

Transneuronal Degeneration in Brains of Monkeys Asphyxiated at Birth

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Brain damage occurring from 10 months to 8 years 9 months after neonatal asphyxiation for 11.5-17 min was assessed histologically in 12 rhesus monkeys. Comparison was made with brains of ten monkeys asphyxiated for brief periods or living shorter times and with those of five nonasphyxiated controls. Very slight damage occurred after 6-7 min of asphyxia; major destruction of relay nuclei in afferent input systems and parts of the basal ganglia, after 11.5-17 min. In the course of time, beginning about 10 months after birth, secondary transneuronal degeneration became evident. This was most clearly seen in the parts of the cerebral cortex which had received projections from the thalamic nuclei destroyed during the asphyxia; also in other thalamic nuclei and the brain-stem reticular formation. Gradual improvement in physical status and in behavioral responses to environment occurred while brain structure deteriorated.

Introduction

The brain damage produced by asphyxia neonatorum was described initially in guinea pigs (21) and later in rhesus monkeys (10, 13). Structural changes of similar nature have been seen in human beings (3). The acute neuropathology of birth asphyxia in the monkey consists of nonhemor-

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rhagic, bilateral, focal lesions, mainly in relay nuclei of somesthetic, auditory, and vestibular systems and in extrapyramidal cell groups.²

The first report of brain damage in the monkey (13) was limited to observations of acute reactions to asphyxia of varying duration in five subjects. The brain sections of more than 50 other animals, examined subsequently, confirmed the original observations (Windle, unpublished). Advent of postnatal respiratory distress (19), hyperbilirubinemia (9), or other complications altered the severity of reaction and led to involvement of other brain regions, including the cerebral cortex.

With few exceptions (22), previous reports dealt with the brains of monkeys surviving asphyxia neonatorum less than 3 months. In the present paper we shall examine the structural deficits in brains of 20 monkeys and the changes that occurred with time in some of them.

Material and Methods

All the subjects were offspring of monkeys (*Macaca mulatta*) in the Puerto Rican breeding colonies. We selected, on the basis of adequacy of our information about the animals and completeness of the histopathologic evaluations, the brains of 12 that had lived for 10 months to 9 years after birth asphyxia. These are listed in the upper half of Table 1 and in Tables 2-4. Supplementing these specimens were the brains of eight monkeys living 6 months to almost 8 years after neonatal asphyxia. They are listed in the lower half of Table 1, but are not represented in the other tables. Brains of five nonasphyxiated monkeys were used as controls.³

Mating procedures have been reported (6, 12). Gestation of the experimental animals was terminated by cesarean section 5 to 12 days before anticipated full term of 168 days (16), except in one instance of a spontaneous breech delivery (5). Four of the nonasphyxiated monkeys had normal spontaneous births. No newborn was premature.⁴

Cesarean section was done under local anesthesia, using procaine hydrochloride, with subjects in the supine position.⁵ As soon as delivery had

² Principally the following nuclei: medial cuneate; sensory trigeminal; superior and medial vestibular; superior olivary; inferior collicular; medial geniculate; subthalamic; and the putamen and external segment of the globus pallidus and nucleus ventralis posterior lateralis of the thalamus.

³ Nonasphyxiated monkeys 7W (4 days), 4 (12 days), 425 (3 months), 52 (11 months) and 244 (22 months) were used as controls.

⁴ The criteria adopted for determining prematurity were birth weight less than 300 g and gestational age less than 150 days.

⁵ The pregnant monkeys were made comfortable, with the head screened from the field of operation. The presence of a caretaker in the animal's view was occasionally required to allay fear. These measures and thorough infiltration of the tissues prevented pain reactions.

TABLE 1
SUBJECTS IN STUDY OF NEUROPATHOLOGIC CHANGES

Monkey no.	Sex	Gestation age (days)	Delivery	Birth weight (g)	Duration asphyxia (min : sec)	Terminal (yr : mo) age
Principal series						
65	M	157	C sect.	486	11:33	4:11
57	F	157	C sect.	390	12:00	0:10
66	M	157	C sect.	423	13:15	4:10
136	M	158	C sect.	426	13:56	3:10
162	M	158	C sect.	Unknown	14:00	3:06
130	M	156	C sect.	471	14:00	3:11
60	F	157	C sect.	588	14:05	8:09
76	M	157	C sect.	461	14:15	4:09
208	M	157	C sect.	470	15:00	2:08
144	M	157	C sect.	398	15:15	3:08
31	M	162	C sect.	472	17:00	5:06
34	F	172	Breech	478	Unknown	1:03
Supplementary series						
13	F	159	C sect.	463	4:35	2:05
56	F	157	C sect.	462	6:05	7:11
11	F	157	C sect.	390	6:08	2:05
7B	M	163	C sect.	442	6:55	2:06
MA	F	Unknown	C sect.	590	13:25	0:06
181	F	156	C sect.	423	15:00	0:08
182	M	156	C sect.	490	15:00	0:08
154	M	159	C sect.	559	15:45	0:06

been completed, the maternal subject was rendered unconscious with intravenous injection of Nembutal to permit surgical closure of the incisions.

