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Perinatal Anoxic Changes of the Central Nervous System

By

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The cerebral changes due to perinatal anoxia and their pathogenesis in the acute, subacute and chronic stages are described. The tolerance by the nervous system of O_2 deficiency in the foetal and perinatal period, intrauterine CO poisoning, the cerebral changes induced by postnatal eclampsia and Alpers' disease are discussed with special reference to histopathologic aspects. Attention is called to the possibility that perinatal anoxia may lead to mental and somatic retardation, because the destruction of the nervous parenchyma is irreversible.

During the perinatal period from the last trimester of gestation till the 2nd or 3rd postnatal week, just as later, anoxia may be stagnant, respiratory, oligaemic and histotoxic. In perinatal age it induces encephaloclastic processes, thus it destroys the fundamentally developed nervous system.

It is known from experimental investigations [49] as well as from human pathological studies (56, 22, 10, 14, 43, etc.) that the developing nervous system with immature myelin responds to injuries more vehemently, with more extensive destructions, than the mature one. In other words, the less mature the nervous system, the more vulnerable it is. Another property of the immature nervous system is that transneuronal degeneration spreads in it much faster than in the mature brain (32.) When a nerve cell degenerates, degeneration of the myelin sheath and of the axon ensue rapidly. During this period secondary ectodermal and mesodermal substitution is insufficient, lagging behind the destructive process; this is true especially in the antenatal period, so that it allows conclusions as to the time of onset and the intensity of the injury. Moreover, in the foetal brain it is the cells of the periventricular matrix that are destroyed in the first place [51]. Immediately before birth and especially during the postnatal period substitution is more effective, though the pattern is far from being characteristic, the boundary is more vague when survival is longer. Thus, in the lack of data concerning early history it is usually difficult or even impossible to determine the time of onset of the lesion. It is similarly difficult to elucidate the causes of anoxia in the absence of relevant evidence. In

general, it is claimed that the cause of antenatal anoxia should be sought in the placenta and umbilical cord, while that of paranatal anoxia in the umbilical cord and the genital tract.

Destruction and substitution by themselves do not supply information as to the cause of the disease, because the dramatic destruction of the prenatal brain washes away eventual vation. In the brain of an 18-months-old infant with Little's disease (Fig. 1), the changes corresponded to a symmetric encephaloclastic porencephaly in the area supplied by the two cerebri media arteries. Destruction of the originally developed matter was proved by the absence of macrophages storing fat at the margin of the pores and of microgyria. It is un-

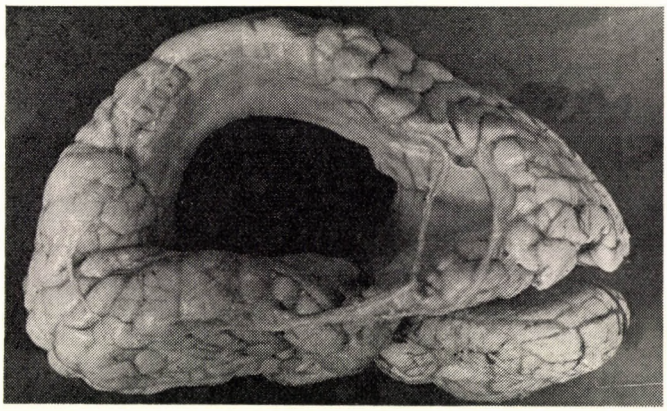

FIG. 1. Symmetrical encephaloclastic porencephaly in the area supplied by the cerebri media arteries. Little's disease of 18 months duration. History unknown

clues, vascular obstructions and emboli. Progressive and regressive glial patterns and inflammatory reactions may be sluggish even in the last trimester. It is a rare error to confound the cells of the perivascular matrix with inflammatory cells. Haemosiderin is only exceptionally detected in the brain which has been damaged antenatally [48].

When there is no relevant history available, it is often difficult to determine the time of onset and the cause of antenatal lesions, as it is illustrated by the following obser- clear how the pores arise; thrombosis, embolism following foetal endocarditis or placental arteriitis, and postnatally a compression of the two cerebri media arteries may explain it. At necropsy we could rule out foetal endocarditis but in the lack of a relevant history all that could be stated was that the holes had arisen following a compression or occlusion of the two cerebri media arteries, although it is difficult to conceive how their simultaneous and symmetric thrombosis could have developed [16].

On the other hand, when there are relevant data in the history, it is easy to put forward a morphogenetic explanation. The following observation shows the vehement destruction of the immature brain and the absence of substitution.

skull. The white matter turned into a multilocular sac (polycystic cerebrum). Intact nerve cells were present exclusively in the hypothalamus. The nerve cells of the cortex were destroyed without exception.

