ANTENATAL AND PARANATAL CIRCULATORY DISORDERS AS A CAUSE OF CEREBRAL DAMAGE IN EARLY LIFE*†‡

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In the past century or more, investigators have made a study of a variety of cerebral lesions of early life in an effort to learn something of their cause. For the most part, this period has been one of confusion and uncertainty because of an inability to understand the nature of the process or processes which initiated the changes. The resulting lesions were evidently responsible for the clinical states of cerebral palsy, mental deficiency and epilepsy, either singly or in combination. As time passed, however, certain pathological entities came to be distinguished and were separated from the larger group. In some instances specific causes could be assigned to some of these lesions. For example, true congenital malformations could, with reasonable assurity, be distinguished from a group of their simul­ators. Certain moderate atrophies with characteristic infiltrations in nerve cells are now known to be due to familial disorders of lipid metabolism (amaurotic family idiocy, and allied diseases). The noxious effects of certain metabolic toxins (severe neonatal jaundice) and transmitted infections (toxoplasmosis) also came to be appreciated. But there still remained a number of gross cerebral lesions of early life and these continued to be a subject of controversy insofar as their etiology was concerned. This situation still applies even to that group in which some sort of circulatory disorder is somehow generally agreed to be responsible.

It is the purpose of this report to place on record the writer's views on the subject of circulatory disorders as the cause of certain of these lesions. The precise types of residual lesions to be considered will be dealt with individually. Finally, the reasons for the writer’s belief that these lesions have their origin in a disorder of circulation will be presented.

TYPES OF RECOGNIZED CIRCULATORY DISORDERS OF THE ANTENATAL, PARANATAL AND POSTNATAL PERIOD

The various possible types of circulatory disorders of intrauterine life, birth, and the postnatal period, may vary considerably but are quite constant for the period concerned. In intrauterine life any disturbances or circulation which might effect the fetal brain are either primarily those influencing the maternal circulation or occur secondary to structural changes in the placenta (table 1). Condi-

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TABLE 1
Circulatory Disorders of Antenatal, Para natal and Early Postnatal Periods

I. ANTENATAL PERIOD—Circulatory disorders of this period almost invariably affect the fetal brain through an anoxic effect. This effect may be exerted in one of three ways:
A. Acting through the Maternal Circulation
1. Anemia, either acute (maternal hemorrhage) or chronic (low blood count or hemoglobin).
2. Toxemias, either exogenous (drugs or poisons including alcohol) or endogenous (pre-eclamptic or eclamptic).
3. Impairment of maternal circulation (persistent low blood pressure or acute circulatory collapse).
4. Action of asphyxiating gases or sedative agents (accidental gas poisoning or action of certain anesthetic agents as nitrous oxide).
B. Acting through the Placenta
1. Diseases of the placenta such as infarction, thrombosis, syphilis or placenta premitis (or its intrauterine counterpart—endometritis).
2. Premature separation in abruptio placenta or placenta praevia.
C. Acting through interference with circulation via the umbilical cord—such as coiling of cord around the neck, stretching of the cord, rupture of the cord, knots in the cord, etc.

II. PARANATAL PERIOD—Circulatory disorders of this period almost invariably act through an anoxic effect on the fetal brain in one of the following ways:
A. Acting through impairment of the maternal circulation through excessive hemorrhage.
B. Acting through the placenta—abruptio placenta or placenta praevia.
C. Acting through the umbilical cord—compression of the cord, premature detachment of the cord, rupture of the cord.
D. Acting through effects on the cardiac, respiratory and vasomotor centers of the fetus itself—influence of anesthetics, sedative drugs on vulnerable center or effects of increased intracranial pressure incident to dystocia or hemorrhage.

III. EARLY POSTNATAL PERIOD—While ill effects of circulatory disturbances may be still acting on the basis of anoxemia, hemorrhage or thrombosis may now play a direct part in the production of cerebral damage.
A. Anoxic effects may still continue either through a disordered respiration and circulation (asphyxia livida or pallida) incident to depressed function of vital centers or to mechanical interference with the respiration due to foreign material in air passages, failure of expansion of lungs or structural changes in the lungs.
B. Intracranial hemorrhage and edema probably continue to act through further depression of vital centers through an increase of intracranial hemorrhage, less likely through hemorrhage into the cerebral centrum.
C. Thrombosis either of the venous channels with secondary red softening of the cortex and subcortex, or less likely of the arterial channels through vasospasm. This is probably less important than was once believed.

Conditions in the mother which may alter the oxygen-carrying capacity of her blood (low blood pressure, anemia from either acute hemorrhage or blood dyscrasia, toxemia, cardiac insufficiency, acute respiratory disorders such as pneumonia, acute cardiac and/or respiratory failure, anesthesia, hypoglycemic episodes, or exposure to carbon-monoxide or other asphyxiating gases) will influence secondarily the circulation of the fetus. If this disturbance is severe enough, it will affect
adversely the development of the very vulnerable fetal brain, tending to damage or destroy the immature nerve cells as well as disrupt with the formation of intercellular nervous connections.

The second group of intrauterine vascular disorders are secondary to those resulting from structural alterations in the placenta which serve to interfere with the gaseous interchange between the maternal and fetal circulations. The most common lesions responsible for this situation are premature separation of the placenta (abruptio placenta) from whatever cause, gross infarction, and disintegration of the placenta. Syphilis of the placenta may be responsible for this condition in rare instances. Intrauterine diseases, particularly suppurative endometritis, may so destroy the placental villi as to impair seriously the oxygen-carbon dioxide interchange between mother and fetus, as Cruveilhier (1) learned so well over a century ago. *

In the birth process the more common circulatory disorders likely to affect the fetal brain are hemorrhage and anoxemia. Hemorrhage into the fetal cranial space may be extradural, subdural, subarachnoid, intracerebral, or intraventricular. Such effusions are usually the direct result of cranial deformations, either primarily due to distortions of the head in the birth canal or secondarily, from compression of the fetal head by forceps. Extradural hemorrhage occurs but rarely at birth and plays no significant role in the production of brain damage.