All but one of the fetuses were asphyxiated intentionally, as previously described (7). One was a spontaneous breech presentation in which the fetal head failed to deliver until manually extracted; asphyxiation time was unknown but, judging from the motion-picture record, may have been as long as 16 min. All the newborn monkeys asphyxiated for 11.5 min or more required resuscitation by positive pressure insufflation of their lungs with oxygen until normal breathing had been established. This varied from 6 to 17 min. The resuscitation and subsequent behavior of the newborn monkeys were recorded on motion-picture film and in case-record books.

The infant monkeys, as a rule, were placed in incubators and given intensive care around the clock until their survival was assured. Most of those asphyxiated for 11.5 min or more had to be maintained for 1 to 7 days under oxygen because they tended to become cyanotic and we feared the threat of respiratory distress, which did occur in six or seven of them.

The monkeys were given neurologic examinations periodically, and in some cases psychologic tests were conducted in effort to evaluate their changing status with passage of time. Fourteen of them reached adolescence or maturity. Four similarly treated monkeys, not included in the present study, are alive 8–10 years after asphyxiation and are currently undergoing tests (14).

The experimental and control animals were killed under deep Nembutal anesthesia by a modified formalin perfusion-fixation method (8).⁶ The brain and spinal cord were removed and placed in the fixing fluid to harden. The spinal cord was separated from the brain stem at C1; the brain stem, from the cerebrum, at the rostral end of the mesencephalon. The cerebrum was divided by frontal slices into three to six blocks; brain stem with cerebellum attached constituted a single block; and representative blocks of spinal cord at C1, C7, T4, T10, and lumbosacral levels were prepared.

Paraffin sections were cut 10 μ thick, the brain stem (with cerebellum) and each block of the cerebrum being sectioned serially. Some loss of tissue occurred between the blocks, but the procedure gave reasonably complete series throughout the brain. All sections were mounted on slides (about 5000 sections per brain); every tenth slide was stained with thionine buffered at pH 4.5; adjacent tenths at selected levels were stained for myelin by the Woccke method. The other slides were held in reserve and stained as required to fill gaps.

Identification of structures in the brain of *Macaca mulatta* was aided by reference to the atlases of Snider and Lee (15) and Olszewski (11).

Results

Principal Series. The structural deficits in the brains of the monkeys listed in the upper half of Table 1 will be considered first. All of them contained scars of the primary lesions that had been caused by the asphyxiation at birth. But this was not all. Early in the study we became aware of cell loss in a more diffuse pattern. Technicians commented that they were having difficulty in obtaining the usual brilliant thionine staining of the cerebral cortex. This was not the fault of the staining method, but was produced by certain structural changes sequential to the initial asphyxial lesions. We have ascribed much of this to transneuronal degeneration.

It was difficult to separate the primary effects of asphyxia from these later atrophic changes in some regions, but in other locations they were clearly differentiated. Lesions of type 1 of Ranck and Windle (13) were easily identified, those of type 2, less so, but those of other types left little or no

⁶ The gum acacia-saline solution, having replaced the blood, and the vascular system, have been filled with the gum acacia-formol-saline solution, the carcass was left untouched until the next day.

TABLE 2
TELENCEPHALIC STRUCTURES SHOWING PRIMARY AND SECONDARY DEFICITS*

REGION	MONKEY NO.											
	65	57	66	136	162	130	60	76	208	144	31	34
Inf. & middle front. gy.	-	++	-	-	-	+	+	-	-	-	-	-
Sup. front. gy.	+	++	-	-	-	+	+	-	-	+	-	-
Med. front. gy.	-	++P +	+	-	-	+	+	-	-	-	-	-
Paracent. lob.	++	++P +	+	-	-	+	+	++	-	++	++	-
Precent. gy.	++	+	+	-	-	+	+	++	+	++	++	-
Postcent. gy.	++	++P ++	+++	+	+	+	++	++P ++	++	++	++	++
Intrapar. sulc. ^b	+	-	++	-	-	+	+	++P +	+	++	++	-
Angular sulc. ^b	-	-	-	-	-	-	-	+++	-	+++	-	-
Insula	-	++P +	++	-	-	-	-	+	-	-	++	-
Dentate gy.	-	-	+	-	-	++	+	++	+	-	-	-
Hippocampus	-	-	-	-	+	++	-	++	+	-	-	++
Caudate nu.	-	++P +	-	-	-	+	+	+P	-	+	-	-
Claustrium	++	++P ++	+	+	+	++	+	++	+	+	-	++
Putamen	++P ++	++P ++	++P ++	+p	-	++p	++P ++	++P +	++P ++	++P ++	++p	+p
Glob. pal. (ext. seg.)	++P ++	++P ++	++P ++	-	-	++p	++P +	++P +	++P ++	++p ++	-	-
Glob. pal. (int. seg.)	-	++P ++	-	-	-	++	+	-	-	+	-	-
Amygdala (basal nu.)	-	+	-	+	-	++	+	++	++	++	-	-

* See text for explanation of symbols. Unusual abbreviations are: gy., gyrus; lob., lobule; nu., nucleus; seg., segment; sulc., sulcus.

