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Maturation of Normal Primate White Matter: Computed Tomographic Correlation

Robert M. Quencer¹

Five infant baboons were examined with computed tomography (CT) during the first year of their lives to determine the rate and degree of normal white matter maturation in frontal, occipital, and parietal areas. The increase in CT numbers with age was correlated with gross and histologic specimens. Two phases of maturation were identified: a rapid phase (first 8–12 weeks) and a gradual phase (after 12 weeks). Frontal white matter was the most immature in the immediate postnatal period but it became equal in attenuation to the other regions by 4 weeks of age. Knowledge of white matter maturation rates may be particularly useful in cases of neonatal hypoxia/ischemia where zones of periventricular hypodensity are identified. The failure of such regions to follow a normal rate of maturation may indicate damage to the white matter and have significant prognostic implications.

Although the measurement of cerebral tissue attenuation by computed tomography (CT) has been the subject of a number of reports within the past few years [1–9], determining the significance of regions of low attenuation in the white matter of newborns has remained a difficult problem. In order to understand the CT appearance of neonatal white matter and to explain its change during the first year of life, knowledge of the rate and degree of white matter maturation during normal infancy is necessary. In this report, infant primates (baboon) underwent a comparative CT/anatomic study of the change in appearance of the frontal, parietal, and occipital white matter with age. Possibly, the accompanying maturation curves will be useful in evaluating immature white matter in human infants and distinguishing normal from leukoencephalopathic processes. Preliminary results of this work have already been reported [10].

Materials and Methods

The brains of five full-term normal baboons (*Papio hamadryas*) were scanned (GE CT/T 8800) and examined grossly and histologically to evaluate, at various time intervals up to 1 year of age, the change in appearance of the frontal, parietal, and occipital white matter. The baboon was chosen for this study because its brain was sufficiently large to allow proper separation of gray from white matter on CT and because the cerebral maturation of primates approximates that of a human infant. The animals were scanned at about 1, 4, 12, 26, and 52 weeks of age (table 1). Because of the clinical demands on the CT unit, these animals could not all be scanned at exactly the same number of days after birth, but, for the purposes of this report, the time of scanning will be referred to as the intervals mentioned above.

Noncontrast CT was performed in the axial plane parallel to the orbitomeatal line with contiguous 5 mm thick sections through the entire brain. The animals were sedated with ketamine before scanning. The CT radiographic factors were 120 kVp, 200 mA, 2.2 msec pulse width, a 9.6 sec scan speed, and a 25 cm field size. A daily calibration check before scanning was performed to ensure the constancy and comparability of the attenuation coefficient measurements.

The periventricular white matter in the frontal lobes, the forceps major in occipital lobes,

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and the parietal centrum semiovale were identified on each scan. These regions were far enough away from the cortical gray matter and the bony calvarium to avoid including these structures with the white matter measurements. CT numbers, expressed as Hounsfield units (H), were obtained by placing a cursor of 0.2 cm² (31 pixels) over each area on an image magnified 2.5 times normal. Ten region of interest samples (CT number $\pm$ standard deviation) were obtained in both the right and left cerebral hemispheres in the frontal, occipital, and parietal regions. No difference in measurements between the two hemispheres was noted. These multiple samples were necessary to minimize the small changes in attenuation coefficients that occur with small shifts in cursor position. The average of the 20 values was tabulated for each region and age (table 2). Variations of CT numbers within each age group are believed to represent biologic and age differences between individual baboons.

For each of the three brain areas, a separate regression analysis was used as a statistical technique to determine the degree to which CT values varied as a function of age. In addition, the use of regression analysis afforded the possibility of deriving the "best" equation for the prediction of CT values from age. Within each regression analysis, the CT value served as the criterion variable, while age served as the single predictor variable.

