



# **Developmental Neuropathology**

**Reinhard L. Friede**

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REINHARD L. FRIEDE, M.D.

Professor of Neuropathology  
Case Western Reserve University  
Cleveland, Ohio

presently

Professor of Neuropathology  
University of Zurich  
Switzerland

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## Preface

The present text was envisioned as a supplement to existing texts on human neuropathology, covering only those aspects of pediatric neuropathology which pertain to and are peculiar of the immature nervous system. No coverage—or only brief comment—is given to diseases commonly found in adults which may, on occasion, occur in childhood or infancy as well. The subject matter is divided into three main categories: 1. The “acquired” lesions dating to the fetal, perinatal or early postnatal periods, 2. the malformations, and 3. the heritable metabolic defects. The first 6 chapters (2–7) are reserved to the lesions most intimately linked to the circumstances of birth. There is some inherent ambiguity in distinguishing between “acquired” lesions and malformations, as, indeed, no sharp distinction can be made between one and the other. Many malformations result from diseases acquired during fetal life and their peculiarity resides in the fact that the organ becomes affected before its development terminates and in such a way that its subsequent development becomes deranged or partly abrogated. A variety of causes acting at the same developmental period or over a common pathogenetic mechanism may produce the same type of derangement, including chemical, physical, infectious or genetic factors, as pointed out repeatedly in the text. Consequently, the definition of a malformation, as differing from an “acquired” residual lesion was made dependant on evidence for the derangement of developmental processes subsequent to the acquisition of the disease. The hemispheric defects of porencephaly, for example, are described among the acquired lesions (chapter 11) while the polymicrogyria that often fringes these defects is described among the malformations (chapter 29) as it clearly results from deranged development of the affected cortex subsequent to the formation of the main lesion. This distinction is carried to a fine point in listing the aplasia of the cerebellar granular layer among the malformations of the cerebellar cortex (chapter 30): recent experimental evidence clearly identified the lesion with a developmental failure subsequent to a destruction of the superficial granular layer of the cortex. In this peculiar instance a derangement of development may still be induced postnatally, at least in the rat. In reporting on the “acquired” lesions and the malformations relatively great weight was given to the original reports and the older literature, as the detailed morphologic accounts published during the nineteenth and early present century often left only details to be covered to later authors. The number of references cited had to be restricted severely for obvious reasons, but it is hoped that those

given will suffice for locating the remainder of the literature. Knowledge on the inherited metabolic defects, covered in the third part, has progressed by leaps and bounds during the past two decades, and much of the labours of generations of morphologists have been negated in the process. Consequently less attention is paid to the older literature, concentrating on the recent insights and the resultant reclassification of diseases. The third part also includes a number of entities of unknown etiology, listed among the inherited metabolic defects according to their morphologic similarities but without pretent of prejudging their true nature.

Completion of this book would have been impossible without the generous help and advice of many colleagues and associates, particularly without the untiring help of Mrs. Frida Wallenstein in preparing and editing the manuscript. The author is also indebted to Dr. Angevine for editing Table 1, and to Drs. Anzil, Barson, Blinzinger, Carpenter, Powell, Lampert, Lindenberg, and Schochet who kindly permitted use of their illustrations.

Zurich, October 1975

R. L. Friede

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## 1. Gross and Microscopic Development of the Central Nervous System

This chapter concerns mainly the gross and microscopic aspects of normal cerebral development during the second half of gestation, that is the period usually encountered by the pathologist. Its purpose is to provide a frame of reference for assessing normalcy in the brain of the fetus and of the newborn, to point out changes of borderline significance, and to establish base lines for the evaluation of gross or microscopic pathologic changes. The chapter does not provide an extensive review of normal embryology of the human central nervous system; developmental principles are cited only to the extent to which they are of help in interpreting abnormal tissue structure, and pertinent data are generally included in the respective chapters of the text.

**Timing of Origin of Various Neuronal Groups.** The time of origin of the neurons of various nuclear groups can be determined from the incorporation of labelled thymidine into the nuclei of dividing cells, as shown by radioautography. The central nervous system of the mouse has been studied in greatest detail, and Table 1 provides a "calendar" of neuronal development in the mouse brain. The timing of origin of neurons in the human brain has not been determined with similar accuracy, but Table 1 permits reasonable extrapolation as to the order in which the various groups form during early fetal development. O'Rahilly and Gardner (1971) tabulated staged timing of developmental events in the central nervous system during the first 8 weeks of fetal life.

