INFANTILE SUBACUTE NECROTIZING ENCEPHALOPATHY WITH
PREDILECTION FOR THE BRAIN STEM*†

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Much progress has been made during the past quarter century in the clarification of the diseases encountered in the brains of newborn and young infants. In those conditions which appear to be pure degenerations of the central nervous system, however, there remains a great deal that is obscure and confused even from a descriptive or nosological standpoint. Often one seems to be dealing only with a type of reaction, peculiar to the immature brain, toward a variety of forms of injury, more or less obvious in the individual patients. Such is the case, for example, in a type of extensive necrotic destruction of the cerebral white matter in infants reported under the titles of Encephalomalacia in Infants by Diamond (1), and Stevenson and McGowan (2), Progressive Degenerative Encephalopathy by Winkleman and Moore (3), Disseminated Encephalomalacia with Multiple Cavity Formation by Ford (4), Multiple Cystic Softening of the Brain in the Newborn by Lumsden (5), and Multiple Cystic Encephalomalacia by Wolf (6). It is generally agreed that this state has no uniform etiology but may be the consequence, at times, of trauma, of anoxia, of arterial or phlebothrombosis or of more hidden causes. It may be said also that among the degenerative encephalopathies in infants those selective for white matter are by far the more numerous and have, therefore, received the most attention. Within the group of leucodystrophies several distinct varieties are now recognized: the infantile form of diffuse sclerosis of Krabbe, late infantile metachromatic leukencephalopathy, and subacute sclerosing leukencephalitis which, to be sure, is probably a form of inclusion body encephalitis. In contrast there are surprisingly few accounts of diffuse or widely disseminated degenerations affecting the gray matter. If one mentions Alpers’ (7) case of diffuse progressive degeneration of the gray matter of the cerebrum, Ford’s (8) similar case of degeneration of the cerebral gray matter, Christensen and Krabbe’s (9) somewhat different case of “poliodystrophia cerebri progressiva (infantilis)” and Neuberger’s (10) case of the same sort the list, at least of well known examples, is exhausted.

The present material, it is believed, augments the data on degenerative polioencephalopathy in a significant way. The report deals with 3 infants of different

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281
families, 16, 7 and 13 months of age respectively, all of whom presented signs and symptoms of widespread devastating disease of the brain for which no source could be found elsewhere in the body. In one of them the condition began at birth; in the other 2 the more obvious symptoms were first apparent at 3 months and at 5 months of age. The clinical features were much alike in all 3 patients. They succumbed from acute respiratory failure after periods of frank illness of 11, 4 and 13 months. The pathological change common to all of the infants was a necrotizing degeneration of neural parenchyma located primarily in the periaqueductal, periventricular and tegmental gray matter of the brain stem in and caudal to the mesencephalon. So alike and characteristic were the changes in these 3 infants, and in 4 others recently described in the literature, that they appear to form a recognizable pathological entity separable from a large nondescript group of cerebral degenerations of infancy and childhood.

CASE REPORTS

Case 1.* History: S.Mc. This patient, a female infant of 16 months, was the offspring of young parents of good health and habits who lived in comfortable circumstances. The blood type of both parents was type A, Rh positive. The only other child in the family was a normal female, 7 years of age. After the birth of the first child the mother had difficulty becoming pregnant and, in 1945, was operated upon at which time a suspension of the uterus, removal of a left ovarian cyst and appendectomy were done. She was told by her physicians that the right ovary was in some way also abnormal. She did not become pregnant for the second time until 1949. There was nothing abnormal about this pregnancy except for the fact that the mother was given iron and vitamin B12 for supposed secondary anemia and quickening appeared somewhat later, and was not as noticeable as in the case of her first pregnancy. Delivery of the infant (the patient) was at full term, after a 7 hour labor, and was accomplished by the aid of rotation because of persistent occiput posterior. Demerol and scopalamine were used in ordinary dosage. The infant breathed normally at birth and exhibited no cyanosis, jaundice or convulsions then or in the early neonatal period. Birth weight was 6½ lbs. She was breast fed for 2 weeks, then weaned because of loose stools and placed upon evaporated milk and cereal supplemented by ascorbic acid 50 mg. and 5 drops of Oleum percomorphum daily. At 6 weeks it was noted that she was a well nourished baby who appeared to be developing normally, was irritable with an exaggerated Moro reflex but no other abnormal findings. Although she presented a feeding problem, she had gained 5 lbs. over her birth weight at 5 months. About this time the patient's mother began to consider that her development was rather slow. Her pediatrician noted only a small-framed, fairly well nourished, pale infant. The diet at this time consisted of evaporated milk, pablum, ascorbic acid and 10 drops percomorph oil daily. She took but little of the vegetables offered to her. On August 1, 1950, at the age of 8 months, she developed a tonic convulsion; both arms were thrown outward and upward, both legs flexed, and respiration was arrested, followed by relaxation and a cry. Such episodes occurred 3 or 4 times a day for about 3 weeks when they ceased under medication with phenobarbital. An examination at age 8 months gave evidence of unquestionable retardation, the behavior resembling that of a 5 month old infant. She rolled over, reached for toys, pulled up to a sitting position, and appeared to be interested in other children. There was no paralysis or spasticity; the patellar reflexes were normal. X-ray examinations of the skull were normal. At 11 months her mental development had not advanced. She then smiled and cooed but did not follow light. The

* The clinical information comes largely from the notes of Dr. Craig Butler who has kindly allowed me to study the brain and report upon this case.
eyes diverged and the pupils reacted poorly. By the time she was 15 months old she could not sit or stand, rarely smiled or cried, and failed to appreciate her surroundings. It was thought that she could neither see nor hear but she would grasp objects. The optic fundi and discs were normal, all tendon reflexes present, brisk and symmetrical. At the age of 16 months she was seen in consultation at a large diagnostic clinic. Here the physical examination was recorded as disclosing a pale, flaccid infant who did not respond to loud noise, bright light or any but painful stimuli which resulted in withdrawal of the arms and legs. She did not cry or grasp objects placed in her hands. The pupils contracted poorly to light. It was the opinion of an ophthalmologist who saw her that the blindness was cerebral.

Roentgenograms of the head and chest were normal as was the electroencephalogram.

Blood count: Hemoglobin 13.2 grams, red blood count 4,430,000, white blood count 7,700;

BLOOD SEROLOGY NEGATIVE.

Course: A short time later she became cyanotic, quickly lapsed into coma and died within 5 hours. In the opinion of her pediatrician food deficiency or malnutrition was never an important consideration at any stage of her illness. The pathologist at the time of the autopsy described the body as that of “a well-nourished white female of normal muscular and skeletal development”. It was thought by all of the consultants who saw the patient that she was suffering from severe cerebral dysgenesis.

Post Mortem Findings: Gross: The external appearance of the brain was quite normal in all respects and there were no abnormalities on the cut surfaces of serial coronal sections through the cerebral hemispheres. On a section through the mesencephalon at the level of the inferior colliculi there were grossly visible areas of gray-red softening. For the most part they were lunate or curvilinear in shape, and frequently appeared to border central areas of relatively unchanged brain tissue in a serpentine manner. The foci were roughly symmetrical on the two sides of the brain stem and were more obvious in the tegmentum. In transverse sections through the brain stem similar changes were present at more caudal levels in the tegmentum of the pons. Here they tended to be less numerous, smaller and round in shape.