^b Damage confined to the depth of the sulcus.

permanent record. Tables 2 and 3 list the pertinent components of the serially sectioned blocks of the cerebrum. Table 4 lists components in the serially sectioned block containing the brain stem and cerebellum. Figures 1 and 2 illustrate the appearance, several years after birth asphyxia, of nuclei at two sites in which primary lesions are most prone to occur; namely, the inferior colliculus and thalamus.

Evaluation of the degree of involvement was qualitative, comparisons being made with brains of nonasphyxiated controls. Where possible to identify the site of a primary lesion by glial and connective-tissue scars, thickening of vascular adventitia, and occasionally cavitation (Fig. 1B), we indicated it in the tables with a capital letter P; where less certainty prevailed and the diagnosis was presumptive, a lower case letter p was employed. We used plus signs (+) to roughly grade the extent of involvement, one plus indicating slightly fewer nerve cells than in the control, four plus indicating nearly total disappearance of neurons. Minus signs (-) indicate that no difference between the brains of asphyxiate and control could be determined; blanks, that no observations were made. Comparison of the tabulated findings in the first 12 monkeys listed in Table 1 show that the brains had undergone extensive structural deterioration with time, for there were

TABLE 3
DIENTEPHALIC STRUCTURES SHOWING PRIMARY AND SECONDARY DEFICITS ^a

REGION	MONKEY NO.											
	65	57	66	136	162	130	60	76	208	144	31	34
Hypothal., paraventric. nu.	+	-	-	-	-	+	-	-	-	-	-	-
Hypothal., dorsomed. nu.	+	+	+	-	-	+	-	-	+	+	-	-
Hypothal., ventromed. nu.	+	+	+	-	-	+	-	+	+	+	-	-
Supraoptic nu.	+	+	+	-	-	+	+	+	+	+	-	-
Mamillary body	-	+	-	-	-	+	+	-	-	+	-	+
Thal., ant. vent. nu.	+	+	+	+	-	+	+	+	-	+	++	++
Thal., vent. ant. nu.	++	+	-	++	++	+	+	+	++	+	++	-
Thal., vent. lat. nu.	++P	++P	++P	++P	++p		++p	++P	++P	+p	++P	++P
	+	++	+				+	+	+		++	+
Thal., retic. nu.	++	++	++	+	++	++	+	++	++	+	+++	++
Thal., lat. post. nu.	+p	++P	++P	++p	++p	++p	+p	++P	++P	-	-	-
		++	+					+	++			
Thal., lat. dors. nu.	-	-	-	+	+	++	+	+	++P	+	-	-
									+			
Thal., vent. post. lat. nu.	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P
	++	++	++	++	++	++	++	++	++	++	++	++
Thal., vent. post. med. nu.	+		++	++		++	-	++p	++	+	++P	++p
							+	+			++	
Inal. vent. post. inf. nu.	+		++	++		+	+	++	++	+	++P	++P
											++	++
Thal., med. dors. nu.	-	++P	++P	++P	++P	+	++	++P	++P	-	++P	++P
		++	++	++	++			+	++		++	++
Thal., cent. medianum nu.	++	+	++P	++	++	+	++p	+	++	+	++P	-
			+								++	
Thal., pulvinar med. nu.	++		+	++	+	+	+	+	+	+	+	+++
Thal., pulvinar lat. nu.	++	+	+	++	+	+	-	-	+	+	+	++
Thal., pulvinar inf. nu.				++	+	+		+	+	+		++
Lat. geniculate body	-	++	++	-	-	++	-	++	+	+	-	-
Med. geniculate body	++P	++P	++P	++P	-	++P	++P	++P	++P	++P	++P	++P
	+	+	+			+	+	+	++	++	++	+
Subthal. nu.	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P
	+	++	++	++			+	+				
Subst. nigra	-	++	++	-	-	+	-	+	-	-	-	-

^a See text for explanation of symbols.

many regions, not usually involved in primary deficits, that exhibited neuronal loss. Some of these regions, such as the frontal and parietal cortex, will be recognized as locations normally receiving the terminations of tracts destroyed by the primary lesions; e.g., the thalamic radiation.

Extensive primary damage by asphyxia at birth led to a reduction in amount of white matter, as in the corpus callosum; this was most marked in monkey 57 in which the cortex had been severely affected.⁷ Then, too, in monkeys 57, 66, and 76, appreciable enlargement of the ventricles was noted (Fig. 1B). These observations were not recorded in the tables.

One point revealed by comparing findings listed in the tables is that the intensity of both primary and secondary defects, but especially the former, was not closely related to the duration of the asphyxia at birth. All the animals had severe brain damage, but some were worse off than others. This may have been due more to early postnatal hypoxic episodes of respi-

⁷ The cortical lesions of monkey 57 were illustrated in previous articles (17, 22).

