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Intrauterine Brain Death

Neuraxial Reticular Core Necrosis

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Summary. Report is given on the first example in which the clinical and electrographic criteria of brain death were obtained at birth. Global destruction of the central nervous system of a type seen only with anoxia and circulatory failure had occurred *in utero* without appreciable disturbance of maternal health. Neuropathologic reaction in fetal tissues was identical with that which has been observed in the child or adult in the brain death syndrome. Functional disturbance of cerebral spinal circulation of sufficient degree to destroy neuronal tissue had happened without change in maternal circulation and without demonstrable lesions in the placenta or the cardiovascular apparatus of the fetus.

Key words: Brain death syndrome – Anoxia – Circulatory failure – Fetal central nervous system – Neuropathologic reaction.

Lesions of necrotic type in the cerebral hemispheres of infants and children, incurred presumably during the last weeks of gestation or the parturitional period, are commonplace. However, considerable controversy surrounds their cause and mechanism. Seldom does the neuropathologist have opportunity to examine the brain at a time appropriate to divulge all the morphological features of the disease. Either death has occurred within hours, in which instance little or no histological reaction has had time to occur, or after months or years when only the relatively undecipherable end-stages of disease remain. And to add to the difficulty, the neuropathologist has been handicapped in the interpretation of lesions in these diverse states because the nervous tissues of fetus and neonate appear to react differently than the mature ones. Immature neurons tend to be more resistent to pathogenic agents, and destructive lesions of all types are disposed to nondescript cavitation with relatively little glial reaction.

As to the causation of lesions, birth trauma, hypoxia, hypotension, placental insufficiency, placenta previa, prolapse of umbilical cord, toxemia of pregnancy, fetal acidosis, and hypoglycemia all appear to have been pathogenic at one time or another, but proof that any one of them was responsible for the lesions has been difficult to adduce. Seldom have the necessary measurements been made at the proper time, i.e., when the disease occurred.

This unsatisfactory state of knowledge of the etiopathogenesis of parturitional cerebral lesions in humans and the difficulty in measuring such important factors as oxygenation, cerebral blood flow, etc., have turned the neuropathologist to the study of the experimental animal. The precise observations of Windle and Myers and their associates, in which the blood flow to the fetal rhesus monkey was completely occluded by clamping the umbilical vessels or was reduced by maternal hypotension, have produced two important neuropathologic syndromes. In one – that of complete temporary ischemia – the lesions consisted of symmetrical foci of necrosis without brain swelling; the inferior colliculi and sensory nuclei of the thalamus were mainly involved. In the other – that of partial temporary ischemia – brain swelling with pale or hemorrhagic necrosis of paracentral regions of cerebrum and also the junctional zones between the middle and posterior cerebral arteries as well as caudate and lenticular nuclei, characterized the morphologic picture. In commenting upon homologies between the cerebral diseases of human and animal, Brann and Myers suggest that the partial ischemic lesions of rhesus corresponds most closely to the pattern of ulegyria (sclerotic microgyria or lobar sclerosis),

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Table 1. Granocchia enfant

Age	Temps	pH	pCO_2	EB	Hgb	pO_2	Glucose	Ca	K	NA	Cl
0	23.26 h										
	0.45 h	7.01	93	−13.0[a]	16.4	34	361	4.5	3.1	142	104
	1.35 h	7.03	100	−10.5		31			3.3	149	
Bi NA 10 ml →											
	1.47 h	7.16	92	+ 5.1		46			3.0	146	
	2.07 h	7.20	88	+ 1.9		48			3.0	154	
Bi NA →											
2 h	2.25 h	7.315	105			55			3.0	149	
2.30 h	2.55 h	7.34	75	+10.5		60			3.3	140	
	8.45 h	7.61	30	+ 9.0	19.2	376	94	5.6	3.6		
11.30 h	11.00 h	7.62	27	+ 8.0						146	101
	15.40 h	7.36	61	+ 3.8[b]							
	18.00 h	7.21	33	−13.8							
19 h	18.40 h	exitus									