Microscopic Examination: Sections from representative areas of the cerebral cortex, basal ganglia and cerebellum were stained with hematoxylin-eosin-azure, cresyl violet and by the Niemer and Klüver-Barrera methods for myelin. Sections of numerous levels of the brain stem from the inferior colliculi to a level caudal to the obex were stained in addition with phosphotungstic acid hematoxylin, and by the Perdrau and Van Gieson methods for connective tissue.

Brain Stem: At the level of the inferior colliculi there was an area of striking parenchymal degeneration of the periaqueductal region which extended in a rather accurately symmetrical fashion on both sides over the dorso-lateral and lateral margins of the conjunctival decussation and involved the thalamo-olivary tracts, the spinothalamic tracts, the medial lemnisci and the caudal extremity of the substantia nigra (fig. 1A, 2A, 2B). The degeneration took the form of incomplete necrosis affecting primarily the ground substance of the parenchyma and ranging from incomplete staining and indistinctness of its texture to more severe disintegration represented by fenestrated areas of vascular shunting (fig. 1D). One of the most striking features was a great increase of area within the affected areas. The most constant and obvious vascular change was varicose enlargement of the capillaries and precapillaries with some irregularity of calibre. The walls of such vessels were somewhat uneven in thickness and exhibited degenerative changes in the form of swelling and early hyaline transformation of collagen but no proliferation of adventitia or endothelium. In Perdrau stains there was only a moderate amount of reticulum in the vessel walls, no proliferation of fibers or evidence of vascular sprouting. A few small precapillary hemorrhages were seen, but were extremely infrequent. While many of the ganglion cells within the lesions showed mild to moderate degeneration, relative sparing of the cell bodies of the neurons was a cardinal characteristic of the lesions (fig. 2C). Often apparently intact neurons with well preserved nuclei and Nissl substance stood out in the midst of far gone devastation of ground substance and nerve fibers. Wherever the parenchyma was
Fig. 1. Case 1. Hematoxylin-eosin-azur stain. A. Mid-brain. Tegmental necrosis, greatest in substantia nigra. B. Pons. Central tegmental necrosis. C. Necrotizing lesion in the tegmentum of the pons. Prominent vascular changes and disintegration of the ground substance. D. Lesion similar to C in tectum of the mid-brain.

affected by edema or sponginess, the myelin fibers in the area also stained poorly or showed more severe disintegration corresponding to the intensity of the other changes. Within the lesions, also, was a quite vigorous microglial reaction with many pleomorphic forms. Where the tissue necrosis was advanced the astrocytes had also succumbed, but at the periphery of such lesions and in areas where the necrosis was less complete there was very active proliferation of astrocytes and the formation of a loose anisomorphic glia fiber scar, in places very extensive.
In the **rostral pons** the entire tegmentum was the site of the same type of degenerative change (fig. 1C). The medial longitudinal fasciculi were demyelinated and on one side were spongy as was the dorsal third of the brachium conjunctivum. The lateral lemniscus was demyelinated on one side, intact on the other. The fibers of the trochlear nerves in their course lateral to the aqueduct were spongy and demyelinated while those in the trochlear decussation were normal.

At the **level of the mid-pons** (fig. 1B) there was, in its central portion, a rounded field 3 mm. in diameter where the necrosis was more complete than at higher levels. The area was well demarcated, completely demyelinated, and was occupied by numerous dilated capillaries, hypertrophic astrocytes, proliferating microglia and many fat granule cells. Even in this region the neurons were relatively well preserved. Beyond this focus, in the tegmentum of the same side and throughout the tegmentum of the opposite side, were degenerative changes less severe than those in the tegmentum at more rostral levels, with sparing of the medial and lateral lemnisci, the posterior longitudinal bundles and the superior cerebellar peduncles.

**Fig. 2. Case 1.** Hematoxylin-eosin-azur stain. A. Destructive lesion of the substantia nigra. B. Higher power of A. C. Reticular formation of the mid-brain. Spongy state with intact neurons. D. Necrotic softening with gitter cell formation in the tegmentum of the medulla.
At the ponto-bulbar junction spongy disintegration and demyelination was limited to the dorsal extremity of the medial lemnisci and the tectospinal tracts bilaterally. Throughout the area vestibularis there was increased vascularity and diffuse gliosis.

At the mid-olivary level of the medulla rarefaction of ground substance and pallor of myelin staining with increased vascularity and diffuse gliosis was apparent throughout the reticular formation bilaterally more marked on one side. Here, dorsal to the superior olive, was a focus of more complete necrosis or softening similar to that in the mid-pons (fig. 2D). There was also some demyelination and fenestration of the formatio reticularis alba, most marked in the tectospinal tracts.

Caudal to the obex the necrosis again reached the intensity of that in the mid-brain and rostral pons and again assumed a well demarcated and symmetrical pattern. The lesion had the shape of an inverted “V” with the apex including the central gray and the limbs extending ventrolaterally to occupy the whole of the reticular formation on both sides. Qualitatively the lesions were identical with those described in the mid-brain.

There was no ependymitis of either the third or fourth ventricles.

Cortex, Basal Ganglia and Cerebellum: There were no noteworthy changes in the neurons, myelin fibers, neuroglia or blood vessels of these areas of the brain beyond diffuse, mild regressive alterations of the ganglion cells of doubtful significance. Certainly there were no areas of focal destruction or vascular reaction in the cerebral or cerebellar hemispheres or in the hypothalamus including the mammillary bodies.

In the proximal portions of both optic nerves, in the chiasm, and in the optic tracts there was advanced demyelination. The loss of myelin fibers in the optic nerves was associated with an increase of hypertrophic astrocytes and marked overgrowth of collagen in the blood vessels. The optic tracts were also completely demyelinated throughout their course posterior to the chiasm and were occupied by fibrillary gliosis.

Summary: The main features of the histological picture were non-systematic, often symmetrical areas of necrosis and subnecrosis which affected the ground substance primarily, without special selection for either gray or white matter, and were restricted in distribution to the tectum and tegmentum of the mid-brain, the tegmentum of the pons, and the central gray and reticular formation of the medulla oblongata (fig. 8). In part the lesions were patchy, in part more continuous extending for long distances in the longitudinal axis of the brain stem. Certain characteristics of this necrosis were outstanding. The invariable alteration, the first to appear in the early lesions and the most intense in the advanced ones, was the breakdown of the interstitial tissue of the neural parenchyma. Such changes ranged, according to the completeness of the necrosis, from edema to the marked rarefaction of a status spongiosus. In most of the affected areas the small blood vessels were greatly dilated, very numerous and somewhat degenerated. In those parts of the lesions that were apparently in the earliest phase of development such vascular changes, together with loosening and beginning disintegration of the interstitial ground substance, were the only alterations. It was noteworthy, too, that even in regions of almost complete dissolution of ground substance, the neurons were surprisingly well preserved. In the areas of necrosis and rarefaction the myelinated fibers had undergone severe damage.

Case 2. History: L.S. This infant was born of healthy parents on October 9, 1950. The father was 38, the mother 25 years of age. There was no history of unusual diseases in either the paternal or the maternal line and the mother had not been ill in any way during the pregnancy. She was para iii. Her first pregnancy resulted in a normal male child, then 3 years of age; the second pregnancy terminated in a miscarriage at 3 months. Delivery was at term under saddle block anesthesia after a labor of 2½ hours. There was no difficulty initiating respiration and no cyanosis; at the time of birth and on leaving the hospital one week later the new born infant was considered to be a normal vigorous female baby. The birth weight of 6 lbs. 3 oz. was regained within a week.