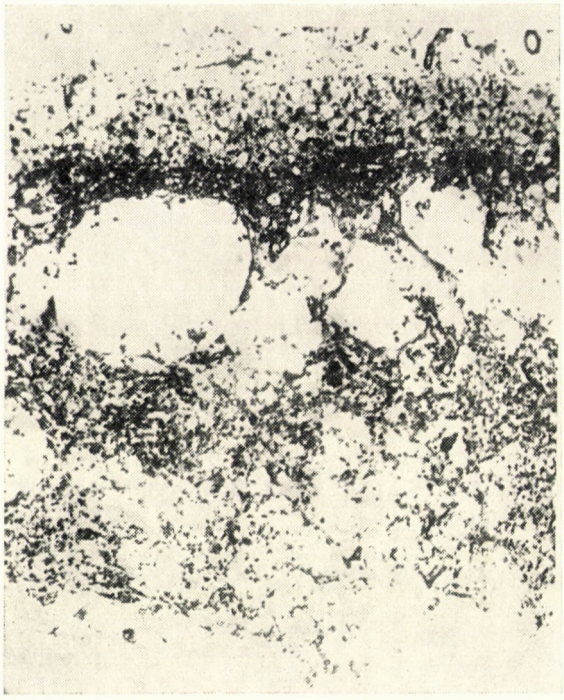

FIG. 2. Intrauterine CO poisoning. The stratum zonale is resistant. Total desorganization with pseudocysts in the cortical-subcortical matter. Survival for about 3 months. Paraffin — Nissl. ×50

A patient aged 28 years attempted suicide with illuminating gas in the 7th month of her pregnancy. She recovered after a short period of unconsciousness and gave birth at full term to a baby, which weighed 1900 g and died of toxic enteritis at the age of 1 month. The brain was fist-sized inside the fully developed

In layers 2 through 5 and subcortically, the structure was loosened micropolycystically (Fig. 2). The stratum zonale increased in diameter and the astrocytes in it were proliferating. The cerebellum was intact.

To this date, 10 similar observations have been reported (for details, see [4]).

Anoxic Changes During the Perinatal Period

It has been widely accepted that cellular defects found in the cortex of newborns were induced by some mechanical action during delivery, such as a compression of the extracerebral arteries, an increase of intracranial pressure, or following a maternal collapse [28, 29]. The prenatal cell losses may be confirmed exclusively when survival is short. Schmidt [45] studied brains from preterm and term newborns, irrespective of the presence or absence of asphyxia in the history. In 38% of 258 brains, selective parenchymal necrosis was demonstrated, more frequently in premature than in mature babies. Veith [53] found selective parenchymal necrosis in the brain of 18% of still-born babies. His findings suggest that dysmaturity rather than premature birth was the factor responsible for the selective parenchymal necrosis. Cell losses may be caused by temporary O_2 deficiency, compression of the umbilical cord, placenta previa, infarction and last but not least, by changes in the placenta.

The experimental investigations yielded results confirming the hypotheses put forward in human pathology. Myers et al. [35] reproduced in the brain of foetal and newborn rhesus monkeys changes well-known in human pathology, such as polycystic necrosis, selective parenchymal necrosis, ulegyria, etc. by inducing incomplete abruption of the placenta or anoxia for a few minutes or for a longer period of time.

As to postnatal injuries, during delivery respiratory and stagnant anoxia may be expected to occur. Histotoxic anoxia, due to drug treatment of the mother, is rare. Apnoea, aspiration, protracted delivery, increase of intracranial pressure are accompanied by anoxia. According to Wohlwill [56], delivery is the most serious catastrophe the nervous system is exposed to during life. This catastrophe is illustratively demonstrated by the Slonimsky-Cunge benzidine test following asphyxia (Figs 3a and b) due to stagnant hypoxia. A consequence of stagnation is an increase of intracranial pressure due to concomitant oedema. Traumatic haemorrhages may also exert a vascular anoxogenic effect, in the paranatal period in the first place: acute subdural haematoma and internal haematocephalus are such changes. It has been mentioned that an increase of intracranial pressure may compress the pial arteries (Fig. 4) [28, 43, 17]. It is easily conceivable that during protracted delivery irreversible, circumscribed lesions may be caused by the compression of a few exposed pial blood vessels [38].

We shall not deal with the mechanical injuries during delivery, haemorrhages, tentorial rupture. They were described in detail by Schwartz [46, 47].

