type: the others consisted of transient loss of consciousness followed by headaches, but further information concerning them and their spacing is not forthcoming. His wife denied that there had been any change in his personality or deterioration in his abilities. In the course of his racing career he had had numerous minor injuries but none severe.

On admission he was noted to be a tall thin man without any obvious injury. He was unrousable, with slow gasping respirations (6 per minute), blood-pressure of 90/70 mm. Hg, flaccid limbs, and complete areflexia. As a possible case of barbiturate poisoning he was treated with bemegride, oxygen, and a noradrenaline drip. Lumbar puncture produced cerebrospinal fluid under pressure, containing 15 lymphocytes per c.mm. and 60 mg. of protein per 100 ml. Barbiturates were not identified in the urine.

The next day he responded to painful stimuli, and became violent when carotid angiography was attempted. The blood-pressure was now 130/85, but respirations were still only 12 a minute. Over the next week his state of consciousness was variable but tended to improve, so that he was able to speak and understand, though he still showed marked lack of attention. For a short period there was a divergent squint, but no obvious visual loss and no other abnormality of the cranial nerves; flaccid weakness of the right arm and leg was present, and spasticity of the left limbs with increased tendon reflexes; plantar responses were flexor. During the third week he deteriorated again, becoming incontinent and uncooperative. The right arm and leg remained weak but were now spastic, and there was an extensor plantar response on this side. He seemed unaware of the right side. It was thought that he had a diffuse lesion, probably inflammatory, involving both hemispheres; other suggestions were of tumour at the hind end of the third ventricle or of basilar artery occlusion.

He was transferred to Maida Vale Hospital, but all attempts to define a localized tumour or vascular lesion proved negative. An E.E.G. was recorded on August 13 when the patient was unresponsive. This showed in all regions irregular delta potentials varying in frequency between $\frac{1}{2}$ c./sec. and 3 c./sec. and with an amplitude of 100–200 μ V. No persistent focus was demonstrated. Super-

imposed on the slow rhythms were some low-voltage faster potentials, mainly at 12–18 c./sec. The E.E.G. was considered to be indicative of severe cerebral disease of undetermined nature but unlikely to be a subacute encephalitis (Dr. H. R. A. Townsend). At this time he had no papilloedema. By August 23, however, he had become inaccessible, with spastic tetraplegia, and had developed bilateral papilloedema with haemorrhages. He died a week later.

Post-mortem Findings

A post-mortem examination (Dr. Frances D. Bosanquet) made seven hours after death revealed the body of a man looking somewhat younger than his stated years. The brain weighed 1,430 g. and showed no evidence of the intracranial pressure having been raised. The vertebral, basilar, and internal carotid arteries and the circle of Willis were devoid of atheroma. Except for the internal carotid artery, these basal vessels were, however, all noted to be rather small, the left posterior cerebral artery, which in this brain arose from the basilar artery, being in fact threadlike. Over the right parietal lobe there was a suggestion of fresh sub-arachnoid haemorrhage, but elsewhere there was no evidence of bleeding, either old or recent. The skull bones showed no evidence of healed fractures. A general examination disclosed confluent bronchopneumonia of both lower lobes, a flabby myocardium discoloured brown, and a small diverticulum of the duodenum but with no evidence of scarring. There was a minimum of atheroma in the aorta and great vessels and in the coronary arteries. A routine histological examination of organs confirmed the presence of bronchopneumonia and revealed early centrilobular necrosis of the liver. In the pars intermedia of the pituitary there was a small cyst.

The brain, after fixation, showed a congestion of the surface vessels over the convexities, with slight thickening of the leptomeninges. Deep to the right Sylvian fissure the substance of the brain felt rather soft, but the convolitional pattern was everywhere normal and there was no atrophy. When the brain was cut coronally, irregular-shaped and sharply cut-out cavities were noted in the white matter of both frontal and occipital lobes (Fig. 1); they tended to

FIG. 1.—Section through frontal lobes of fixed brain to show cavities in white matter.

be symmetrically disposed and there was a suggestion in their pattern that some had been formed as a result of a confluence of small ones. The white matter of the centrum semiovale was generally softer than normal, and in places it appeared to be a little opaque. Plaques of the type seen in multiple sclerosis were not noticeable in the unstained slices.

The brain was studied in frozen, paraffin, and celloidin preparations, the following stains being employed: haematoxylin and eosin, haematoxylin and van Gieson, Mallory's

phosphotungstic acid haematoxylin, Heidenhain, Nissl, Luxol blue, Scharlach R, Holzer, Nile blue, Cajal, Penfield-Cone, Bielschowsky, Davenport, and Glees.

The myelin sections showed extensive pallor of the white matter, notably in the frontal (Fig. 2), occipital, and temporal lobes, and in the central white matter.

