PELIZAEUS-MERZBACHER DISEASE*†

A Study in Nosology

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Seitelberger (1) has remarked that knowledge of Pelizaeus-Merzbacher disease parallels the evolution of neuropathology in general. After Pelizaeus (2) had recognized the uniqueness of the disease clinically, Merzbacher (3) secured its separate nosologic position by pathomorphologic observations. He interpreted the lesion to be congenital aplasia of the myelin sheaths, but Spielmeyer (4) asserted that the absence of myelin resulted from demyelination, thus implying a progressive rather than a static disease. Bielschowsky and Hennegue (5) then classified it as a "leukodystrophy", assuming disturbed myelin metabolism as the pathogenesis. In keeping with classical concepts of neuropathology, Seitelberger concluded "the neuropathologic differentiation of nosologic entities... is one prerequisite for the recognition of specific genetic and enzymatic factors responsible for the degenerative processes (1)."

On the basis of personal observations, we want to examine the validity of these concepts. Admittedly, the merits of classical neuropathology are implicit in the classification of neurologic disorders by morphologic criteria. Nevertheless, in comparison to other disciplines, morphologic neuropathology has been somewhat less than successful in elucidating etiologic and pathogenic mechanisms. There is no better example for demonstrating this point than mongolism. The discovery of 21 trisomy (6) almost nullified the efforts of scores of neuropathologists whose punctilious studies contributed nothing to the understanding of the etiology. On occasion, the classic neuropathologic approach has even hindered progress in nosology. For example, the morphological similarities between Tay-Sachs and Batten disease have perpetuated the notion that the two conditions are variants of the same basic process, although clinical, biochemical, and genetic observations have established the fallacy of such a conclusion (7, 8). Although pathomorphology fills a real need, its preeminence in nosographic studies may yield to an approach which draws from a wider range of information.

These reflections are derived from clinical and post mortem studies on 3 patients identified in Figure 1 by Nos. 1, 2 and 3, belonging to a family extensively studied by one of us (9). Twenty-one males were definitely affected with Pel-

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Fig. 1. Pedigree. The black squares indicate the affected males; the circles with bars represent females with neurologic defects not suggestive of Pelizaeus-Merzbacher disease.

Pelizaeus-Merzbacher disease. All died before reaching the age of 6 years. The condition was inherited as a sex-linked Mendelian recessive; consanguinity was absent. Three females also suffered from neurologic deficits, which clinically did not resemble Pelizaeus-Merzbacher disease, but the final diagnoses remain unsettled. In a fashion which vividly recalls the pathos of the disease as related to Merzbacher (3) by his informant, Mrs. Hetzer, the mothers usually had established during the first 3 months of life whether a male infant was affected. Since genetic and clinical data will be dealt with in a separate communication (9), only the more important aspects are discussed here.

The pathoanatomical studies were done on material inherited by this laboratory except for brain $3$ which was kindly placed at our disposal by Dr. Scharenberg, University of Michigan. No fresh, unfixed tissue was available. Fixation in bromformalin of one brain and embalming of another further limited the scope of the morphologic studies. In general, however, the material sufficed to support the clinical diagnosis and to investigate some of the more important morphologic aspects of the condition.

CASE REPORTS

Patient $1$. (NP 58-29)

This male infant was born on March 14, 1955 and died on April 1, 1958 at 3 years of age. The mother noted shortly after his birth that his hands turned inward towards the midline, and that his cry was abnormally weak. Roving movements of the eyes were first observed at the age of 3 months, and the infant failed to gain head control. He never learned to sit up,
walk or talk. When he was 16 months old neurologic examination revealed questionable pallor of the optic disks. Pupillary reflexes and eye movements were prompt; there was no true nystagmus but the eyes wandered continuously in a searching fashion. The infant would move his limbs but not in a purposeful way. Respirations were irregular. The myotatic reflexes were difficult to elicit; yet there were bilateral Babinski signs. The spinal fluid was normal on routine examination; electrophoresis was not done.

The child died from severe dehydration due to continuous vomiting, complicated by multilocular bronchopneumonia. Autopsy diagnoses: Emaciation and dehydration; bronchopneumonia; congestion and edema of lungs; hyperplasia of hilar lymph nodes; nodular hyperplasia of adrenal cortices.

The brain was unusually firm and weighed 1000 gms, which is too light for this age but within normal limits in relation to the body length of 84 cm. Although small, the brain stem was well shaped. In coronal brain sections, the ventricles appeared dilated with rounding of their lateral angles. The area occupied by cerebral white matter was reduced; the corpus callosum, for example, measured only 3 mm in width. The various subdivisions of basal ganglia, brain stem, and spinal cord were difficult to recognize because the dull, gray white matter afforded poor contrast. The spinal cord was small.