**Mass Growth of the Brain.** The growth of the central nervous system is exceptionally rapid during the early fetal period; for example, the increase in its volume between the 2nd and 3rd month amounts to 416 percent, while it amounts to only 42 percent at the end of gestation (Mikhailets, 1952). The rapid initial growth of the CNS is precocious when compared with other body tissues; its weight comprises 21 percent of body weight at the 6th month, 15 percent at term, and 3 percent in the adult (Wilmer, 1940). The overall growth of the CNS is the composite product of different growth rates for its main portions. The increase in the volume of the cerebral hemispheres is slow and steady between the 2nd and early 6th month and accelerates thereafter. The brain stem grows most rapidly between the 2nd and the end of the 6th month, less rapidly thereafter. The cerebellum grows slowly between the 2nd and 5th month; then an exceptionally rapid increase in volume begins and continues until the 6th postnatal month (Dunn, 1921). The main portions of the brain thus constitute different fractions of total weight at different phases of development. For example, cerebral hemispheres, cerebellum and

Table 1. *Timing of Origin of Neurons in Mouse Brain*

Nucleus	Site of Origin	Time of Origin (days)	Author
<i>Brain stem</i> (most nuclei completed by day 14)			
Cranial motor nuclei	Primitive ependyma	10 and earlier	Taber, 1963, 1964
Secondary sensory neurons	Primitive ependyma	10 and 11	Taber, 1963, 1964
Reticular formation	Ependyma and rhombic lip	10 and earlier	Taber, 1963, 1964
Inferior olivary nucleus	Rhombic lip, caudal	10	Taber, 1963, 1964
Pontine gray matter	Rhombic lip, caudal	10-16	Taber Pierce, 1966
Nucleus reticularis tegmenti	Mostly primitive ependyma of pons	12-13	Taber Pierce, 1966
Cochlear nucleus	Rhombic lip, middle portion	Large neurons, 10-12; medium and small, 11-13; granular cells, 12-18	Taber Pierce, 1967
<i>Cerebellum</i>			
Purkinje cells and roof nuclei	Subependymal germinal layer (direct outward migration)	10-13	Uzman, 1960
Golgi II neurons of granular layer	Subependymal germinal layer (direct outward migration)	10-15	Miale and Sidman, 1961 Miale and Sidman, 1961
Superficial granular layer	Rhombic lip, migrates to cerebellar surface	Beginning of migration, 13 days; continued division	Miale and Sidman, 1961
Granule cells	From superficial granular layer by inward migration	Late embryo to 15 days postnatal	Miale and Sidman, 1961
Small cells of roof nuclei		13 days to 1st postnatal week	Miale and Sidman, 1961
<i>Cerebral Hemispheres</i>			
Thalamus: ventral lateral, zona incerta, dorsal lateral, geniculate, posterior pretectal, lateral, posterior ventral	Primitive ependyma of third ventricle; general gradients in timing caudal-rostral, ventral-dorsal, lateral-medial	10-15	Angevine, 1970
Thalamus: anterior group; paratenial, paraventricular, reuniens, rhomboides		10-15	Angevine, 1970
Habenula	Ventricular matrix	10-16	Angevine, 1970
Amygdaloid nucleus	Ventricular matrix	10; peak 12	Sidman and Angevine, 1962

Basal cortical nuclei and claustrum	Ventricular matrix	10; peak 12-13	Sidman and Angevine, 1962
Caudate nuclei and putamen	Ventricular matrix	10; peak 12-13	Sidman and Angevine, 1962
Medial septal nuclei	Ventricular matrix	12-15	Sidman and Angevine, 1962
Olfactory bulb:			
Triangular cells	Local matrix	10-11	Hinds, 1966
Mitral cells		11-13	Hinds, 1966
Rest of cells (inside out order)		11-20	Hinds, 1966
Granule cells		11-20 postnatal	Hinds, 1966
Hippocampal region:			
Entorhinal, subicular region,		11-15	Angevine, 1965
hippocampal sector CA <sub>2</sub>		Continues to day 19 (birth)	
Hippocampal sector CA <sub>1</sub> , CA <sub>3</sub>			
Granule cells of fascia dentata			
(outside in order)			
Convexity cortex:			
Deep layers	Periventricular matrix	11	Angevine and Sidman, 1962
Upper layers	Periventricular matrix	13-15	Angevine and Sidman, 1962
Most superficial layers	Periventricular matrix	17	Angevine and Sidman, 1962