One baboon was sacrificed at each of the intervals, 1, 4, 12, 26, and 52 weeks of age, using 161 Euthansia solution. The brain was removed intact from the skull, weighed, fixed in formalin for 2

weeks, cut in a series of 1-cm-thick sections parallel to the plane of the CT scan, and inspected for changes in the appearance of the white matter. Staining of tissue specimens from each of the regions with hematoxylin-eosin luxol fast blue allowed visualization of the myelin that was present. Mishandling of the 4-week-old brain caused loss of some frontal cerebral tissue. These gross and histologic specimens were compared with the CT sections and the CT values (table 2).

Results

In figure 1, graphs of the change in average CT values as a function of age are presented for each area of the brain. Similar maturation curves were found for the three areas. Specifically, the white matter matured rapidly during the first 8–12 weeks of life and then more gradually thereafter. Highly consistent results were also obtained from the three regression analyses, namely, CT values associated with each area were found to be logarithmic functions of age, having the form: $CT\ number = a + b (\log_{10} age)$, whereas a = the CT number at 1 week of age and b = the rate of change of the CT numbers.

For each of the three white matter areas, the following functions were derived: Frontal white matter— $CT\ number = 15.8 + 10.4 (\log_{10} age)$; occipital white matter— $CT\ number = 19.6 + 6.7 (\log_{10} age)$; and parietal white matter— $CT\ number = 18.4 + 6.6 (\log_{10} age)$.

Since these equations were calculated by regression analyses and represent the best fit line to the data, the a values are the predicted CT values at 1 week and, therefore, are not expected to be exactly equal to the average observed values. This explains why the a values from these equations for the frontal, occipital, and parietal white matter are 15.8, 19.6, and 18.4 and differ slightly from the observed values of 15.0, 19.4, and 18.8, as shown in table 2. The regression analyses also allowed computation of the

TABLE 1: Ages of Baboons When Scanned and Ages and Weight of Brain When Sacrificed

Baboon	Ages (days)*		Weight at Sacrifice (g)
	At Scanning	At Sacrifice	
A	7	7	76
B	11, 32	32	82
C	8, 29, 92	92	91
D	6, 27, 83, 181	181	104
E	10, 32, 87, 185, 367	367	125

* Ages at scanning and sacrifice correspond roughly to 1, 4, 12, 26, and 52 weeks, respectively.

TABLE 2: White Matter CT Values

Region: Age (weeks)	CT Values (H) ($\pm$ SD) of Baboon:					
	A	B	C	D	E	Average
Frontal:						
1	13.4 (2.0)	15.4 (2.0)	15.9 (2.0)	16.3 (2.7)	14.1 (2.0)	15.0 (2.2)
4	...	22.7 (2.5)	23.0 (2.6)	24.3 (2.1)	22.6 (2.4)	23.2 (2.4)
12	...	...	27.0 (2.0)	28.1 (2.4)	28.5 (2.2)	27.9 (2.2)
26	...	...	...	30.8 (2.0)	29.4 (2.0)	30.1 (2.0)
52	...	...	...	...	31.1 (2.0)	31.1 (2.0)
Occipital:						
1	19.4 (2.1)	19.8 (2.9)	20.5 (2.7)	20.1 (2.9)	17.7 (2.4)	19.5 (2.6)
4	...	24.5 (1.7)	22.8 (2.0)	25.1 (2.0)	22.5 (1.9)	23.7 (1.9)
12	...	...	25.4 (1.7)	27.9 (2.0)	27.2 (1.9)	26.8 (2.0)
26	...	...	...	28.5 (1.8)	30.1 (1.9)	29.3 (1.9)
52	...	...	...	...	30.6 (1.5)	30.6 (1.5)
Parietal:						
1	18.2 (2.5)	19.0 (1.8)	19.3 (1.9)	19.7 (1.9)	17.5 (2.1)	18.8 (2.0)
4	...	22.1 (1.8)	21.1 (2.3)	22.7 (2.1)	20.1 (2.0)	21.5 (2.1)
12	...	...	26.0 (2.0)	26.1 (2.1)	25.3 (2.1)	25.8 (2.1)
26	...	...	...	27.2 (1.8)	28.8 (1.8)	28.0 (1.8)
52	...	...	...	...	29.6 (1.7)	29.6 (1.7)

Note.—For purposes of this investigation, average number of days for each category of weeks are: 1 week = 8 days; 4 weeks = 30 days; 12 weeks = 87 days; 26 weeks = 183 days; and 52 weeks = 367 days.