**Histopathologic Findings**

Coronal sections from 3 forebrain levels stained with buffered cresyl violet revealed a more or less normal cytoarchitecture. The morphology of the neuronal perikarya was unremarkable. Leptomeninges, ependyma, and choroidal plexus were normal. The central canal of the spinal cord was open. Basal ganglia, diencephalon, midbrain, pons, and medulla oblongata were relatively small due to a marked reduction of the area occupied by white matter. The spinal ventral horn cells were reduced in number; some of those remaining showed cytoplasmic vacuoles. In the white matter, the ratio of astrocytes to oligodendrocytes approximated 1:1. Characteristic rows of interfascicular glial cells were not encountered. No inclusion bodies were seen in glial nuclei.

Sections stained for myelin utilizing hematoxylin lakes, copperphaloeyanin, and sudan black B failed to demonstrate a single myelinated fiber in 3 cerebral and 2 cerebellar hemisphere celloidin sections (figs. 2 and 3). Twenty paraffin and 6 frozen sections from various regions of brain and spinal cord. This finding contrasted sharply with the normal myelin stainability of the cerebrospinal nerve roots (fig. 4). Like other central neural white matter, the optic pathways were unstained. Peripheral nerves were not available.

Silver carbonate impregnations showed numerous axons, with no evidence of degeneration. Nevertheless, each medullary pyramid contained only 374,000 axons, as estimated by a random sampling method with an expected error of not more than ±8 per cent (10). The mean number of axons per pyramid in 3 neurologically normal children who were 3½, 2½ and 3½ years old was 1,106,000, which approximates the adult mean number of pyramidal axons of 1,087,000. Since the expected normal range for 85 per cent of the population is between 749,000 and 1,435,000 pyramidal axons (11), the value of 374,000 in our patient is pathologically low. The deficit was predominantly at the expense of medium and large-sized fibers, which were absent. Likewise, in the pontocerebellar fiber systems no large fibers were recognized. On the other hand, the 3 year old, as judged by comparison with normal controls, displayed a full range of fiber sizes.

Frozen sections stained with oil red O and with sudan black B revealed diffusely distributed, exceedingly small droplets of neutral fats within the cytoplasm of fibrous astrocytes. An occasional perivascular space contained a few macrophages laden with huge sudanophilic droplets. Interstitially, the only macrophages to be found were in the cerebral peduncles (fig. 5). The white matter exhibited a dense isomorphic cleiosis as revealed by silver impregnations and polarized light, but not nearly as well by Holzer stains.

**SUMMARY**

This 3 year old male suffered from a congenital neurologic disorder which was clinically and genetically diagnostic for Pelizaeus-Merzbacher disease. The
neuraxis showed slight, diffuse atrophy. Not a single myelin sheath could be stained by conventional technics, in contrast to a normal staining of myelin sheaths in the cerebrospinal nerve roots. Although axons displayed a normal distribution, the corticospinal tracts contained none of the thick fibers normally beginning to appear prominently by 3 years of age, and the number of axons in the pyramid was 4 standard deviations below the mean. The only indication of active myelin breakdown was found in the cerebral peduncles, although astrocytes containing minimal amounts of neutral fats were regularly present in the sclerosed white matter.

*Patient #2 (NP-80-83)*

This boy, born on 13 July 1949, died on 18 December 1954 at the age of 5 years and 5 months. He was born prematurely and weighed 4 lbs. and 5 oz. His cry was weak and was associated with an inspiratory wheeze. He never gained weight properly, although he ate well and had no obvious dysphagia. Rolling eye movements were noticed within a few weeks after birth. He could not sit or stand, but was able to raise his head feebly from the mat-
tress. He never talked, and was considered to have decreased vision and hearing. Since the age of 1½ years, he had frequent grand mal seizures, usually occurring in series, with free intervals lasting a week or more. Because of the seizures, he was hospitalized several times. He made no useful voluntary movements. The eyes wandered aimlessly in all directions. Myotatic reflexes were absent, and no extensor toe signs were observed. All skeletal muscles were hypotonic to the point of flaccidity. Spinal fluid was normal. The seizures were unsuccessfully treated with diphenyl hydantoin and phenobarbital.

The boy died at home under unknown circumstances. An autopsy was performed on the embalmed body. Autopsy diagnoses: Bronchopneumonia of lower lobes of both lungs; amyotonia congenita.

