DIFFUSE SCLEROSIS WITH PRESERVED MYELIN ISLANDS:

A PATHOLOGICAL REPORT OF A CASE, WITH A NOTE ON CEREBRAL INVOLVEMENT IN RAYNAUD'S DISEASE.

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PELIZAEUS (1885) described a family of which five members exhibited a rather uniform clinical symptomatology, consisting of tremor of the head, nystagmus, spastic paraplegia, etc. He thought he was dealing with an atypical familial form of disseminated sclerosis. Twenty-five years later Merzbacher (1910) investigated the same family and found the symptoms in twelve members, representing four generations. Symptomatology and clinical course of the condition was, in all patients, approximately identical: onset within the first months of life, rapid progression within the first six years, slowing down later considerably, death after twenty to thirty years due to intercurrent disease. The symptoms were tremor of the head, nystagmus; later paraplegia, ataxia, visual and auditory disturbances, involuntary movements, etc. The emotional and intellectual sphere remained comparatively unimpaired. The heredity was found to be recessive: the mothers, though themselves spared by the disease, pass it on to their sons (though among the twelve cases of Merzbacher there were also two females). In the one case investigated histopathologically by Merzbacher a diffuse demyelinization was found, particularly marked within the occipital region, distributed symmetrically in both the hemispheres and characterized by the persistence of myelin islands, often around vessels, which gave the condition the appearance of a tiger's skin. Merzbacher thought he was dealing with an hereditary aplasia of axis cylinders and myelin fibres, and called the condition *aplasia axialis extracorticalis congenita*.

Since then a few more pathologically verified cases have been described by Spielmeyer and Liebers (1928) of the family previously investigated by Merzbacher, by Bodechtel (1929), Bielschowsky and Henneberg (1928), Loewenberg

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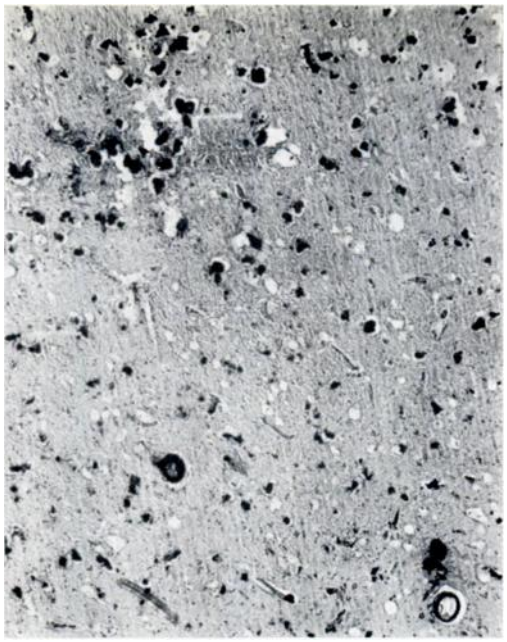

FIG. 9.—Van Gieson stain. Globus pallidus.

FIG. 10.—Nissl stain. Globus pallidus.

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but understands a little. Good-tempered, very simple, destructive. Does very little work. Low-grade imbecile.

In 1935 there was a sudden collapse. She was pulseless; had very cold cyanosed extremities. Died of acute cardiac failure on March 24, 1935.

Blood, cerebrospinal fluid and urine did not show any pathological signs on several examinations.

Post-mortem findings.—Body is fairly well nourished. The skull is of average thickness. Weight of brain 670 grm. Dura mater thickened, adherent to base. Cerebrospinal fluid not increased. Slight enlargement of the ventricles. Simple pattern of convolutions. Depth of cortex without abnormality. The basal ganglia and internal capsule appear rather small. Corpus callosum and fornix in right proportion to the size of the brain. Substantia nigra very conspicuous on both sides.

There is some œdema within the lower lobes of both lungs. The heart does not show pathological change. Aorta is of small calibre. Coronary arteries patent. Capsule of liver (21 oz.) slightly thickened, but liver otherwise normal. Spleen (2½ oz.) pale pink, soft. The left kidney has a fairly large cyst in the pyramidal zone; cortex and pyramids are pale and poorly differentiated. Ovaries and uterus infantile. Adrenals, pancreas, thyroid and pituitary without abnormalities.