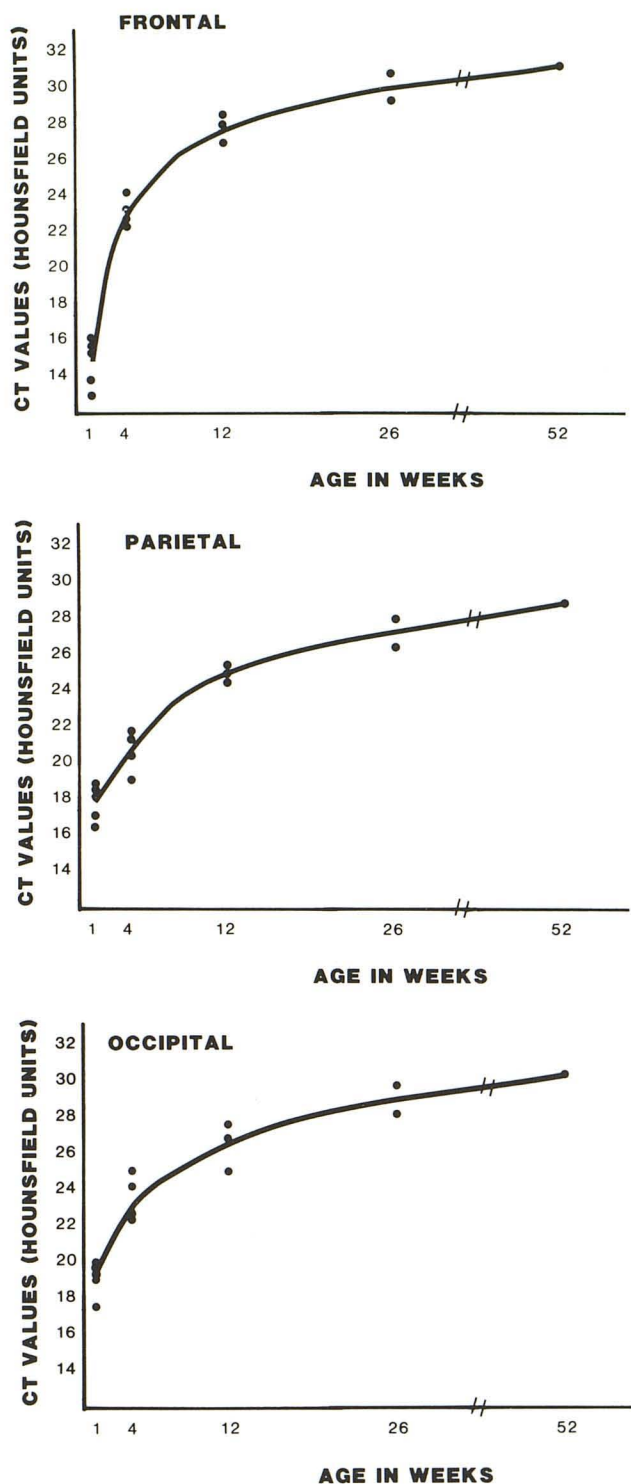


Fig. 1.—Graphs of age versus white matter attenuation demonstrate a logarithmic relation between the two variables. Compressing the distance between 26 and 52 weeks visually deemphasizes the nearly asymptotic relationship of the curve to the y axis after 12 weeks of age. Although there are some differences among the three curves, they can be roughly divided into two phases: rapid maturation (first 8–12 weeks) and gradual maturation (after 12 weeks). Equations expressing this plotted data are the Results.

rate of change in CT numbers (b value) and indicate that the rate of change is 10.4, 6.7, and 6.6 in the frontal, occipital, and parietal areas, respectively.