In the acute, subacute and chronic stages of perinatal anoxia, the pattern of changes in the brain depends upon 3 factors, *viz.*

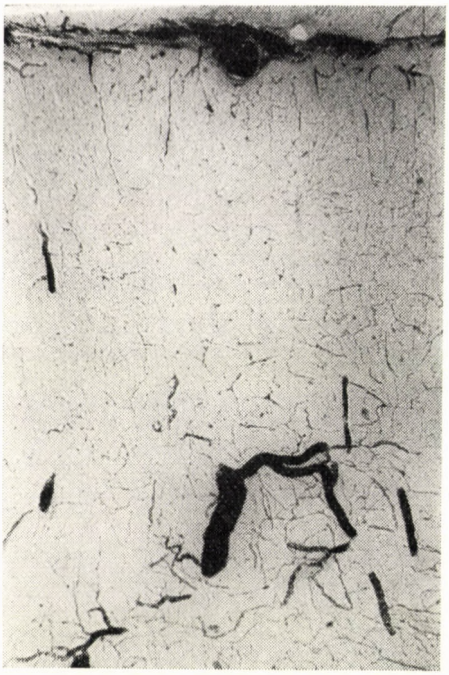

FIG. 3/a. Slominsky–Cunge method. Cerebral cortex of a newborn with algid asphyxia. Stagnation pattern of blood distribution. Post-mortem study 2 hours after death. × 14

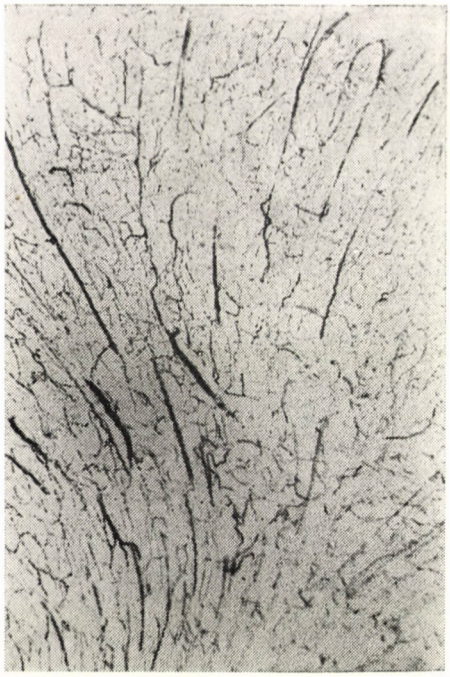

FIG. 3/b. Normal vasoarchitectonic pattern. Newborn brain cortex × 14

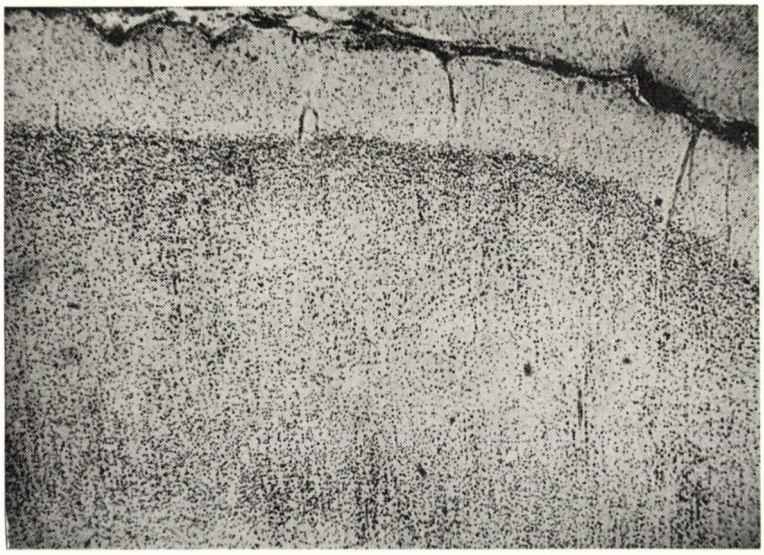

FIG. 4. Part of opercular cortex. Nerve cells lacking in strata 3 to 5. Eleven days after birth, acute internal haematocephaly, intracranial compression. Celloidin—Nissl. × 14

intensity of hypoxia,
duration of exposure,
survival time.

(a) In the case of acute hypoxia, the specific ischaemic cell forms appear also in newborns, but the nerve cells are so closely packed in the cortex that the single cell forms cannot be detected. In neonatal age a reliable sign of anoxia is a focal

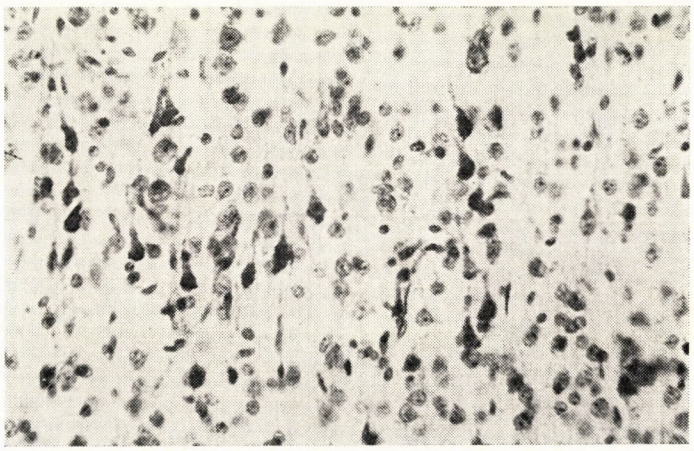

FIG. 5. Hyperchromic, pycnomorphous nerve cells in stratum 5 of the frontal cortex. Dysmature newborn with hypoglycaemia. ×160

or laminar cell loss, followed a few days later by the onset of ecto-mesodermal substitution: proliferation of the vascular wall and of the glia. It is at about 10 days that decomposed lipids and macroglial fibre formation can be detected.

