DYSMYELINATION IN "QUAKING" MOUSE
ELECTRON MICROSCOPIC STUDY

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INTRODUCTION

During recent years, the basic pathological mechanism of several human genetic disorders involving the central nervous system has been elucidated by electron microscopic and biochemical investigations. However, the pathogenesis of certain disorders of central myelin sheaths such as sudanophilic leukodystrophy (1, 2, 3), Cockayne's syndrome (4, 5), and Pelizaeus-Merzbacher disease (6, 7), remains enigmatic, despite intensive research utilizing up-to-date investigative methods.

A potential model for such human disorders is the "quaking" mouse, an autosomal recessive neurological mutant. This disease is characterized by tremulousness and tonic and/or clonic seizures. The onset of clinical signs at 10 days of life approximately coincides with the beginning of myelination in the normal mouse (8). The neurological signs are completely manifested by 30 days, when the normal brain is fully myelinated. In spite of stunting and the persistence of the neurological disorder, the mouse can be maintained and propagated with relative ease. The pathological findings in "quaking" mice were first described by Sidman et al. (9), who found a paucity of myelin sheaths throughout the central nervous system, but failed to detect abnormalities in those myelin sheaths that were present.

In a previous report (10), we demonstrated significant alterations of oligodendrocytes manifested morphologically as perinuclear residual bodies, abnormal myelination and vacuolar demyelination. Similar vacuolar changes were observed by Berger (11), who also encountered numerous spirally formed myelinated axons in the spinal cord and optic tract. Samorajski et al. (12) examined 45-day-old "quaking" mice and demonstrated "hypomyelination" in both peripheral and central nerve fiber systems.

This report presents detailed morphological accounts of oligodendrocytic dysfunction which appear in the "quaking" mouse in the form of production and disintegration of irregular myelin-like membranes.

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DYSMYELINATION IN "QUAKING" MOUSE

MATERIALS AND METHOD

Breeding stock of "quaking" mice, strain C57BL/J-6QK, was obtained from Jackson Laboratory, Bar Harbor, Maine, and bred in our facilities. The mutant homozygotes (qk qk) were ascertained at the age of 10 days, when they developed the characteristic quaking tremor. Affected females were used for propagation; affected males, age 10, 17, 19, 23, 35 and 40 days, were utilized for this study. Unaffected male littermates, namely, heterozygotes (+qk) and homozygotes (+/+) served as controls.

The mice, anesthetized by intraperitoneal injection of 0.03 ml of 5 percent sodium pentolobarbital (Nembutal sodium), were sacrificed by quick decapitation with a razor blade. The entire head was sectioned at right angle to the longitudinal axis and the cut surface of the brain was fixed for 3 hours at 4°C in a solution of 1 per cent paraformaldehyde, 3 per cent glutaraldehyde in 0.081 M phosphate buffer of pH 7.4. Well-fixed portions of the corpus callosum and adjacent tissue and trigeminal nerve roots were dissected and post-fixed in 1 per cent osmic acid in 0.1 M phosphate buffer of pH 7.4 for 2 hours at room temperature. The blocks were dehydrated in a graded series of ethanol and propylene oxide and embedded in Epon 812. 1.5 micron sections were stained with toluidine blue and examined with a light microscope. As judged by the incidence of dense cells, the superficial first millimeter from the cut surface was optimally fixed for electron microscopic examination. The remaining portions of the brains were used for histological study. For the electron microscopic demonstration of acid phosphatase activity, a brain from a 23-day-old affected was fixed in 4% paraformaldehyde in 0.1 M cacodylate buffer of pH 7.4 for one hour. The blocks were soaked in dimethyl-sulfoxide according to Zagyry et al. (13) and quenched in liquid nitrogen. Sections, obtained by cryostat, were incubated in a 5'-cytidylic acid substrate solution after Novikoff (14).

GROSS AND LIGHT MICROSCOPIC OBSERVATIONS

Grossly, the white matter of the affected animals was considerably reduced in volume, softer than normal, and translucent gray instead of the normal shiny white. The gray matter appeared normal.

Light microscopic study of paraffin sections and of frozen sections revealed normal cytoarchitecture of the gray matter and diffuse paucity of the myelin sheaths throughout the white matter as previously described by Sidman et al. (9). Furthermore, a myelin-like material and vacuolar changes, described below, were observed in the Epon sections of the corpus callosum of young mutants.