Subdural hemorrhage may be either dorsolateral or mesoinferior (2). The

* Cruveilhier shows the disastrous effects of placental infarction in one of his lithographs (Folio VI, Plate 6, figs. 1 and 2). Twins at sixth month of gestation were delivered with their placental attachment intact. One of the fetuses was notably smaller than its sibling. Its umbilical cord was attached to that part of the common placenta which was grossly infarcted (see fig. 1). In less serious lesions of the placenta, the vulnerable fetal brain might alone feel the effects of an impaired maternal-fetal oxygen interchange.
latter, which is almost invariably fatal owing to pressure of the blood clot on the
brain stem, probably follows tears of the vein of Galen at the point of its entrance
into the straight sinus. The dorsolateral hemorrhages, if severe, may also be
fatal if not surgically evacuated. If of minor degree, the blood clot tends to be­
come encapsulated, exerting secondary effects on the brain (cortical softening
or atrophy due to interference with the regional circulation) which appear only
after weeks or months have elapsed.

Subarachnoid hemorrhage, although a common complication of birth (3),
probably plays no significant role in the ultimate production of residual lesions,
either meningeal or cerebral.

Intracerebral hemorrhage as a result of difficult labor sometimes occurs. Such
hemorrhages, however, are usually small and not numerous and tend to occur
in the deeper portions of the cerebral centrum. If at all severe, they prove to be
fatal within a matter of days.

Intraventricular hemorrhages are not particularly common and the only sig­
nificant complication is that of obstructive hydrocephalus (5). This result follows
organization of a clot within the aqueduct of Sylvius or adhesions about the
exits of the fourth ventricle.

The second and probably the most significant circulatory disorder of the birth
process is that of anoxemia. The great importance of this type of circulatory
disorder lies in the fact that it may be the factor which initiates any one or more
of a variety of gross deforming lesions of the brain, as the present writer pointed
out a number of years ago (6). Anoxia at birth may be due to a severe hemorrhage
from premature separation of the placenta (as in placenta previa), this situation
usually follows depression of the fetal cardiac and/or the respiratory centers by
an increase in intracranial pressure. There is reason to believe that cardiac and
respiratory failure during birth is also definitely favored by excessive use of
sedatives and anesthetics (7) at the time of delivery. If the respirations alone
fail at this time (asphyxia livida) the outlook is less serious, but if both respir­
atory and cardiac activity are depressed (asphyxia pallida) the likelihood of
residual brain damage in the infants who survive is greatly increased.

Venous Thrombosis and Deforming Cerebral Lesions of Early Life: Several
chronic lesions of the brain in early life have been attributed to thrombosis of
the superior longitudinal sinus and its afferent veins and/or the internal venous
system of Galen. Norman (8) was inclined at first to believe that focal cortical
atrophy (ulegyria) was to be accounted for on the basis of this lesion. More
recently he has expressed his belief with others in a possible arterial component
(Norman, Urich and McMenemey (9)). Marburg and Casamajor (10) have
concluded that this lesion is the cause of chronic cystic degeneration of the
cerebral white matter. Benda (11) and Malamud (12) believe that status mar­
moratus may also have its origin in such a process, particularly after an occlu­
sion of the internal system of Galen, because the resultant hemorrhages following
such an occlusion are found to have a similar distribution. The present writer
is preparing a paper which presents evidence against this thesis.

Postnatal circulatory effects as a cause of cerebral damage, is probably not
particularly significant. Yet, one does occasionally see severe alterations in the brain “dating back to birth” which are almost certainly the result of arterial occlusion (13). This is indicated both by the classical defect in the cerebral cortex and subcortical white matter (usually along the course of the middle cerebral artery) and the presence of a marginal irregularly atrophic cortex.

**EVALUATION OF CEREBRAL LESIONS DATING TO EARLY LIFE IN TERMS OF ETIOLOGY**

In any attempt to discover the cause of a given chronic deforming lesion of the brain of early life, it is necessary to recognize that, as a rule, the process which brought about the terminal changes has been quiescent for some time. The lesion is, therefore, the end result of a process that has previously ceased to act. The early students of the problem, unfamiliar with the course of cerebral disease, could only theorize about causes and almost every possible etiological factor was considered. The passing years have progressively changed this situation not only because of a better understanding of the pathology of the lesions themselves but also of the nature of disease processes in general. The experimental production of these lesions has also contributed measurably to their comprehension. It would seem, therefore, that after almost a century of effort in this direction, it is legitimate to attempt an evaluation of their genesis.

What factors should enter into any such evaluation? A review of the situation suggests the following possibilities: (1) consideration of the antenatal, natal, and early postnatal history in a given case or series of cases, (2) significance of certain maternal and fetal lesions or abnormal states during pregnancy or evident at the time of delivery, (3) cognizance of the length and course of survival period in the affected individual, (4) comparison of the cerebral lesion under consideration with similar ones of later life of known etiology, (5) evaluation of associated lesions of the brain, (6) structural alterations in the nervous tissues as observed on microscopic study, and (7) information gained from experimental production of a similar lesion. It will be seen that the evidence supporting the possible circulatory etiology in the group chosen for evaluation comes from more than one of these sources of information.

As for the history of untoward events influencing pregnancy or delivery, it has long been known that a negative history is quite useless in such instances. The present writer has found that absence of positive information insofar as the patient’s hospital record is concerned, is often reversed when a patient search is instituted for more complete information from the parents, the obstetrician, and the records of the lying-in hospital. On the other hand, the history of “birth injury” cannot be accepted as positive proof that a given cerebral lesion is to be explained on this basis. Many an infant has not only survived such an episode but has grown up to be a perfectly normal individual. At most, it is possible only to say that a history of difficult delivery and/or respiratory aberrations shortly thereafter suggests the possibility of a traumatic and/or anoxic genesis for the cerebral lesion.

Certain maternal states during pregnancy (i.e., marked anemia and toxemia) and some lesions encountered at the time of delivery (i.e., placenta praevia, gross
diseases of the placenta) which are capable of producing serious circulatory disorders in the fetus cannot be lightly dismissed as possible causes of brain damage. The same is true of some lesions of the umbilical cord (i.e., knots, ruptured cord, or coils of cord about the neck of the fetus).