[a] Acide lactique 11.2 mE/l
[b] Acide lactique 3.8 mE/l

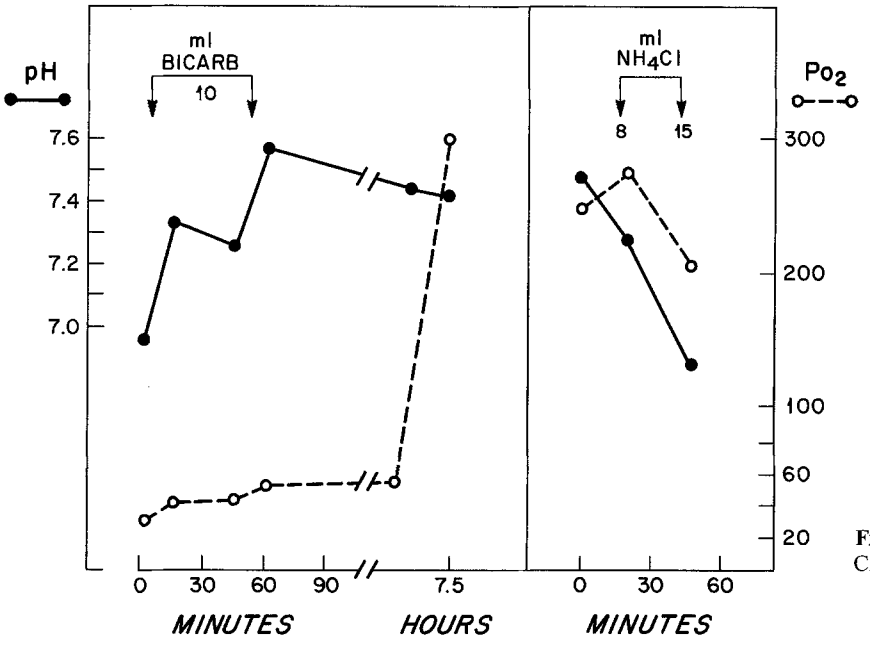

Fig. 1
Chart of blood gases and pH

diffuse white matter sclerosis, and status marmoratus of basal ganglia in man, the triad which Malamud associates with "perinatal injury". In contrast, the symmetrical brain stem necrosis of total asphyxia has been observed only infrequently in humans. Noteworthy also, is the fact that diffuse white matter cavitation and diffuse mantle sclerosis, which Benda and Wolf and Cowen believe to be the more common types of perinatal injury, have not been reproduced in the primate experiments, nor have the periventricular cavities of Schwartz and the "white-spots" of Banker and Larroche.

These discrepancies between the human and animal models of cerebral disease arising in the perinatal period should motivate further study, particularly of human cases in which the circumstances of parturition have been carefully observed and documented.

The following observations are pertinent in this respect and are of interest for another reason—that the case in question manifestly illustrates a universal pannecrosis of brain and spinal cord, corresponding to the so-called *brain death syndrome* of older children and adults but here occurring in utero. Inasmuch as there was survival of seven to ten days after the inception of the brain injury, the pathological material discloses, to a striking degree, the reactive capacities of the interstitial tissues of the fetal brain.

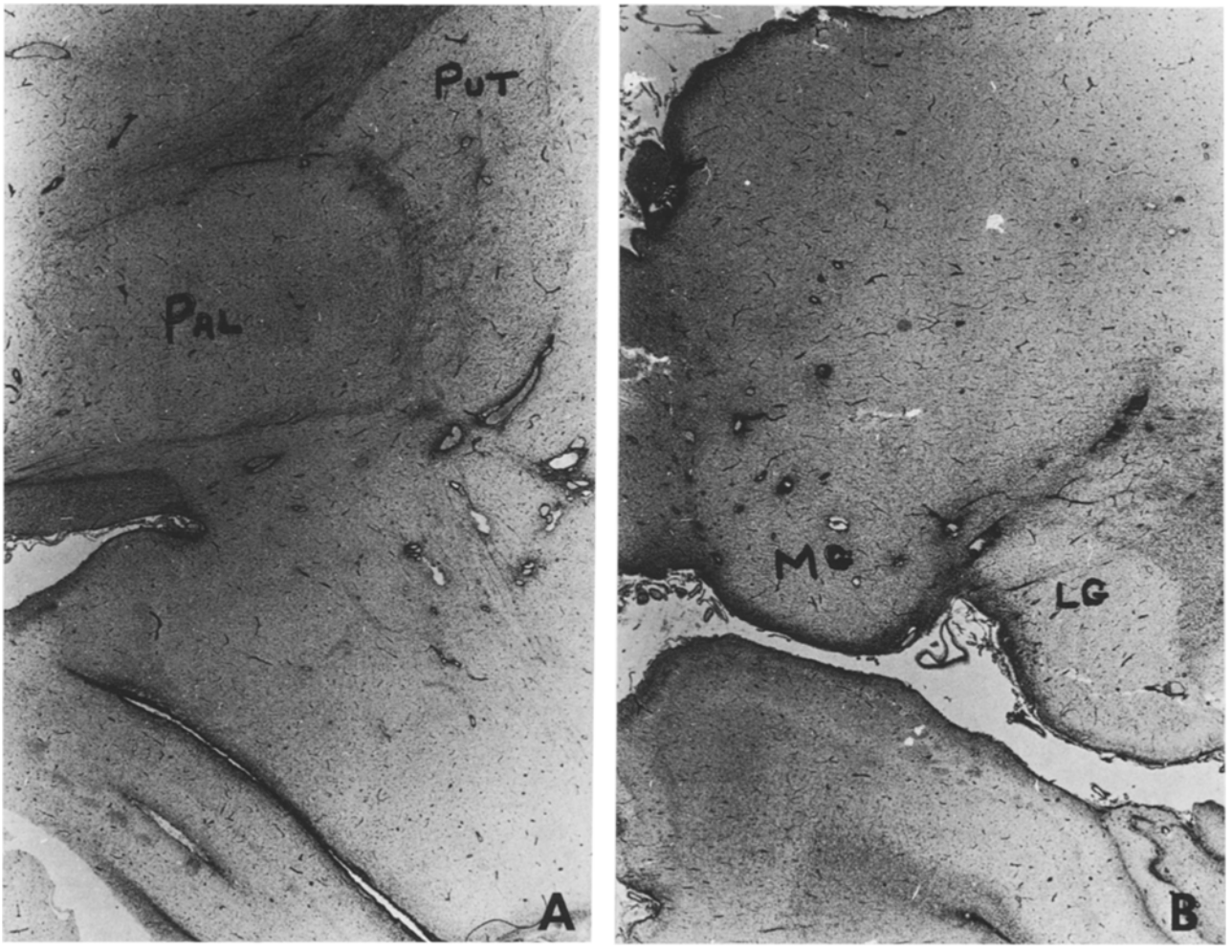

Fig. 2. A Nissl stain of globus pallidus and putamen (upper half) and amygdaloid nuclei (lower half) showing loss of all neurons. **B** Nissl stain of optic thalamus, medial and lateral geniculate bodies (center) and hippocampus (lower) all devoid of neurons