Re-examination of the previously sectioned brain, the weight of which had not been recorded, revealed a diffuse dilatation of the lateral ventricles with blunting of their angles. The entire brain was rubbery. The gyral pattern appeared normal but the white matter was small in relation to the gray, the corpus callosum having a thickness of 3 mm. Basal ganglia and diencephalon were slightly smaller than expected from the overall dimensions of the brain; midbrain and pons were markedly reduced. The white matter appeared dark, obscuring anatomical landmarks usually provided by the subcortical gray matter (fig. 6). The cerebellar cortex was severely atrophic, the folia being as thin as knife blades and separated by gaping sulci. The spinal cord was thin. The medulla oblongata was not available.
Histopathologic Findings

Sections were cut from 3 coronal cerebral hemisphere and 2 parasagittal cerebellar hemisphere slices embedded in celloidin, from 15 paraffin embedded blocks, and from 7 blocks of wet tissues, representing various areas of brain and spinal cord. The cerebral gray matter had a normal cytoarchitecture. Leptomeninges, blood vessels, ependyma, and choroidplexus appeared normal; the spinal canal was open. The spinal cord ventral horn cells were reduced in number, some showing small vacuoles. The spinal commissures contained a few conspicuous neuroplasmic swellings (fig. 7). The cerebellar cytoarchitecture was severely disturbed (fig. 8). Purkinje, granule, and basket cells were depleted. Astrocytes were diffusely overgrown, especially in the molecular layer.

Sections from all blocks were stained for myelin with hematoxylin, phthalocyanin, and sudan black B. Not a single myelinated fiber was found in the neuraxis (fig. 9), whereas myelin sheaths of the cerebrospinal nerve roots were well stained. The efferent nerve likewise showed a normal pattern of myelin, and the striped muscles were unremarkable. Silver impregnations revealed a normal distribution and spacing of axons throughout fore- and midbrain. The intrinsic cerebellar fiber systems, particularly the corticothalamic axons were greatly reduced, but there was little evidence of active axonal breakdown in the form of neuroplasmic swelling and axonal fragmentation. No baskets were seen in the Purkinje cell layer. In the cervical spinal cord and midbrain, the corticospinal tract fibers were of small caliber, not having differentiated into groups of varying diameters. In contrast, the lemniscal fibers were well differentiated. Sections stained with sudan black B and oil red O showed a diffuse distribution of minute droplets of neutral fats. Occasionally, macrophages loaded with neutral fats were noted in the perivascular spaces, but none were found interstitially. The white matter displayed a diffuse isomorphic gliosis.

SUMMARY

This patient suffered from a neurologic disorder possibly present at birth, but certainly manifest within a few months, characterized by severe physical and mental retardation. The neuraxis contained no stainable myelin, in contrast to the normal appearing roots and peripheral nerves. The cerebellum was severely degenerated. Although no count of pyramidal fibers could be made in this brain, a comparison of the supra- and inframedullary parts of the corticospinal tracts indicated a reduced number of pyramidal axons, as in Patients 1 and 3.

Patient #3 (NP-63-51)

This boy, born on 7 December 1954, died on 3 June 1957 at the age of 2\(\frac{1}{2}\) years. He was never seen by a neurologically experienced physician. The mother noticed immediately that he was affected, although the characteristic eye movements were not definitely observed until the age of 6 weeks. He never developed normally, and had dysphagia. Unable to talk, he expressed his feelings by crying, especially when hurt. Except for continuous eye motions, he displayed no spontaneous activity. He, occasionally, had a grand mal seizure. He died under unknown circumstances at home. An autopsy was done on the embalmed body.

No report of the autopsy findings was available. The brain was fixed in bromformalin and was forwarded to this laboratory after an extensive dissection. Its weight was estimated to be 900 gms. All white structures were small in contrast to the normal appearing gray matter.

Histopathologic Findings

Cerebral gray matter was essentially normal as revealed by 2 coronal hemisphere sections. The cerebellar cortex showed focal loss of Purkinje cells in the pattern of central lobu-
Fig. 6. Brain 2. Level of mesencephalic diencephalic junction after 6 years in formalin fixation. Note the conspicuous formation of fatty plaques and the washed out appearance of the cut surface. The corpus callosum is extremely thin, the lateral ventricles are moderately dilated. The other two brains presented an identical appearance; $\times 0.9$.

Fig. 7. Spinal Cord 2. Posterior commissure and dorsal nucleus. Hematoxylin and eosin stain. Note neuroplasmic swellings. These were also observed in Case 1 and 3 but to a lesser extent; $\times 200$.

Fig. 8. Brain 2. Cerebellum. Lillie-Weil stain for myelin showing atrophy of cortex and absence of stained myelin sheaths; $\times 2.4$. 