FIG. 2.—Left frontal pole stained for myelin to show widespread general loss but with preservation of the subcortical arcuate fibres. In the areas of softening there is no myelin at all. Heidenhain's stain for myelin. Celoidin at 30 μ .

This pallor tended to be symmetrical, and, while it sometimes impinged on to the central grey matter, the subcortical arcuate fibres were spared and stood out prominently, in great contrast to the sub-jacent pallor. In general the white matter of the occipital lobes and of the anterior part of the frontal lobes showed a greater loss of myelin than did the parietal lobes and the posterior parts of the frontal lobes, but in these latter areas the loss was greater towards the centre than

peripherally. The cavities already noted stood out prominently in the myelin preparations as areas of complete demyelination.

In the internal capsules an occasional area of complete demyelination could be seen, but for the most part they were intact and there were no patches of partial demyelination. There was slight demyelination in the corpus callosum just anterior to the splenium and mostly on the right, but none in the optic tracts or optic nerves. The white matter of the hippocampal gyrus and of the first temporal convolution on each side was well preserved in comparison with that of the second and inferior temporal convolutions and the gyrus fusiformis. In the occipital cortex myelin was well preserved in the "U" fibres surrounding the calcarine sulcus, in the pericalcarine white matter, and in the optic radiations, though here were to be seen a few small lesions of the type found in multiple sclerosis. At no place did the cavities in the occipital white matter transgress the cortico-medullary junction.

Inside the cavities were large numbers of histiocytes containing sudanophilic fat: also astrocytes, mostly rather small, with scanty cytoplasm the edges of which tended to be concave; a few, however, had swollen bodies. Fibres were few in number. Coursing through these cavities could be seen occasional axons, mostly deformed and with bulbous swellings upon them. There were also innumerable slender blood-vessels, all of them seemingly patent. In the areas of partial demyelination phagocytosed sudanophilic fat was present in great quantities, while swollen astrocytes were to be seen, sometimes with abundant well-formed glial processes: in general, however, as in the cavities, the astrocytes were rather small, their nuclei being not prominent and their processes indefinite. There were many more intact axons in this part of the white matter than in the completely softened areas: in fact, it appeared that the axons were little disturbed by this demyelinating process. At the cortico-medullary junction the astrocytes were hypertrophied and provided something of a glial wall. In one or two situations, notably in left F.1, F.2, and F.3 posteriorly, this gliosis was, in Holzer sections, visible to the naked eye.

Within the partially demyelinated areas in the frontal lobe could be seen, in addition to the major areas of softening, irregularly defined patches of more intense myelin loss, sometimes with occasional accentuation of the surviving

myelin at the periphery of these paler areas. While very often a vessel could be seen in or near the centre of these areas of demyelination, sometimes one noted a ring of relative myelin preservation around a blood-vessel (Fig. 3), a feature which was especially evident immediately adjacent to the cortico-medullary junction. Exceptionally there was endarteritis, but, in general, vessels were not thickened; neither was there any necrosis of vessel walls.

Some of the blood-vessels were cuffed with lymphocytes and histiocytes, but very few fat-filled histiocytes seemed to have gravitated to the perivascular spaces. Eosinophils and plasma cells were not noted. The oligodendroglia were reduced in numbers and in the white matter were confined to the areas which showed little or no demyelination: here they presented no unusual features. They were virtually absent from the areas of complete demyelination, but when present were often surrounded by a halo, while occasionally the nuclei had swollen to such an extent as to make it difficult to distinguish them from those of astrocytes. The cortex appeared normal, except in the posterior part of the right calcarine fissure, where there was a laminar necrosis.

In an adjacent part of the calcarine cortex two penetrating arterioles were seen, associated with a slender surround of softened cortex (Fig. 4). Near to the point of entry of one

FIG. 3.—White matter of left frontal lobe to show patchy nature of demyelination with survival of myelin around many of the blood vessels. Heidenhain's stain for myelin. ($\times 35$.)

FIG. 4.—Localized softening around penetrating arterioles in the right calcarine cortex. There is a solitary thickened arteriole in the leptomeninges. See arrow. Haematoxylin and eosin stain. ($\times 42$.)

of them there was a small grossly thickened but not occluded arteriole in the leptomeningeal space, which it was felt had, because it was thickened, been predisposed to relative stagnation and eventual occlusion: in short, the infarction was believed to be a secondary phenomenon due to the fact that the vessel led into an area of disease characterized by fatty degeneration and general swelling of white matter. The only abnormality in the medulla was a small collection of glial cells in the fasciculus cuneatus. The cerebellum, pons, and spinal cord were normal.