Table 2. *Brain Weight Related to Gestational Age* (Modified, Gruenwald and Minh, 1960)

Gestational Age (weeks/days)	Brain Weight (gm)	Body Weight (gm)	Body Length (cm)	Number of Cases
23/5 ± 2/3	70 ± 18	500	29.4 ± 2.5	317
26/0 ± 2/6	107 ± 27	750	32.9 ± 3.0	311
27/5 ± 3/1	143 ± 34	1,000	35.6 ± 3.1	295
29/0 ± 3/0	174 ± 38	1,250	38.4 ± 3.0	217
31/3 ± 2/3	219 ± 52	1,500	41.0 ± 2.7	167
32/4 ± 2/6	247 ± 51	1,750	42.6 ± 3.1	148
34/6 ± 3/2	281 ± 56	2,000	44.9 ± 2.8	140
36/4 ± 3/0	308 ± 49	2,250	46.3 ± 2.9	124
38/0 ± 3/2	339 ± 50	2,500	47.3 ± 2.3	120
39/2 ± 2/2	362 ± 48	2,750	48.7 ± 2.9	138
40/0 ± 2/1	380 ± 55	3,000	50.0 ± 2.9	144
40/4 ± 1/6	395 ± 53	3,250	50.7 ± 2.6	133
40/4 ± 1/5	411 ± 55	3,500	51.8 ± 3.0	106
40/6 ± 2/3	413 ± 55	3,750	52.1 ± 2.3	57
41/4 ± 1/3	420 ± 62	4,000	52.4 ± 2.7	31
41/2 ± 2/1	415 ± 38	4,250	53.2 ± 2.5	15

brain stem respectively constitute 88.6, 3.1, and 8.3 percent of total brain weight at the 3rd month, 92.7, 5.8, and 1.5 percent at birth, and 88.0, 10.1, and 1.9 percent at the age of 20 years. The weight of the whole brain more than doubles during the first 9 months after birth and reaches over 90 percent of the adult weight by the 6th year (Scammon, 1933). The postnatal increase in cranial circumference serves as a convenient clinical parameter of normalcy in cranial development (Silver and Diemer, 1948; Nellhaus, 1968; Kantero and Tiisala, 1971).

**Cerebral Cortex.** The development of the cerebral hemispheric surface proceeds gradually from the flat (lissencephalic) brain of the fetus to the gyral pattern of adults. The Sylvian fissure is apparent at approximately 14 weeks gestation, forming a shallow indentation into the smooth hemispheric surface. The opercula are formed by the growing cortex next to the Sylvian fissure eventually concealing the insula. Indentations of the cortical surface leading to the formation of the Rolandic and calcarine fissures appear between 24 and 26 weeks, followed by the demarcation of the superior temporal and the pre- and postcentral gyri. Formation of the cortical gyri proceeds rapidly at the 30th week of gestation, and the entire hemispheric surface is gyrate by approximately 32 weeks; the gyri, however, are less numerous than in the adult brain. Pryse-Davies and Beard (1973) demonstrate that the gestational age can be estimated by counting the number of convolutions crossed by a line from the frontal to the occipital pole above the insula and adding 21 to the gyral count; this gyral index is most reliable between 28 and 37 weeks, less reliable between 37 weeks and term. The cortical surface area of the newborn measures approximately 679 cm<sup>2</sup>, of which 61 per cent is intrasulcal (Hessdoerffer and Scammon, 1935). The hemispheric surface more than doubles during postnatal growth, to reach an adult value of approximately

1,600 m<sup>2</sup>. This growth is accompanied with an increase in the size and number of gyri, so that the intrasulcal portion of the adult cortex is about the same as that in the newborn. The adult cortical surface is reached by the 2nd year of life.