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Fig. 9. Brain 2. Frontal section at level of medial thalamic nucleus. Lillie-Weil stain for myelin demonstrating complete absence of stainable myelin sheaths; × 1.6.

lar sclerosis restricted to the ansiform lobes. The white matter of fore- and hindbrain showed a 1:1 ratio of oligodendrocytes and astrocytes. The latter appeared to be slightly activated as demonstrated by an increased stainability of the cytoplasm and by large, pale nuclei. No rows of interfascicular glia and no nuclear inclusion bodies were found. In the white matter some widened perivascular spaces, often containing a few lipid filled macrophages, were present. Otherwise, the vascular system, ependyma, and meninges were not remarkable. The central canal was patent.

Sections stained with hematoxylin-lakes, copper phthalocyanin, and sudan black B showed segments of a few myelinated fibers in the pallidorubral system and the cerebellar white matter, but no myelinated fibers were found in the remainder of the neuraxis (figs. 10, 11), in contrast to the well-stained nerve roots. In silver impregnated sections, the pattern and arrangement of axons appeared, for the most part, within normal limits. The brain stem, in particular the pons and medulla oblongata, was small, and counts of pyramidal axons done as in Case 1 revealed a total of 520,000 fibers in one pyramid, or only about 50 per cent of normal. Again, the corticospinal tracts contained only small-sized fibers (fig. 12). Sections stained with sudan black B and oil red O showed no neutral fats in the parenchyma
Fig. 10. Brain 3. Frontal section at level of red nucleus. Note the small size of the white matter and the absence of grossly visible areas of stained myelin sheaths; Lillie-Weil stain; $\times 1.5$.

and only a few fat laden macrophages in the perivascular region of some vessels. Proliferation of glial fibers throughout the areas covered by white fiber tracts was conspicuous under polarized light and in Holzer preparations.

**SUMMARY**

This 2½ year old boy suffered from a congenital neurologic disorder genetically and clinically conforming to Pelizaeus-Merzbacher disease. The neuraxis contained almost no stainable myelin, in contrast to a normal myelin stainability in peripheral cerebrospinal nerves. Evidence of active myelin breakdown was extremely scant if present at all.

A number of additional physicochemical studies on the myelin lipids in these
brains and on control material were carried out. The results can be presented in summary, since they were identical for all 3 brains.

A conspicuous gross feature was the huge quantity of the fatty plaques originally described by Laignel-Lavastine and Tinel (12) (figs. 2, 6, 9, 10). Although these plaques have been correctly identified as fixation artefacts (13), their magnitude and simultaneous occurrence in these brains, preserved in 3 different laboratories, suggests that the artefact may be of significance. This is particularly true in reference to Brain §1 which was fixed in formalin for only 2 years prior to our examination, whereas plaques have not been found in brains fixed for less than 6 years (13).

Another interesting finding, probably related to the fatty plaques, was the formation of a conspicuous surface scum as soon as the formalin-fixed tissues were immersed in water. The scum was taken off and stained on chemically clean slides. Reactions for cholesterol and cholesterol esters (14) were positive. The material also reacted positively with PAS, phosphomolybdic acid-stannous chloride and sudan black B. These observations indicate that the scum might contain non-water-soluble, unformed myelin lipids. In frozen tissue sections, the same staining reactions were peculiar. The phosphomolybdic acid-stannous chloride technic as well as the PAS stain gave a diffusely positive reaction throughout the
Fig. 13. Brain 3. Silver carbonate stain for axis cylinders. Dorsal motor nucleus of vagus. A. Transmitted light; B. Polarized light. Note the birefringent sheathing of axis cylinders as well as of the dendrite in the center; × 440.

cortex, but only a faint, finely granular reaction throughout the white matter. This behavior was precisely opposite to what one sees in normal tissue. In no instance were periaxonal sheath-like structures stained by these techniques.

Because the myelin sheaths were almost universally unstainable with conventional techniques, we studied frozen and paraffin sections under polarized light. In general, we could confirm Seitelberger's report of a delicate birefringent sheath surrounding axons bare of a stainable myelin sheath (15). This birefractive property was also observed around the demyelinated axons of a brain with sulfatide lipidosis, and we found it surrounding dendrites (figs. 13A, B). It is, therefore, improbable that this anisotropic material is pathognomonic for Pelizaeus-Merzbacher disease; nor can it represent a myelin sheath of abnormal composition.