Case Report

Clinical Data

The patient was the second born infant of parents, each 31 years of age, who had been concerned about infertility in the first years of their marriage. No known nervous disease had been observed in their antecedents and there was no question of consanguinity.

The pregnancy had proceeded without mishap except for a mild albuminuria which was detected on the last prenatal visit two months before delivery. A reduction in salt intake was advised. No other symptom or sign of toxemia appeared. Fetal movements which were never vigorous were thought in retrospect to have diminished in the last week or two of pregnancy; but, when questioned carefully after the death of the infant, the mother and father recalled no unusual illness or symptom which could have warned of the distress of the fetus in utero. No medications were taken. The mother had no fever. No animal contact was remembered.

The mother presented herself in labor at the Lausanne Cantonal Hospital on the 290th day of the pregnancy. Soon after entering the Obstetrical Clinic the membranes ruptured, revealing an amniotic fluid that was strongly stained with meconium. The fetal heart rate was 140–148 and showed none of the usual physiologic oscillations with uterine contractions. The fetus was in a transverse position. The mother's blood pressure was 140/80 and the general examination was negative.

Because of evidence of fetal distress and the abnormal fetal position a Caesarean section was performed and the delivery was accomplished in 3 min. The infant was covered with an unusually thick, viscid meconial-stained fluid which filled the mouth and nares. The umbilical cord was wrapped tightly around the neck. The skin had desquamated over large areas. The infant was flaccid and cyanotic and the only sign of life was a heart rate of 100. The fontanelle bulged and the sutures were separated. The body weight was 2600 g (10%); the body length 49 cm (10–25%); the cranial circumference 33.5 cm (22–50%). The Apgar scores were 1–1–2. There were no spontaneous respirations hence intubation of the trachea was performed immediately and 100% oxygen given. The pH of the blood was 7.3

After 30 min the infant was still in the same precarious condition and did not breathe spontaneously. The legs were held in firm flexion and did not move. The pupils were dilated and fixed to light. No ocular movements could be evoked. Sucking, grimacing, and grasping reflexes were absent. There was no