The *length and course of the survival period* of the victim of gross brain damage of early life is of considerable importance in trying to understand the nature of the underlying lesion. On this basis, the lesions or lesion-complexes may be divided into two, possibly three groups. In the first, the responsible lesions for this state are usually those resulting from a profound ischemia. This seems to be the case in instances of hydrencephaly, gross total or subtotal cerebral softening, central cystic degeneration, and large porencephalic cavities or gross areas of nodular cortical atrophy. In the second group, there may be little or no evidence of cerebral damage in the early months of life, other perhaps than occasional convulsive episodes. But as the child develops, deficits in the motor and intellectual spheres become manifest. In such cases, the development of the lesion is slow and progressive, eventually arriving at a stage of total or almost total quiescence. In this group are the cases of localized nodular cortical atrophy or porencephalic defects, as well as focal cortical scars and cysts which are responsible for epilepsy. A possible third group of incompletely understood lesions are those which result in central demyelination. Some of these lesions (infantile cases of diffuse sclerosis) certainly belong in this group of cerebral lesions originating in early life. After a period of latency, infants so affected survive a progressive downhill but chronic course to a fatal issue. The remarkable likeness of such lesions to a similar latent degeneration of the central white matter after anoxia opens up a wide field of speculation on the etiology of diffuse sclerosis.

Comparison of early cerebral lesions with lesions of known etiology of later life has been depreciated by some as a source of evidence, but in a number of instances the logical conclusion seems inescapable. One needs only to point to the occurrence of porencephalic-like defects and of nodular cortical atrophy in the cerebral hemispheres of later life to recognize comparable lesions in case of damage dating back to early life. The remarkable similarity of other early lesions of the cerebral cortex and centrum to those consequent to known cerebral anoxia of postnatal life makes it difficult for all but the prejudiced or ignorant to see comparable processes at work.

Another important factor in the evaluation of individual lesions is the *possible significance of other associated lesions and structural changes*. When alterations in the basal ganglia in the form of cystic degeneration or demyelination (status dysmyelinisatus) are found together with porencephalic defects or areas of nodular atrophy known to be of ischemic etiology, it is fair to raise the question whether all of these defects should not be accounted for on the same basis. The frequent occurrence of such complexes in instances of gross brain damage of early life furthermore demands some other explanation as to why this association takes place, if all of the individual alterations are not to be explained on identical or sequential causes.

Information gained from a critical *histological examination of the cortical,*
central and ganglionic changes is also helpful. This is true, not only in determining positive evidence of certain processes such as circulatory ones, but also in eliminating certain others, particularly those of inflammatory origin. The presence of focal and laminar cortical necrosis, changes so characteristic of the anoxic state, and regressive changes in the globus pallidus with similar connotations should lead the pathologist to consider this process as the essential one. Cortical scars in nodular cortical atrophy reminiscent of those incident to arterial occlusion should merit consideration of a similar mechanism at work in the early months of life.

Evidence gained from animal experimentation clearly points out the precise origin of a number of these early lesions. The production of identical changes in the form of hydrencephaly, generalized cerebral softening, and of porencephalic defects has been effected by embolic occlusion of the larger cerebral arteries of newborn animals. This is also true of generalized atrophy, hemispherical atrophy and lobar atrophy which are found to be the residuals of experimental natal anoxias in guinea pigs. It is also possible that the answer to the pathogenesis of status marmoratus will be found in the same fashion as the work of Morrison (14) would suggest. On the other hand, it is too much to expect that the entire answer to the etiology of these various lesions will be found in experimental pathology.

This brief introduction to the evaluation of available lesions suggests that no one source of information is sufficient to explain all of the various cerebral lesions of early life. Nevertheless, this evidence proves to be very valuable in an understanding of residual changes by an analysis of how they are produced by disturbances of circulation. When one realizes that the tissues of the brain tend to react to noxious processes in accord with a well defined pattern, it is possible to interpret the residual alterations whenever they are encountered. If the investigator is experienced enough to recognize these processes as manifested by the various steps in the development of the lesion, he should be able to unravel some of the complexities of its etiology. This is precisely what the present writer will attempt to do in discussion of the following group of lesions.

**THE EVIDENCE FOR THE CIRCULATORY GENESIS OF CERTAIN GROSS MORBID LESIONS CAUSING CEREBRAL PALSY**

With this background the investigator is now prepared to analyze the various individual residual lesions which he may find at autopsy in individuals who have been afflicted with disturbances of mentation and motor function, and which have been suspected by someone or at some time of having a circulatory origin. The specific lesions which should be subjected to critical scrutiny on this basis are the following: (1) generalized or hemispheric atrophy; (2) a group of diffuse cerebral lesions including (a) cortical or cortical-subcortical degenerations, (b) widespread cortical softening, and (c) subtotal or total cerebral softening; (3) the various individual lesions included under the term of nodular cortical atrophy (focal cortical scars, sclerotic microgyria, lobar sclerosis, sclerosing hemispheric atrophy); (4) porencephaly, (5) chronic cystic degeneration of the
cerebral white matter, (6) diffuse sclerosis, and (7) certain striatal disorders including status marmoratus and dysmyelinisatus.

The General Cerebral Atrophies: In this group of cases is included both a moderate generalized atrophy of both cerebral hemispheres and a unilateral or hemispheral atrophy. It is not difficult to understand how atrophy of the brain as a whole could result from some generalized circulatory process such as anoxemia. In the case at hand, however, the atrophy affects selectively the cerebrum, the cerebellum and brain stem being normal in size. This suggests per se that those parts of the brain supplied by the carotid system as opposed to that irrigated by the vertebral-basilar system have been subjected to the influence of an impaired oxygenation. This fact would further suggest the interposition of some factor, perhaps one acting through vasoconstriction, which limits sufficiently the amount of blood passing through the carotid arteries.