The infant was brought to the Bob's Roberts Hospital of the University of Chicago Clinics at the age of 6 months because her parents thought that she was not developing normally and also because she was not eating well and had lost some weight. Feeding had been by
breast for 4½ months and was then changed to bottle feedings of whole milk because the baby did not nurse well. Solid foods were begun at 2 months and were accepted rather better than liquids. The diet had been supplemented throughout with vitamins (Zymadrops, Polysvisal and extra B12). It was noted that, when feeding, the infant made snorting noises and for a period of several weeks, at the age of 4½ months, regurgitated a good deal. It was then thought that there was some difficulty in swallowing and it was said, on the basis of examination in another hospital, that there was spastic constriction of the throat. She began to hold up her head and suck her thumb at the age of one month but ceased to do either from 3 months on, and from that time appeared to be generally weak. At 3 months she had been given a single immunizing injection of DPI which was not followed up by others, and shortly before this age and again shortly after she had a very mild upper respiratory infection of no seeming importance.

**Examination:** A physical examination disclosed a moderately well nourished (weight, 13 lb.), well developed baby who was quiet and unresponsive to any stimuli except pain. She paid no heed to sudden movements of objects before her eyes or to loud noises and gave the impression that she could neither see nor hear. The pupils did not react to light. The ocular fundi were normal except for a slight greenish tint of the optic discs. The tongue was kept in a protruded position. When the infant was placed in a sitting position she was completely unable to hold up her head or support her body, but collapsed like a rag doll. All tendon reflexes of the arms and legs were increased in activity and the plantar responses were extensor. There were no abnormalities of the chest or abdomen. The temperature was 37°C. The blood count showed: white blood count 9,000, red blood count 4,800,000, hemoglobin 12.5 grams. X-rays of the skull were normal.

**Course:** The patient was readmitted to the hospital one month later for the purpose of experimental treatment with ACTH. At this time her physical signs had not changed appreciably. She had gained 8 oz. in weight. She was given 10 mg. of ACTH daily in divided doses. On the seventh hospital day she began to exhibit episodes of twitching of the muscles of all extremities associated with some cyanosis. These were interpreted as abortive major convulsive seizures and medication with ACTH was discontinued. In the subsequent 3 days such attacks became more frequent. By the tenth hospital day severe respiratory embarrassment had appeared, and she expired from this cause on that day at the age of 7 months. The clinical diagnostic impression had been diffuse cerebral sclerosis (form Krabbe).

**Post Mortem Findings:** The abnormalities in the general autopsy were: Bilateral upper confluent acute bronchopneumonia; patent foramen ovale; mesenteric lymphoadenopathy of undetermined etiology; slight adrenal enlargement; a clear cyst, 4 mm. in diameter, over the left ovary. The body was described as that of "a well developed and well nourished female child."

**Brain. Gross:** The only abnormality in the external appearance of the brain was a narrowing of both frontal lobes due principally to lack of development in their posterior parts in the region of the operculum. The unusual shape was the same in both cerebral hemispheres, and there were no other obvious abnormalities of the convolutional development. At all levels from the extreme rostral to the extreme caudal extremity of the striatum the entire area of the caudate nucleus and putamen was softer than the rest of the brain and stood out clearly because of its white color (fig. 4A). The globus pallidus and the thalamus, on the other hand, appeared to be normal in color and consistency.

**Microscopic Examination:** Sections were prepared of representative blocks of the cerebral cortex, basal ganglia, cerebellum, optic chiasm, and six levels of the brain stem. The stains employed were hematoxylin-eosin-azure, cresyl violet, the Niemer and Klüver-Barrera methods for myelin, and the Van Gieson and Perdrau stains for connective tissue.

**Brain Stem. Mesencephalon:** Rostrally, at the level of the oculomotor nucleus, in the area of the dorsal tegmental nucleus and extending laterally from it for some distance was a well circumscribed focus of parenchymal destruction in which the ground substance appeared homogeneous and took the stain poorly. Within the area were many greatly dilated
FIG. 3. Case 2. Cresyl violet stain. A. Lesion in the dorsal tegmental nucleus of the midbrain. B. High power from A. Varicose changes of capillaries, disintegration of ground substance, relatively intact neurons. C. Necrotizing lesion in the substantia nigra. D. High power from C.

and prominent capillaries and precapillaries, the walls of which were thickened not only from edema but also from endothelial and adventitial proliferation of moderate degree (fig. 3A). These vessels contained only moderate amounts of collagen and showed no evidence of proliferation of reticulum fibers. Neuroglial nuclei were comparatively sparse, large and vesicular, and poor in chromatin. While relatively few neurons were present, those which remained stood out as comparatively intact structures in an otherwise greatly devastated parenchyma (fig. 3B). The neurons of the neighboring oculomotor nucleus were entirely normal in number and appearance, but throughout the nucleus and limited to it was an intense proliferation of astrocyte and microglial nuclei without accompanying increase of vascularity. The medial portion of the substantia nigra was altered in such a way as to resemble the necrotic lesion in the dorsal tegmental nucleus (figs. 3C, 3D), while the lateral part presented gliosis like that in the oculomotor nucleus. Throughout the nigra there was extensive loss of neurons, and those remaining in the medial portion were severely degenerated.

At the level of the trochlear nuclei were several well demarcated destructive lesions more or less symmetrical on the two sides. In the midline, ventro-lateral to the inferior portion of the aqueduct, the ground substance of the periventricular gray matter was almost unstained and contained many dilated and engorged capillaries with some adventitial proliferation. In this field there was also some increase of astrocytic nuclei which were pale, vesicular and poor in chromatin from degenerative change. The lesion implicated the area of the dorsal tegmental nucleus and was actually a caudal extension of the damage to this structure present at more rostral levels. A similar lesion was present in the tectum of one side following the contour of the dorso-lateral border of the inferior colliculus in the region of the tract and nucleus of the lateral lemniscus. There was great proliferation of both astrocytic and microglial nuclei in the region among which were many fairly well preserved
neurons. The vascular reaction here was comparatively slight. In an exactly similar location in the opposite colliculus was another more advanced lesion with very intense proliferation of neuroglia and blood vessels and a spongy state of the ground substance. Even here there were a number of nerve cells in a good state of preservation. In the whole extent of the substantia nigra of both sides, practically limited to the area of these nuclei, were lesions similar to the above and similar, also, to each other in size, shape and character. Here, too, the persistence of fairly intact ganglion cells in the midst of great disintegration of nerve fibers and interstitial tissue was striking.

In the rostral pons were two rather small rounded lesions placed quite symmetrically in the dorsal tegmentum, involving almost the entire locus coeruleus. The areas were partially destroyed; the ground substance appeared pale and glassy and contained a number of dilated and somewhat hyperplastic capillaries. There was little if any increase of neuroglial nuclei, but all of the astrocytic nuclei were large, vesicular and poor in chromatin. Except for mild sponginess in the reticular areas of both sides there were no other changes at this level.

At the midpons there were no changes. More caudally in the pons at the level of the facial nuclei some proliferation and hyperplasia of neuroglial nuclei was found together with slight increase of capillary vascularity diffusely throughout most of the extent of the vestibular nuclei.

In the medulla oblongata at the level of the inferior third of the olive no noteworthy changes were observed.

The myelin pattern of the entire brain stem was normal except in those specific areas, such as the dorsal tegmental nucleus and the substantia nigra, where the destructive process was well developed. At no level of the ventricular system was there evidence of ependymitis.