In the white matter of 10-day-old mice, myelin sheaths were scarce, both in the mutants and in the control animals, and histological differences were not encountered. Mutants aged 17 to 23 days did display numerous vacuoles (fig. 1) of variable size, some reaching 15 micra in diameter. These were distributed randomly throughout the white matter and in the nerve fiber bundles of the gray matter. In contrast to the dense myelination in the control brains, those of the mutants contained no myelin sheaths. Instead, osmiophilic bodies, resembling myelin, were encountered sporadically (fig. 1). Some of the myelin-like bodies were U-shaped and others very irregular in configuration. Often they formed rings surrounding a vacuole. Changes in the oligodendrocytes occurred in the form of cytoplasmic swelling, dense osmiophilic spherical inclusions and vacuoles. The intracytoplasmic vacuoles and myelin-like bodies were smaller than comparable intercellular structures. In paraffin sections, the density of
glial nuclei in the white matter was normal and no significant alterations in the ratios of the various cell types could be detected. In frozen sections stained with Oil Red O, only a few fine granules reacted positively.

At the age of 35 to 40 days, the vacuoles were fewer and smaller than at younger ages. Likewise the number of myelin-like structures was conspicuously reduced, but no definite myelin sheaths were visible. The majority of the oligodendrocytes at this stage were morphologically similar to those of age-matched controls and were arranged in a typical interfascicular pattern. The astrocytes appeared normal.

ELECTRON MICROSCOPIC OBSERVATIONS

a. Control Brains

At 10 days of age, many cells of the cerebral white matter could not be identified as to type. Typical oligodendrocytes had voluminous cytoplasm filled with abundant free ribosomes intermixed with microtubules. These cells contained more rough endoplasmic reticulum and mitochondria than more mature forms. The cytoplasmic processes of these cells were arranged in parallel along the axons and contained microtubules and a cytoplasmic matrix denser than those of adjacent axons. The processes only occasionally surrounded axons with a mesaxon and formed a compact myelin sheath with either a single or several major dense lines. The inner and outer loops contained a few ribosomes not arranged in rosettes. The diameters of myelinated axons ranged from 0.8 to 1.8 micra, those of non-myelinated axons measured from 0.2 to 1.8 micra in diameter. Their respective axolemmas were in contact with each other.

Fig. 1. Corpus callosum of a 19-day-old affected mouse. An oligodendrocyte in the center is swollen and contains numerous vacuoles and osmiophilic bodies. Normal myelin sheaths are lacking. Occasional myelin-like structures (arrows) show various configurations. Epon-embedded 1.5 micron thick section stained with toluidine blue. × 1,400.
Fig. 2. Typical young oligodendrocyte. The abundant cytoplasm is filled with numerous organelles among which are numerous microtubules. 17-day-old normal control mouse. × 14,500.

In the corpus callosum of a 17-day-old control animal the glial cells were larger and their nuclei were two to three times the size of those at 10 days of age. The cytoplasm of these presumably young oligodendrocytes had increased in volume and become filled with abundant organelles, such as microtubules, rough endoplasmic reticulum, mitochondria and Golgi complexes (fig. 2). The population of large axons had noticeably increased.

In the 21-day-old control brain, axons in the process of initial myelination were often seen. They were surrounded by an oligodendrocytic process which formed a mesaxon but no myelin structure. This phenomenon was considerably reduced in frequency by the 26th day of age when myelination had advanced. At this time, the oligodendrocytes were smaller, the cytoplasmic organelles decreased in number, and the cytoplasmic matrix appeared condensed. The nuclei showed peripheral clumping of chromatin.

At 35 to 40 days, most oligodendrocytes were of the dense, mature type. Myelin sheaths occupied a large area of the white matter. Axons showing initial myelination were rarely seen. Numerous small axons remained unmyelinated.

b. Brains of “Quaking” Mice

In all specimens examined, the gray matter adjacent to the corpus callosum showed no recognizable alterations of nerve cells or of synapses. In the white matter, the blood vessels appeared unaltered and there was no evidence of
infiltration or proliferation of macrophages or of other mesenchymal cells. Astrocytes contained a normal number of fibrils and glycogen particles. Axis cylinders also appeared to be normal in number, size, and structure. Normal myelin sheaths were not found in animals aged 10 through 23 days; however, thin myelin sheaths were observed occasionally at the ages of 35 to 40 days. The oligodendrocytes displayed striking changes to be described in detail below.