That this possibility is not one of theoretic interest alone is indicated by the fact that occasionally one finds in mentally deficient, epileptic and even in cerebral palsied individuals, a cerebrum which is obviously small as compared to the cerebellum (fig. 2, A). Although it is not always possible to learn of any anoxic episode at birth, the discovery, that there is a reduction in cortical nerve cells in the same cell laminations (III to VI) affected by anoxemia, is suggestive. The demonstrations by Windle and his associates (15) that a general cerebral atrophy can take place after experimental birth anoxia is also significant.

The problem becomes somewhat more involved in the case of uniform moderate cerebral hemiatrophy. Nevertheless, this condition is sometimes exposed at autopsy in the case of mild mental defectives or epileptics from birth (fig. 3, A). One such case of cerebral hemiatrophy as a consequence of a severe anoxemia of later life came to the writer's attention in the recent past (fig. 3, B). The generalized loss of cortical nerve cells following a laminar pattern is also pertinent. The demonstration after simulated birth anoxia of hemiatrophy of the brain in guinea pigs by Windle and his associates (15) seems to support the assumption of its anoxic etiology.

Diffuse Cortical or Cortical-Subcortical Degeneration: This change characterizes a veritable hierarchy of cerebral lesions which differs from the general or hemispheral atrophies in that the cortex alone or the cortex and subcortical tissues are visibly altered by actual softening*. Although this category as a whole includes some of the rarer types of gross brain damage, several fairly well defined subgroups are to be made out. As a more acute lesion there is to be found a disorder designated by Alpers (16), as a "chronic progressive degeneration of cerebral gray matter," widespread cortical-subcortical necrosis, subtotal softening of the brain, and finally, in its most extreme form, hydrencephaly. All of

* This particular group of cases was made the subject of a separate study, recently published (17). It was the object of this study to show that the characteristic and more or less uniform loss of the cortical parenchymatous elements and, in severe cases, of the entire intermediate cortex indicated an anoxemic type of circulatory disturbance as its basic cause. When this process was the result of total occlusion of the carotid arteries, all nervous tissues were affected and subtotal cerebral softening or hydrencephaly was the inevitable result.
Fig. 2. Uniform Cerebral Atrophy. A. General atrophy of the cerebral hemispheres in a 20-year-old mental defective and spastic girl with history of "birth injury." Note widened sulci and large ventricles. B. General atrophy of brain of guinea pig consequent to anoxia; upper figure shows brain of normal size, lower figure, atrophic brain 6 weeks after asphyxiation (Windle, Becker and Weil: J. Neuropath. & Exper. Neurol., 3: 244, 1944).

Fig. 3. Cerebral Hemiatrophy. A. Atrophy of left cerebral hemisphere in a 32-year-old lifelong epileptic. B. Atrophy of right cerebral hemisphere (compare occipital lobes) in a woman of 27 years with death 9 months after cerebral anoxia incident to cardiac standstill.
these lesions seem to represent a progressive series of disorders characterized by impairment of the carotid circulation, for the brain stem and cerebellum are usually quite normal. In the most serious lesion, hydrencephaly, it is clear that a more or less total obstruction of the carotid system must exist, for at autopsy the residual fluid filled sac is made up alone of the leptomeninges and ependyma. Only isolated islands of nervous tissue are to be found between these membranes. Because the posterior cerebral arteries are usually derived from the vertebrals, the convolutions of the basilar temporal lobe and parts of the basal ganglia, are still present. In these cases, the carotid arteries may be missing entirely or greatly reduced in size.

The mechanism of production of hydrencephaly is generally accepted to be essentially that of total cerebral ischemia. This seems to be proved by the ex-

![Fig. 4. Generalized Subtotal Cerebral Softening. A. Total softening of the cerebral hemispheres in an infant of 4 months, described as being "weak" since birth; cortical markings are still apparent. B. Total softening of brain of a 30-year-old woman who died after four days in a respirator. Cortical markings intact but interior of brain was entirely disintegrated.](http://jnen.oxfordjournals.org/)

![Fig. 5. Cortical Softening. A. Widespread selective cortical softening in a 16-months-old infant spastic since birth. B. Extensive selective cortical softening in a 50-year-old male who survived for one month after a severe episode of cardiorespiratory failure under spinal anesthesia.](http://jnen.oxfordjournals.org/)
experimental work by Becker (18). By injecting droplets of wax or oil into the carotid arteries of newborn animals, this investigator was able to produce an immediate softening of the cerebral tissues. The ultimate residual lesion in the animals that survived from 9 months to 1 year consisted either of a genuine hydrencephaly or a severe degree of porencephaly with knotty convolutions (microgyria) bordering the defects. Immaturity of the nervous tissues of the newborn animal probably explains why there is no counterpart of this lesion as a result of the anoxias of later life.

The second subgroup of generalized softenings is characterized by an advanced degree of necrosis of one or both cerebral hemispheres, depending upon the extent of involvement of the vascular system (vertebral and/or carotid complexes). The convolutional pattern of the cerebellar and/or cerebral cortex can still be made out, but all the nervous tissues, both gray and white, are found to be undergoing advanced degrees of degeneration (fig. 4, A). Death usually occurs in a quadriplegic infant during the first year of life. This lesion is simply a less profound degree of ischemic softening than that which occurs in hydrencephaly. The nearest approach to this type of cerebral lesion occurs in individuals who die some days after experiencing an acute respiratory and cardiac failure. The brain in these early cases is found to be in a condition of more or less advanced total softening, at times with sparing of the brain stem and cerebellum (fig. 4, B).

The next lesion in this category consists of advanced degrees of selective widespread cortical softening which is grossly quite evident. These cases are relatively rare. Although the cortex of practically the entire brain may be affected (fig. 5, A), the degree of the lesion is sometimes more marked in one hemisphere or that part of a hemisphere usually supplied by one of the major cerebral arteries. This fact alone suggests that the alteration has for its basis a profound degree of ischemia. It is likely that association with cerebral anoxia is suggested by its close resemblance to the brain of individuals who have experienced a severe anoxic episode (as acute cardiorespiratory failure under anesthesia), and yet survive for a considerable interval. This interval makes possible the appearance of a widespread laminar softening of the cerebral cortex (fig. 5, B).