Discussion

The histological findings are in keeping with what is now generally called sudanophilic diffuse sclerosis. Its relationship to multiple sclerosis is uncertain, but some authors (Kufs, 1931; Heeranu *et al.*, 1945; Lhermitte, 1950; Lumsden, 1950; Poser, 1957) regard them as variants of the same disease, for many cases of "Schilder's disease" have been recorded which have shown characteristic plaques of multiple sclerosis (such instances have been called "transitional sclerosis" by Poser). When, however, the lesions are confined to the cerebrum and are diffuse in nature, and when the characteristic clinical features of multiple sclerosis and especially its relapsing nature are lacking, then it seems appropriate to speak of the disease as diffuse sclerosis.

The histological findings in the present case, which indicate at least two episodes in the evolution of the process, are believed to be compatible with a total duration of as little as five weeks, and they are comparable with certain cases in the literature to which reference is made below. In view, however, of the history of the fits, a well-recognized early symptom of Schilder's disease, more especially in younger people, the likelihood of some pathological process existing throughout the 12 months cannot be excluded. In this connexion the presence of the subcortical Holzer-positive gliosis might be thought to indicate a chronic process, but it has to be remembered that on occasion it may be met with in as little as one month after the onset of post-traumatic oedema of the white matter (Klatzo *et al.*, 1958) and after a severe anoxic episode (W. Krücke, 1959, personal communication).

The usual course of this condition is a steady march of symptoms characterized by mental deterioration with blindness or spastic paralysis, progressing to coma and death in a period of 3 to 12 months. Headache is frequent, and transient attacks of unconsciousness may occur; ocular symptoms are almost always complained of, and swelling of the optic-nerve head, is common. In some cases the onset is acute, and the course more rapid.

Bouman (1934) collected details of 94 cases, four of these patients having died in under one month from the onset of symptoms. Of the recorded instances with rapid evolution and with histological changes of a comparable order the following may be epitomized. Case 3 of Stewart *et al.* (1927) was a woman aged 43 in whom sudden blindness in both eyes was apparently the first symptom eight days before death. The brain showed acute swelling of the astrocytes but with little fibre formation except in the occipital areas, and then only in relation to vessels. Sheldon *et al.* (1929) reported rapidly developing focal symptoms with raised intracranial pressure in a 27-year-old woman who six and a half weeks previously had given birth to her first child, to be followed first by puerperal sepsis lasting three weeks and then by blindness which developed over a period of one week. The true nature of the disease became manifest during craniotomy. Necropsy four

days later disclosed marked demyelination of the left occipital lobe with preservation of the "U" fibres and local involvement of the corpus callosum and right temporo-parietal and occipital lobes with implication of the arcuate fibres on this side. There was extensive destruction of axis cylinders.

In Case 1 of Bini and Spaccarelli (1947) the patient, a boy of 9, became paralysed and demented in a week from the onset of symptoms. The distribution of the lesions was not dissimilar from the case we have described but the emphasis of destruction was in the occipital regions. There was a general weak staining of the myelin noticeable almost everywhere, though the "U" fibres were spared. A few islets of preserved myelin were noted and also confluent halos of demyelination around vessels. Axis-cylinder loss was not as marked as the loss of myelin. There was some perivascular infiltration with lymphocytes and also small perivascular bleedings, not necessarily in the areas where the pathological process was to be seen. The astrocytes showed moderate hypertrophy, fibre formation in the Holzer preparation being described as "very modest."

Környey (1952) described the case of a woman aged 21 who became somnolent eight days after a cold and five days after the appearance of an urticaria-like rash, lapsing into coma and dying seven days later. The lesions anteriorly were diffuse and massive, but posteriorly they were multiple. The demyelination was uneven and not always complete, the most defective areas being centred around small blood vessels. The author describes some loss of axis-cylinders and spindle-like swelling on others, with lymphocytes and plasma cells cuffing vessels, and moderate hypertrophy and hyperplasia of the neuroglia. Braitenberg and Callieri (1955) report an illness of 12 days' duration in a boy aged 13 with dementia and bulbar signs. A large subcortical lesion was found in the right frontal lobe, but the medulla was not examined.

The present case is therefore another example of the disease exhibiting a rapid evolution, but the lapse into coma in so few hours would appear to be exceptional. The ictal onset in a man of this age had naturally in life suggested the presence of a cerebrovascular lesion, and when the destruction of white matter was noted the diagnosis of Binswanger's (1894) disease was considered. The finding of two disordered transcortical arterioles in the occipital lobes with softening of the contiguous grey matter lent some support to this suggestion, but a more detailed study failed to demonstrate any of the thickening of the arterioles in the white matter which has been noted by those who have reported such cases (Nissl, 1920; Grünthal, 1929; Farnell and Globus, 1932; Davison, 1942; and Pilleri and Risso, 1959). Neumann (1947) is of the opinion that some cases of reported Binswanger's disease may be no more than instances of Schilder's disease occurring in arteriosclerotic subjects. The very occasional thickening of the blood-vessels noted in the present case was believed to be secondary to the stasis and to the accumulated products of myelin breakdown.