**Perinuclear Granulomembranous Vacuoles**

At all ages, but with variable frequency, oligodendrocytes contained vacuolated dense bodies in the perinuclear cytoplasm (fig. 3 and 4). The majority were almost spherical and measured up to 1.3 micra in diameter. The individual bodies were surrounded by a trilaminar membrane and contained dense granular material and vacuoles. The granules were of variable density and seemed to aggregate under the limiting membrane. The large central area was occupied by a spherical vacuole; some vacuoles contained a granular or amorphous substance while others harbored membranous structures. Very often, the limiting membranes displayed a loose concentric lamellation. These vacuolated bodies tended to coalesce and form polycyclic configurations. Occasional bodies showed very irregular shapes.

Except for these granulomembranous vacuoles, the remaining subcellular organelles of the oligodendrocytes were identical with those seen in controls at the age of 10 days. Thus, their cytoplasm contained a comparable number of discrete microtubules dispersed among the abundant ribosomes. At the age of 17 days the oligodendrocytes were swollen and contained numerous granulomembranous vacuoles as described above, whereas ribosomes were significantly reduced in number and microtubules were scarcely seen in the perinuclear cytoplasm although they were still abundant in the periphery.

**Aberrant Myelination**

Oligodendrocytes showed striking abnormalities in the arrangement of their processes (fig. 5 and 6). Redundant cytoplasmic extensions surrounded a single axon in a random fashion and eventually compacted to form a structure reminiscent of a myelin sheath. The outer processes tended to undergo compaction first, whereas stout processes remained in proximity to the axon. This type of myelination resulted not only in a sheath of variable thickness but also in unmyelinated axonal segments covered only by enlarged oligodendrocytic processes. These processes contained numerous microtubules. The axons appeared normal in structure. Occasionally, both an axon and astrocytic process were encircled together by a myelin-like structure (fig. 5). Due to the irregular arrangement of the oligodendrocytic processes, it was often impossible to correlate faulty myelin membranes with a certain axon.

Several oligodendroglial processes were encountered which were many times larger in diameter than the thick axis cylinders (fig. 7). Some of these were surrounded by myelin-like sheaths. The apparent lack of association with an axon may perhaps result from the angle of cutting. In any event, these findings
Fig. 3. Perinuclear granulomembranous vacuoles in oligodendrocyte of 17-day-old affected mouse. × 24,000.

Fig. 4. Perinuclear granulomembranous vacuole showing polycyclic configuration. 17-day-old affected mouse. × 37,500.
Fig. 5. Aberrant myelination. At least six oligodendrocytic processes (marked 1 to 6) surround an axon (Ax) in an irregular fashion. Random compaction of the processes results in variable thickness of the myelin-like sheath, which also encircles an astrocytic process (Δ). 35-day-old affected mouse, × 34,500.

Fig. 6. Aberrant myelination. This micrograph shows redundancy of oligodendrocytic processes with compaction of the outer members which form a myelin-like sheath. 17-day-old affected mouse, × 26,400.
Fig. 7. Myelin-like structure surrounds a stout oligodendrocytic process which is much larger than the neighboring axons. A vacuole, at the top, is bounded by regularly arranged concentric membranes. 17-day-old affected mouse. X 20,500.

Fig. 8. A higher magnification of the rectangular area in Fig. 7 reveals the limiting membrane of the vacuole to resemble a myelin sheath. Arrows indicate intermediate lines. V: vacuole. OL: oligodendrocytic cytoplasm. X 118,000.

Fig. 9. Small vacuoles in the oligodendrocytic processes contain osmiophilic granules and concentric membranes. V2 shows double concentric membranes clearly. V1 and V4 the membranes are arranged rather irregularly. 17-day-old affected mouse. X 28,600.
are further indications for the irregularity in thickness and the aberrant arrangement of the oligodendrocytic processes.

**Vacuolar Disintegration in Oligodendroglial Processes**

In those oligodendroglial processes which abutted axons, vacuoles were noted frequently (fig. 9). The smaller ones measured approximately 0.5 micron in diameter and contained fine granular material which tended to aggregate at the periphery. Some vacuoles were surrounded by a single limiting membrane (fig. 11) but others were bounded by concentric lamellae with an electron density similar to that of myelin. Most concentric membranes were irregularly compacted (fig. 9) but occasional ones were arranged regularly with a repeat period of 150 Å, approximating the periodicity of major dense lines of normal myelin (fig. 7, 8, and 9). In rare instances, structures suggestive of intermediate lines were also observed (fig. 8).