The development of the laminar architecture of the cerebral cortex has been studied extensively, and only the most essential features are reviewed here. During early embryogenesis (the 5th to 6th week) the hemispheric wall consists of an inner layer of matrix tissue (the germinal layer) and a superficial, acellular zone (the Randschleier). The cerebral cortex separates from the matrix tissue by the 7th week, as neuroblasts migrate from the matrix to the surface of the tissue. A layer of low cell density forms between cortex and matrix tissue, increasing subsequently in width to become the white matter. The cortical cell population is fed by the continued proliferation of matrix cells located in the periventricular tissue, reaching the cortex by their successive migration across the white matter. Autoradiographic studies (Table 1) have shown that the cortical layers develop from inside out from successive waves of neuroblasts, the first one forming the deep cortical layer and the later waves migrating sequentially past their predecessors to the cortical surface (Angevine and Sidman, 1961; Sidman and Angevine, 1962). In the rat, the 5th and 6th cortical layers form at the 16th and 17th days, the fourth layer on the 18th day, and the second and third layers on the 19th to 21st days (Berry and Rogers, 1965). The observations of Rakić (1972) suggest that the migration of neuroblasts toward the cortex is guided by their movement along ependymo-glia processes which extend from the ventricular walls across the white matter to the cortical surface. The speed of migration of neuroblasts was estimated as 15 to 30  $\mu$ , that is once or twice the length of the cell body, per hour (Hicks and D'Amato, 1968). Altman (1966) determined speeds of 50 to 750  $\mu$  per day in rat olfactory bulb and cerebellum.

The cerebral cortex of the 5-month-old fetus shows a molecular and a cell layer; the latter is divided into a thin outer portion of high cell density and a thick inner portion of low cell density. The six-layered neocortex begins to emerge from this pattern by the 6th month, first with a gradual differentiation of the fifth and sixth layers. The first neurons to mature are the pyramids of the deep cortical layers; they exhibit, with conventional staining methods, large cytoplasmic perikarya and vesicular nuclei when most of the remainder of the neuronal population is still in the neuroblast stage. Illustrations of typical cortical profiles at various stages of fetal development were published by Larroche (1962). The changes in cortical laminar architecture are accompanied with a corresponding redistribution in the activity of several oxydative enzymes (Friede, 1966).

The rearrangement of cortical layering is accompanied with a progressive decrease in the packing density of nerve cells, a universal feature of maturation of gray matter. It results from the increase in the volume of neuropil, which, in turn, is due to the dendritic growth and to the ramification of afferent processes in the tissue between the neuronal perikarya. The growth in the thickness of the cerebellar and hippocampal molecular layers is equivalent to the growth of neuropil in cerebral cortex.

A peculiar aspect of cerebral cortical development is the transient appearance of a superficial granular layer in the form of a thin lamina of matrix cells immediately underneath the leptomeninges. This layer appears first at the 12th to 13th week of gestation in the basal allocortical zones, where it derives from columns of cells ascending from the periventricular matrix (Brun, 1965). It spreads into the isocortex during the 13th to 14th week and covers the entire convexity by the 16th to 18th week, reaching greatest thickness by 22 weeks. Subsequent involution of the superficial granular layer seems to result from the migration of cells into the cerebral cortex. The layer disappears in the insula and anterior cingular cortex by 27 to 29 weeks, in the precentral cortex by 32 weeks, in the calcarine cortex by 33 weeks, in the postcentral and posterior cingular cortex at 36 weeks, and in the frontal and occipital cortex at 39 weeks. Remnants of the superficial granular layer persist in term infants at the inferior temporal and orbital cortex. Brun thought that persistence of the superficial granular layer in certain malformations, such as in polymicrogyria, constitutes a marker of the teratogenic determination period; he also considered the layer the source of various types of abnormal cellular hyperplasias of the cortical surface (Chapter 29).

The Ammon's horn is generally considered a phylogenetically old portion of the cerebral cortex, but radioautographic studies have shown that at least part of its neurons originate late in development (Angevine, 1965). A peculiar aspect of the maturation of the Ammon's horn are marked differences in the rate of maturation of the neurons in its sectors. The neurons of the so-called "resistant sector" mature first, followed closely by those in the "endplate". In term infants, these neurons have vesicular nuclei and significant cytoplasmic bodies; whereas, those in Sommer's sector are still neuroblasts (Fig. 1). Development of the cells in Sommer's sector progresses from outside in, starting in the outermost portion of the cell layer; maturation is concluded by about the 2nd year. The immaturity of the Sommer's sector in newborns is a potential source of error in identifying perinatal asphyctic lesions. The segmental differences in cellular maturation may well explain patterns of selective vulnerability of the Ammon's horn characteristic of kernicterus (Chapter 8) or of pontosubicular neuronal necrosis (Chapter 7).

**White Matter.** The hemispheric white matter grows slower than the cortical gray matter during fetal development, but the growth of white matter continues postnatally long after the gray matter has reached its definite volume. The growth of the cortex subsides by the 2nd year of life; that of the hemispheric white matter continues until after the first decade because of continued accumulation of myelinated fibers and increase in their calibers (Scammon, 1933). Because of the differences in the rate and the timing of growth of gray and white matter, their proportions change during development. Between the 6th and 18th postnatal month for example, the volume of white matter is relatively small when compared with the nearly fully developed, deeply gyrate cortex. This normal aspect of cerebral development should not be mistaken for hypoplasia of white matter, but it may persist in certain diseases (Chapter 41).