Each of the above functions was found to be highly significant ($p < 0.0001$). Moreover, results of the regression analyses indicated that nearly all the variance in CT values is explained by the logarithmic transformation of age. The proportions of explained variance in CT values for frontal, occipital, and parietal white matter areas were 95.2%, 94.1% and 94.4% respectively. A statistic that reflects the degree of prediction accuracy associated with each function is the standard error of estimate. For the purposes of this study, the standard error of estimate indicates the standard deviation of the actual CT values from those predicted. Extremely low standard errors of estimate were found in the regression analyses to be associated with the three derived functions and, thereby, indicate relatively high degrees of prediction accuracy. The standard errors of estimate for frontal, occipital, and parietal white matter areas were 1.4, 0.97, and 1.4, respectively. These standard errors show that the average error that would be committed in predicting CT value from age using one of the above equations would only be about 1 H. In addition, it is important to note that the standard deviations of the obtained CT values were found to be relatively uniform at each of the ages within the three brain areas.

These equations and the graphs indicate that in the immediate postnatal period the frontal white matter has lower CT values than either the occipital or parietal white matter and that the rate of increase of CT values of the frontal white matter is more rapid than the white matter in either the occipital or parietal regions. By 4 weeks of age, the CT values in all three areas became nearly equal, and, after 12 weeks, the curves that relate CT values to age (fig. 1) reach a virtually asymptotic relationship with the CT values. With increasing age, the skull thickens and the brain enlarges, resulting in a beam-hardening effect. The result of this phenomenon is that, in the older animals, the CT values are lower than they would have been had the skull remained as thin and the brain as small as it was in the newborn. Were CT values of maturing white matter obtained without the effect of beam-hardening, the points displayed for the older animals in figure 1 would be greater than shown. Therefore, although comparing *absolute* CT numbers of maturing infants is a theoretical drawback, because increasing skull thickness is normal with aging, relative CT value comparisons can be made. With visual inspection only, the differences in densities between the three regions at any given time period or change in density of a given region over a span of time cannot be appreciated (fig. 2), which dictates that CT numbers must be used when determining relative changes over a period of time.

Both gross (fig. 3) histologic (fig. 4) specimens show a significant change in the appearance of the white matter over the first 3 months of life, but no visible change for the rest of the first year of life. The lack of a significant myelin stain and the absence of broad bands of white matter is evident in the 1-week-old baboon. There is faint myelin staining and formation of white matter bands in the 4-week-