The larger vacuoles, with a diameter up to 4 micra, often harbored several spherical structures of multilayered and/or single membranes, as well as granular material (fig. 10 and 11). When the compacted myelin-like membranes bounded vacuoles, they were usually loosened (fig. 11). Sometimes concentric membranes were folded upon themselves forming U-turns with a collapsed lumen (fig. 10 and 11), presumably due to compression by the expansion of neighboring vacuoles.

The largest vacuoles, measuring up to 15 micra in diameter, possessed walls partly consisting of oligodendrocytic cytoplasm and partly of myelin-like membranes (fig. 12). The membranes facing the lumen were loosely arranged, whereas their outer laminae were tightly compacted. The axons surrounded by these irregular membranes were normal (fig. 12). Although, most frequently seen in peripheral processes, vacuolar disintegration was also observed in the oligodendrocytic perikarya (fig. 13).

**Specific Alteration in Relationship to Age**

At the age of 10 days, the initial phase of myelination in the form of spiral wrapping of the axons by oligodendrocytic processes was never found. Only a few vacuoles with concentric membranes were encountered in the peripheral processes. Well-differentiated oligodendrocytes contained abundant microtubules and ribosomes, and some of these cells harbored granulomembranous vacuoles in the perinuclear region.

During the second and third week, the corpus callosum invariably showed the above-described major alterations in the oligodendrocytes characterized by abundant perinuclear cytoplasm harboring numerous polycyclic granulomembranous vacuoles which produced an irregular cell outline (fig. 13). Vacuoles containing disintegrated membranes were most numerous and largest at this time. Abnormal myelin formation with irregularly arranged redundant oligodendrocytic processes was also at a peak.

At the age of 35 to 40 days, these alterations were still present but much less frequent (fig. 14). The vacuoles were markedly reduced in number and size.
Fig. 10. This large vacuole contains aggregates of granular substances and several groups of loosely arranged membranes. The surrounding myelin-like sheaths are compact. Arrows indicate two U-turn points of the multilayered membranes of the collapsed vacuoles. 19-day-old affected mouse. × 23,000.

Fig. 11. The large vacuole on the left could have been formed by coalescence of several small vacuoles. Two loosened membranes surrounding a vacuole show U-turns (arrows). The oligodendrocytic process on the right harbors a vacuole surrounded by a single membrane (V). The myelin-like lamellae are wavy and lack compaction. 17-day-old affected mouse. × 25,000.
Fig. 12. The wall of this very large vacuole is formed by oligodendrocytic cytoplasm (OL) and also by myelin-like membranes (M). The sheaths of two intact axons (A) extend into the vacuole where they appear to be disintegrating. 17-day-old affected mouse. × 17,000.

Fig. 13. Corpus callosum of 10-day-old affected mouse. The oligodendrocytic cytoplasm contains a large vacuole (V) and many granulomembranous bodies. Aberrant myelination and vacuolar disintegration are seen in the right side of the picture. N: nucleons of oligodendrocyte. × 8,500.
Fig. 14. Corpus callosum of 35-day-old affected mouse. Two rows of interfascicular oligodendrocytes are seen. Perinuclear granulomembranous bodies are still present as shown in the left upper corner. Demyelinating vacuoles are small and rare (arrows). Some axons in the left side of the picture are ensheathed by very thin myelin. × 5,000.

Fig. 15. Longitudinally cut axon ensheathed by spiral myelin. The terminal (also known as "lateral" and "paranodal") loops are irregularly arranged. Two of them contain membranous vacuoles (V). Ax: axon. 35-day-old affected mouse. ×25,500.
Redundancy of oligodendrogial processes was likewise less common than in the younger affected animals. Some oligodendrocytes still contained a few perinuclear granulomembranous bodies, whereas others showed normal cytoplasm. They were arranged in typical interfascicular fashion. The majority of axons remained unmyelinated. A few axons, however, were surrounded by a thin sheath with from 3 to 6 major dense lines (fig. 14). These myelin sheaths showed a relatively uniform thickness. On longitudinal section, however, the lateral loops were still stout, arranged in slightly asymmetrical fashion, and contained an occasional small vacuole (fig. 15).

*Acid Phosphatase Study*

In the cerebral cortex, lead phosphate precipitation was observed in the Golgi complexes and in some small vacuoles or lysosomes of the nerve cells. This was interpreted as being normal.