Exceptionally, in the perinatal period even a survival of hypoxia for a few hours may induce the so-called hyperchromic, pycnomorphous cell, or the dark neurone, demonstrable by Nissl's technique (Fig. 5). The cells are elongated, pyramid-shaped, the nucleus and the cytoplasm are strongly basophilic, confluent. NISSL termed this pattern cell sclerosis, chronic cell degeneration. The picture may be reproduced experimentally by inducing acute anoxia [25]. The contradictory opinions concerning these cells have been reviewed in detail by HAGER [21]. Several authors claim them to be artifacts, but more think them to be intravital changes. According to COLMANT [9] both origins are conceivable. KÖRNYEY [26], on the other hand, claims that they constitute an early specific change following some anoxic incident. Ultrastructural studies, too, have confirmed the assumption that the increased basophilia is a result of water loss.

Fig. 5 shows a newborn boy, delivered by Caesarean section, weighing 3700 g. The newborn showed signs of dysmaturity, the mother had

rheumatic carditis. Three days after birth the baby was cyanosed and had only traces of blood sugar, and in spite of adequate measures died a few hours later. Post-mortem examination showed hypoplasia of the aorta and of the left ventricle.

The extreme destruction of the nervous system by acute anoxia is demonstrated by the following observation.

mesencephalon, pons and medulla showed similar changes. Mesenchymal substitution was marked (Fig. 6), but there was hardly any glial proliferation. The cerebellum was intact. In the white matter there was oedematous dissociation. Sudan staining revealed traces of fat in a few macrophages only. Myelin sheath staining and axon impregnation disclosed only exceptionally some single degenerated myelin sheaths or broken axons.

Thus, an extensive and severe destruction of ectodermal elements and simul-

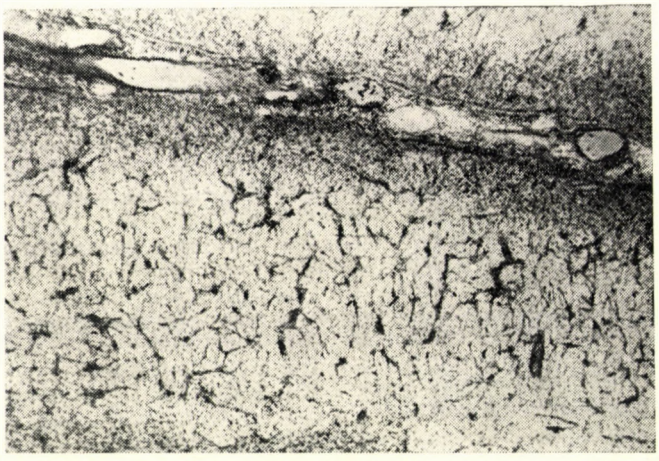

FIG. 6. Part of parietal cortex of a newborn kept alive for 8 days after pallid asphyxia. Mesenchymal proliferation at the site of destroyed nerve cells in strata 2 to 6. Celloidin—Nissl. ×18

P. L., was born at term with livid asphyxia. Spontaneous respiration and crying started after 30 minutes resuscitation. The umbilical cord was only 20 cm long. Twenty-four hours later hyperpyrexia developed, the pulse could not be counted. Respiratory rate was 96 per minute, tonic convulsions appeared in the upper extremities. Gradually the infant became soporous and died on the 8th day. At autopsy, swelling of the brain, flattened gyri, and subarachnoidal suffusions were found.

Microscopically, there was a total cell loss from the frontal to the occipital pole. The basal ganglia, Ammon's horn, the

taneous mesenchymal proliferation were demonstrated. Ultimately, the pattern is that of an infarction extending to the entire cerebrum. Similar changes have been attributed to thrombosis of the deep venous system [31].

The clinical data suggested that the destruction dated back to 8 days, but the histopathologic changes justified the assumption that the anoxic insult had taken place prenatally, eventually as a result of an early detachment of the placenta, explained by the shortness of the umbilical cord. Even so, the process could not have been longer than 9 to 10 days in duration.

Foetal and neonatal tolerance to O_2 deficiency is a controversial problem. The pertaining experimental results and human observations are at variance. The former would suggest that the foetal nervous system tolerates hypoxia much better than the mature one [35]. It is unlikely, however, that these experimental results should be valid without restrictions for the human foetus. There are namely observations indicating that while the mother and foetus are exposed to the same noxa — for example, CO poisoning during pregnancy — the mother may fully recover and the foetal brain may be destroyed. At the same time, it has been known for thousand years that a live offspring may be taken out from a dead mother.