DISCUSSION

Diagnostic Considerations

Morphologist have often claimed that the diagnosis of Pelizaeus-Merzbacher disease can be made only by pathologic examination. The usurpation of clinical diagnosis by morphologists has paid handsome dividends in some instances, but
has proved to be a cumbersome burden in others. As a lucid example, illustrating both theses on the same subject, we cite the problem of “diffuse cerebral sclerosis” which for decades harbored a hodgepodge of different conditions because of their morphologic likeness which, by more refined histochemical and genetic investigations, could finally be separated into different nosologic entities (16). It should be remembered that morphologically delineated nosologic entities may cause a variety of clinical syndromes, and that one etiologic agent may produce different morphological manifestations. It is for this reason that we re-examine the problem of the diagnosis of Pelizaeus-Merzbacher disease in greater detail.

Clinical Aspects

Originally, Pelizaeus (2) stated that the disorder manifested itself during infancy by aimless, wandering eye movements, usually noticed by the mothers or by some experienced member of the family and referred to as “dancing,” “trembling,” “roving,” etc. Although sometimes designated as nystagmus, the eye movements are usually not rhythmic. The next clear-cut sign of the disease is failure of the infant to develop normal head control. These two absolutely stereotyped findings have always been present in every incontestable instance of the disease. Their pathophysiological basis is not understood. In addition to these almost diagnostic signs, the mothers note a general lag in development: the affected children grow more slowly and do not gain weight as rapidly as their healthy siblings. All patients in whom the diagnosis is unquestioned have had a small head size, in the low normal or microcephalic range, and a body length below the 3rd percentile.

The further evolution of the condition seems to vary somewhat between and within families. In general, all extremities become spastic, and purposeful movements are restricted if not impossible. Mentation is subnormal and may range between idiocy and moronic levels. In contrast to the impaired motor system, the sensory system is usually well preserved. Optic atrophy, however, is common, although Merzbacher (3) denied its occurrence. Spinal fluid is invariably normal (8). Skeletal abnormalities, such as osteoporosis, kyphoscoliosis, etc. may either result from the chronic motor disorder or they could be a reflection of the genetic defect. The latter is less probable because skeletal abnormalities invariably occur after the disease has been manifest for many years.

The course of the disease is eminently chronic, but clinically it is difficult to say whether the patients regress or whether their symptoms are due to a congenitally defective nervous system. Some of Pelizaeus’ patients lived to be almost 60 years old. There are, however, a dozen or more males who died before the age of 6 years, and as far as can be ascertained, came from families in which no affected individual lived for a longer time (1, 17). No doubt, all patients have increasing difficulties as they grow older, but this in itself is not sufficient reason to assume an underlying progressive disorder. Clinicians and parents often notice that children with static cerebral lesions, such as those associated with cerebral diplegia, may seem to get worse as spasticity or athetosis increases during matura-
tion. Taken together, a number of observations suggest that progression is not a prominent clinical feature. Little if any discrepancy is usually noted between the size of the brain and the intracranial volume. This observation agrees with the characteristic clinical finding of a small head in Pelizaeus-Merzbacher disease. Another point favoring only minimal, if any, progression is the normal spinal fluid. These clinical facts also agree with the minimal pathologic evidence of active parenchymal breakdown.

Considering its stereotyped clinical signs, fairly characteristic, exceedingly torpid course, and its sex-linked recessive inheritance, the disease is not difficult to diagnose, clinically, if a full genealogy is available. These criteria should suffice to weed out a number of patients who have been erroneously diagnosed as Pelizaeus-Merzbacher’s disease. It is more than historically interesting that Merzbacher (3) already decried the laxity with which the disease was being diagnosed clinically, Pelizaeus (18) himself being an offender. Cases which, on account of the clinical picture, must be excluded from the list of Pelizaeus-Merzbacher disease, are in the first place, those published by Camp and Löwenberg (19), often considered to represent an “adult form” or a “dominant type” of the disease (20). Although the brain lesions are superficially similar to those in this disease, the clinical and genetic findings do not support a diagnosis of Pelizaeus-Merzbacher disease. On clinical grounds, we would question the cases of Bodechtel (21), Bielschowsky and Henneberg (5), Schefelt (22), Perkins (23), Josephy (24), Forsberg and Strømme (25), Einarson and Neel (26), Hagen and Sult (27), Sherman and Liebert (28), Blackwood and Cumings (29), and of Lüthy and Bischoff (30). Likewise, the famous “Würzburger Fall” should finally be discarded as an example of Pelizaeus-Merzbacher disease if one accepts Zahn’s (31) excellent clinical report. Incidentally, the first pathoanatomical description is often erroneously ascribed to E. Müller (32) who probably never saw this brain and certainly did not describe it! According to W. Müller (33), the correct reporter, and to Merzbacher (3) the brain had some similarity to Pelizaeus-Merzbacher disease, but Merzbacher very carefully underscored the differences. The most questionable diagnosis of Pelizaeus-Merzbacher disease has been made by Kastan (34), whose paper is widely quoted. He diagnosed the condition clinically in a 34 year old chronic alcoholic with a toxic cerebellar ataxia. One son of the propositus died of “encephalitis periaxialis of Schilder”, and another son’s demise was due to “Krabbe’s Disease of the Bogaert-Scholz type”. The propositus had a cousin with “Strümpell’s spastic lateral sclerosis” and the whole family then was afflicted with “diffuse sclerosis”, and propositus having the “chronic type”, his children the “acute”, and the cousin the “spinal type”. These diagnoses were based solely on clinical and historical data, and were made on some patients whom he could not personally examine and whose neurologic status he admittedly guessed at.