Cause of death given: Pulmonary œdema.

Macroscopic Inspection of the Hardened Brain.

There was no gross change of the convolutional pattern, which was of simple type.

In addition to the changes already described there was found an irregular brownish discoloration of the white matter, more marked in the anterior regions. Within the degenerated white matter numerous white islands of myelin were recognizable on naked-eye inspection.

Histological Examination.

Only the brain was available. The spinal cord had not been taken out nor were pieces of the organs preserved.

The leptomeninges were thickened generally, in some places, particularly over the cerebellum, to a considerable degree. There were inflammatory changes neither in the meninges nor elsewhere. The walls of the meningeal blood-vessels were greatly thickened (Fig. 1), some hyalinized; in others concentric lamellæ of proliferated connective tissue were seen. Only occasionally the intima participated in proliferation, giving rise to narrowing of the lumen and splitting and proliferation of the elastic fibres. Though the blood-vessel change was most marked in the meninges, capillary and precapillary fibrosis was present throughout the cortex, white matter and brain-stem.

The cytoarchitectonics of the cerebral cortex studied in Nissl sections of 25μ thickness were preserved everywhere. The layers were of normal depth and cell density and no outfall of cells was noted. There were slight degenerative changes in the ganglion cells with formation of vacuoles, the initial stages of what has been called by Nissl simple shrinkage. These changes were not confined to layers or areas and, as a rule, they had provoked only slight glial reaction, though occasionally the number of proliferated astrocytes and the degree of subpial gliosis was remarkable. Substances stainable by Scharlach R. were found neither in nerve-cells nor in the glia or mesodermal cells. In contrast to the cell structure the myelin fibres of the cortex were rarefied. In addition, circumscribed areas were seen in which the myelin was stained more deeply, in contrast to others in which

the staining was inadequate (Fig. 2). The myelin picture thus had a rather patchy appearance which superficially recalled that of *plaques fibro-myéliniques*. Closer analysis showed, however, that there was no hypermyelinization. The deeper staining was produced by unusual uptake of the hæmatoxylin by the ground tissue, in a similar way as that described by Liebers (1928) in his case of Pelizaeus-Merzbacher disease. There was a diffuse symmetrical demyelinization of the white matter extending from the occipital to the frontal pole, nowhere intense, but more marked in the frontal than in the posterior regions. The demyelinization involved to a great degree also the subcortical fibres. The characteristic features were sharply demarcated myelin islands, which gave the appearance of a " tiger's skin " (Figs. 3, 4, 5). These islands were of varying size (up to the size of a pea). They had no uniform shape, some being round, others elongated. Within the islands the myelin fibres were well preserved. There was no constant perivascular arrangement of the myelin islands, as has been described in previous cases of Pelizaeus-Merzbacher disease. Since some of the islands were of considerable size the occasional finding of one or two vessels need not be significant. Many of the smaller microscopical islands, however, showed the perivascular situation well. The axis cylinders were preserved throughout both in the demyelinated areas and in the islands. Neither in the glial cells nor in endothelial and adventitial cellular elements could an appreciable amount of fatty or other breakdown substances be detected by means of Scharlach R., Nile blue, Kossa, Turnbull and azocarmine methods; nor were products found stainable by hæmatoxylin as described in Pelizaeus-Merzbacher disease by Bielschowsky and Henneberg (1928). With Holzer stain a diffuse proliferation of the glia fibres could be demonstrated (Fig. 6). The gliosis was in parts dense and poor in glia-cells; in others it had more of an astrocytic appearance, as brought out particularly well by the Globus-Cajal method (Fig. 7). As a rule the gliosis was more dense in the central parts of the white matter, and of a more astrocytic appearance in the peripheral parts adjacent to the cortex. Specimens stained for fibrous glia often revealed a similar " tiger-skin " appearance with the difference that the place of the myelin islands stood out as less heavily sclerosed. Nissl pictures showed a striking number of heterotopic ganglion cells in the white matter which were evenly dispersed. No circumscribed accumulation of heterotopic cells were found. The oligodendroglia and microglia were little changed both qualitatively and quantitatively. Here and there some swelling of the oligodendrocytes was seen, but mucoid degeneration was nowhere found. The myelinization of the basal ganglia and brain-stem was as a whole preserved. The internal capsule was undamaged, though small. Within the globus pallidus some patchy demyelinization was seen. Fig. 8 shows this well in a section stained with the Weil method after paraffin embedding. The globus pallidus contained a very large amount of pseudocalcium precipitations within the media of the arteries and in the adventitial spaces, and as concretions lying free in the tissue (Fig. 9). Fine pseudocalcium deposits were dispersed in some ganglion cells. The pigment of the globus pallidus and that of the zona rubra of the substantia nigra was definitely increased (Fig. 10), and gave together with the concretions in the globus pallidus a strong iron reaction. The ganglion cells were not diminished in number nor did they reveal significant changes, nor was there a considerable fibrous glia reaction, though the protoplasmic macroglia showed considerable signs of proliferation.