TABLE 4
BRAIN-STEM AND CEREBELLAR STRUCTURES SHOWING PRIMARY AND SECONDARY DEFICITS *

REGION	MONKEY NO.											
	65	57	66	136	162	130	60	76	208	144	31	34
Interpedunc. nu.				—	—		—	—	+	+	+	—
Oculomotor nu.	++p	++p	+p	—	—	—	—	++p	—	—	—	—
Tectum sup. coll.	+	+	++	+	—	+	+	—	—	—	++	++P
Red nu. (parvocell.)	+	+	++	++	—	++	++	++	+	+	++	++
Retic. form. (mesenceph.)	+	—	+	+	+	++	—	—	+	+	++	++
Nu. inf. coll.	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P
	++	++	++	++	++	++	++	++	++	++	++	++
Nu. lat. lemniscus	—	++P	++p	+p	++P	++P	—	++P	+p	++p	—	—
		++			++	++		++				
Trigem. sens. nu.	++p	++P	++p	++p	++P	++p	+p	++P	+p	++p	++p	++p
		++			+			+				
Sup. olivary nu.	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P	+p	++P
		+		++	++		+	+	+			
Vermis	++P	++P	+P	++P	—	—	+p	++P	++P	—	++P	++P
		++						+	+			
Cerebellar nu. ^a	+p	++P	+p	+p	+p	+p	++p	++P	++p	+p	+p	++p
		++						+				
Sup. & med. vestib. nu.	+p	++P	++p	+p	++p	—	+p	++P	+p	++p	+p	++p
		++						+				
Dors. cochlear nu.	—	++	—	+	+	—	—	++	—	+	—	++
Vent. cochlear nu.	—	++	—	++	++	—	++	+	++	+	+	++
Inf. olivary nu. ^c	+	++	+	+	+	—	++	+	+	+	++	++
Lat. retic. nu.	++	+++	++	+	++	+	++	+	—	+	++	++
Retic. form. (bulbar)	+	++	+	+	+	—	+	+	+	+	++	++
Cuneate nu.	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P	++P
				+	+		+		+			
Nu. spinal tr. trigem.	++p	++p	—	++p	++P	—	—	—	—	—	++p	—
					+							
Gracile nu.	—	++P	—	++P	++P	+p	—	—	+p	++P	—	+p
		++										

* See text for explanation of symbols.

^b Dentate, fastigial and interpositus.

^c Inferior olivary, medial and dorsal accessory nuclei.

ratory distress than to differences in the length of time the intentional asphyxia was permitted to endure. Note, for example, that primary lesions were found in the cerebral cortex of monkey 57 which had been asphyxiated for only 12 min, whereas no primary cortical lesions were present in monkey 31 which had been asphyxiated for 17 min at birth. Monkey 57 periodically became so cyanotic between the second to fifth days after resuscitation that it had to be kept in oxygen. Monkey 31, on the other hand, did not suffer from such prolonged distress postnatally. Its cerebral cortex was free from primary lesions; nevertheless, it showed marked atrophy (Fig. 3) of the cortical regions, associated with extensive primary lesions in the thalamus. On the other hand, monkey 66, with 13 min 15 sec of asphyxia almost 5 years previously, had less primary thalamic damage than monkey 31, and its precentral and postcentral cortical gyri exhibited a laminar pattern of transneuronal degeneration (Fig. 4).

Parts of the cerebral cortex escaped primary damage and showed little or no secondary changes. The occipital lobes of the cerebrum contained no