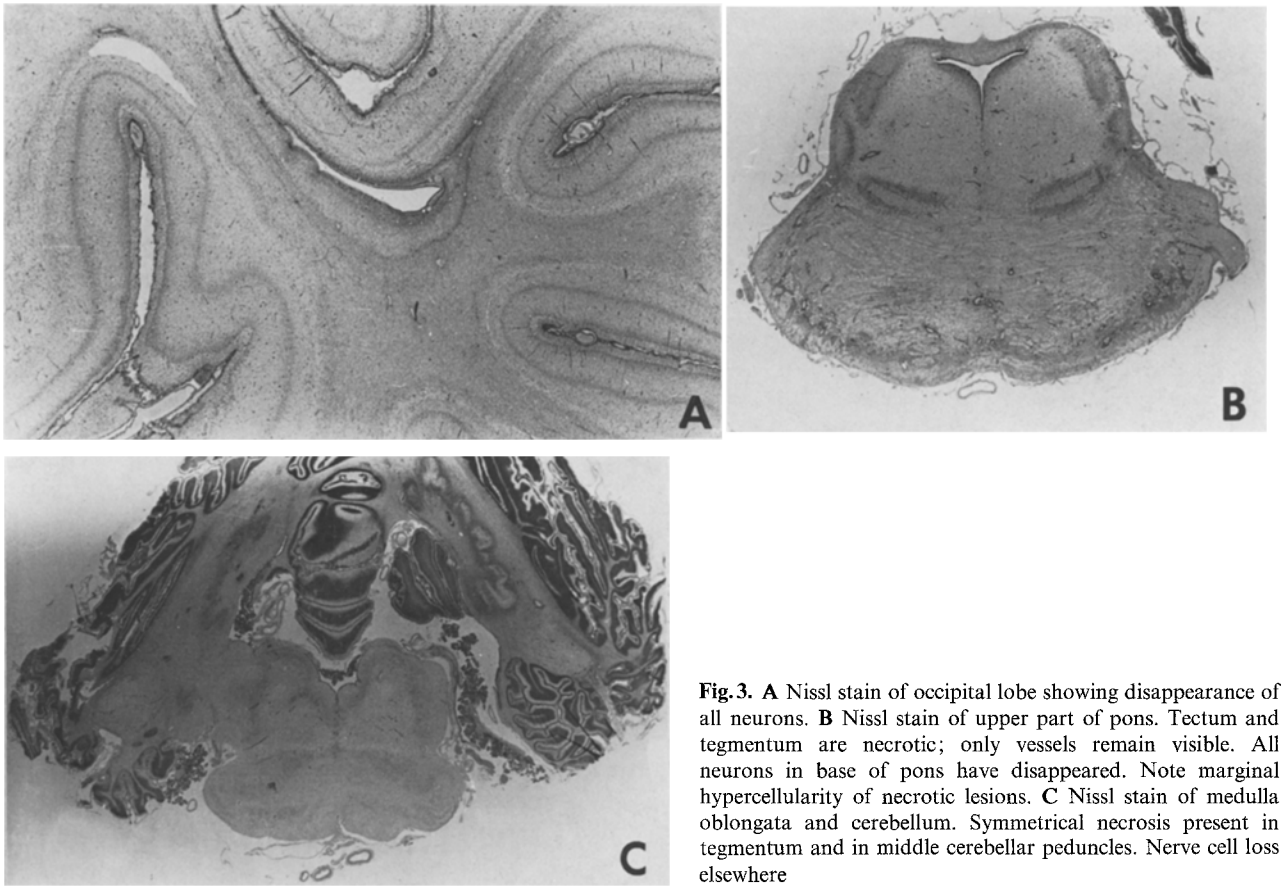

Fig. 3. A Nissl stain of occipital lobe showing disappearance of all neurons. **B** Nissl stain of upper part of pons. Tectum and tegmentum are necrotic; only vessels remain visible. All neurons in base of pons have disappeared. Note marginal hypercellularity of necrotic lesions. **C** Nissl stain of medulla oblongata and cerebellum. Symmetrical necrosis present in tegmentum and in middle cerebellar peduncles. Nerve cell loss elsewhere

Moro response, no support reaction, and no steppage movements or incurvation of trunk on stroking the skin of the back. The tendon reflexes were absent.

The electroencephalogram taken at the ninth hour postnatally was isoelectric even at the highest amplification.

The pH of umbilical blood had fallen to 7.01 at 30 min after birth; the pO_2 was 34 mm Hg, the pCO_2 was 93, and the other biochemical measurements were as indicated in Table 1.

Attempts to correct the lactic acidosis and the abnormal blood gases by alkalinization during the first $7^1/_2$ h of postnatal life are shown in Figure 1 (left side). Later when it was certain that there was no chance of survival the effects of acidification with NH_4Cl were recorded (right side).

The cardiac action slowed and a slight cardiomegaly developed. The cord continued to pulsate for more than 30 min. None of the normal neonatal reflexes or automatisms returned. The limbs were now completely flaccid. The heart action ceased at the 19th hour of life.

Pathological Findings

The only abnormality outside the nervous system was bronchopneumonia and evidence of aspiration of amniotic fluid and meconium in the bronchial passages and alveoli and necrosis of epidermis. The placenta was found to be normal upon gross and microscopic examination. There was no clear evidence of cardiac, renal or hepatic damage from circulatory insufficiency.

The brain was both swollen and congested when sectioned after formalin fixation. There was manifest increase in volume as reflected in the flattening and obliteration of sulci and smallness of ventricles. Aside from softness and friability of the cerebral tissue, no other macroscopic change was observed.

Microscopically the lesions were of two types; one in which global necrosis of tissue had occurred, the other in which neurons alone had been destroyed.

The tissue necrosis was diffuse and symmetrical. It involved most of the thalamus and basal ganglia as well as symmetrical zones of the tectum and tegmentum of midbrain, pons, and medulla, and the central gray matter of the spinal cord (see Figs. 2, 3 and 4). In Nissl, H and E, axis cylinder, and myelin stains, the only surviving elements in the necrotic zones were capillary walls and endothelial cells. The pyknotic remnants of oligodendrocytes and astrocytes could be distinguished only with difficulty from those of destroyed neurons. What must have been neurons were reduced to shrunken pale cells with collapsed nuclei. The endothelial cells of capillaries had proliferated, rendering the capillaries strikingly visible, and small numbers of macrophages had migrated short distances from the cellular vessels (Figs. 5 and 6). Large vessels, arteries and veins, had unusually cellular walls owing to increase in number and size of both endothelial and adventitial cells. The borders of the lesions were also marked by a hypercellularity wherein large numbers of macrophages had accumulated (Fig. 6). Astrocytes, too, had increased slightly; some of their nuclei were paired but no plump or fibrous forms were seen.

The necrotic lesions were notable with respect to the parts of the neuroaxis which were left untouched. The ependyma and ad-