It is known from BARCROFT's investigations [5] that the partial pressure of O_2 in the cord vein is low, corresponding to that measured at about 10000 metres (Everest in utero). The O_2 tension of the adult is 90 mm Hg, while during the last trimester that of the foetus is 26 to 30 mm Hg. In the adult the arterial blood contains 19 vol per 100 ml of oxygen, as compared to 10 vol per 100 ml in the umbilical vein of the mature foetus [55]. This does not, however, mean that the foetus is exposed to hypoxia, because that amount of O_2 suffices for its metabolism, because, among others, the red blood cell count may be as high as 6 million. In CO poisoning, depending on the amount of CO haemoglobin, the O_2 tension and content fall below the critical value sooner than in the mother, because there is less excess O_2. O_2 saturation of blood decreases in the same way. This time again the duration of exposure to CO is of primary importance. If we add to this the increased vulnerability of the foetal nervous system and last but not least the increased O_2 demand in the last trimester, this mechanism may explain the reversibility of the changes in the maternal nervous system and the irreversibility of the damage to the foetal nervous system. The permeability of foetal blood vessels plays hardly any role, because we have been unable to find evidence indicating that the CO haemoglobin contained in foetal blood would exceed that found in the mother's blood. Anaerobic glycolysis plays no major role, either, because it is only for a short time that it may replace a 10% O_2 deficit, while it may suffice when Caesarean section is performed on the dead mother.

Thus, we believe that PEIFFER's view [39] is well-founded: during the second half of gestation till birth the foetus tolerates O_2 deficiency less and less. In neonatal age the rate of metabolic processes decreases, so that a hypoxia is tolerated better and this tolerance is the newborn's adaptation with the gradual development of pulmonary respiration. Those described above may explain the higher risk in premature and dysmature neonates. In prematures the risk is increased by the immaturity of the lungs, in cases of overdue birth by the fibrosis of the capillary system of the

villi, due to te decreased O_2 tension of venous cord blood. Therefore, paranatal cerebral injury due to anoxia, trauma or haemorrhage will carry a very poor prognosis. As to the cerebral complications following Caesarean delivery, PHILIPP [41] is right in stating that it is not the operation that causes the complications but is the complications that justify the operation. It should therefore be performed when there are early symptoms preceding the complications.

(b) The subacute stage of perinatal cerebral anoxia is usually postnatal and it mostly appears in the brain of asphyxic newborns difficult to keep alive. In the place of the nerve cells which had been destroyed by the hypoxia, there are the early signs of glial-adventitial scar formation and of a decomposition of neutral fat. The fat had not yet passed in the perivascular spaces, it is found in the place of parenchymal necrosis in microglial cells and macrophages. When necrosis occurs in small foci the hardly pepper-sized intractions may be visible to the naked eye. Later, ulegyria develops at those sites. In the case of total necrosis, the nerve cell or eventually glial destruction extends to every layer of the cortex, reparation lagging behind destruction. It is at this time that we see the early signs of the development of cortical cysts. Even in the case of total cortical anoxia the stratum zonale is usually resistant to necrosis, which may be explained by its structure, its O_2 demand being much lower than that of the other cortical layers.

V. J., 1-month-old, was born with 3700 g following protracted delivery in algid asphyxia and was difficult to resuscitate. Sucking and swallowing reflexes were extremely weak. Artificial feeding had to be instituted. Eclamptic seizures appeared 2 days after birth. Following frequent episodes of vomiting, diarrhoea and gradual atrophy, the infant died at the age of four weeks.

At necropsy, papillary necrosis of the kidneys was found. After fixation the brain weighed 415 g, it was not smaller than usual and presented no changes visible to the naked eye. Microscopic study revealed a marked dissolution of the architecture deep in the sulci because the nerve cells had been replaced by glial foci in strata 3 and 5 (Fig. 7) in the frontal, temporal and parietal lobes. The occipital lobes, basal ganglia, pons and cerebellum were intact. Sudan staining revealed cells storing fat evenly distributed in the destroyed cortex and the subcortical white matter, without perivascular accumulation. Fat accumulation was the most marked in the areas of cell loss. Cajal's gold sublimate method revealed a proliferation of astrocytes in the areas of selective parenchymal necrosis. Axon and myelin sheath stainings failed to disclose such changes; the latter may be explained by the immaturity of myelin.

This case has once again confirmed the view that histopathological studies must be done even in the absence of gross anatomical changes.