The microscopic structure of the developing cerebral white matter is

determined to a large extent by two successive events occurring with considerable overlap. The passing of waves of migrating neuroblasts on their way to the cortex is the dominant feature of early fetal white matter. It is superseded and replaced toward the end of gestation by the proliferation of glial tissue associated with myelination (myelination gliosis). The following sections refer to these two events.

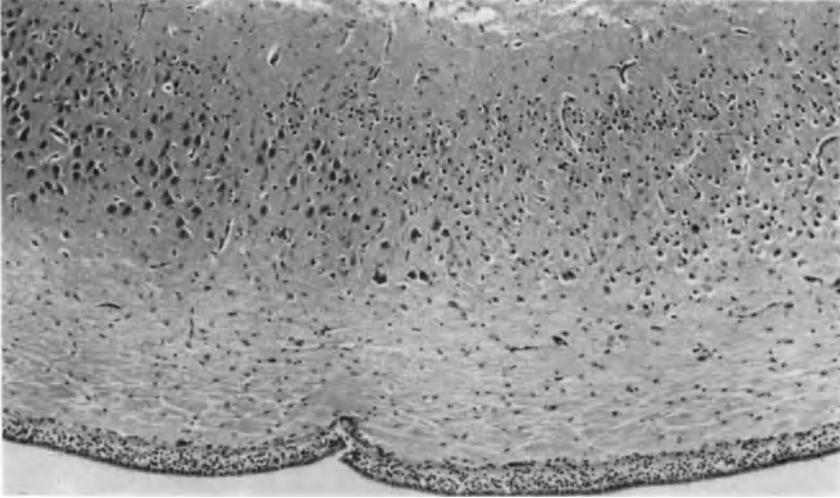


Fig. 1. Difference in neuronal maturation between Sommer's and resistant sectors of the Ammon's horn in a term newborn; H & E  $\times 80$

**Periventricular Matrix Tissue.** The matrix tissue of the lateral ventricles forms a subependymal layer of tightly packed immature cells extending over the entire ventricular wall up to 30 weeks of gestation. At this time, the layer begins to thin out and it loses continuity first at the fornix and the corpus callosum, the dissolution progressively extending toward the corners of the lateral ventricles where the solid layer breaks into islands of cells by the 36th to 39th week. Matrix cells often persist longest in perivascular tissue. Term infants show only scattered islands of tightly packed matrix cells in the ventricular wall, except for a thick cushion at the ganglionic eminence between the thalamus and the caudate nucleus. This cushion becomes fragmented during the first 3 postnatal months, and nearly all of the matrix tissue normally disappears by the first year of life. Nests of matrix cells also occur in the basal portions of the frontal lobe, off the ventricular surface.

Waves of migrating cells may produce a marked layering of cell density in the early fetal white matter. This pattern persists longest in the occipital lobe, where a concentric periventricular halo of increased cell density may encompass the occipital horn, being separated from the subependymal matrix tissue by a zone of lower cell density. Undifferentiated cells are scattered

throughout the hemispheric white matter up to and shortly after the dissolution of the periventricular matrix. The presence of these cells needs to be considered when assessing pathologic changes in the newborn white matter, as they are superficially similar to migrating microglia. The identification of necrobiotic changes in migrating cells is also difficult as their nuclei are normally small and dense and their cytoplasm is too sparse to allow evaluation with conventional stains.

**Myelin Formation, Fine Structure.** Myelin formation, in a narrow sense, consists of the helical wrapping of surface membranes of Schwann cells, or of oligodendroglia, respectively, around axons (Geren, 1954). This phase of sheath formation, however, merely constitutes the end product of a series of cellular and chemical events involving the sheath cell population as well as the axon during the myelination period.