**Basal Ganglia:** In the caudate nucleus, putamen, globus pallidus and nucleus subthalamus of both sides there were extreme degenerative alterations (fig. 4B). The changes were

![Fig. 4. Case 2. A. Lesions in caudate nucleus and putamen. B. Complete selective destruction of caudate and putamen. Woelke myelin stain. C. Necrotizing lesion of the caudate nucleus with marked vascular reaction. Cresyl violet stain. D. More advanced necrosis in the putamen. Hematoxylin-eosin-azur stain.](http://jnen.oxfordjournals.org/)

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essentially the same in all of these gray masses, and consisted essentially of incomplete but severe necrosis affecting the neurons, the neuroglia and to a lesser extent the blood vessels. There was some variation in degree of necrosis in different areas of the respective gray nuclei, but in general it presented a loss and marked regressive change of ganglion cells, myelinated fibers and neuroglia with swelling and loss of chromatin of the astrocytic nuclei (Figure 4C). The ground substance of the affected areas showed merely paleness of staining except in the lateral parts of the putamen where it was disintegrated and spongy (fig. 4D). Generally the capillaries and the arterioles were prominent only from endothelial swelling, but in some there were proliferative changes of the walls. There were some regions almost devoid of neurons but crowded with degenerated glial nuclei, suggesting neuroglial reaction followed by beginning necrosis. It was noteworthy also that in some fields the neurons, while severely degenerated, were better preserved and present in greater numbers than would be expected from the degree of degeneration of the neuroglia. In the thalamus and hypothalamus there were only mild regressive changes of the neurons and no alterations of neuroglia or blood vessels, except for a few scattered foci of partial necrosis in the ventral part of the pulvinar. The mammillary bodies were quite free from changes. Staining of myelin in the striatum and pallidum was grossly deficient but was normal in the internal capsule and deep white matter of the hemispheres.

Although there was diffuse non-specific neuronal degeneration in the cerebral cortex, there was nowhere focal cortical necrosis.

The optic nerves had been divided very short at the chiasm. In Woelke myelin stains, however, the optic chiasm, the rostral portion of the optic tracts and what remained of optic nerves showed great reduction in number of myelinated fibers, and those remaining were pale stained.

Summary: The definitive lesion here, as in Case 1, was a disseminated necrotizing process of varying intensity involving primarily certain areas of gray matter and nuclear masses of the brain stem. In general, the lesions were symmetrical on the two sides, were best developed in the rostral brain stem (basal ganglia, nuclei of the tegmentum), and decreased in number, size and intensity caudally (fig. 9). Special features of the lesions were the relative integrity of the neurons in the areas of partial necrosis and the prominence of numerous greatly widened and somewhat hyperplastic capillaries within them.

Case 3. History: K.McK. This patient was the only child of a mother who previously had 3 successive spontaneous abortions during the second or third months of pregnancy. In this pregnancy, also, there was threatened abortion in the second month. Otherwise there was nothing remarkable about the gestation except that fetal movements, which began at the fifth month were always slight and were almost absent in the last month of pregnancy. The infant, a male, was delivered 3 weeks before estimated term after a normal 4 hour labor. The birth weight was 6½ lb., and there were no convulsions, cyanosis or jaundice at birth or in the neonatal period. On the first day of life it was noted by the nursing staff, however, that he did not suck properly.

The infant was admitted to the Bobs Roberts Hospital of the University of Chicago Clinics on 8/13/47 at the age of 10 months. His mother, a physician, stated that all his life he had trouble taking food, necessitating frequent small feedings. There had also been a good deal of vomiting and at times regurgitation of food through the nose. At the age of 6 months he was studied in another hospital where x-ray examinations were reported to have shown greatly delayed emptying of the stomach. Nevertheless, with careful attention, he did reach a weight of 15 lb. at 8 months. He had never been able to lift his head, to sit up or turn over in bed, and his cry had always been feeble. Until recently he appeared to be normally aware of his surroundings and would laugh and play, but in the past 6 weeks he had become more inactive and quiet.

Examination: The physical examination at the time of admission to the hospital showed a puny (15 lb.) infant who was obviously seriously ill. He responded only to painful stimuli. He lay without moving, the arms abducted to 90° at the shoulders, and the forearms directed cephalad with the hands clenched. The posture of the legs was normal. The pupils reacted
slowly and incompletely to light; the ocular fundi including the optic discs were normal. Movement of the palate was greatly restricted, the palatal reflexes were not obtained; the infant apparently could not swallow, did not suck, and had a feeble cry. No atrophy of the muscles of the extremities or the trunk was observed. There was some variability of muscle tone in different examinations, but in general the arms and legs appeared to be spastic with greater tonus on the left side than on the right. The tendon reflexes were all brisk, somewhat more so on the right side. The right plantar reflex was flexor, the left extensor. There were no abnormal findings in the chest or abdomen. The admission temperature was 37°C. Blood count: white blood count 9,850, red blood count 6,000,000, hemoglobin 15 grams. The blood Kahn reaction was negative. X-rays of the skull and chest were normal. The spinal fluid was under normal pressure, contained no cells and 50 mg. per cent of protein.

Course: During the hospital stay of almost 12 weeks, the status of the patient was essentially unchanged. He lay absolutely motionless in bed, seemed to be perpetually crying without any sound coming from the throat, and continually drooled small amounts of saliva. He remained afebrile. At the time of admission he was placed on tube feedings with a high vitamin supplement. On this regime he gained 2 pounds. From time to time there were episodes during which the infant ceased breathing, became cyanotic, arched the back and had convulsive movements of the arms and legs. Such attacks became increasingly more frequent and severe until it often seemed that he was about to die in them and was restored only by artificial respiration and the administration of oxygen. On 11/1/47 he was found dead at the age of 13 months.

It is of interest that a brother of the patient’s mother had also died at the age of 13 months of a condition that she thought was quite similar to that of her child. Unfortunately the autopsy records of this case are not available.

Post Mortem Findings: In the general autopsy the only significant changes were those of bilateral acute and organizing bronchopneumonia, moderate hypertrophy and dilatation of the heart and moderate cor pulmonale. The adrenal glands were normal. The body was described as that of a “well developed, well nourished white male infant.”

Brain. Gross: The brain weighed 930 grams. The leptomeninges were normally thin and transparent. On the lateral and inferior surfaces of both temporal lobes were numerous pin point to pin head-sized discolorations. On coronal sections through the frontal lobes at the level of the heads of the caudate nuclei there were irregular cavitations which reached from the subcortical white matter of the first and second frontal convolutions into the deep white matter for a distance of 2 cm. These regions were roughly symmetrical and were of about the same size, 2 x 3 cm in greatest dimension. The wall of the cavities was rough and shaggy. In serial coronal sections through the cerebral hemispheres posterior to this level there were many scattered irregular areas of softening involving the cortex and the subcortical and deep white matter (fig. 5D). These appeared to be of varying ages. Some of them were cystic, sunken from the surface, and lined by a web-like membrane. Others, more recent, were soft, discolored gray pink, and lay almost flush with the surface of the cortex. Where the cortex was involved it was discolored gray yellow, and had a slightly stippled appearance, and the demarcation between cortex and white matter was indistinct. Such regions often extended through the entire width of the cortex to encroach upon the convolutional white matter. The basal ganglia, particularly the putamen, contained large, rather ill-defined softenings, pink to light brown in color. In sections through the cerebellum and brain stem there were two symmetrical curvilinear areas of light brown discoloration in the pes pedunculi and tegmentum of the mid-brain. They lay in the position of the substantia nigra and extended caudally into the stratum profundum of the rostral part of the pons. Here the brain tissue appeared granular and was slightly depressed from the cut surface. In the lowermost portion of the medulla oblongata there was a similar area of partial necrosis lying centrally in the region of the medial lemniscus, and the entire dorsal half of the medulla was slightly softened.