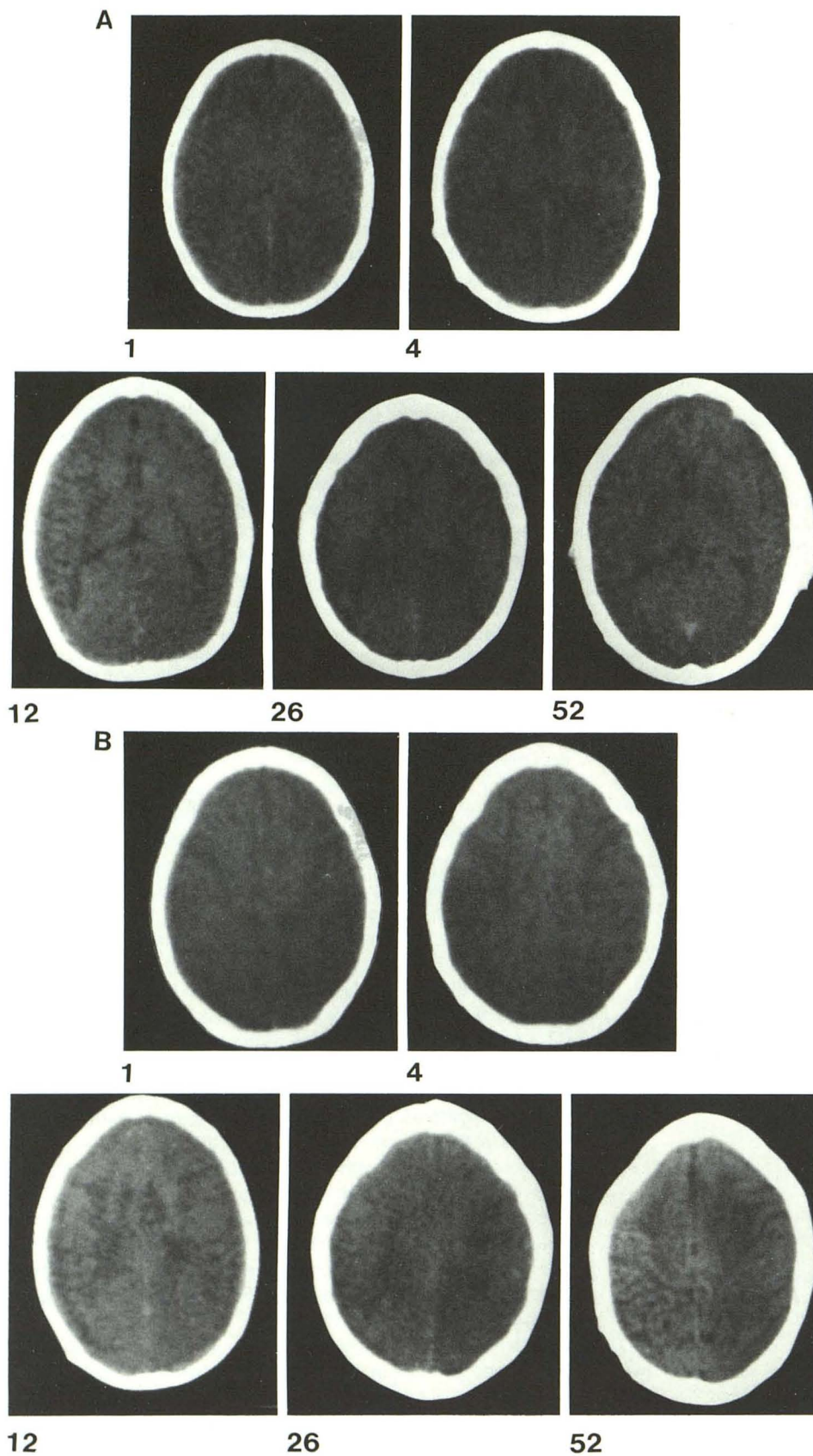


Fig. 2.—Frontal and occipital (A) and parietal (B) areas at 1, 4, 12, 26, and 52 weeks, respectively. Window width is 150 and window level is +40 (scale = -1,000 to +1,000). Measurements in prefrontal white matter, forceps major, and parietal centrum semiovale are described in Materials and Methods. Even though visual differences are not readily apparent when 1-, 4-, and 12-week-old sections are compared, significant differences in CT numbers did exist (see table 2 and fig. 1).