A less serious form of these cortical softenings, chronic progressive degeneration of the cerebral gray matter, was introduced by Alpers (16), who described the brain of an infant with widespread cortical softening characterized by areas of focal necrosis, laminar loss of nerve cells and vascular cortical scars. A number of cases have since been described, including one more recently reported by Christensen and Krabbe (19). The association in these cases of changes in the globus pallidus, subcortical demyelination, and cyst formation and laminar type of cortical necrosis, and the occasional history of asphyxia at birth (Somoza, cited by Alpers), suggests its close relationship to cerebral anoxia. Moreover, classical counterparts of this situation have been described by the present writer (20) in cases of anoxia after nitrous oxide anesthesia.

"Walnut Kernel Brain": A lesion with similar widespread changes in the cortex, but with progressive cortical gliosis consequent to a loss of parenchymatous element should also be considered in this connection. The individual convolutions show a more or less uniform atrophy with severe sclerosis. The extent of change
tends to vary in degree in the different arterial zones suggesting again that ischemia plays an important role in its production. This lesion is obviously one of slower evolution than in cases of progressive softening described above.

In surveying this group of lesions as a whole one is immediately impressed with the ischemic nature of the more severe lesions and with the close analogy between the detailed changes in the cerebral gray matter in cases of less severe lesions and those of anoxemia as a generalized circulatory state.

_Nodular Cortical Atrophy (Mantle Sclerosis):_ Regardless of the extent of the cerebral cortex affected (cortical scars, lobar sclerosis or sclerosing hemispherical atrophy), it is obvious that the basic change characterizing all of these lesions is essentially the same. The writer has previously pointed out (13) that this lesion is identical with the irregular cortical atrophy consequent to partial arterial occlusion as by embolism in later life. One is prepared, therefore, to accept the concept of an arterial genesis as its cause. The writer has also suggested in previous studies (13, 20) that cerebral anoxia, as a process, is capable of provoking a local arterial ischemia probably chiefly through its action on the vasomotor center, but possibly also on the artery itself. This is indicated by the occurrence of areas of cortical-subcortical softening regions several weeks after severe exposure to carbon monoxide asphyxia. The larger arteries supplying these softened areas are not found to be occluded when studied at autopsy.

The evidence in favor of a primary anoxic factor in cases of nodular cortical

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**Fig. 6. Nodular Cortical Atrophy.** A. Nodular cortical atrophy about a residual parnatal ischemic defect. B. Nodular cortical atrophy in an adult male 16 years after asphyxiation with carbon monoxide (Meyers, 1926). Both myelin sheath preparations.
atrophy may be stated as follows: (1) the occurrence of a similar type of nodular
cortical atrophy when no other factor than anoxia was known to exist (case of
Meyer (21) (fig. 6, A and B); (2) the occurrence of other lesions of suggested
anoxic etiology (general cortical atrophy, subcortical cysts) (Siegmund (22),
Benda (23)), areas of central demyelination (Kotschetkowa (24), Koppen (25)),
ocurrence of associated porencephalic defects (Schaeffer (26), Koppen (27),
Richter (28), Siegmund (22)), and alterations in the basal ganglia (Bielschowsky
(29), Onari (30), Norman (31), Malamud (12)) as well as microscopic alterations
reminiscent of an anoxic origin, and finally its association with (3) the clinical
picture of Little’s disease presumably due to bilateral upper central foci of
sclerotic change in individuals with a history of asphyxiation at the time of
birth (Friedman and Courville (32)). Under these circumstances, it is difficult
to assume any other ultimate cause than anoxia for this type of cortical change.

Porencephaly as a Circulatory Lesion: Some investigators have divided the
larger cerebral defects or cysts commonly known as porencephaly into two
groups; (1) the schizencephalies, which are defined as a congenital failure of de­
development of portions of the cerebral cortex, and (2) encephaloclastic or destruc­
tive lesions (Yakovlev and Wadsworth (33)). These defects are now usually
considered to be the result of occlusions in utero of one or more of the major
cerebral arteries. There can be little doubt about the validity of a vascular gene­
sis of the second group as suggested by the location of these defects within the
individual arterial fields. But if any uncertainty still exists, the similarity of less
advanced types of porencephaly to old gross lesions in adults are obviously
incident to arterial ischemia (fig. 7, A and B). Such lesions also have a thin
membrane covering the defect and with bordering convolutions undergoing
atrophy (20). As a final proof the development of identical lesions in new-born
animals, after injection of foreign material into the carotids, would seem to
settle the matter beyond equivocation (Becker (18)).

Cortical-Subcortical Cysts and Cerebral Anoxia: Penfield and Erickson (34)
have called attention to certain small cortical cysts and scars which have epi­
leptic potentialities. The nature of these scars with focal and laminar cell loss
or actual necrosis, suggest a lesion of vascular or anoxic etiology. In grossly de­
deformed brains of cerebral palsied children, it is not unusual to find cortical-sub­
cortical cysts (“pseudoporencephaly”) which are but one of a group of lesions
responsible for the clinical state. The writer has assumed in the past that these
lesions, too, are of anoxic etiology. To support this hypothesis, a case studied by
the writer (Courville, Case 9 (35)), may be cited, namely, that of a man of 69
years of age who had been asphyxiated with carbon monoxide some 50 years
before. The brain disclosed a well-defined cortical-subcortical cyst in the left
motor area associated with old cystic cavitations in the globus pallidus. Since
focal cortical-subcortical foci of softening have also been observed in this region
in more recent cases of carbon monoxide without actual arterial disease or evi­
dences of physical occlusion, it was assumed that this effect was the result of
arterial spasm secondary to cerebral anoxia. The presence of such cysts in the
altered brains of crippled children who had been asphyxiated at birth, further
emphasizes the likelihood of this relationship.
FIG. 7. Porencephalic Cavitation. A. Upper central defect, one of bilateral porencephalic cavities in a 3-year-old male child. B. Defect in brain of 65-year-old woman with an old occlusive vascular lesion. Both lesions were associated with nodular cortical atrophy.
One must conclude by inference that there remains the definite possibility that the larger porencephalic clefts or cysts, as well as the smaller cortical-subcortical cysts, may be the result of an anoxic insult to the brain. Anoxia is capable of provoking arterial spasms resulting in a transitory but effective occlusion, usually occurring particularly in the distribution of the middle cerebral arterial tree.