(c) The chronic form of perinatal anoxia exhibits progressive fatty degeneration and regressive scarring. Depending on the intensity and duration of anoxia, extensive cortical areas may be devoid of nerve cells (Fig. 8). The destroyed nerve cells

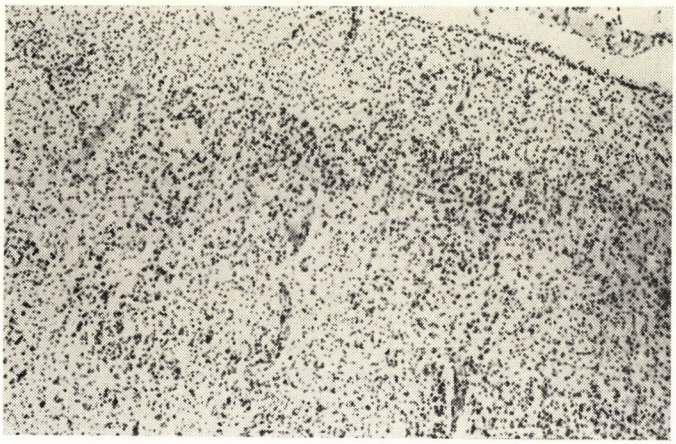

FIG. 7. Wall of parietal sulcus from an infant who survived pallid asphyxia for 1 month. Groups of residual nerve cells in strata 2 to 6. Glial proliferation at site of destroyed cells. Celloidin—Nissl ×50

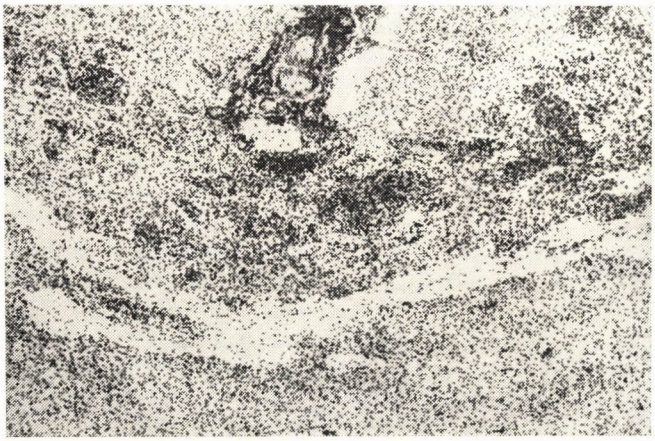

FIG. 8. Two-months-old infant. Total disorganisation of architectonics deep in the insular sulcus. Glial-mesenchymal substitution. The oligocellular strip at the cortico-medullary boundary is sudanophilic debris. Cerebral birth injury. Celloidin—Nissl. ×28

are replaced by glial scars. The cortico-medullary junction is hardly discernible. In general, the gravest nerve cell destruction is found deep in the sulci. When the microcystic structure develops, it presents with pseudocysts hardly filling a visual field, that merge, become rounded and contain intraluminar masses of fat cells. The wall of the cyst is a dense glial fibrous barrier. In such cases the anoxic insult affects not only the nerve cells, but also the intercellular white matter. When the brain is examined after months or even years, we may be able to follow up the

degeneration of the myelin sheaths and axons of the destroyed nerve cells, which lends a progressive character to the disease. The compound granular cells along the degenerated myelin enter the perivascular spaces, whence they may migrate into the subarachnoid space or the cerebrospinal fluid. Sometimes minute granulomata containing cholesterol crystals and foreign body giant cells may also be visible, together with large amounts of birefringent crystals. Gomori's silver impregnation demonstrates at the site of desorganisation the fine fibrous adventitial network (Fig. 9). Thus, the characteristic features of chronic perinatal anoxia are a neutral fatty disorganisation and glial-mesodermal restitution at the site of the destroyed nervous parenchyma, furthermore the absence of inflammatory reactions. The latter is important in differential diagnosis, because changes similar to those described above may occur in parasitic or viral diseases, for example in the chronic stage of toxoplasmic encephalitis and cerebral cytomegaly.

The cortico-medullary disorganisation, when it has lasted several months or a few years, may exhibit ecto-mesodermal tissue substitution and cysts in the place of the gradually absorbed neutral fat: it is in this way that the well-known pattern of polycystic brain develops (*e.g.*[13]). The brain may be reduced to one-third or one-fourth of its original size, the gyri are narrowed and the sulci are broad (Fig. 10). Its clinical manifestation is idiocy with cerebral palsy. In adult age such a severe phthisis of the brain is incompatible with life. The cells of the mesencephalon and hypothalamus are much more resistant to hypoxia, therefore they survive.