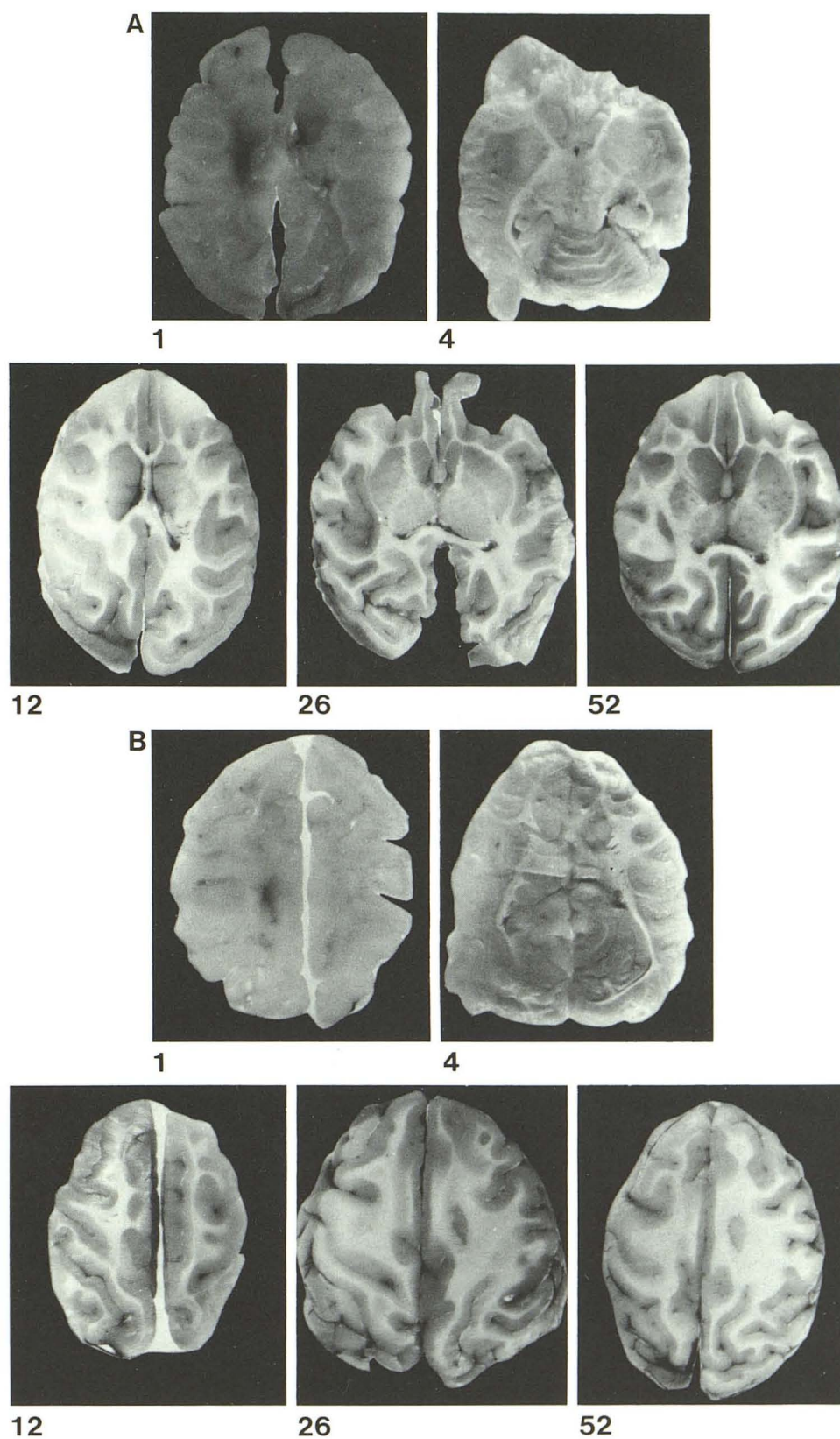


Fig. 3.—Gross specimens. Frontal and occipital (A) and parietal (B) white matter at sacrifice: 1, 4, 12, 26, and 52 weeks of age, respectively. There are no well defined bands of white matter in the 1-week-old, but there is a definite appearance of white matter by 4 weeks. Improper handling of the 4-week-old specimen resulted in loss of some left frontal cerebral tissue. White matter is broader and better defined by 12 weeks. No striking changes were seen after that.