Genetic Aspects

The original observations of Pelizaeus (2) were suggestive of a sex-linked recessive mode of inheritance. This concept was ostensibly vitiated when Merz-
bacher (3) found 2 affected females in the family. One female patient’s brain examined by Spielmeyer (4) and re-studied by Liebers (35) was similar to the brain of an affected brother (3). In most of the subsequently described families no females have definitely been affected (3, 17, 36, 37, 38, 39), but in the family of Falls (9) from which the present cases originated and another unpublished family (40), females with neurologic disorders dissimilar to Pelizaeus-Merzbacher disease were observed. As the pedigree of the latter family (40) now stands, 15 males are known to be affected. Whether the patients of Nolan (41), 2 females and 5 males in 2 generations were affected by neurologic disorders, and those of Friedmann and Scheinker (42) had Pelizaeus-Merzbacher disease, remains uncertain.

A neurologic disorder, stereotyped clinically and inherited as a sex-linked recessive represents a windfall for investigation. Unfortunately, the 2 proven female cases (3, 4, 35) and possibly others seem to invalidate the assumption of a sex-linked recessive pattern. This is, however, not necessarily the case because the Lyon hypothesis (43) provides a logical explanation for a female to present the phenotype of an X-chromosome linked recessive genetic defect. Since this hypothesis has possible morphologic implications, it will be fully discussed in this context. For the moment we might state, that the sex-linked recessive mechanism of inheritance in Pelizaeus-Merzbacher disease provides further support for eliminating the families of Camp and Löwenberg (19) and of Kastan (34) from the roster of this condition.

Pathologic Considerations

By applying rigid criteria to the clinical and genetic aspects of Pelizaeus-Merzbacher disease, only a few incontestable cases remain which have been studied morphologically. Since they represent a clinically uniform group, it is perhaps surprising to note diversity in the pathologic picture. Probably no experienced neuropathologist would have diagnosed Wicke's case (44) as Pelizaeus-Merzbacher disease without having known that the patient came from Bostroem's family (37), because myelin stains revealed only minimal deviations from normal. On the other hand, the almost complete loss of myelin stainability found in other brains (1, 17, 45) has prompted Norman and Tingey (46) and Bargeton et al. (47) to assume that their patients belong to a different disease entity termed “sudanophil leucodystrophy”. Nevertheless, the process in all of these brains, including the present ones, is basically the same, namely a lack of myelin stainability without clearcut evidence of myelin breakdown.

A few special pathomorphologic features require further discussion. The diffuse cerebellar cortical atrophy in the brain of Patient 2 and the lobular atrophy in the brain of Patient 3 correlate with the clinical fact that these 2 patients suffered from repeated generalized seizures. The predilection of the cerebellar cortical neurons for suffering seizure-induced damage is well documented (48). Accordingly, cerebellar cortical lesions are probably not a primary feature of Pelizaeus-Merzbacher disease. However, the reduced number of pyramidal tract axons, first documented here, must be considered characteristic. It partially explains
the spasticity in all four limbs. That it is in contrast to the apparently normal development of the lemniscal systems agrees with the relatively normal function of special and general somatic afferent systems. The reduction in number of pyramidal fibers although apparent in illustrations (44, 45), is rarely mentioned in the literature, but it did not escape Merzbacher who stated: "In respect to the pyramidal tracts one can say that they are present; however, they are markedly reduced both in mass as well as in respect to the size of the individual fibers (3)."

In conclusion, Pelizaeus-Merzbacher disease is pathomorphologically characterized by a lack of stainable myelin and hypoplasia of axonal systems. Evidence of myelin catabolism is scant. The severity of the process spans a wide spectrum ranging from almost complete preservation to almost complete loss of myelin stainability. To designate the latter cases as "sudanophil leucodystrophy" is not warranted, since they are clinically and genetically concordant with the patients from the original Pelizaeus-Merzbacher family.