**Etiology of Chronic Cystic Degeneration of the Cerebral White Matter:** In 1867, Virchow (36) described a central cystic lesion in infants which he designated as "congenital encephalitis." Almost twenty years later Limbeck (37) reported another case and called attention to its possible relationship to porencephaly. Köppen (25) found the co-existence of microgyria with this lesion in one instance and its association with a chronic subdural hematoma in another (38). Sachs and Peterson (39) believed that trauma at birth was its chief cause, a conclusion supported by others (i.e., Schmincke (40)). In the case reported by Jakob (41), these lesions had developed in an infant with a history of asphyxia at birth who died at the age of 10 months. Schwartz (42) believes however, that the cysts found in the cerebral white matter are the result of hemorrhages incident to birth and that these, in turn, are consequent to natal traumatic thrombosis of the venous channels, and with this conclusion others appear to be in agreement (i.e., Marburg and Casamajor (10)).

The history of difficult labor has led some to conclude that dystocia is a prominent factor in the etiology of cystic degeneration (Stevenson and McGowan (43),

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**Fig. 8.** Cystic Degeneration of Cerebral Centrum. A. Horizontal section of a 5-months-old spastic infant with history of postnatal respiratory irregularities. B. & C. Multiple central cyst formation as a delayed residual of carbon monoxide asphyxia.
Benda (44). The occurrence of a similar type of lesion in a disease of lambs ("swayback") has resulted in another theory that the disorder may be due to a disturbance in the metabolism of copper.

The lesion in question is a well-defined one in which all or most all of the cerebral white matter has been transformed into a larger number of confluent spaces (fig. 8, A). These spaces are traversed by strings or "girders" which are blood vessels of the white matter. The cortex may also show minor changes in the form of focal or laminar loss of nerve cells. The occurrence of these central cysts in infants born after difficult labor has convinced many students of the problem that dystocia is perhaps the major causative factor (Sachs and Peterson (39), Schwartz (42), Stevenson and McGowan (43), Benda (11, 44), and Malamud (45)). But there is no agreement as to the precise mechanism by which physical violence is able to produce these cysts. Most favor the idea that the white matter was the original seat of hemorrhages secondary to occlusion of regional venous channels with secondary rupture of the afferent veins (Schwartz (42), Marburg and Casamajor (10)). One disturbing feature about this assumption is that the lesion is sometimes already advanced in children who die shortly after birth (46).

The present writer favors the conclusion that infantile cystic degeneration either begins (1) in utero with some situation favoring anoxemia in the fetus or (2) at the time of birth incident to anoxia attendant on dystocia. At times, however early, postnatal disturbance in circulation may be responsible. As for the intrauterine factors, severe anemia in the mother or a disruption of the oxygen-carbon dioxide interchange in the placenta (traumatic displacement of the placenta (Seitz (47)); syphilis of the placenta (Schob (48)); endometritis (Courville (35))). It is also likely that asphyxia at the time of birth sets up a vasomotor disturbance with delayed breakdown of the cerebral white matter which results in cyst formation. The demonstration that cerebral anoxia of various causes can result in the formation of cysts in the white matter has been proven both experimentally (by carbon monoxide (Yant et al. (49)); (by cyanide poisoning (Hurst (50, 51)) and in man (asphyxia after nitrous oxide anesthesia) (Abbott and Courville (52)), after carbon monoxide poisoning (Courville, Case 11 (35)) (fig. 8, B). Finally, the association of cystic degeneration with other lesions suspected of being anoxic in etiology (microgyria (Köppen (25), Probst (53), Diamond (54), Marburg and Casamajor (10)), and focal cortical subcortical necrosis (Köppen (27), Diamond (54), Winkelman and Moore (55)) seems to support this conception.

The writer, therefore, agrees with Benda (11) who concludes that asphyxiation (at birth) with anemic necrosis is the most important factor in the pathogenesis of this condition.

**Diffuse Sclerosis:** This demyelinizing disorder is one which is characterized clinically by a steadily progressive downhill course, more often occurring in infancy or childhood but, occasionally, in adults as well. However, the disease seems to have essentially the same nature regardless of the age of the patient. It is characterized by a loss of myelin beginning in the central portion of the
white matter then spreading to the periphery (fig. 9, A). It ultimately comes to affect considerable extents of the cerebral hemispheres, although the occipital, parietal and temporal lobes are most characteristically involved. The earlier in life the disease occurs, the more rapid tends to be its clinical course. The disorder was first described as a special entity by Schilder (56), who reviewed the literature on this subject. When the subject was reviewed 20 years later by van Bogaert and Scholtz (57), 70 cases had been reported.

No consistent cause has been found for the disease. It has been considered to be a form of encephalitis (Schilder (56)), the result of a circulatory disorder (Wohlwill (58)), specifically an obstruction of venous drainage (Marburg (59)). Grinker (60) called attention to its similarity to the end-result of myelopathy after severe exposure to carbon monoxide, a conclusion reached also by Meyer (61). The occurrence of central myelin degeneration after temporary complete arrest and circulation (Grant, Weinberger and Gibbon (62)), after chronic cyanide poisoning (Jedlowski (63), Hurst (50, 51), Lumsden (46)) as well as after asphyxia incident to carbon monoxide as noted in a number of case reports reviewed recently by the writer (64) demands consideration of its origin in some sort of an anoxic-ischemic basis (fig. 9, B). This conclusion seems to be supported by experimental evidence as well (65).

The association of central myelinopathy with other lesions under consideration in this connection also warrants an evaluation. For example the presence of central cyst formation associated with degeneration of myelin in both animals (Yant et al. (49), Hurst (50, 51)) and man (Abbott and Courville (52)) in known cases of anoxia is sometimes also reproduced in diffuse sclerosis (Schaltenbrand (66), Josephy and Lichtenstein (67)). Less apparent, but still very significant of its possible anoxic genesis, is the presence of laminar cell degeneration in some cases of Schilder’s disease (Russell and Tallerman (68), Jervis (69)).