In the white matter, the oligodendrocytes displayed significant activity of the enzyme in the perinuclear granulomembranous bodies. The reaction product was precipitated on the granular material and on the membranous structures as well as in the vacuolar spaces (fig. 16). In the vacuoles which contain degradation products of myelin, acid phosphatase reaction product was hardly identifiable, due to a large amount of non-specific lead precipitate around the myelin-like membranes.

*Fig. 16.* A granulomembranous body in the subcortical white matter of the cerebrum from a 23-day-old affected mouse. Acid phosphatase reaction product occurs on the granular matrix and membranous material as well as in the vacuoles. × 81,000.
c. "Quaking" Peripheral Nerve

Only the intracranial portion of the trigeminal nerve from an affected mouse aged 19 days was examined. The majority of the axons were myelinated in normal fashion, but a few abnormal Schwann cells contained granulomembranous bodies similar to those in the oligodendrocytes. A few unmyelinated large axons and myelinated axons with partial compaction, as described by Samorajski et al. (12), were also observed.

DISCUSSION

The observations of the corpus callosum of affected animals at varying ages enabled us to recognize and to study the evolution of three major pathomorphologic changes in oligodendrocytes: abnormal myelin formation, vacuolar disintegration of faulty myelin and accumulation of granulomembranous bodies in the perinuclear cytoplasm.

The following investigators: Kruger and Maxwell (15), Caley and Maxwell (16) and Mori and Leblond (17, 18) have described normal oligodendrocytes which may be identified by a regular, round or oval nucleus and cytoplasm rich in ribosomes and microtubules and having relatively few fine processes. They noted a wide variety in cell size and in nuclear and cytoplasmic density; however, most cells were dark. Microtubules in the cell body and processes were observed to be prominent by others (19 to 23). In the brain of the 10-day-old "quaking" mouse, the oligodendrocytes showed the above appearance despite the presence of perinuclear granulomembranous vacuoles. At the age of 17 days many oligodendrocytes of the "quaking" mice were considerably swollen and their cytoplasm was loaded with granulomembranous bodies which made them resemble macrophages. The microtubules, which were abundant at the age of 10 days, were rarely seen in these swollen cells. A resemblance of oligodendrocytes to macrophages had been observed by Maxwell and Kruger (24), with an extensive accumulation of pleomorphic osmiophilic granules in the swollen reactive oligodendrocytes in the irradiated rat brain.

The perinuclear granulomembranous bodies were identified as lysosomes by their acid phosphatase activity. These secondary lysosomes most likely represent autophagosomes and their residual bodies, presumably resulting from the degradation of abnormal myelin. Similar structures, also containing granules and membranes were likewise present in the peripheral oligodendrocytic processes but in larger numbers and of greater size, suggesting that degradation of defective myelin is carried out in the processes rather than in the perikaryon.

Our morphological observations indicated that the digestive activity of lysosomes is normal in the "quaking" mouse brain, because vacuolation is most prominent at 3–4 weeks of age, but is markedly reduced by the age of 6 weeks. Abnormal myelin is abundant in the young animals, but has disappeared by the 6th week leaving the majority of the axons naked. Perinuclear lysosomes are still present at the age of 40 days but they are not increased in number and in size after the 23rd day of life.

The conclusion that the lysosomal activity in the brains of "quaking" mice is
normal, is supported by the results of biochemical studies. Siakotos et al. (25) measured the activity of several lysosomal hydrolases and observed no significant differences between mutants and controls. This is in contrast to Kurz and Kanfer (26) who reported a reduction of alpha-mannosidase and aryl-sulfatase in mutants.

Normal myelination in the central nervous system proceeds by spiral wrapping of oligodendrocytic plasmalemna with retention of cytoplasm forming inner, outer, and lateral loops (22, 23, 27 to 40). The oligodendroglial cells of “quaking” mice do not produce the normal regular spiral wrapping but rather generate irregular myelin-like structures by random compaction of multilayered processes, perhaps the result of structural molecular defects in the oligodendrocytic plasmalemma. Biochemical support for this hypothesis is extrapolated from the work of Baumann et al. (41) and Jaque et al. (42), who demonstrated a marked reduction in the ratio of long chain fatty acids to short chain fatty acids in the brains of “quaking” mice. Baumann has recently shown (43) that even normally formed myelin, i.e., by spiral wrapping, contains extremely low amounts of C24 fatty acids. Therefore, failure of spiral wrapping cannot be attributed to an absence of C24 fatty acids alone, but some other structural defects in the myelin membrane must be postulated. Nevertheless, it remains to be shown whether a myelin synthesizing enzyme is deficient or whether a structural protein is abnormal in the brain of “quaking” mice. It is interesting to note that there is marked reduction in the activity of cyclic 2',3'-AMP phosphohydrolase, an enzyme that occurs exclusively in myelin, in mutant mice (25, 44), although the exact role of this enzyme is not known.