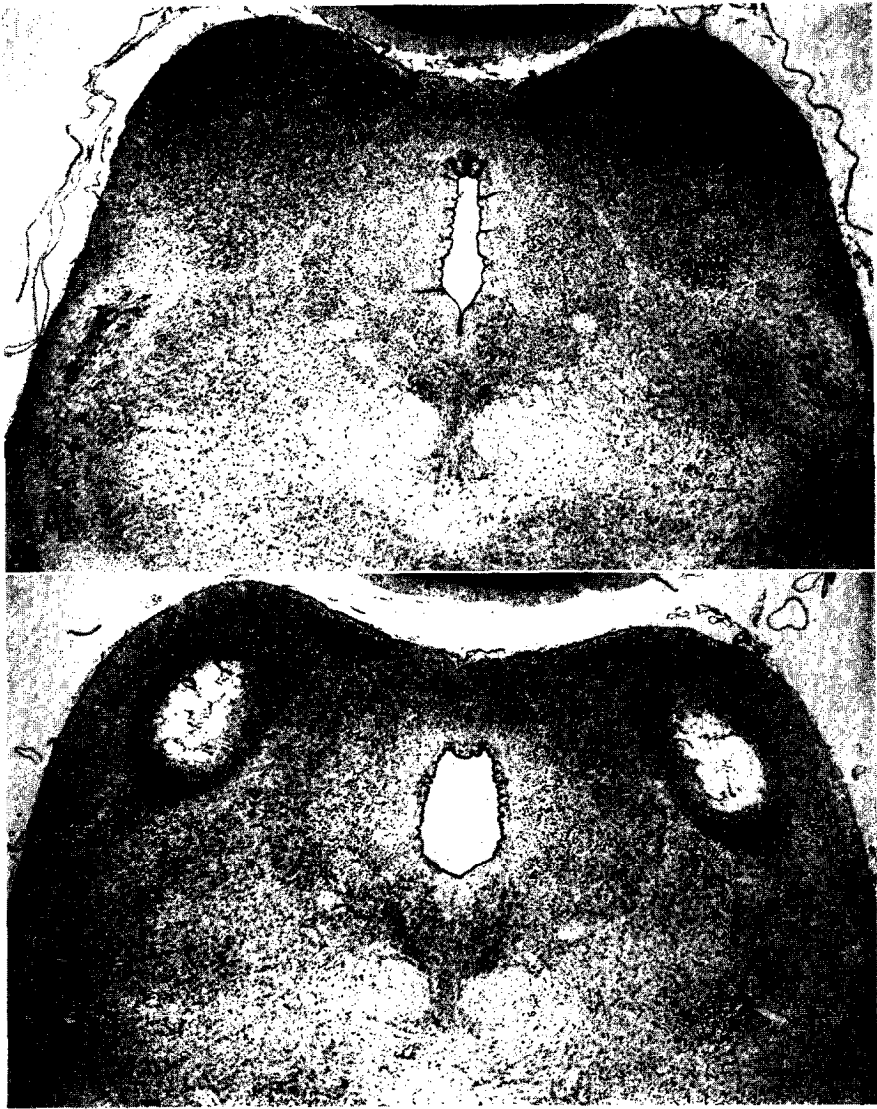


FIG. 1. Sections through the mesencephalon at the inferior colliculi; thionine stain; 10 $\times$. A. Nonasphyxiated monkey (No. 52). B. Asphyxiated monkey (No. 76) with cavitation in the scars of primary lesions in the nuclei of the inferior colliculi. Comparison with A shows general atrophy of the colliculi with slight enlargement of the aqueduct. Note especially the periaqueductal gray matter and the lateral tectum.

lesions, and we could detect no atrophy; the geniculocalcarine tracts appeared to be intact.