Microscopic Examination: Sections from representative areas of the cerebral cortex, cerebellum and basal ganglia, from five levels of the brain stem, and from cervical, dorsal
and lumbosacral levels of the spinal cord were stained with cresyl violet, hematoxylin-eosin, the Niemer and Klüver-Barrera methods for myelin and by the Van Gieson and Perl-drau stains for connective tissue.

**Brain Stem:** The whole of the tegmentum of the mid-brain presented a spongy state (fig. 5A). In the trochlear nuclei it was apparent that the early and primary changes were of the ground substance and nerve fibers, the ganglion cells being in large part intact. Within the areas of the trochlear nuclei a few capillaries showed some evidence of proliferation but in the remainder of the spongy tegmentum there were no vascular changes. In the substantia nigra and dorsal portion of the pes pedunculi the necrotizing process had led to much greater destruction with softening and early cavity formation (fig. 6A). The lesions were quite symmetrical in shape and extent on the two sides, and within them there was the same variety of vascular reaction observed in areas of equivalent damage elsewhere. Over the whole cross section of the mid-brain there was almost universal paleness, loss and degeneration of myelinated fibers including those of the medial longitudinal bundles, medial lemnisci and pes pedunculi. Only the brachium conjunctivum and its decussation had escaped to a considerable degree. In the mid-brain the relative preservation of neurons in nuclear areas where the nerve fibers and ground substance had undergone advanced degeneration was striking (fig. 6A). Thus, in the substantia nigra many ganglion cells in fairly good condition lay in the empty spaces of the devastated parenchyma.

In the rostral and mid-pons virtually the entire brain stem presented a fenestrated...
spongy state affecting the gray and white matter of both tegmentum and stratum profun
dum. Upon this background were patchy and confluent areas of more intense necrosis of differing grades. The medial longitudinal bundles and some of the transverse pontine fibers were the site of extreme degrees of status spongiosus. The gray matter of the ventromedial reticular formation and some of the nuclei pontis showed great disintegration of ground substance, advanced regressive change and loss of neurons, and swelling and degeneration of the capillary endothelium. In the descending fiber bundles of the stratum profundum and in some of the adjacent pontine nuclei were small scattered foci of softening with gitter cell formation or larger fields of vigorous proliferation of microglia. Only in such locations was there any noteworthy proliferation of blood vessels. It was evident in the myelin stains that the destructive process was neither selective nor systematic. For example, the superior cerebellar peduncles were quite well preserved while their decussation

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which lay adjacent to the more severe necrosis in the tegmental gray showed great loss and impairment of staining of myelin fibers. Similarly, some of the transverse pontine fibers were almost normal, but where they lay in or near extremely spongy areas they were sparse, pale, attenuated and beaded with varicose swellings. At the level of the caudal pons the spongy transformation of the parenchyma was less severe and was restricted to the reticular area of the tegmentum and the descending fibers near the midline of the stratum profundum. Otherwise the only changes at this level were mild regressive alterations of a few of the neurons of the abducens nuclei and the reticular formation. Myelin stains were likewise normal except for pale staining of those medial descending bundles which showed a spongy state and of the transverse fibers in their immediate vicinity.

In the medulla oblongata at the level of the eighth nerve, there was in the central tegmentum an area of status spongiosus involving the ventral part of the medial lemniscus and the ventro-medial reticular formation symmetrically on either side of the median raphe. Here the blood vessels were moderately prominent, the ground substance loosened, the myelin fibers pale and reduced in number, but with neuronal cell bodies in good condition. In the caudal medulla at the level of the nuclei gracilis and cuneatus there was again a well marked spongy state of the entire cross section of the brain stem and superimposed upon this a central area of symmetrical patterned necrosis. The whole of the central gray matter was involved by complete necrosis with cavitation (figs. 5B, 6C, 6D). Laterally on both sides the necrosis extended as a less complete softening involving all of the gray matter containing the cells of the nucleus ambiguous, dorsal motor nucleus of the vagus and nucleus supraspinalis. Within these areas was a vascular reaction similar to that described elsewhere and an energetic proliferation of microglia with some production of gitter cells. Ventromedially, in the region of the caudal pole of the inferior olives and the dorsal parts of the pyramids on each side were additional symmetrical foci of necrosis in which the neuroglial and vascular reactions were even more intense. The neurons of the nuclei gracilis and cuneatus and descending trigeminal nuclei showed well marked degenerative changes. While there was also loss and degeneration of the neurons of the central and anterior gray matter, it was again striking how many of these remained fairly intact in the midst of complete interstitial destruction. Myelin staining was everywhere grossly deficient with best preservation of the posterior columns. In the Kluver-Barrera stains with Luxor blue there was in the brain stem, in addition to the loss of myelin already noted, a rich felt-work of neuroglial fibers in the spongy areas (fig. 7D). Such fibrillary gliosis tended to be most dense in the ventral marginal zone of the brain stem. Perdrau and Van Gieson stains revealed no increase of collagen or reticulum fibers in the reacting blood vessels of the lesions. There was no ependymitis of any portion of the ventricular surface.

Basal Ganglia: The striking changes within the basal gray nuclei were best exemplified at the level of the anterior commissure and were most outstanding in the corpus striatum (fig. 5C). Here, in the head of the caudate nucleus, was a large focus of necrotic softening, 6 x 2 mm. in dimension with its long axis parallel to the wall of the ventricle. It presented as an area of incomplete cavitation in which no neurons or ground substance remained and was occupied by a framework of thickened and proliferating capillaries along and between which were scattered macrophages of medium to large size (fig. 7A). In the putamen were two similar lesions, one 2.5 x 8 mm., the other 5 mm. in diameter. Associated with the frank softenings were other areas in which the parenchymal disintegration was not so advanced; there was great overgrowth of capillaries and a more solid cellular reaction of macrophages, microglia and histiocytes. There were also two small hemorrhages in the putamen. The globus pallidus was relatively intact and had a normal complement of neurons but most of them were somewhat degenerated and there was an appearance of edema and early breakdown of the interstitial tissue. Such changes were more obvious in the lateral part of the pallidum especially in proximity to the lesions in the putamen. In the anterior nucleus of the thalamus the destructive process was still less advanced. Ventrally all of the neurons had disappeared, there were regressive changes of glial nuclei and the endothelium of the capillaries was swollen but not proliferated. Dorsally in the nucleus there was merely diffuse regressive change both of neurons and neuroglia.
Although there were extensive fields of malacic necrosis in the ventrolateral thalamic nuclei at the level of the mammillary bodies, the corpora mammillaria themselves were normal except for the mildest degree of prominence of capillaries from swelling of the endothelium.

Virtually no myelinated fibers were stained in the caudate nuclei or putamens and those in the globus pallidus were greatly reduced in number and were degenerated. There was diffuse paleness of myelin staining, together with thinning out of the fibers in the internal and external capsules, optic tracts, fornix, anterior commissure and centrum ovale. The ansa lenticularis, however, was well stained.