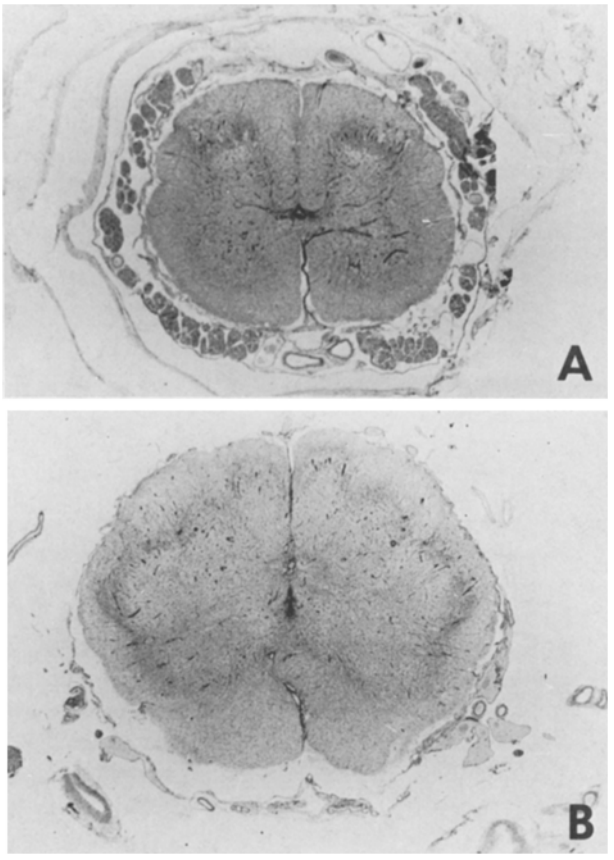

Fig. 4. A Nissl stain of lumbar spinal segment showing destruction of anterior and posterior horns of any matter as well as intermediate zones. **B** Nissl stain of spinal cord at decussation of pyramids. Symmetrical necrosis of entire gray matter

jacent periventricular zones appear to have been identified (Fig. 7). The subpial zone and meninges were intact in all places. The cerebral white matter, cerebellar white matter, base of the midbrain, pons and medulla and the tracts of the spinal cord were spared. (Presumably these are the parts least vulnerable to diminished blood flow.)

Neuronal degeneration was also widespread in regions of the brain which escaped necrosis. The cerebral and cerebellar cortices pictured in Figures 2, 3, 4 and 5 are illustrative of this lesion. Neurons had disappeared in all layers of the cerebral cortex (Figs. 5 and 8). With depth focusing under subduded light, one could barely discern cell remnants. "Vascular hyperplasia" with prominence of endothelial cells, and large numbers of macrophages, particularly in the pia and outer layers of cortex (Figs. 5 and 6), were also noteworthy findings. Again astrocytic hyperplasia, though present, was minimal. In the cerebellar cortex the external and internal granular layers were spared; the Purkinje cells had disappeared and the macrophage reaction was prominent throughout the molecular layer (Fig. 6). Neuronal loss was nearly complete in all the thalami nuclei and basal ganglia.

The cerebral and cerebellar white matter, by contrast, was much less affected, and here the interpretation of microscopic change was more difficult. Oligodendrocytes were relatively preserved and pale medullated fibers were seen in the parietal lobes, internal capsules, and in the cerebellum near the dentate nuclei. Pleomorphic histiocytes were relatively numerous (Figs. 5 and 6). The cells of the matrix zones were damaged in places but most of them survived. "White-spot" type of necrosis of the centrum ovale and destructive paraventricular lesions could not be identified.

In the brain stem relatively few neurons were seen to have survived outside the necrotic lesions. All the nerve cells of the ocular nuclei, facial nuclei, nuclei ambiguus, reticular formations basis pontis, cochlear and vestibular nuclei had vanished, usually with no neuronophagic reaction (Fig. 7). A few nerve cells remained in the lateral part of the inferior olivary nuclei (Fig. 7).

In the spinal cord few anterior horn cells remained and many of those in the posterior horn cells had also disappeared. Ependymal cells of the central canal persisted.

Cranial and spinal roots were unusually cellular but retained their medullated fiber populations.

Discussion

With respect to the clinical status of the patient it can be said that every vestige of cerebral nervous function was in abeyance at the time of birth and in the hours that preceded cardiac arrest. All the brain stem reflexes and all primitive reactions and neonatal automatisms were absent. This was reflected not only in the low Apgar scores but in the findings at all subsequent clinical examinations. Persistent flexor posture, noted in the legs soon after delivery, was presumably maintained by disinhibited surviving alpha motor neurons in the spinal cord.

These clinical data in conjunction with the isoelectric electroencephalographic tracing comprise a clinical picture which corresponds to that of brain death as defined by the Harvard Committee. Receptivity and unresponsivity, suppression of all reflex activity and the absence of electrical activity in a properly performed electroencephalogram in a patient whose nervous system has suffered damage from circulatory arrest and hypoxia (not intoxication) are the denominative qualities of this syndrome of brain death which is now being critically examined on a national scale in the U.S.A.

The idea that a global, irreversible encephalomyelopathy of this magnitude might occur in utero is not in any sense novel. Cases abound in which an accident around the time of birth has caused permanent impairment of cerebral function, leaving the patient in a state of helpless idiocy. Maresch, Neuburger and Hallervorden have also described cases in which the fetus was damaged in utero when the mother unsuccessfully attempted suicide by inhalation of carbon monoxide. Interestingly, the mother could recover even though the brain of her infant was virtually destroyed. Also the fetal brain was the only organ to suffer injury. Of course, the usual stillborn macerated fetus has also suffered brain death but usually all other organs are destroyed as well. The point so dramatically made by our patient is that the functioning neurons of the entire nervous system may