Traditionally, the purkinje cells of the cerebellum and the so-called Som-

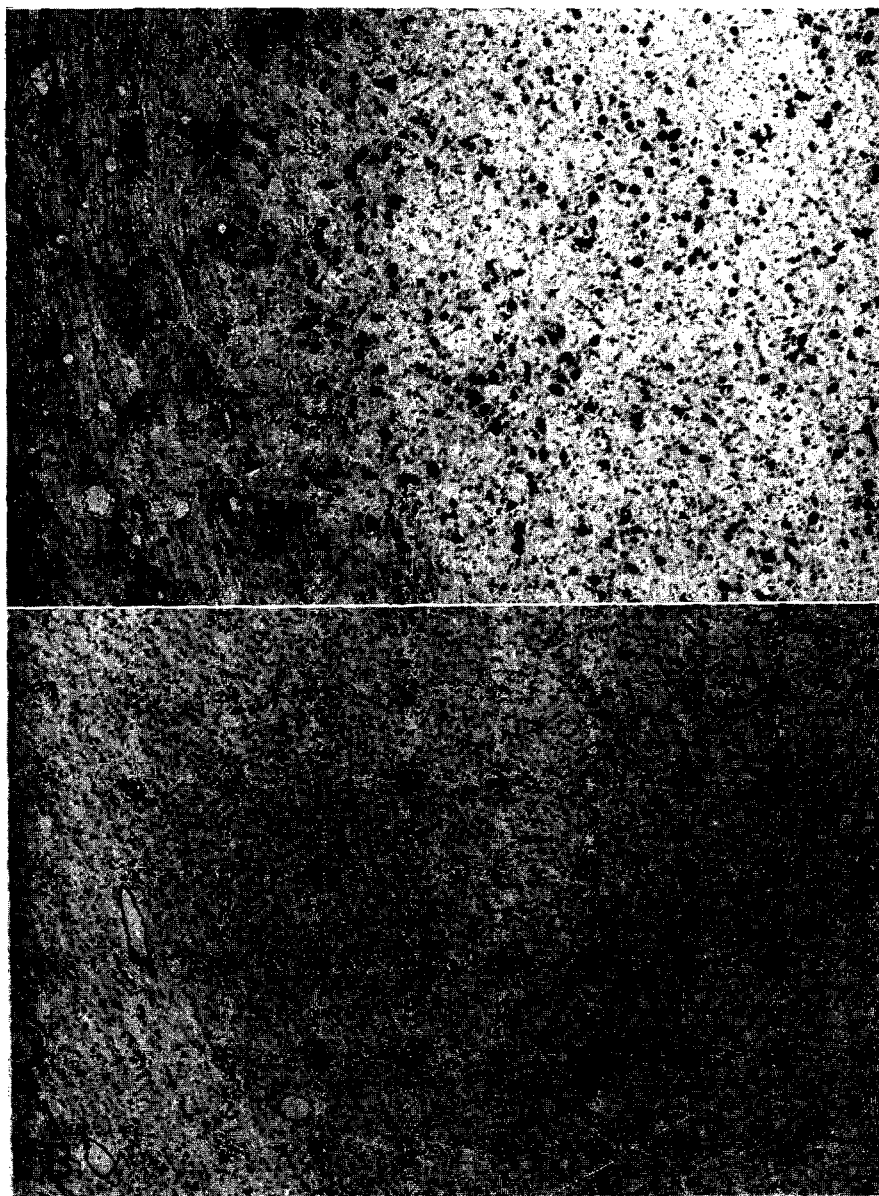


FIG. 2. Comparable portions of the left nucleus ventralis posterior lateralis of the thalamus. A. Control monkey (No. 52). B. Monkey (No. 76) asphyxiated for 14.25 min, 4 years 9 months previously. Internal capsule on the left in both. Comparison shows total loss of nerve cells in B, leaving what amounts to a pure population of neuroglia cells. Thionine stain; 40 $\times$.

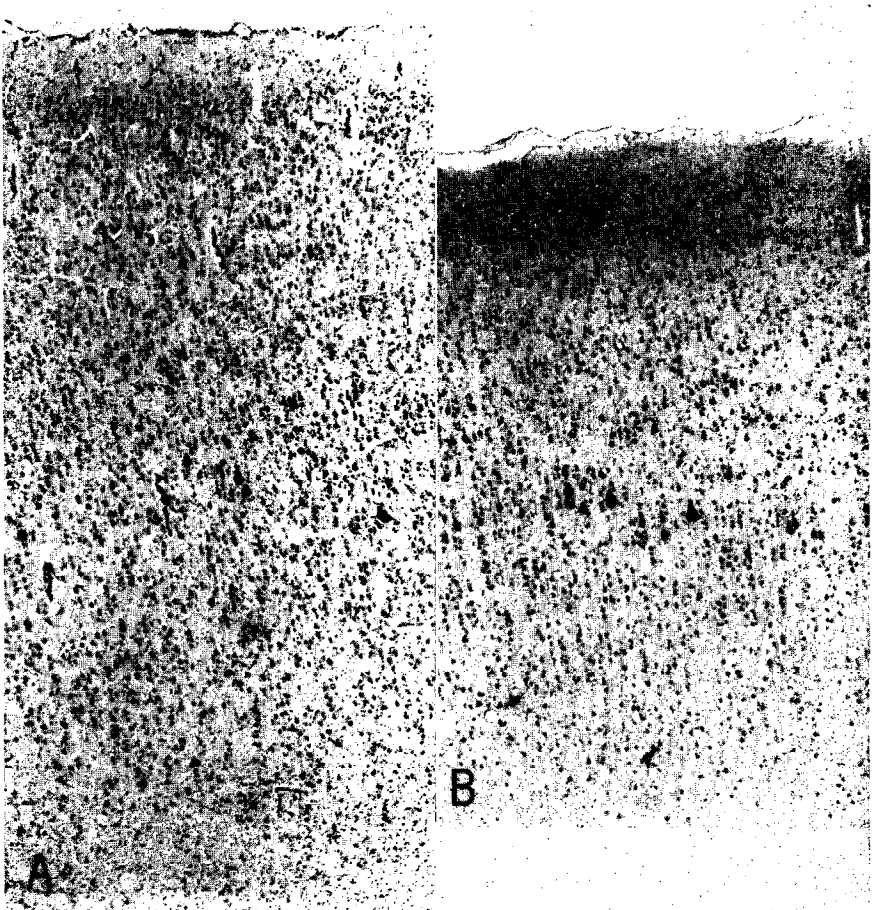


FIG. 3. Precentral gyrus of the cerebral cortex of (A) a control monkey (No. 244) and (B) a monkey (No. 31) asphyxiated for 17 min 5.5 years previously. Comparing Fig. 3B with Fig. 4, shows greater atrophy in the former; this reflects greater primary damage in the thalamus. Thionine stain; $40\times$.

mer's sector of the hippocampus are considered to be especially vulnerable to anoxia in the adult. We did not find this so in the brains of monkeys. Figure 5 shows nearly maximum damage encountered in the hippocampus. This may have been primary.

To what extent the damage observed in basal ganglia was secondary could not be determined. We are inclined to view most of that in the putamen and globus pallidus as primary; perhaps the cell loss in other nuclei was too. If the initial asphyxiation was not responsible for all of the defects seen, the postnatal hypoxic episodes during respiratory distress may have