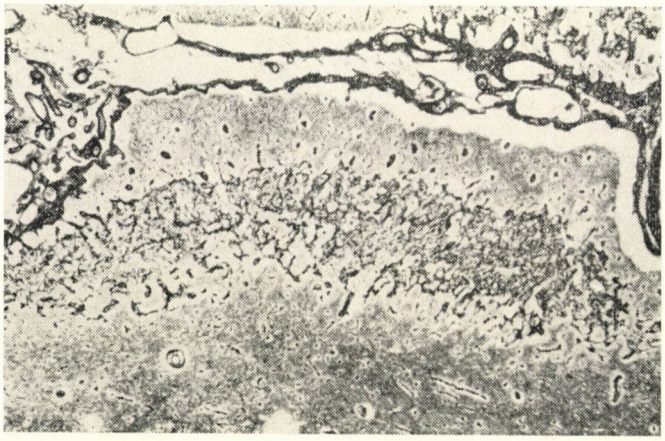

FIG. 9. Mesenchymal substitution in cortex on the convexity of a gyrus. Postnatal cerebral lesion of 2 months duration. Paraffin—Gomori's impregnation. × 14

In the acute and subacute stages there are no changes in the vascular wall. They occur only when the duration of the disease is long. We then see in the pial blood vessels a subintimal proliferation, considerably narrowing the lumen. This change seems to be a secondary one: the lumen is narrowed because the loss of brain matter is associated with a decrease of blood flow.

FIG. 10. Idiocy in 15-month-old infant. Forceps delivery, epileptic state since birth. Polycystic destruction in parietal lobes. The two temporal lobes are intact. Celloidin — Nissl disk at chiasmatic level.

HYPOXIA IN THE POSTNATAL PERIOD

The hypoxic changes occurring in the postnatal period are degenerative in nature, corresponding to encephalopathy or encephalomalacia. The cerebral changes are caused by respiratory and/or stagnant anoxia. The latter is a consequence of the haemodynamic imbalance. The former may be explained by hyalin membrane, interstitial plasmocytic pneumonitis, bronchopneumonia, i.e. by dyspnoea associated with respiratory distress.

In the neonatal period, hyalin membrane pneumonia and hypoglycaemia are the characteristic hypoxic complications. Hyalin membrane pneumonia leads to a pure respiratory anoxia, causing discrete lesions only owing to short duration. Purkinje's cells may be lost, or eventually there may be selective parenchymal necrosis [44, 53]. The persisting cerebral injuries in the babies of diabetic mothers are due to hypoglycaemia [3].

The injury caused to the nervous system by tonic-clonic convulsions (eclampsia, epilepsy, "Fieberkrampf") is again widely discussed these days.

Investigations [50, 39, 15, etc.] have shown that especially in the immature nervous system the convulsive states may give rise to selective parenchymal necrosis, followed by glial scarring. Repeated convulsions may increase the number of cells lost and gradually persisting neuropsychiatric symptoms may develop. The conclusion that the anatomic changes are a consequence and not the cause of the disease has been generally accepted [37, 30, etc.], so that the problem seems to be settled. PETERS [40] claims outright that it cannot be questioned. On the other hand, VEITH [54] made observations on a large material and claims, relying partly upon the investigations of SCHMIDT [45], that the selective parenchymal necrosis is not a consequence, but the cause of epilepsy, because he demonstrated it in the brain of infants who had no convulsions. ("Es ist nicht erwiesen, daß selektive Parenchymanekrosen Krampffolgen sind": it has not been proved that selective parenchymal necrosis is due to convulsions.) VEITH [54] explaines the development of necrosis or scars by prenatal and postnatal hypoxia due to disorders of the placenta and umbilical cord, etc.

The brain of chronic epileptics is less suitable for study in this respect. After acute epileptic states, acute febrile infantile convulsions [15] or therapeutic convulsive treatments causing death, ischaemic nerve cells could be demonstrated proving the role of anoxia. Further human evidence is for example the focal or laminar necrosis demonstrable after fatal eclampsia of pregnancy [26], as well as the fact that in two cases of eclampsia of pregnancy without convulsions no specific cellular changes were found [7].

The pathogenetic explanation of hypoxia connected with convulsions is not uniform. A critical fall of blood pressure, vascular spasm due to smooth muscle contractions, apnea, increased O_2 demand, acidosis, one by one or combined, may all cause anoxia. The problem is further complicated by the fact that the hypoxia-induced antenatal and postnatal cerebrocortical scar tissue may cause eclamptic convulsions. The seizures may then give rise to further scarring. Experimental results as well as the clinical experience that protracted eclampsia and epilepsy may be associated with dementia are merely mentioned here. As it is almost impossible to make a thorough study of the cerebral cortex by serial sections, a negative finding cannot be relied upon.

Finally, it should be mentioned that EEG studies [19] recorded permanent cortical changes following an epileptic state.

From our own investigations and from data in the literature it may be concluded that recurrent tonic-clonic convulsions, but especially an epileptic state may cause anoxic cell losses much more easily in the immature than in the mature brain. Our pathogenetic explanation is that particularly in the immature brain the cell losses are due to an increase of

intracranial pressure caused by the oedema accompanying the convulsions.