Another finding in diffuse sclerosis which implies a circulatory genesis of some kind is the not infrequent occurrence of recognized alterations in the blood vessels. Thickening of the intima and adventitial proliferation leading to formation of new capillaries have been described by many contributors (Schilder (56), Siemerling and Creutzfeld (70), Shelden, Doyle and Kernohan (71)). Gasul (72) went so far as to conclude that demyelination was actually the end-result of these vascular changes. Such vascular alterations were also found in three typical cases in the writer’s series (35).

The writer’s particular contribution to the pathogenesis of this disease consists in again pointing out the marked similarity between the demyelination resulting from carbon monoxide and that found in diffuse sclerosis (64). These points of similarity include the occurrence of perivascular demyelination, sparing of the subcortical arcuate fibers, decreased numbers of capillaries in the areas of demyelinations, the decrease in numbers of oligodendroglia and the occasional occurrence of “islands of preservation” in the periphery of the degenerated areas. It would seem that so many points of resemblance between the two conditions must have some significance with respect to its pathogenesis (table 2).

What are the chief arguments against an anoxic origin of diffuse sclerosis?
Fig. 9. Diffuse Sclerosis. A. Low power photomicrograph depicting section of cerebral centrum in case of diffuse sclerosis showing irregular demyelination. B. Low power photomicrograph of section of white matter showing delayed effects of carbon monoxide asphyxiation. Both myelin sheath preparations.

Fig. 10. Status Dysmyelinisatus. A. Low power photomicrograph of lenticular nucleus showing demyelination of external capsule (status dysmyelinisatus) in a 27-year-old male with double athetosis born after use of forceps in difficult labor. Brain also showed bilateral parietal foci of microgyria. B. Low power photomicrograph of lenticular nucleus showing demyelination of external capsule in case of delayed death incident to cerebral anoxia from excessive rectal bleeding (anemic form of anoxia) in a 43-year-old man.
# Table 2

Comparison between Details of Demyelination in Diffuse Sclerosis and Carbon Monoxide

<table>
<thead>
<tr>
<th></th>
<th>Diffuse Sclerosis</th>
<th>Carbon Monoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precip. Factor Course</td>
<td>? acute infections</td>
<td>Anoxemia</td>
</tr>
<tr>
<td>Initial lesion</td>
<td>Status spongiosus central white matter</td>
<td>Progressive after delayed onset</td>
</tr>
<tr>
<td>Interval lesion</td>
<td>Patchy demyelination</td>
<td>Patchy demyelination</td>
</tr>
<tr>
<td>Ultimate lesion</td>
<td>Practically total demyelination</td>
<td>Practically total demyelination</td>
</tr>
<tr>
<td>Location of lesion</td>
<td>Most common in posterior cerebral centrum</td>
<td>Most common in posterior cerebral centrum</td>
</tr>
<tr>
<td>Characteristics of</td>
<td>Sparing of arcuate fibers</td>
<td>Sparing of arcuate fibers</td>
</tr>
<tr>
<td>demyelination</td>
<td>Sparing of P.V. islands of fibers</td>
<td>Sparing of P.V. islands of fibers</td>
</tr>
<tr>
<td></td>
<td>Areas of total demyelination</td>
<td>Areas of total demyelination</td>
</tr>
<tr>
<td></td>
<td>Absence of oligoglia*</td>
<td>Absence of oligoglia</td>
</tr>
<tr>
<td></td>
<td>Focal cyst formation at times</td>
<td>Focal cyst formation</td>
</tr>
<tr>
<td>Degenerative products</td>
<td>Usual products lipidoid degeneration; at times metachromatic staining</td>
<td>Usual products lipidoid degeneration; ? metachromatic staining</td>
</tr>
<tr>
<td>Vascular changes</td>
<td>Loss of capillaries in demyelinating areas; endothelial proliferation; collapse of penetrating cortical arteries†</td>
<td>Loss of capillaries in areas of demyelination; endothelial proliferation; collapse of penetrating cortical arteries</td>
</tr>
<tr>
<td>Cortical changes</td>
<td>Loss nerve cells; focal scars§</td>
<td>Patchy and laminar necrosis; scars</td>
</tr>
<tr>
<td>Ganglionic changes</td>
<td>Present at times</td>
<td>Almost the rule</td>
</tr>
<tr>
<td>Familial tendency</td>
<td>Increasingly more marked in older age group</td>
<td>Recurrent cases of natal anoxia not uncommon in two or more siblings</td>
</tr>
</tbody>
</table>

‡ Courville; Contribution to Study of Anoxia, 1953.

The argument that the lack of history of asphyxia at birth or even difficult labor, is probably not valid. In the writer's experience this negative history is often worthless (35). Even if present, the significant factor may have been some unknown disorder which affected the fetus in utero, via the maternal circulation or some disfunction of the placenta.

Perhaps the most cogent argument of all against such an assumption is its occasional familial incidence (59). This is particularly true in those instances in which the onset of the disorder is late in life (Pelizaeus-Merzbacher disease). However, it is entirely possible that two or more siblings may have been exposed to similar or identical situations in utero which favored a relative anoxia and resulted ultimately in bearing the fatal fruit of demyelination. It is now recognized that more than one child in a family can develop cerebral palsy, either with identical or entirely different deforming lesions of the brain (35). Thus, the
familial incidence of diffuse sclerosis does not entirely exclude anoxia (natal or otherwise) as its cause, although it is recognized that the burden of proof continues to rest on proponents of this theory. Perhaps one reason for doubt lies in the delayed onset of symptoms and signs of this disease. This may be explained in the case of infants and children by the fact that demyelination after carbon monoxide is also a delayed process (six years to fatality in Case 4 of de Hehoczy (73)). In cases with onset in adults this answer is scarcely satisfactory and some other cause for anoxemia not clinically evident may be its cause.