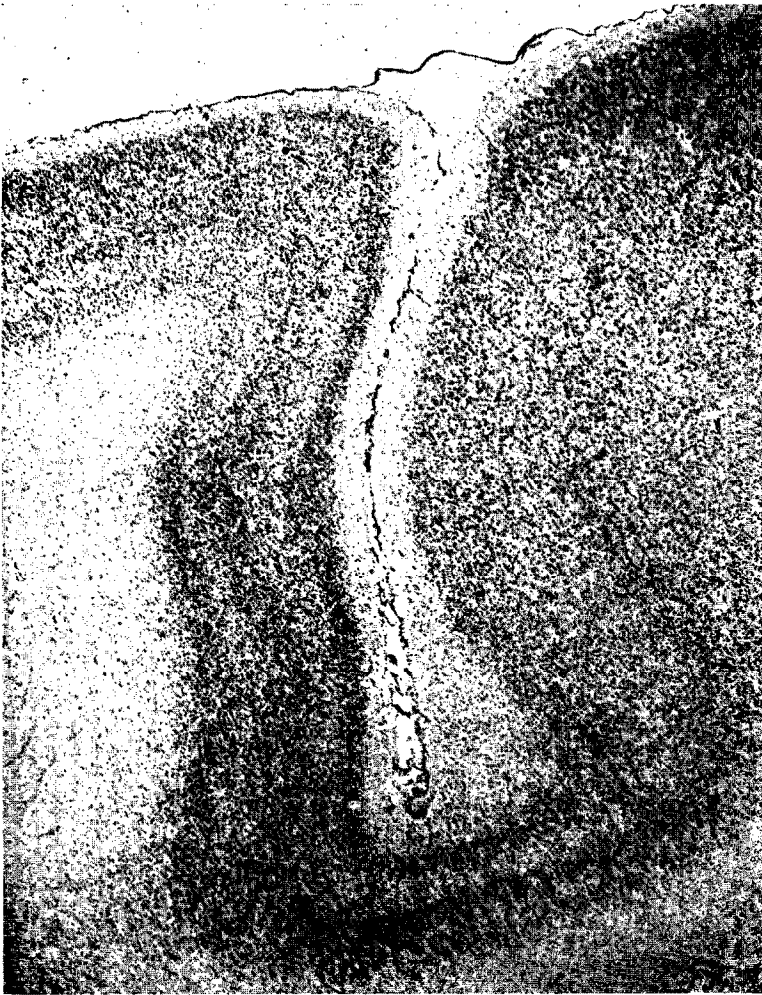


FIG. 4. Precentral (right) and postcentral (left) regions of the cerebral cortex of monkey (No. 66) asphyxiated for 13 min 15 sec 4 years 10 months previously. Laminar degenerative changes, interpreted as transneuronal, are secondary to extensive primary lesions of the thalamus. Thionine stain; $10\times$.

contributed to the damage. Extensive destruction of tissue in this region was noted by Ranck and Windle (13), 8 and 9 days after resuscitation of two monkeys asphyxiated for nearly 16 min.

Large focal primary lesions in the thalamic nuclei—mainly ventralis lateralis, ventralis posterior lateralis, and lateralis posterior—were followed in time by degeneration in other thalamic nuclei—notably the anterior ven-



FIG. 5. Hippocampus of monkey 34 (breech delivery) showing cell loss especially at arrows. Thionine stain; composite photomicrograph by Dr. E. Hibbard; 20 $\times$.

tralis, ventralis anterior, centrum medianum, and pulvinaris. Here, too, we are uncertain that all of it resulted from transneuronal degeneration.

Primary lesions in the brain stem tended to be confined to specific nuclei of the lateral tegmentum. But with time, there developed a thinning out of neuron populations in the reticular formation and medial regions. Note the loss in periaqueductal gray matter and mesencephalic reticular formation in Fig. 1B.

We saw no indications of primary asphyxial lesions in the spinal cord. In most of the animals its structure appeared to have been unaffected, but atrophy of the dorsal gray columns of cervical and thoracic regions was quite distinct in monkeys 31, 57, and 76. The intermediolateral column also was involved in monkey 31, in the spinal cord of which atrophy amounted to about 50%.

Primary asphyxial lesions were encountered in the cerebellar vermis of eight or nine of the 12 monkey brains, located deep to the surface and involving granule even more than purkinje cells. Such lesions were illustrated previously (22). If secondary atrophy occurred in the cerebellum, we were unable to determine it.

The cochlear nuclei underwent changes with time that were somewhat different from those seen in most regions of the monkey brains. Nerve cells were smaller than in these nuclei of nonasphyxiated monkey brains; some loss of cells took place but it was scattered and never complete. Other nuclei in the auditory pathways—superior olive, lateral lemniscus, inferior colliculus, and the medial geniculate body—had primary focal lesions, but

most neurons of the cochlear nuclei seemed to remain viable although reduced in size.

Primary motor neurons of most nuclei were unaffected by the asphyxia and no secondary degenerative changes were detected. Only the oculomotor nucleus is listed (Table 4) because it had deficits, probably of a primary nature, in four brains. A partial loss of motor neurons was noticed in the trigeminal nucleus of monkey 34. No deficits were encountered in the motor nuclei of other monkeys.

Supplementary Series. The first four specimens in the supplementary series of Table 1 were used to check the effects of time in monkeys with neonatal asphyxia of short duration. However, all regions of the brain of monkey 13, asphyxiated for only 4 min 35 sec and killed at 2.5 years of age, appeared normal, so we used this specimen as a control along with the non-asphyxiated ones.