Cerebral Cortex: In all areas of the cortex from which blocks were taken there were extensive, severe destructive changes in the form of various degrees of necrosis ranging from advanced regressive changes of nerve cells and fibers to complete loss of neural parenchyma with cavitation. Both the cortex itself and the convolutional white matter were affected in a patchy way by the necrotizing process, the cortex to a considerably greater extent. The cortical degeneration was almost always somewhat laminar, the usual picture being as follows (fig. 7C): The molecular layer was transformed into a solid rim of hypertrophic astrocytes and in this form was everywhere intact and unbroken. In the second and third cortical laminae the destruction was equally complete but different in quality. Here there was total destruction and loss of nerve cells and fibers with replacement of the parenchyma by a slit-like cavity parallel with the cortical surface, occupied by a framework of blood vessels, occasional macrophages and the nuclei of free cells difficult to identify. In places the outer cortical layers were occupied by a more solid cellular reaction. In the latter case greatly thickened capillaries were proliferating actively from the adventitia and the interstitial cellular reaction was composed of a few large macrophages and occasional astrocytic nuclei, but mostly of small dark crinkled nuclei with no visible cytoplasm, resembling "reduced" gitter cells. There were also variable numbers of pleomorphic microglial nuclei. In the deeper layers of the cortex there were likewise no nerve cells or fibers, but instead large numbers of hypertrophic astrocytes lying in a matrix of spongy ground substance. Fields of varying grades of necrosis and reaction merged one with another in a geographic way and would also abut sharply upon reaches of cortex where frank necrosis had not yet occurred and neurons were still present in almost normal numbers. In such relatively spared areas of cortex, however, there was always edema, and the neurons had suffered extreme regressive changes resembling the severe cell disease of Nissl. In a few areas the necrosis extended from the cortex into the white matter which then had completely disintegrated leaving either a ragged empty cavity or a pavement of very large macrophages lying in the meshes of what remained of the ground substance. Otherwise the usual change in the white matter was a spongy state in which hypertrophic astrocytes lay among the meshes of loosened fibrillary ground substance. Both the spongy state and the astrocytic reaction were greatest in the convolutional white matter and became less toward the centrum ovale. No myelinated fibers were present in the cortex and those in the white matter which had not disintegrated were greatly attenuated, beaded and broken up. The stains with Luxor blue revealed also in the areas of less complete necrosis more or less dense heteromorphic fibrillary gliosis. This was densest in the narrow subpial zone of cortex overlying regions of laminar cortical necrosis. Aside from the reaction of the blood vessels within the lesions themselves there were no vascular alterations and no hemorrhages, perivascular or otherwise in the gray or white matter.

Cerebellum: All parts of the cerebellar cortex exhibited mild to moderate regressive changes of the Purkinje cells, some thinning out of the granule cells and, even more marked, edema and a sieve-like spongy state in the white cores of the folia. Certain restricted cortical areas exhibited much more advanced degeneration with severe regressive changes of Purkinje and granule cells, even greater disintegration of folial white matter, and activation of microglia with formation of scattered large macrophages. Marked overgrowth and hyperplasia of capillaries, involving first proliferation of endothelium and later of adventitia, was an even more striking feature of such areas. Similar vascular change was found in the small vessels of the meninges overlying badly damaged areas of cortex and in the arterioles
FIG. 8. Drawings projected from sections to illustrate the topography of the lesion at representative levels. Solid black indicates complete necrosis, cross hatching less advanced change. In this case the changes are confined to the tegmentum of the brain stem. Note the bilateral symmetry of the lesions at most levels. a—caudal mid-brain, b—rostral pons, c—caudal pons, d—mid medulla, e—caudal medulla.

Passing from meninges to cortex. In general the necrosis was not selective but affected the molecular, Purkinje and granule cell layers equally (fig. 7B). While the neurons of the dentate nucleus showed moderate to rather severe degeneration, there were no foci of necrosis in the deep nuclei or deep white matter. Myelin stains demonstrated a great deficit and thinning of the fibers of the folial cores but normal staining of the deeper white matter.

The spinal cord was essentially normal at cervical, dorsal and lumbosacral levels except for secondary degeneration of descending tracts in the lateral columns.

In longitudinal sections through the left optic nerve, the chiasm and optic tract there
Fig. 9. Same as Figure 8. In addition to the lesions in the brain stem there is necrosis of the caudate and lenticular nuclei. a—Basal ganglia b—mid-brain c—rostral pons d—caudal pons e—rostral medulla f—caudal medulla.
was complete demyelination of these structures with advanced astrogliosis and glia fiber formation.

Summary: The entire cerebral neuraxis was involved in a patchy focal necrotizing encephalopathy (fig. 10). The process varied greatly in intensity from place to place, and showed wide gradations in degree within the same lesions; where most severe, there was actual softening with cavitation. Where necrosis was less complete a loose spongy state of the ground substance had developed associated with demyelination and regressive change of neurons and glia. In such areas and in others still less affected there was proliferation

Fig. 10. Same as Figure 8. Not only are there necrotizing changes in the brain stem tegmentum similar to Cases 1 and 2, and in the striatum similar to Case 2, but also in the cerebral and cerebellar cortices. a—frontal cortex b—basal ganglia c—cerebellum d—midbrain e—rostral pons f—caudal pons g—caudal medulla.
of astrocytes and fibrillary gliosis together with varying microglial reaction. Within most of the lesions, but not all, proliferated blood vessels were prominent. It was remarkable that the neurons were not the elements most affected by the damage, but were often left relatively intact when other components of the parenchyma had undergone advanced dissolution.

Although the lesions were regional in distribution rather than selective for gray or white matter, they were in general preponderant in the gray matter. In the brain stem, necrotic foci were distributed in essentially the same manner as in Cases 1 and 2, being most evident in the mid-brain tegmentum and substantia nigra, the tegmentum of the pons, the reticular formation of the medulla, and the central periventricular gray throughout the brain stem. In this case, however, the destructive process was equally well developed in the corpus striatum, and in disseminated regions of the cerebral and cerebellar cortices. Associated with the necrosis of the gray matter of the cerebral hemispheres were lesions of multiple-cystic encephalomalacia in the white matter.

**DISCUSSION**

In the brains of all 3 infants the salient and constant pathological changes were foci of necrosis in the brain stem which affected the ground substance primarily without sharp selection for gray or white matter. Within the brain stem the lesions were restricted to the periaqueductal and periventricular gray, the tectum and tegmentum of the mid-brain (always including the substantia nigra), the tegmentum of the pons, and the central gray and reticular formation of the medulla oblongata. In part they were patchy, in part continuous, extending for long distances in the longitudinal axis of the brain stem; often they were strikingly symmetrical. Certain characteristics of the necrosis were outstanding and were the same in all of the cases. The invariable alteration, the first to appear in the early lesions and the most intense in the advanced ones, was the breakdown of the interstitial tissue or ground substance of the neural parenchyma. Such changes ranged, according to the completeness of the necrosis, from defective staining and edema to the marked rarefaction of a status spongiosus; rarely was there softening with mobilization of fat granule cells. In most of the areas that were affected to any considerable degree the small blood vessels, notably the precapillaries and capillaries, were very numerous, greatly dilated and somewhat degenerated. The essential vascular change was varicose dilatation and engorgement, although there were also variable degrees of endothelial swelling and adventitial proliferation. The great vascularity suggested new growth of small vessels, but actually there was probably no vascular sprouting, an impression supported by the absence of increase of reticular fibers and of intervascular bridges in silver stains. While the hypervascularity was perhaps the most obtrusive feature of the lesions, it formed only one aspect of the reaction to tissue injury. Proliferative as well as regressive alterations of the astrocytes and microglia were variable in degree, but were present in most of the lesions and were often pronounced. Non-specific regressive changes of nerve cell bodies, especially of the smaller ones, was common in and near the lesions, but the astonishing preservation of neurons within areas otherwise almost completely destroyed was a remarkable characteristic of the necrosis. Although the myelinated fibers were extremely vulnerable and were greatly degenerated wherever
they lay within the confines of a lesion, and although there was edema and some sponginess of white matter in many areas, especially in fiber tracts lying near foci of necrosis, the destructive process was predominantly selective for areas of gray matter in the brain stem tegmentum. In this sense the condition may be considered as a polioencephalopathy.