Similar increase of the pseudocalcium was seen in the dentate nucleus, though there again no gross change of the ganglion cells nor glial increase was noticed. Nor was there any gross architectonic impairment of the cerebellar cortex. In the white matter of the cerebellar lobules a slight increase of fibrous glia was noted. There was, as already described above, a considerable thickening of the meninges, with marked hyalin change of the blood-vessels. In the medulla and the dentate nucleus recent diapedetic hæmorrhages were rather frequently seen without any reaction of the surrounding tissue. The principal tracts, including the pyramidal pathways, did not show secondary degeneration.

Discussion.

The outstanding pathological finding of the case is the demyelinizing process of the white matter, with preservation of myelin islands. The preserved myelin islands are visible on naked-eye inspection of the brain fixed in formalin.

This constitutes the main pathological feature of Pelizaeus-Merzbacher disease, which is also suggested by the apparently early onset, choreiform or tremor-like movements, the integrity of the axis cylinders, the negligible amount of fatty breakdown products and the gliosis. There was no heredity in this case, but the experiences of Bielschowsky and Henneberg (1928), Loewenberg and Hill (1933) and Schenk (1934) show that this is not indispensable for the diagnosis.

With previous observations of Pelizaeus-Merzbacher disease the case has in common the fact that the demyelinization is not a sign of aplasia, but the result of a process as illustrated by the underlying gliosis. The case is distinguished, however, by atypical features and complications. Firstly the clinical symptomatology is surprising. The case was labelled as an able-bodied idiot. The neurological investigation was, however, never very complete, and certain neurological signs, particularly hyperkinetic movements of a choreiform and tremor-like nature, common in Pelizaeus-Merzbacher disease, are reported, and, apparently, were present at an early stage of the disease. In the last years of life some progress has been noted, manifesting itself in unsteadiness of gait and mental deterioration, though with the supervening Raynaud's disease it is difficult to assess what is due to the latter and what to the demyelinizing disease. The nature of the pupillary symptoms remains uncertain because of the iritis, the ætiology of which has never been ascertained. No spasticity ever developed and, in agreement with this, no degeneration of the pyramidal tracts was found. This is strange, but may find its explanation in the fact that the demyelinization as a whole was slight, the axis cylinders were fully preserved and the whole process more pronounced in the frontal lobe (Fig. 3).

A further atypical sign is the widespread independence of the large myelin islands from the blood-vessels. In previous cases there was a definite perivascular preservation of myelin, and the same has been seen in transitional cases (Meyer and Pilkington (1936)). However, microscopically many perivascular islands could be seen in this case also.

Another unusual feature is the involvement of the globus pallidus, which showed a patchy demyelinization and a considerable amount of pseudocalcium, certainly pathological in degree.

A special consideration is necessary with regard to the microcephaly and the terminal Raynaud's disease. Microcephaly has not yet been reported in

Pelizaeus-Merzbacher disease. It is difficult to decide whether it is a feature of the demyelinizing process which may have commenced earlier than usual, or whether it is a complication independent of the (supervening) demyelinizing disease. It is impossible to give a satisfactory answer to this question. The simple type of the convolutional pattern, the relative smallness of the basal ganglia, the striking number of heterotopic ganglion cells certainly point to an arrest of development. Hydrocephalus of the degree found in this case is also uncommon in demyelinizing processes. It would be difficult to make an attempt at assessing how much of other findings, such as a certain scarcity of myelinization in the cortex and the gliosis of the white matter, may be attributed to the microcephalic or the demyelinizing component, if both should be regarded as independent.