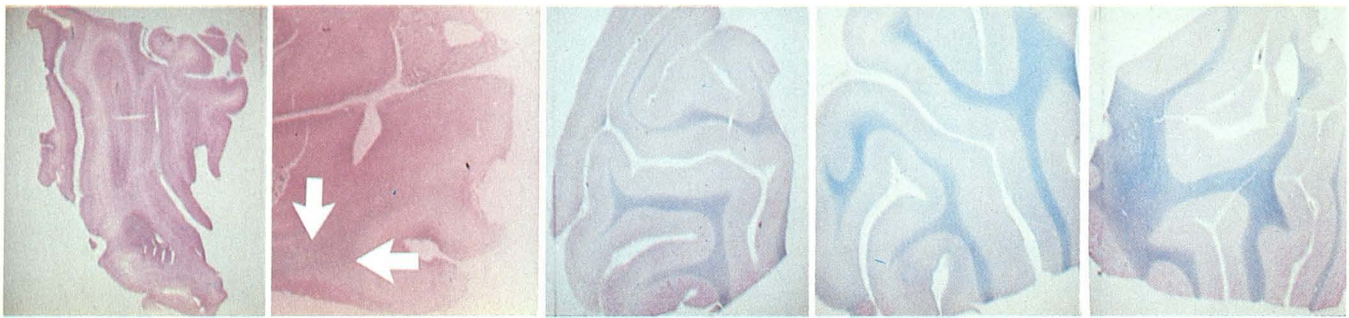


Fig. 4.—Histologic specimens from occipital lobe are representative of simultaneous changes in frontal and parietal regions at 1, 4, 12, 26, and 52 weeks of age, respectively. H and E luxol fast blue stains myelin blue. At 1 week of age, there is a lack of any significant myelin stain; at 4 weeks, there

is faint staining (between arrows); and at 12 weeks, there are well defined bands of myelin. There is no significant change in staining characteristics at 26–52 weeks.

old and this becomes even more noticeable in the 12-week-old. There is no significant change after that. This correlates well with the CT changes described above, that is, a rapid change during the first 3 months and more gradual changes thereafter. The fact that there is an increasing myelin stain over the first 12 weeks is not due simply to water loss but to more complicated changes.

Discussion

The change in photon attenuation of the newborn human brain with age is a result of a complex series of chemical alterations. The major changes include a decrease in water content, which creates a 50% increase in the dry weight of the brain during the first 6 months of life [6, 11] and an increase in both the lipid and protein content [1, 11].

Dobbing and Sands [11] used changes in whole brain cholesterol levels to judge the degree of brain myelination. They found a doubling of the cholesterol levels in the first 6 months of life, then a continued steady increase to 2 years of age, followed by a gradual leveling off of the cholesterol levels thereafter. However, since cholesterol is not a myelin-specific lipid, they recognized that this method of judging progressive myelination is imprecise. At the time their work was published in 1973, they believed no satisfactory morphologic method existed for measuring the rate and degree of myelination.

Since that time, various investigators have used CT to characterize features of normal infant brain tissue. Brant-Zawadski and Enzmann [1] and Schrupp et al. [12] found a decreasing difference between white and gray matter photon attenuation with age. Serial measurements indicate that while there is no significant variation in gray matter attenuation because it is relatively mature at term, there is an increase of white matter tissue attenuation with age [1]. Both water loss and myelination within the white matter contribute to this changing brain density.

Brooks et al. [13] explained that white matter appeared more lucent than gray matter on the basis of differences in their atomic structures. They showed that at typical CT

energies, average gray-white differences of 5.5 H relate to the lower water content (8% less oxygen) and the higher lipid content (8% more carbon) of white matter. This lower water content and higher lipid content means that oxygen, with its higher atomic number, is less abundant, and carbon, with its lower atomic number, is more abundant in the white matter than in the gray matter. The result is less photoelectric absorption and, hence, lower photon attenuation of the white matter. Differences in blood supply and actual variation in tissue densities of these two areas were calculated to have made only minor contributions to their appearance on CT [13]. It is clear, therefore, that the CT changes of white matter during infancy is a result of more than simple myelination. They reflect overall maturation of the cerebral white matter.

Agreement exists that decreased brain tissue attenuation, particularly in the periventricular regions, is a normal finding in normal premature infants [2, 3, 14]. Even with these reports, there remains a number of unanswered questions: (1) what is the lowest CT number for white matter that can be considered as normal; (2) at what rate does the CT number of white matter change; (3) is the rate of change of the CT number of white matter constant or does it vary at different ages; and (4) at what age does the CT number of white matter reach an adult value? To answer these questions, repetitive scanning of a group of normal human neonates and infants would be desirable but cannot be ethically justified. Therefore, despite the fact that at birth the non-human primate brain is more mature than the human brain [15], the baboon was chosen as an experimental subject to determine the rate and degree of white matter maturation.