The phenotypical alterations of the “quaking” mutant mouse are in contrast to those of the human leukodystrophies, such as the metachromatic type (45, 46) and the globoid cell type (47), which result from a deficiency of certain hydrolytic enzymes of the lysosomal system. Demyelination in these conditions may be attributable to the dysfunction or death of the oligodendrocytes due to an accumulation of substrate in the residual bodies. However, the abnormalities in brains of “quaking” mice seem best described by Poser’s concept of “dysmyelination”, being an inborn error of metabolism of myelinogenesis which results in an aberrant constitution of the myelin sheaths (48) and subsequent deterioration.

In the corpus callosum, we found a few thinly myelinated fibers with normal arrangement in 6-week-old mutants, but no such structures were present at the ages of 2 to 4 weeks. Others who examined older mutants (11, 12), also observed normally formed but thin myelin sheaths in other parts of the central nervous system, for instance in the spinal cord, optic nerves and the corticospinal tracts of the medulla oblongata. It therefore appears possible that two morphologically different types of dysmyelination occur in the brain of the “quaking” mouse. The first variant we call deformed dysmyelination which is initiated by a nonspiral configuration of oligodendrocytic processes, followed by production of sheath-like structures and terminating in vacuolar disintegration of the aberrant myelin. The second we term spiral dysmyelination, in which the myelin occurs as spiral wrapping of oligodendrocytic plasmalemna as in nor-
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...mal myelination but the completed sheaths appear much thinner than normal. Our observations indicated that "deformed dysmyelination" precedes "spiral dysmyelination", at least in the corpus callosum. This phenomenon appears to be associated with oligodendrocytes laden with perinuclear lysosomes. As the occurrence of "spiral dysmyelination" coincides with the appearance of interfascicularly arranged oligodendrocytes, these two events, in turn, might be causally related.

A human genetic disorder which is manifested by abnormal myelin formation similar to that found in the "quaking" mouse is Pelizaeus-Merzbacher disease (6, 7). This sex-linked recessive disorder is manifested by an onset in early infancy followed by extremely slow progression of the illness. Neuropathologically, Pelizaeus-Merzbacher disease is marked by a widespread absence or paucity of myelin sheaths throughout the central nervous system with sparing of the peripheral nervous system. There is no evidence of demyelination; the "quaking" brain shows similar alterations in the older mutants, as seen in the corpus callosum after 6 weeks of age. The peripheral nervous system is seemingly spared. In both disorders, the primary phenotypical manifestation is considered to be the dysmyelination, although the early changes in Pelizaeus-Merzbacher disease remain unknown. Since the pathognomonic morphologic alterations might be present for only a short period of time, as is the case in the mouse, it might be difficult to find similar changes in the human brain biopsied in random fashion. Absence of myelin sheaths (6, 7), "status hypomyelinicus" (12), and gliosis, might well be the end stages of a process, the evolution of which remains unknown. By using an animal model we could follow the entire evolution of the disorder and thus provide new insight into the problem of dysmyelination and possibly of sudanophilic leukodystrophy as reviewed by Poser (48).

SUMMARY

The pathognomonic change of the brain of the "quaking" mouse is a dysfunction of the myelin-forming system, manifested by changes in the oligodendroglia. In the 3rd and 4th weeks of life the irregularly arranged plasmalemma randomly forms myelin-like structures which disintegrate immediately thereafter and are digested in vacuolated lysosomes. Simultaneously with these alterations in the terminal processes, granulomembranous bodies representing digestion vacuoles accumulate in the perinuclear cytoplasm. During the 7th week of life, faulty myelin and vacuoles have disappeared, but the axons remain unmyelinated, except for occasional tardy myelin formation in the form of ordinary spiral wrapping with a small number of lamellae. The disturbance in myelin formation in the "quaking" mouse occurs in the form of "deformed" and of "spiral" dysmyelination, presumably resulting from structural molecular defects of the oligodendrocytic plasmalemma.

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