Prior to the onset of myelination there are few sheath cells in the white matter, both in terms of their number per volume tissue or of their number per density of nonmyelinated axons. Proliferation of sheath cells is initiated before the onset of sheath formation and may reach its peak before myelinated fibers become discernible by light and electron microscopic methods (Schonbach *et al.*, 1968). The proliferating sheath cells contact the axons and engulf the axis cylinder with their cytoplasm. Formation of the sheath begins with the wrapping of the mesaxon of the sheath cell around the axis cylinder, first in the form of a loose spiral of alternating layers of cytoplasm and of cell membranes. This wrapping is followed by obliteration of the intracellular compartment; the inner surfaces of the cell membranes fuse and form the major dense line of the sheath by their coalescence (Peters and Muir, 1959). The process of sheath formation is associated with metabolic activation of the sheath cells, evident from radioautographic and enzyme histochemical data and from changes in the density of cytoplasmic organelles. Attachment of the sheath cell to the axon occurs with the onset of axonal growth and may be triggered by initial axon enlargement; it is, however, not rigidly linked to a specific dimension of the axon (Matthews and Duncan, 1971). The mechanism responsible for the initial contact between sheath cells and axis cylinder and for triggering the formation of the initial turns of the sheath cell membranes around the fiber are not known. The subsequent deposition of additional turns of myelin sheaths occurs in proportion to the growth of the axon (Friede and Samorajski, 1968; Samorajski and Friede, 1968); axon growth, in turn, occurs in proportion to the growth of the perikarya of the neurons (Martinez and Friede, 1970). Experimental data suggest that the amount of myelin formed by the sheath cell is controlled by the rate of expansion of the growing axis cylinder (Friede, 1972).

The basic aspects of myelin formation are similar for peripheral and central nerve fibers, but there are differences in the types of relations established between the sheath cell and the axon. A Schwann cell in a peripheral nerve attaches its perikaryon to one given fiber, and forms a sheath only around the engulfed segment of this one fiber. An oligodendroglia cell projects processes to a number of axons which it myelinates; estimates of the number of fibers myelinated by a given oligodendroglia cell vary considerably,

from 4 or 5 (McFarland and Friede, 1971) to more than 50 (Matthews and Duncan, 1971).

**Regional Timing of Myelination.** Myelination of any given fiber system involves all the events described above, but different fiber tracts myelinate at different developmental periods; even the component populations of a given tract may differ in timing (Matthews and Duncan, 1971). Myelination of tracts proceeds, generally speaking, in a caudo-cranial order earlier in the spinal cord than in the cranial portions of the CNS. The schedule of myelination was first elaborated by Flechsig (1876), and useful reviews were published by Lucas Keene and Hewer (1931) and, more recently, by Riggs and Rorke (1969).

The following fiber systems begin to show myelin sheaths by 14 weeks gestation: Posterior and anterior spinal roots, tractus cuneatus (Burdach), direct cerebellar tracts, Gower's tracts, anterior ground bundle, medial longitudinal bundle, and all cranial nerves except the cochlear, the optic and the sensory trigeminal.

At 22 to 24 weeks, myelination is also seen in the tractus gracilis (Goll), the lateral and posterior ground bundles, the connecting fibers of the gray matter in the cord, the olivary and cerebellar connections, the tractus retroflexus, ansa lenticularis, and the cochlear and sensory trigeminal nerves.

Just before birth, myelination commences in Lissauer's bundle, the cortico- and rubrospinal tracts, the external arcuate fibers, the pontine fibers, cortico-cerebellar fibers, striothalamic bundles, Meynert's commissure, and the optic nerve and radiation. Myelination of the hemispheric white matter commences gradually during the first 2 postnatal years and continues to juvenile age; postnatal myelination by the 5th to 9th postnatal month is also observed in the retroflex tract, the olivo-spinal tract and the fornix.

Myelination of peripheral nerves generally occurs during fetal life, at about 14 to 16 weeks in the brachial and sciatic plexus; its electron microscopic features in human fetuses (Cravioto, 1965) resemble those known from the examination of laboratory animals. The peripheral portion of the nerve root beyond the glia-Schwann cell border stains much more intensely with conventional myelin stains than its central portion. The difference is due to the different proteolipid-protein composition of peripheral and central myelin; it may give the misleading impression of a much earlier onset of myelination in the distal portion of the root.

**Myelination Gliosis.** The stage of myelination can be assessed in routine sections of white matter, even without myelin stains, from the extent of proliferation and the density of glia cells, or myelination gliosis (Roback and Scherer, 1935). Counts in the human internal capsule show a more than six-fold higher density of glia cells per volume tissue at term than at the 6th fetal month; similar but smaller differences are found in the hemispheric white matter (Friede, 1961). Maximum cell density at the peak of myelination gliosis may be greater than in the adult brain for some tracts as the glia cells become dispersed later on by the growth in the caliber of the myelinating fibers.

The proliferating glial cells of myelination gliosis have not acquired the