Considerations on Pathogenesis

Since Spielmeyer’s paper (4), theories of pathogenesis in Pelizaeus-Merzbacher disease have centered around demyelination. Today, his interpretation is still considered a triumph over Merzbacher’s contention of a congenital aplasia (3). Blackwood and Cumings (29) proposed that myelination is arrested at a chronological age of approximately 2 years. This hypothesis has found little support, presumably because their case did not show the pattern of myelination one finds in the brain of the 24 month old infant (49). Furthermore, it is doubtful whether their patient, a 14 year old female, in fact, suffered from Pelizaeus-Merzbacher disease. The clinical history is fragmentary and does not suggest onset of the difficulty in infancy. Pathoanatomically, the case is very similar to M.J. 29. 76 of Hallervorden (50), a dysplastic diffuse sclerosis.

The demyelination theory of pathogenesis in Pelizaeus-Merzbacher disease was modified by Bielschowsky and Henneberg (5) who suggested that the myelin breakdown in this disease is similar to that of “Familial Diffuse Sclerosis” of Scholz (51). To distinguish this type of demyelination from that of multiple sclerosis and of Wallerian degeneration they coined the term “leucodystrophy” implying a faulty myelin metabolism, a pathogenetic mechanism originally conceived by Scholz (51). Disturbances of the myelin sheath due to inborn errors of metabolism have been extensively discussed by Poser (52) under the title “dysmyelination”. Such general hypotheses are not without danger, because they create the notion that a general principle has been discovered which seemingly demonstrates a generic relationship of different nosologic entities (53).

Seitelberger (15, 54) lifted the hypothesis of dysmyelination as applied to Pelizaeus-Merzbacher disease to a more sophisticated level by suggesting that the demyelination, which allegedly begins in the center of the hemispheric white matter and spreads peripherally, results from the formation of lysocompounds of the glycerophosphatides of the myelin sheaths. This metabolic fault involving loss of a fatty acid by hydrolysis he considers to be located in the neuron. Edgar (53) asked whether the faulty composition of the “dysmyelinated neurons” is
sufficient to produce demyelination or whether additional pathogens are required to lead to this end.

All of these speculations, no matter how plausible and truthful, miss the problem because they do not encompass the clinical and genetic aspects, and do not pay full attention to all of the pathomorphologic facts. The hypothesis of a glycerophosphatide dystrophy (54) is weakened by the fact that these lipids are widely distributed throughout the body. They constitute a considerable percentage of peripheral nerve myelin which in contrast to the central nervous system myelin is stainable. Nevertheless, the concept of a lipid dystrophy in the form of the dysmelination theory (52) is still a tempting one. In keeping with this hypothesis, it could be suggested that the chemical fault lies not with the glycerophosphatides but with the proteins and proteolipids, the latter showing a high specificity for central nervous myelin, where they occur in a concentration about 30 times that of peripheral nerve myelin (55). This hypothesis also explains why sphingomyelin, cerebrosides, and cholesterol are found in the central white matter in concentrations much higher than would be expected from the lack of myelin stainability, since the latter results almost completely from changes in the proteolipids and the neurokeratin (15, 56). Again, this hypothesis neglects clinical and genetic facts. It offers no explanation for the lack of pyramidal axons; nor does it “permit” islands of normally stained myelinated fibers.

In the following, we present ideas on the pathogenesis which resolve some of these objections. Beginning with clinical observations, we first consider the early onset of neurologic deficits in relation to pathomorphologic events. It has been assumed that demyelination begins in utero (1), or that it occurs during the early months of life and progresses rapidly (16). In the light of Conel’s work (57), one wonders how much substrate for demyelination there is in the fetal or infantile brain. In a patient who died at the age of 7 months (47) one would have expected to see more evidence of demyelination in those areas which have just been myelinated such as the medullary cores of the frontal lobes. The fact, however, is that regardless whether the disease lasted for more than 20 years (3, 44), or for only 7 months (47) the amounts of alleged products of demyelination are always the same; they are invariably inconspicuous and compound granular corpuscles are virtually absent. This is in contrast to any other experience with demyelinating lesions. Since there is no proof that these brains were ever myelinated, the concept of demyelination is speculative. This conclusion makes the original contention of Merzbacher (3) no more correct. What can be assumed, however, is that the central nervous tissue is defective at birth. This defect is expressed by a faulty myelination rather than by demyelination and by a hypoplasia of neuronal systems, in particular the corticospinal tracts.