The 3 cases reported here are not only entirely similar among themselves as regards the pattern and the kind of tissue reaction in the brain stem, but are identical also in this respect with 4 others recently reported in the literature. The first of these was described by Leigh (11) and 3 others by Feigin and Wolf (12). No other comparable reports are on record. Leigh’s patient was a 7 months old infant with normal birth and early development whose rapid clinical course of 6 weeks was marked by general inactivity and lethargy, sweating, spasticity of all limbs, absent tendon reflexes, and normal spinal fluid. Pathologically the main changes were located in the tegmentum of mid-brain andpons and the central gray matter of the lower medulla, were remarkably symmetrical, and were identical in all histopathological details with those of my cases. Of Feigin and Wolf’s 3 patients one was 12 months of age with a clinical course of 7 months, one 21 months old with symptoms for 4 months, and the other 4 years of age, the duration of the illness being at least 2 years. The clinical syndrome observed in this group of cases, generally speaking, was that of lack of development, inertia, mental deficiency, and drowsiness, motor weakness, ataxia, altered muscle tone with spasticity in one patient and hypotonia in another, and a variety of cranial nerve signs. The pathological alterations in the 3 cases of Feigin and Wolf were quite uniform, consisting essentially of extensive but discontinuous, frequently symmetrical fields of partial necrosis in the tegmental and reticular areas of the brain stem from the preoptic region to the caudal medulla oblongata. The tissue reaction of the lesions conformed in every particular to that of my cases.

Pathologically the common denominator of this group of 7 cases was a necrotizing process in the brain stem having a uniform pattern of distribution and a uniform tissue response. In some of the patients, as in my Case 1 and Feigin and Wolf’s Cases 1 and 2, the necrosis was present only in the brain stem, but in others it exceeded these limits. In this respect there is much variability among the individual examples. Thus, in my Case 2 there was extensive necrosis of the deep gray masses of the cerebral hemispheres, greatest in the corpus striatum but present also in globus pallidus, pulvinar of the thalamus, and subthalamic nuclei. In Case 3 not only were the basal ganglia similarly involved but also the cerebral and cerebellar cortex. In Leigh’s case foci of necrosis were encountered in the anterior, dorsomedial, submedial nuclei and pulvinar of the thalamus, and in Case 3 of Feigin and Wolf in the dentate nuclei. Leigh mentions also destruction in the posterior columns of the cord at cervical and dorsal levels. In my Case 3, apparently the only other one in which the spinal cord was examined, it was unaffected. This case, however, differed from all the others by showing an attack upon the white matter of the cerebral hemispheres where the process took the form of liquefaction necrosis and cavitation and produced the picture
of multilocular encephalomalacia. Striking as such changes were in this brain, they should not be allowed to obscure its identity with the other cases which it resembles in all essential respects. It might be contended, rather, that one has here another example to support the view that multiple cystic softening in infants has no single cause or pathogenesis, but is merely a type of reaction displayed by the cerebral white matter of infants to a variety of injuries.

Two details concerning the localization of the necrotizing process in the 7 cases attract special attention. In all of them the substantia nigra was the site of intense and extensive symmetrical destruction. On the other hand, in none of them were the mammillary bodies affected although the gray matter of the lateral walls of the third ventricle was involved in several. It is also of great interest that there were signs indicative of a defect of the visual system and corresponding degenerative changes in the optic pathways of most of the infants. My cases all appeared to be blind, the pupillary light reflexes were slow or absent, and there was complete demyelination of the proximal portions of the optic nerves and tracts, and of the optic chiasm. Leigh's case had optic atrophy with unreacting pupils and the optic nerves were demyelinated. Case 1 of Feigin and Wolf had absent light reflexes with no mention of the optic system in the pathological description; optic atrophy was noted in Case 2 with unspecified lesions in the optic chiasm and tracts and similar lesions (demyelination?) in Case 3.

The stretches of focal necrosis in the cerebral cortex of my Case 3 raises the question of the relationship of this entire group to the "Poliodystrophia Cerebri Progressiva" of Christensen and Krabbe (9) and to Alper's (7) "Diffuse progressive degeneration of the gray matter of the cerebrum". As to the former there seems little doubt that the 2 conditions are quite distinct. The case of Christensen and Krabbe as well as the one like it described by Neuberger showed no changes outside the cerebral cortex and there was none of the vascular reaction so prominent in my cases. It is more difficult to judge about Alper's case. The cortical changes were very like those in Case 3, those in the striatum and pallidum similar to Case 3 and Case 2 and there were foci of necrosis in the pons with prominent vascular reaction. So far as can be decided from the published account, however, it appears that the brain stem changes differed both in arrangement and quality from those under consideration here.

The symmetrical necrosis of the caudate nuclei and putamens in Cases 2 and 3 is reminiscent also of that reported by Verhaart (13) in 4 Chinese infants under 1 year of age. But in each of these patients, death followed a brief acute febrile illness and the pathological changes in the lower brain stem appear to have been less constant, less severe and not so sharply patterned as in the present cases.

The 3 cases resembled each other also in their main clinical features which included, prominently: the early appearance and persistence of feeding difficulties associated with dysphagia, inadequate sucking, and regurgitation; slowness or lack of behavioral development with failure to support the head, to sit up, to stand or even to turn over when in the recumbent position; eventual deterioration of simple sensori-motor and postural behavior; impaired or absent pupillary
light reflexes; the appearance of blindness and deafness as judged by the failure to pay heed to such stimuli; very brisk tendon reflexes, extensor plantar responses and, in one patient, spasticity; and convulsions of comparatively late onset in the course of the disease. The clinical similarity extends also to the cases of Leigh and of Feigin and Wolf. Taking the 7 cases together it may be said that the disorder is exclusively one of early infancy, the earliest age of onset being at birth, the latest at 2 years and the earliest demise at 4 months, the latest at 4 years. The shortest duration of symptoms was 6 weeks, the longest 2 years. All 7 patients presented feeding difficulties, failure of proper development and mental and motor deterioration. Five of them had impaired pupillary light reflex, 4 were blind and 4 deaf. Six of the group exhibited motor weakness with spasticity in 3, hypotonia in 2, increased tendon reflexes in 4, and decreased reflexes in 2. Ataxia was noted in only 2 cases and convulsions, present in each of my cases, were not mentioned in the others. Apparently the spinal fluid was examined in only 2 of the 7 cases and in them it was normal. The clinical state, common to all of the cases, was that of diffuse or widely disseminated brain disease and does not serve to distinguish them from other types of polioencephalopathy or from the leucodystrophies. It will always be difficult and usually impossible to make the diagnosis of this condition during life by any clinical methods now available, and it is probable that most of the cases will continue to be regarded as some form of leucoencephalopathy.

Presumably there may be a common cause at work behind such a specific pathological reaction as the one described here, but about this one can only speculate in the most general terms. It seems clear in the first place that the process is a purely degenerative one. The uneventful births and the normal state and development of the infants during the early weeks of life in most instances, as well as the selection of the process for the brain stem, make it most improbable that trauma, anoxia or dysgenesis have played any part in bringing about the disorder. Likewise the complete lack of inflammatory reaction in the lesions and the absence of changes in the larger vessels exclude infection or vascular occlusion as factors in pathogenesis. The basis for a necrotizing degeneration of this sort can scarcely be anything but metabolic either induced by a toxin or present as an inborn metabolic error or deficiency.