A similar difficulty is encountered in ascertaining the part played by the terminal Raynaud's disease in the production of changes in the brain. A group of cases of Raynaud with a general vasomotor lability, including the vasomotor system of the brain, has long been recognized (Cassierer and Hirschfeld (1935), Guttmann (1937)), and pathologically verified cases showing apparent histological involvement of the brain have been described (Ruhemann (1928), Assmann (1929)). In our case the very marked vascular proliferation in the meninges and brain substance surpassed what might naturally be expected in a chronic demyelinizing disease, and might well be an expression of an involvement of the brain. The sudden collapse has been attributed to œdema of the lung. This may well be so, but there is also a possibility that the fresh hæmorrhages frequently seen in the medulla and cerebellum have been instrumental in bringing about the collapse by means of a breakdown of the vasomotor regulation, in a similar way as sudden death in post-encephalitic conditions has been interpreted (A. Meyer (1929)).

It would be mere speculation to ask what other part of the histological picture might be attributed to an involvement of the brain in Raynaud's disease. It is at least safe to say that the absence of signs of acute breakdown does not particularly encourage any speculation that the demyelinizing process itself might have been caused by the terminal disease. Nor is there, in this case, any substantial evidence for a cerebral origin of Raynaud's disease, the possibility of which has been occasionally discussed in the literature.

In so far as Pelizaeus-Merzbacher disease is based upon the characteristic histological appearance in the brain the case obviously belongs to this group. Beyond this much remains doubtful with regard to its classification and interpretation. Though it would be a mistake to discuss on the basis of this very complex and puzzling case the problems of Pelizaeus-Merzbacher disease at large, in a wider sense the case might prove a valuable contribution to future research on demyelinizing diseases.

Summary.

A case is described which shows the cardinal symptom of demyelinization with preservation of myelin islands characteristic of Pelizaeus-Merzbacher disease. The case was complicated by microcephaly and terminal Raynaud's disease. The difficulties of interpretation and classification are emphasized.

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References.

(1) Assmann, H,—*Klin. Wochenschr.*, 1929, ii, p. 1342.
(2) Bielschowsky, M., and Henneberg, R.—*Journ. f. Neur. u. Psychol.*, 1928, xxxvi, p. 131.
(3) Bodechtel, G.—*Zeits. f. d. ges. Neur. u. Psychiat.*, 1929, cxxi, p. 487.
(4) Bouman, L.—*Diffuse Sclerosis*, London, 1934.
(5) Cassierer, R., and Hirschfeld, R.—*Handbuch der Neurologie* (O. Bumke and O. Foerster), Berlin, Springer, 1935, xvii, p. 246.
(6) Guttmann, E.—*Journ. Ment. Sci.*, 1937, lxxxiii, p. 542.
(7) Hallervorden, I., and Spatz, H.—*Arch. f. Psychiat.*, 1933, xcviii, p. 641.
(8) Liebers, M.—*Zeits. f. d. ges. Neur. u. Psychiat.*, 1928, cxv, p. 487.
(9) Loewenberg, K., and Hill, T. S.—*Arch. Neur. Psychiat.*, 1933, xxix, p. 1232.
(10) Merzbacher, O.—*Zeits. f. d. ges. Neur. u. Psychiat.*, 1910, iii, p. 1.
(11) Meyer, A., and Pilkington, F.—*Journ. Ment. Sci.*, 1936, lxxxii, p. 812.
(12) Meyer, A.—*Arch. f. Psychiat.*, 1929, lxxxix, p. 27.
(13) Pelizaeus, A.—*Ibid.*, 1885, xvi, p. 698.
(14) Ruhemann, E.—*Zeits. f. d. ges. Neur. u. Psychiat.*, 1928, cxv, p. 443.
(15) Schenk, V. W. D.—*Acta Psychiat. et Neurol.*, 1934, ix, p. 187.