The assumption of faulty genesis of the neuraxis is in agreement with the indolence of the clinical process, the smallness of the head, and the general lag in development. Otherwise, in the patients dying during infancy and early childhood, one would have to assume that myelin broke down as fast as it was produced. Certainly, there is progression in this condition, but mostly on account of intercurrent complications such as generalized seizures, infections, and ali-
mentary disturbances, rather than being due to progressive demyelination. Astrocitic scar formation, even if restricted to the regions of faulty myelin stainability, is not conclusive evidence for demyelination, since glial fibers are formed without parenchymal damage or loss (58). That the disease ostensibly becomes arrested after the affected individuals survive infancy and childhood (2, 3, 37, 39, 40) again suggests that the critical stage coincides with myelinogenesis. This would mean that the genetic deficit of Pelizaeus-Merzbacher disease affects the deposition rather than the maintenance of myelin. Whether this enzymatic deficit is neuroglial, neuronal, or systemic is not known.

One notes that the brains of all patients dying in the first 7 years of life had little or no stainable myelin, in striking contrast to the considerable amount of stainable myelin observed in patients dying during adulthood (3, 4, 35, 44). There are at least 2 explanations for this finding. One is the assumption that the severe and ubiquitous lack of myelin stainability indicates a more severe or "double dose" genetic defect (50) in comparison to the cases with at least partial myelin stainability. The other possibility is that adults have acquired stainable myelin following the maturational transition from myelogenesis to myelin maintenance. That the pathogenetic principle is less active during adolescence and adulthood is supported by clinical data, but the deficit in neurons is, of course, not overcome, since the large corticofugal fibers remain absent even though myelinated fibers can be abundant by comparison (3, 44).

A further understanding of these problems is provided by more recent genetic information. Since Pelizaeus-Merzbacher disease is inherited as a sex-linked Mendelian recessive, the faulty gene is located in the maternal X-chromosome. Because they possess a paternal as well as maternal X-chromosome, females should not be affected. The infantile and juvenile cases with practically complete lack of myelin stainability were all males, and, thus, follow the expectations. On the other hand, the 2 females of the Pelizaeus-Merzbacher family seem to defy it, but an explanation may be provided by the Barr body. The Barr body is thought to be an X-chromosome in a genetically inactive, heterochromatic state. Therefore, both males and females have only one active X-chromosome per cell. The heteropyknotic inactivation of X-chromosomes may randomly involve the paternal in one and the maternal X-chromosome in another cell. Since this develops as early as the sixteenth day of gestation, it results in clusters of cells with either maternal or paternal X-chromosomes (43). This hypothesis explains, for instance, the dappled coat color of certain heterozygous female mice or the mosaic coat of the tortoise-shell female cat. The temptation to analogize the tigroid pattern of myelin stainability with the tigroid pattern of the coat colors of heterozygous female animals is almost irresistible. Unfortunately, a similar myelin pattern has been found in adult males (3, 44), a fact which can be explained only by making further, presently unsupported assumptions. Nevertheless, application of the Lyon hypothesis to Pelizaeus-Merzbacher disease at least explains the occurrence and the apparent mitigation of the disease in females and suggests that the patches of myelin might reflect groups of genetically different, more fully equipped, cells.
Although we are presently unable to propose a satisfactory, encompassing hypothesis on the pathogenesis of Pelizaeus-Merzbacher disease, the implications are clear. Any further probing into the basic nature of this disease or, for that matter, of any other genetically controlled degenerative disease, must take into consideration all aspects of the disease. This necessitates a rigid definition of the nosologic entity. Pelizaeus-Merzbacher disease is particularly simple to delineate nosologically because of its clearcut genetic and clinical picture. In contrast, the pathomorphological pattern of faulty myelination is much less stereotyped, rendering unsatisfactory any pathogenetic theory based solely on pathomorphologic findings.

SUMMARY

Three brains from patients with Pelizaeus-Merzbacher disease were almost completely lacking in stainable myelin, in contrast to a normal myelin stainability in the peripheral nerves. There is no need to consider these cases as different from Pelizaeus-Merzbacher disease or to designate them "sudanophil leucodystrophy".

In discussing the pathogenesis, we point out that the pathomorphologic diagnosis of the disease has been overestimated while insufficient consideration has been given to clinical and genetic data. Although unable to present a completely adequate pathogenic theory, we suggest that presently discussed theories fail to explain the total phenomena of the disease. Basically the pathogenetic mechanism is not demyelination, but a disturbance in myelination and possibly neurobiotaxis. The tigroid pattern of myelin stainability, an intriguing finding, can be set in analogy to similar coat-color patterns of heterozygous females by applying the Lyon hypothesis of heteropyknotic inactivation of X-chromosomes. Since myelin stainability has been shown to be linked to the presence of proteolipids and other myelin proteins, it may be more promising to investigate these substances rather than glycerocephosphatides, because the former occur almost exclusively in the central nervous system, while the latter are ubiquitous in the body.

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