Favoring the toxic view is the fact that I have been able to produce in the monkey necrotizing lesions essentially similar to those of the infants, symmetrically selective for nuclear masses of the brain stem, by intoxication with quinoline compounds (14) and in the globus pallidus and substantia nigra with carbon disulfide (15). In the experimental lesions, which in general were somewhat more circumscribed than those of the infants, one encounters the same partial, usually profound, breakdown of the parenchyma including the ground substance and the same if somewhat more vigorous productive reaction of the neuroglia and of the mesodermal capillary bed within the confines of the lesions. It may be mentioned, too, that the tissue reaction of carbon monoxide poisoning in man and in experimental animals as observed by Meyer (16) is similar in all essential particulars to that of the infants.

On the other hand, Leigh, who considered the possibility of a toxic agent in
his case, was struck by the close resemblance of the lesions to those of Wernicke's disease and Feigin and Wolf were even more impressed by it. This suggestion must be taken very seriously. There are objections, however, to considering the disorder simply as infantile Wernicke's disease, that is, specifically, as the effect of thiamine deficiency. Although the 3 infants were “feeding problems” from early infancy with symptoms of defective sucking and regurgitation, all were children of intelligent devoted mothers (one a physician), who compensated in large part for the nutritional deficiency by zeal in forced feeding and large supplements of vitamin under the supervision of a pediatrician. It is noteworthy, too, that the necropsy protocol of each of the infants stated explicitly that the body was that of a well-nourished child. One gains the impression in these cases, as did Feigin and Wolf in theirs, that the difficulties with feeding were the consequence rather than an important cause of the disease. The situation of the lesions in the bulbar brain stem would be expected to produce trouble with sucking and deglutition. In the literature dealing with the neurological complications of avitaminosis from nutritional deficiency reference is made to the disorder known in the Orient as “breast milk intoxication”, a condition in which the ophthalmoplegic and other cerebral symptoms tend to clear with supplementary feedings and thiamine, and appear to be the result of dietary avitaminosis. Tanaka (17) has given the only reasonably clear pathological account of the syndrome. He described parenchymal degeneration in the gray matter of the brain stem, to be sure, with increase and hyperplasia of capillaries but the process was outstandingly hemorrhagic, there was no neuronal sparing and it is not possible from Tanaka’s illustrations to identify the lesions of his case with those of mine.

Furthermore, there are important differences pathologically between my cases and those related to it on the one hand and Wernicke's encephalopathy as it is manifested in the adult on the other. In Wernicke's disease the mammillary bodies are heavily involved with great regularity, although not invariably. Thus Campbell and Biggart (18) found them affected in all 12 of the cases examined; Neubuerger (19) likewise in his 12 cases; Bender and Schilder (20) reported them involved in all 6 of their patients regardless of clinical type; and Riggs and Boles (21) in 21 of 23 cases of alcoholic Wernicke's disease. Gamper (22) found them constantly involved in all 16 of his alcoholic cases and stated that "Das Corp. mamm. scheint gerade zu den Knotenpunkt des ganzen Processes zu bilden". In my 3 cases, on the other hand, mammillary bodies were entirely spared; the same was stated to be true of Leigh's case and of one of Feigin and Wolf's, while these structures were not mentioned in their other 2. Considering the greater susceptibility generally shown by the infant's brain to most varieties of injury it would be strange, indeed, if Wernicke's disease in the infant differed in this particular respect, i.e., sparing of the mammillary bodies from that in the adult. Moreover, the single infantile example in Riggs and Boles study of 29 cases of Wernicke's disease did exhibit changes in the mammillary bodies but none in the brain stem except for the periaqueductal gray of the mesencephalon. Conversely the substantia nigra which is only exceptionally the site of change in Wernicke's encephalopathy was a principal locus of damage in all 7 cases of the infantile encephalopathy under consideration here.
Still another point of difference between the two conditions is to be found in
the predominantly hemorrhagic character of most of the recorded lesions of
Wernicke’s disease, particularly those in the rostral brain stem, whereas petechial
hemorrhages are few and insignificant at any location in all of the cases of this
variety of infantile encephalopathy. A further discrepancy between the two
pathological states is seen in the total absence of ependymitis in the infants in
contrast to the prominence of the ependymial reaction in cases of Wernicke’s
disease, as was pointed out especially by Bender and Schilder.

From the qualitative standpoint it is the striking vascular reaction in the
lesions of the infants’ brains that is perhaps most reminiscent of the Wernicke
process. But it will be generally agreed that such changes, compounded of stasis
and varicose dilatation, degeneration and hyperplasia of the capillary walls
are not diagnostic of any single disease or manner of pathogenesis. They are
seen in association with partial necrosis of gray matter in a number of different
conditions, in the necrotizing lesions of various intoxications as already mentioned,
in certain types of infarcts, in encephalopathy from avitaminosis, in some of the
lesions of hepatolenticular degeneration, and have recently been described by
Innes and Plowright (23) in a necrotizing poliomyelopathy, selective for the
anterior spinal gray matter, in sheep. Little is known of the nature or the second­
ary consequences of vascular alterations of this kind, but it seems probable that
they are not the primary change, however much they may dominate the picture,
but are merely the mesodermal component of a particular kind of tissue reaction
in a particular place, provoked by the underlying localized metabolic failure,
by the surrounding breakdown of neural parenchyma or both.

Although it appears that the encephalopathy herein described cannot be
classified properly as infantile Wernicke’s disease, there are good reasons for
thinking that it may be of the same general nature. In any event it seems likely
that the parenchymal and vascular reactions are in response to failure of an
enzymatic pathway, whether by poisoning of enzymes or an inborn enzymatic
deficiency. Certain facts suggest that the underlying metabolic defect is, indeed,
inborn and genetically determined. Cases 2 and 3 of Feigin and Wolf were siblings
and a brother of the mother of my Case 3 died at 13 months of a disease that
she (a physician) considered similar to her son’s condition.

SUMMARY

1. The histories of 3 infants, aged 16, 7 and 13 months respectively, are pre­
sented. The clinical features were similar in all 3 patients and were indicative
of severe diffuse brain disease, progressive and fatal.

2. Pathological examination of the brain was made in each case and revealed
foci of necrosis in the brain stem as the salient and constant pathological change
in all. The outstanding characteristics of the necrosis was its restricted localization
to the tegmentum of the mid-brain, pons and medulla oblongata and often its
symmetry, the breakdown of the interstitial tissue of the neural parenchyma
with relative preservation of the cell bodies of the neurons, and the prominence
of the small blood vessels in the lesions. In one case there was, in addition, ex­
tensive focal necrosis in the caudate nucleus and putamen, and in another not
only this but also irregularly distributed foci of necrosis in the cerebral and
cerebellar cortices and in the white matter of the cerebral hemispheres. De­
myelination of the optic nerves, chiasm and tracts was found in all of the brains.

3. Attention is called to the close similarity that exists clinically and, especially,
pathologically not only between the 3 cases themselves but also with 4 others
which have been reported recently. So alike and characteristic are the changes
in all the cases that they appear to form an identifiable pathological entity
separable from a large nondescript group of cerebral degenerations of infancy
and childhood.

4. It is suggested that the basis for the disorder lies in an endogenous toxemia
or an inherent metabolic defect, possibly enzymatic.

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