Åström *et al.* (1958) have described an unusual form of demyelination in two patients with chronic lymphatic leukaemia and in one case of Hodgkin's disease in which the nuclei of the oligodendrocytes were frequently swollen and densely basophilic and those of the astrocytes were markedly hyperchromatic and irregular. The distribution of lesions in these brains was not so typical of Schilder's disease as in the present case, and

the unusual changes they described in the astrocytes were not found by us. Christensen and Fog (1955) have reported a case of Schilder's disease in a 59-year-old man whose illness lasted five months and was associated with sarcoidosis of the lungs, spleen, lymph nodes, and kidney; and they advance the suggestion that both the cerebral and the systemic diseases may have been co-ordinated allergic reactions. When the sarcoidosis was treated with A.C.T.H. the brain disease progressed rapidly, but the possibility of coincidence could not be excluded. They believe that the primary lesion in the brain was a degeneration of the oligodendroglia.

In the present case the paucity of oligodendrocytes in the affected parts was striking, but on histological grounds it is not possible to say whether their dissolution preceded or followed that of the myelin. The demyelination which follows cyanide intoxication may, however, be due to a derangement of enzyme activity in the oligodendrocytes (Lumsden, 1950), so it is reasonable to suppose that a similar mechanism may obtain in certain other forms of demyelinating disease. In the present case, apart from the unexplained early centrilobular necrosis of the liver, there was no evidence of intoxication, anoxia, or infection, but the history of fits and blackouts is consistent with recurrent "allergic" episodes of a functional character, preceding the acute destructive process in the brain. Myelin preservation noted in this case around some of the vessels in the central zone has been previously reported by Meyer and Pilkington (1936).

In general, demyelination seemed to occur most in the areas of late myelinogenesis; thus demyelination was pronounced in the frontal lobes and the middle and inferior temporal gyri, whereas the first temporal and hippocampal gyri were spared. But the diffuse involvement of the occipital lobe proved to be an important exception to this generalization, though the relative integrity of the pericalcarine white matter, apart from the few small and young plaques, was noteworthy.

Summary

A case of demyelinating disease of the brain in a man of 45 years presented with an apoplectic onset, followed by fluctuating signs of bilateral cerebral disorder and ending in death after a total period of six weeks.

The brain showed diffuse, irregular cavitation of the white matter, with extensive patches of demyelination, sparing the subcortical arcuate fibres. The histological changes were those of sudanophilic diffuse sclerosis, a condition usually associated with a slowly progressive clinical course.

Reference is made to other acute cases in the literature.

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GIANT FOLLICLE LYMPHOMA OF THE SPLEEN

RECOVERY AFTER SPLENECTOMY

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This paper is concerned with four patients with the following features: (1) Massive splenomegaly without enlargement of superficial lymph nodes. (2) Lymphocytosis without any great increase in total leucocytes, and with the presence of abnormal and immature mononuclear cells in the circulating blood. (3) Large numbers of lymphocytes in bone-marrow aspiration films. (4) In the two cases in which bone-marrow biopsy was carried out there were numbers of lymphocyte foci in active marrow. (5) Excellent clinical result of splenectomy. (6) In the course of time the abnormal and immature mononuclear cells in the circulating blood disappeared and the leucocyte count returned to normal, the lymphocytosis disappearing. (7) In the three cases in which liver biopsy was carried out at the time of splenectomy there were abnormal lymphocyte accumulations in the portal tracts. (8) No superficial lymph-node enlargements occurred during the periods of observation, and the patients remained well (one patient died of pneumonia 13 years after splenectomy and no sign of any lymph-node disease was found at necropsy).

The histological appearances of the spleens in Cases 1 and 2 were typical of giant follicle lymphoma, and the lymph nodes which were removed with the spleens showed the same histological changes. In the spleens in Cases 3 and 4 the follicles were large and ill-defined; there were large numbers of lymphocytes and lymphoblasts in the splenic pulp, and the histological appearances were thought to be those of lymphosarcoma or lymphatic leukaemia. However, these two cases were exactly similar in all other respects to Cases 1 and 2 with regard to symptoms, signs, response to splenectomy, and subsequent progress, and this, together with the known close relationship of giant follicle lymphoma to lymphatic leukaemia and to lymphosarcoma, indicates that the same disease process was present in all four cases. Summaries of the four cases follow.

Case 1

A woman aged 34 was first seen in September, 1952, with lack of energy for 18 months and increasing abdominal swelling for two months. The spleen reached to the mid-line and half-way between the umbilicus and the symphysis pubis. There was no anaemia. Leucocytes numbered