In the 1-week-old baboons, consistently and significantly lower CT values were found in the frontal white matter than in the occipital and parietal white matter. This is seen not only in table 2 but also in the regression equations (see Results) of three regions. Note that the prediction of the CT value at 1 week for the frontal white matter is 15.8 (i.e., a value), whereas it is 19.6 and 18.4 for the occipital and parietal areas, respectively. These data correlate well with previous observations [3, 5, 14], where zones of low atten-

uation were found mainly in the frontal region in both normal premature and full-term human infants. In the baboon, this regional difference in CT numbers no longer exists at 1 month of age and thereafter. The discrepancy between these observations and the prior clinical work on premature human infants [3], which indicated that the frontal periventricular area remains low density for a long time, is not surprising since the brain of a 4-week-old full-term normal baboon is more mature than that of a 4-week-old premature human. The fact that the CT numbers of frontal white matter are low at 1 week but reach levels similar to that of the occipital and parietal white matter 3 weeks later is reflected in the *b* values of the calculated regression equation (see Results). The *b* values for the frontal area is 10.4, whereas it is 6.7 and 6.6 for the occipital and parietal regions, respectively.

These regression equations may be useful in predicting the white matter CT values at different ages early in life. Inspection of figure 1 shows that, in all three regions, a relatively rapid maturation phase exists during the first 8–12 weeks of life, followed by gradual maturation thereafter. This gradual maturation appears to correlate with the work of Penn et al. [6] and Brant-Zawadzki and Enzmann [1], who found a continual change in whole brain CT measurements [6] and differences in gray-white attenuation [1] up to about 6 months of age in human. The small changes that figure 1 does show from 12 weeks onward may correspond to the fact that total myelination is not complete until the second decade of life [16].

The gross anatomic (fig. 3) and histologic (fig. 4) specimens also show a similar pattern of white matter change with time. In all three regions (fig. 3), barely discernible bands of white matter in the 1-week-old give way to the broadening areas of white matter in the 4- and 12-week-old. After 12 weeks of age, no visual difference is seen in the gross specimens. Representative histologic specimens (fig. 4) reflect more vividly the white matter maturation by showing part of that maturation process, namely its myelination. There is no significant myelin staining at 1 week of age, faint staining at 4 weeks and increased staining at 12 weeks. No change is seen after that. From a visual standpoint, these increases in myelination parallel the white matter maturation curves (fig. 1).

Clinically, these considerations are important when evaluating the periventricular hypodensity in neonates who have suffered hypoxic/ischemic brain damage [2–5, 9, 12, 17, 18]. A number of authors have tried to determine the significance of these regions by correlation with the eventual clinical outcome [2, 4, 12, 17]. Although moderate to severe periventricular leukomalacia in neonates commonly results in abnormal motor and mental development [4, 12], reversal of similarly affected regions of white matter with a normal follow-up CT scan [18] and with a good clinical outcome has also been reported [17]. In addition, since mild forms of decreased brain tissue attenuation are generally accepted as normal [2, 3], it is apparent that in the spectrum of mild to severe periventricular low density, a point is reached that should be considered abnormal. In practice, this judgment is reached by a qualitative rather than a quantitative assess-

ment and, therefore, is subject to a significant variation on the basis of the observer's experience. Since it is the change in attenuation with time rather than the value of a single measurement that is important, the use of maturation curves like those presented here may be helpful. From a practical standpoint, if an area of hypodensity in the white matter is visualized and is suspected of being abnormal, accurate CT numbers of that area could be compared with subsequent measurements of the same area some weeks later. The failure of that area to show increasing CT numbers with time and to parallel normal maturation curves may indicate significant damage to the white matter.

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