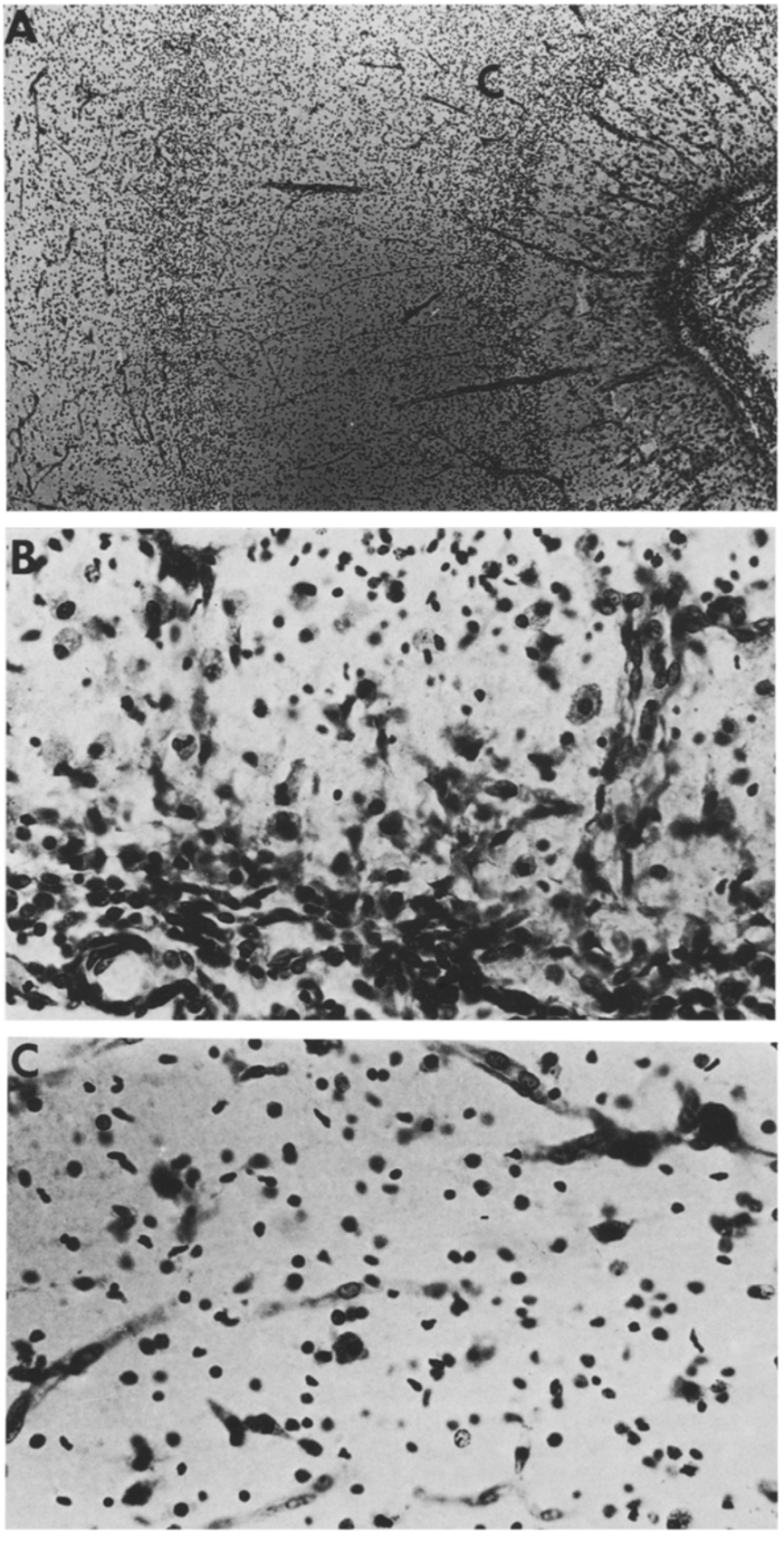

Fig. 5
A Nissl stain of cerebral cortex revealing loss of neurons, cellular vessels and histiocytes in molecular layer and pia.
B Nissl stain of molecular and 2nd layers of cerebral cortex (meninges on Rt.). Cell remnants are seen on left side; huge numbers of macrophages on right.
C Nissl stain of cerebral white matter. Endothelial cells of capillaries increased in number and size. Some oligodendrocytes are pyknotic. Scattered macrophages are visible