Critical examination of the brains of the three other animals asphyxiated for less than 7 min and allowed to live approximately 2.5 to 8 years revealed that slight primary brain damage had occurred in such regions as ventrolateral thalamus and inferior colliculus. We could find no transneuronal secondary changes in, for example, the cerebral cortex and reticular formation.

Another kind of check was provided by the specimens from four severely asphyxiated monkeys killed at 6 to 8 months of age. They contained distinct primary focal lesions characteristic of neonatal asphyxia. However, we found little or no indication that secondary atrophic changes had set in. The precentral and postcentral gyri did not exhibit laminar degeneration, even though extensive thalamic lesions were present in monkeys 154 and 181. The brain stem tegmentum, too, appeared to retain its normal structure.

Discussion

Animal brains that are severely damaged by disease or trauma before development is complete are apt to become atrophic. Those of the monkeys in the present study exhibited that condition. To what extent was it due to the loss of tissue at the primary sites of asphyxial damage? The present study demonstrated that the process was complicated by a secondary degeneration beginning at a later time. This was not detectable during the first 6–8 months after asphyxiation, but apparently began 10 months or more after birth of monkeys that had incurred extensive destruction of major afferent relay centers. The atrophy was most clearly seen in the part of the cerebral cortex to which thalamic nuclei had projected before they were destroyed by the asphyxia.

This secondary degeneration appeared to be transneuronal. It doubtless involved many other regions of the brain but could be most clearly seen in

the thalamic projection areas of the cortex. The reticular formation was another region showing changes with time. The occipital cortex, on the other hand, showed no such change, for the geniculocalcarine projection remained intact.

The meaning of these findings in terms of brain function is speculative. The monkeys developing atrophic secondary brain damage had been severely affected by the primary neuronal loss incurred with the birth asphyxia, and in early life exhibited symptoms comparable with human cerebral palsy (18). The symptoms gradually disappeared with time (as is strikingly shown in motion picture records of some of them). The course of improvement in physical condition and behavior of the monkeys in the present report was described in an earlier article (20). Four similarly asphyxiated monkeys with severe neurologic deficits initially, now after nearly 10 years, appear overtly normal, although close observation reveals that they have poor manual dexterity and short memory spans (14).

Similarity between the monkey whose physical condition and response to surroundings improve with time and the human infant who displays neurologic deficits at birth and throughout his first year, but by 4 years presents no detectable neurologic signs (2), is noteworthy. It is clear that the monkeys of the present study adapted to their environment in spite of severe initial brain damage and subsequent transneuronal atrophy of important systems concerned with conveying signals to the higher centers. One wonders whether human beings showing similar improvements with time do so because they were given the benefit of intensive, time-consuming (and costly), therapeutic patterning regimens, or because their brains undergo progressive changes with time similar to those in the rhesus monkeys. The monkeys received no comparable therapeutic measures.

The present study extends previous histologic observations of primary brain damage from asphyxia neonatorum (13, 17, 18, 22). One notable difference pertains to animals asphyxiated for less than 7 min. We had not previously noticed changes in the brains of these, but slight neuronal loss and gliosis were detected in the specimens from monkeys 2 years 5 months to 7 years 11 months old. The extent of the loss was so limited that it may have created no functional deficits. However, it adds emphasis to the view that birth asphyxia need not be prolonged to the point requiring resuscitation of the offspring (about 8.5 min in monkeys) to leave its mark on the brain. This suggests that the asphyxiated human infant who may not have required resuscitation at birth, nevertheless, may have been minimally brain-damaged. What effect this may have on intelligence we can only guess.

Another point in connection with minimal injury relates to the absence of brain lesions in monkeys asphyxiated in nitrogen on the first day or two of life, as reported by Jacobson and Windle (7). We examined the brains of

two additional nitrogen-asphyxiated monkeys (No. 24 and 83) that had lived for 2.5–4 years. These showed no signs of primary asphyxial lesions and no atrophy even though they had breathed the gas for sufficient time to have caused some degenerative changes in their brains had they been asphyxiated in their fetal membranes. The in-membrane asphyxiation of the fetus did not allow dissipation of carbon dioxide, whereas the nitrogen asphyxiation did. Brain damage by asphyxia neonatorum is not a function of anoxia alone. Dawes, Hibbard, and Windle (20) demonstrated a reduced level of brain pathology in asphyxiated monkeys infused with solutions of alkali and glucose to offset the development of metabolic acidosis.

How closely do conditions in rhesus monkeys resemble those in other animals, especially human beings? There are species differences in response to asphyxia neonatorum. The acute vulnerability of the central nucleus of the inferior colliculus in the monkey was not found in the guinea pig, but thalamic nuclei were destroyed by asphyxia in both species (1). The human brain at birth appears to react much as does that of the monkey (3). It may never be possible to trace the full sequence of changes in the brain of the human asphyxiate, and it is doubtful that transneuronal degeneration can be so clearly observed. The monkey brain offers the closest comparison available.

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