In the past decade, "hypsarrhythmia" has become a key word in conjunction with postnatal encephalopathies accompanied by convulsions. To this concept belongs the infantile epilepsy showing characteristic EEG changes (Fig. 11). In a number of postmortem studies destructive perinatal and postnatal anoxic changes have been described. However, hypsarrhythmia has no pathological equivalent, because characteristic EEG patterns may be produced not only by destructive changes, but also by tuberous sclerosis, malformations, enzymopathies, or even inflammatory processes, etc. The morphological aspect of the syndrome has been dealt with by JELLINGER [24].

In the entities discussed so far anoxic aetiology could be demonstrated with more or less certainty, or could reasonably be suspected.

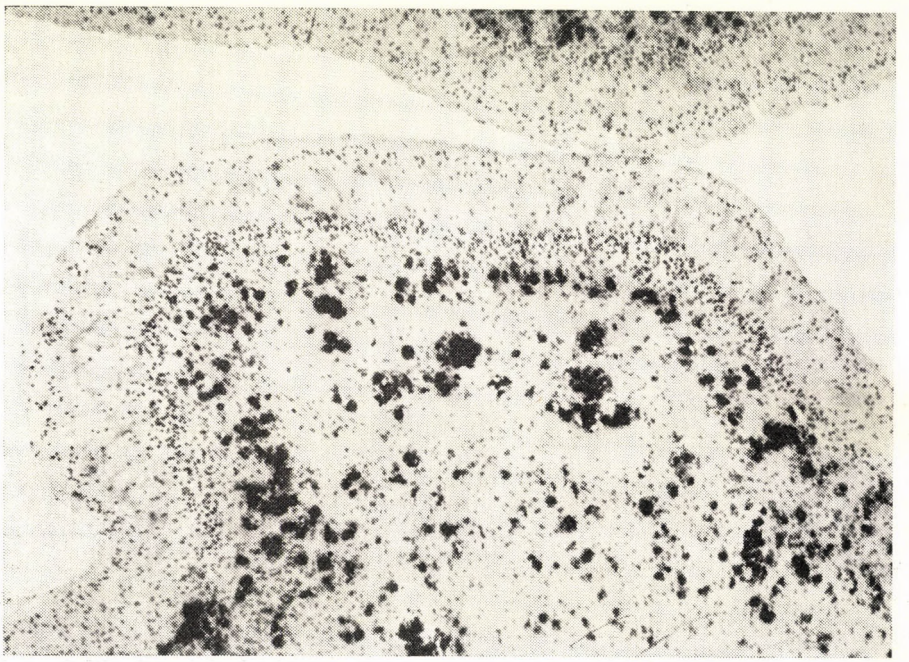

FIG. 11. Part of occipital convexity. Sudan staining. Breakdown of neutral fat in the area of cortical destruction. Infant aged 1 year, progressive hypsarrhythmia since birth. Postnatal encephalodystrophy. ×24

But the immature nervous system has also a postnatal dystrophy of unknown aetiology, named after ALPERS [1], who was the first to describe it under the name of diffuse progressive degeneration of the gray matter of the cerebrum or progressive cerebral degeneration of infancy. In the early stage the disease cannot be diagnosed histologically, as the

changes may resemble those following perinatal anoxia. Some authors [10, 12, 36] therefore do not consider it an independent primary dystrophy, but attribute it to anoxia not demonstrable or not detected at birth. The diagnosis may be facilitated by the data concerning its familial occurrence [6, 52).

Alpers' disease appears after a few weeks or months of apparently normal growth. There is no evidence of previous anoxia, the spongious disorganisation is selectively cortical, encephalomalacia and cyst formation are absent, the changes are symmetrycal, degenerative and progressive. Like Little's disease, it is accompanied by mental and somatic retardation. Under given conditions it may be mistaken for subacute perinatal anoxia, but not for chronic anoxia which is followed by cortical — subcortical — medullary micropolycystic sclerosis. Familial incidence supports the claim that Alpers' disease is a nosological entity, but histopathologically it fits into the group of anoxic lesions [6, 5, 2].

* * *

During life the nervous system is exposed to the greatest danger in the perinatal period. Complications of placental, maternal and neonatal origin may arise, which may lead to hypoxia, one by one or combined. The cell losses caused by hypoxia decimate the nervous parenchyma, consequently they are accompanied by mental and somatic retardation. The final result is an idiocy with cerebral palsy. There are no therapeutic methods to cure the hypoxia-induced changes of the brain, because the central nervous system does not regenerate. Prevention is the only way toward success. The preventive measure should extend to the placental, maternal and perinatal complications and, last but not least, to the prevention of preterm delivery, because the developing nervous system is more vulnerable than the mature one.

Acknowledgement. The author is indebted to Professor K. Frank and Dr. A. Vidos for clinical data.

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