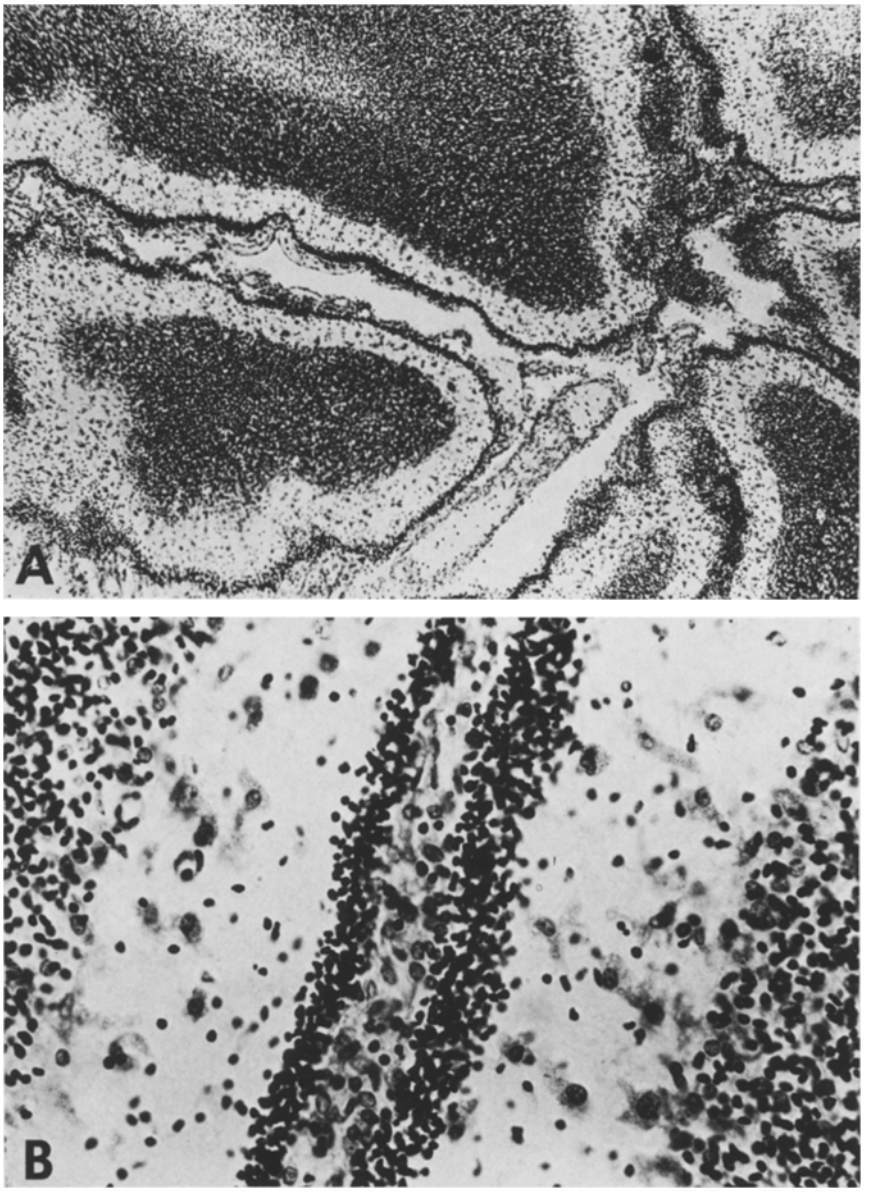

Fig. 6
A Nissl stain of cerebellar cortex. All Purkinje cells have disappeared. Part of external granular layer is destroyed whereas inner one is intact.
B Nissl stain of cerebellar cortex showing disappearance of Purkinje cells and slight astrocyte proliferation in Purkinje cell bed. Many macrophages seen in molecular layer and pia

be destroyed by a disease which causes no important microscopically visible changes in other organs even with survival for a week or more.

The biochemical findings are in line with both tissue alterations and by the consequent lack of oxygen in the nervous system. Lack of oxygen, forcing organismic reliance on anerobic mechanisms, is known to give rise to an accumulation of lactic acid—a lactic acidosis. The inadequacy of pulmonary ventillation prevented the usual respiratory alkalosis which compensates for this. The beneficial effect of alkalinization is shown in Table 1. Low arterial oxygen and elevation of CO_2 were presumably the direct consequences of impairment of the ventillatory surface of lung parenchyma and surely they were a continuing source of cerebral injury.

The explanation of the neurological status was obvious enough—a virtually complete destruction of the reticular core of the brain stem and spinal cord from the thalamus to the sacral segments of the spinal cord. The involved tissue lay within the territories of carotid, vertebral basilar and spinal vascular circuits; and since it would be inconceivable that occlusion could occur in all vessels simultaneously a general circulatory or hypoxic factor must be postulated. The neurologic and electroencephalographic pictures correspond to those described by Alderete et al. in the adult nervous system.

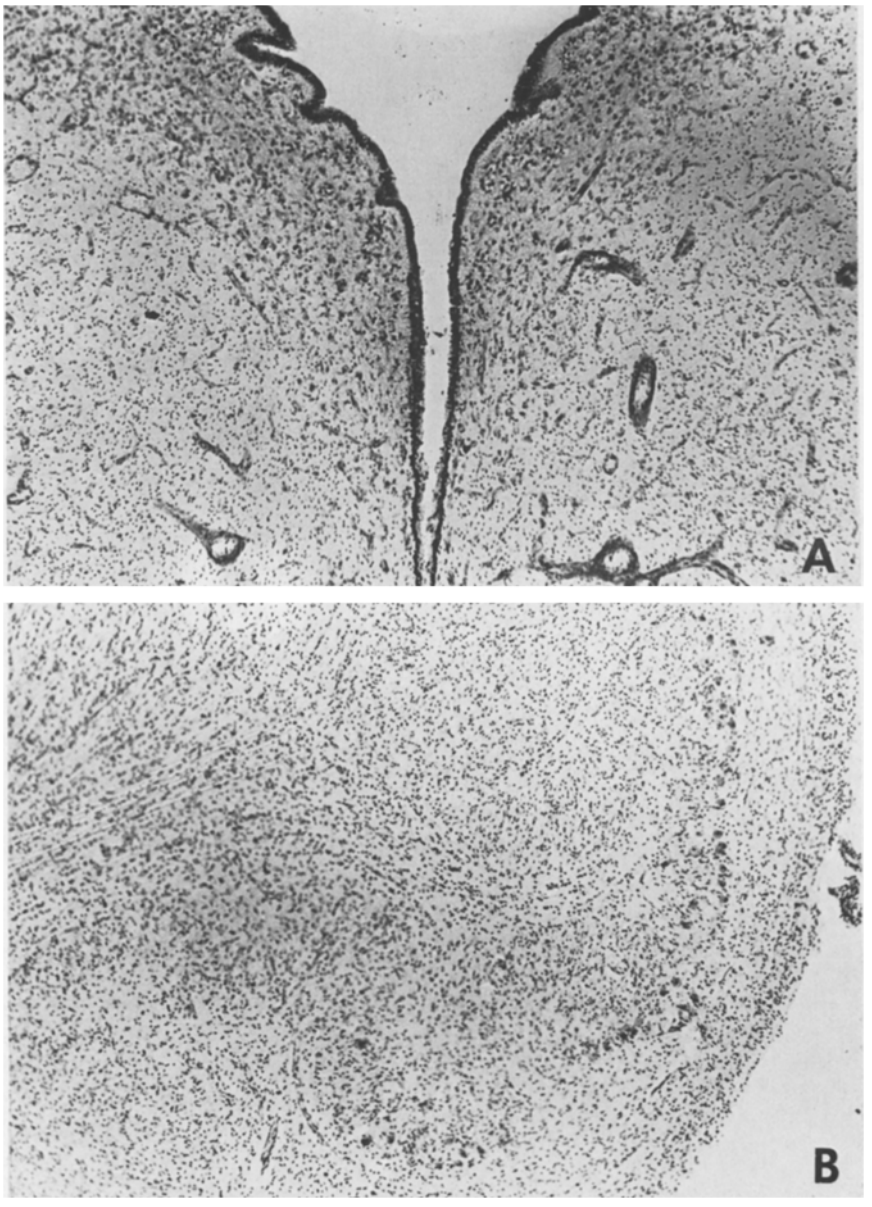

Fig. 7
A Nissl stain of posterior margin of necrotic zones in medulla. Cell remnants and cellular vessels are visible within the lesions. Histiocytes are numerous in the margins. Ependyma and subependymal regions are intact.
B Nissl stain of inferior olivary nucleus. Some of neurons in lateral part have survived. Where neurons have disappeared microgliacytes and to a lesser extent astrocytes have proliferated

Of considerable interest was the neuropathologic lesion, which might be described best as a *neuraxial reticular core necrosis*. The reticular formations from the basal ganglia to the lower end of the spinal cord had undergone a pan-necrosis, affecting medullated fibers, neurons and supporting tissues alike. This corresponds to what Schneider et al. had observed in anoxic encephalopathy in 7 newborn children who suffered perinatal and postnatal accidents. In their cases also there was variable necrosis of the cerebral and cerebellar cortices. The general topography of this lesion differs from that of the other two more familiar perinatal anoxic lesions, namely the subcortical ganglionic necrosis syndrome of Windle et al. and the cortical-basal ganglionic syndrome of Myers et al. that leads eventually to état marbré and lobar sclerosis. The pathogenesis of these three hypoxic syndromes is not fully understood. Variations probably depend on degrees of hypoxia, hypotension and lactic acidosis.

The most frustrating feature of this case was our failure to determine the cause of the cerebrospinal lesion. Our interpretation of the morphological changes as representative of an hypoxic-hypotensive insult can hardly be questioned. Their very nature excludes the action of all known toxic and infective

agents. Yet at the time this disaster must have occurred, as estimated from the reactive changes in the nervous system, the circulation and oxygenation of the mother's body were presumably normal. And, since the placenta and umbilical vessels were later grossly and microscopically normal (at the time of birth), one cannot incriminate disease of these structures. This leaves only the rather vague possibility of a devastating functional disorder of the fetal circulation sufficient to destroy both brain and spinal cord but leaving all other organs unscathed. In this instance the neuraxial disturbance was incompatible with survival but in other instances a lesser degree of a similar neurological disorder might well be responsible for a life-long imbecility, cerebral palsy or epilepsy.

Finally, we would emphasize that the recognition of cerebral death at the time of birth, through clinical, electrographic, and biochemical examinations, appears now to be entirely feasible. If this can be achieved by a completely reliable clinical methodology it will surely require a new orientation towards the value of supportive measures and therapy in critical care units of nurseries. Society will be confronted with some of the same moral and ethical problems as in the adult brain death syndrome.

The purpose of this brief report is to call attention to the phenomenon of brain death occurring during the late period of intrauterine life.

A patient exemplifying this condition was unable to survive postnatally and a complete postmortem examination confirmed the global destruction of the cerebrum, brain stem, cerebellum and spinal cord. The vigor of the vascular, histiocytic-microglial reaction to neuronal necrosis was of such degree as to indicate that the cerebral lesion had occurred at seven to ten days before birth, yet careful questioning of the mother failed to disclose awareness of any symptoms or illness in herself that reflected the catastrophic injury to her fetus. Moreover, examination of the placenta, the umbilical vessels and other organs yielded no signs of disease which could have been responsible for the failure of circulation and oxygenation of the nervous system.

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