With these data in mind, the present writer wishes to restate a conclusion reached 5 years ago (35); “This disease (diffuse sclerosis) is the result of a widespread ischemic mechanism whose precipitating cause, insofar as can now be determined, is usually anoxemia of some sort.” And at least in the instances of this condition occurring in infancy and early childhood, the likelihood of its incipiency in some anoxic episodes in late fetal life or during delivery is more than possible. In the examples occurring in later life, it is also possible that some other cause as yet unknown is capable of precipitating a similar profound and widespread vasomotor phenomenon which initiates the disease process and perhaps keeps it going as well.

The Striatal Disorders: There are 2 relatively rare lesions of the corpus striatum, status marmoratus, and status dysmyelinisatus, which warrant scrutiny in this connection. The fact that the lenticular nucleus, particularly the globus pallidus, is so commonly the seat of structural damage as a consequence of anoxemia itself suggests that some sort of residual postanoxic striatal lesions are to be expected. Moreover, the clinical observation of typical symptom-complexes in young individuals who have experienced difficult deliveries (74) is encountered. Verification of the lesion at autopsy cannot be entirely ignored in individuals who have had “birth injuries.” Malamud (12) also seems to support this conclusion. It would also be difficult to show how any purely mechanical factor could possibly cause the lesions.

Insofar as status marmoratus is concerned, the evidence of a truly mechanical effect is defective in the sense that the essential feature of the lesion is an apparent increase in number and size as well as the abnormal arrangement of the myelinated nerve fibers. Morrison (14) has found that this process occurs in the basal ganglia of young animals when portions of the overlying cortex has been resected, which suggests a form of “release” phenomenon. This conclusion is further supported by the observation that similar changes may take place as part of the irregular cortical changes occurring in nodular atrophy. The association of status marmoratus with other lesions is assumed by the writer also to be the result of anoxia at birth (cerebral hemiatrophy and microgyria (29), focal and laminar cortical necrosis (30), with lobar sclerosis (75, 76, 77), cyst formation in the white matter (77) and central demyelination (75, 78), and finally with scar formation in the lenticular nucleus (75)) makes this seem a reasonable deduction. By way of summary, therefore, it can be said that the clinical history of dystocia in these cases suggests that status marmoratus is probably a consequence of cerebral anoxia at the time of birth. The statement by Benda (44) to
the effect that "asphyxiation is the most common cause of this type of pathology" seems a reasonable one.

The second of the two striatal conditions described by the Vogts (79), \textit{status dysmyelinisatus}, is characterized pathologically by a marked atrophy of the globus pallidus, and to a less marked degree, the corpus luysi and the thalamus, associated with a loss of myelinated nerve fibers (fig. 10, A). The caudate nucleus and putamen are also affected in some instances. The striatal symptoms appear early in life and progress to the time of death of the patient which usually occurs in late childhood or adolescence. The clinical picture often resembles that of Little's disease. The early age of onset of symptoms and the association of other manifestations of cerebral palsy are to be viewed in the light of the well-known fact that damage to various portions of the corpus striatum are a common finding in cerebral anoxia (80). In addition, the loss of myelinated nerve fibers in the external capsule and lenticular nucleus after severe anoxic episodes are direct counterparts of the findings in status dysmyelinisatus (81, 82, 35) (fig. 10, B).

In view of this evidence, it would seem difficult to postulate any other cause for this disorder than anoxia occurring just before or during the natal episode.

Atrophy of the lenticular nucleus or actual cystic degeneration of this body can even more readily be compared to anoxic lesions of adult life.

\textbf{SUMMARY}

This survey of a group of individual cerebral lesions originating in early life and which are the evident cause of crippling clinical states (cerebral palsy, mental deficiency and epilepsy) was made with the primary objective of determining their etiology and pathogenesis. Selection of the lesion to be evaluated was based upon the opinions of previous investigators and the present writer's own experience in the realm of anoxic and ischemic lesions of the brain. After what seems to be a fairly comprehensive effort to elicit evidence from various sources, certain of these lesions (uniform and widespread cerebral atrophies, cortical, cortical-subcortical, subtotal and total cerebral softenings, nodular cortical atrophy, porencephaly, chronic cystic degeneration of the cerebral white matter, diffuse myelinating disorders of early life, and certain striatal disorders), were believed to have their origin in generalized or localized disturbances in the circulation.

The nature, value and completeness of the evidence pointing to this conclusion vary in the individual groups of lesions. For example, the anoxic origin of the widespread and uniform cerebral atrophies rests chiefly on the demonstration of similar changes in experimental animals after simulated natal anoxemia. The generalized softenings on the other hand appear to be due either to an impairment of the carotid circulation (as incident to absent or small carotid arteries) or to severe anoxemia (as demonstrated in the counterparts of these lesions of anoxic etiology in later life). This conclusion seems to be further supported by similar lesions produced by experimental carotid occlusion in young animals. Nodular cortical atrophy and porencephalic defects, quite commonly associated in a single specimen, are almost certainly the result of arterial occlusion as indi-
icated both by the disclosure of similar lesions in later life and by their experimental production. The circulatory (anoxic) genesis of chronic cystic degeneration of the white matter is still somewhat in question as is widespread myelinopathy of early life. Comparative studies on similar lesions of postnatal life as residuals of severe anoxemia brings out comparisons which should not be lightly ignored. Similar lesions have also been produced by cerebral anoxia in experimental animals. The anoxic etiology of structural changes in the corpus striatum and thalamus, producing somewhat less common but typical clinical syndromes of early life, is suggested by the well known vulnerability of these structures to oxygen want. The nature of the resultant lesions (with the exception of status marmoratus) in both early and late cases are quite similar which strongly implies a common pathogenetic mechanism. In the isolated case of status marmoratus, there are no comparable lesions in adult life to guide one in evaluating either its etiology or pathogenesis. In this instance, the unusually high incidence of a history of dystocia with “brain injury” suggests either a traumatic or anoxic origin. Experimental findings suggest that the aberrant location and the hypertrophy of the myelin sheaths as well as an increase in their number in the basal ganglia may be the result of a parenchymatous deficit in the regional cortex. This lesion may therefore be an indirect or secondary one resulting from a primary anoxic or ischemic disorder. Its genesis in a venous thrombosis with resultant hemorrhages in the affected structures seems most unlikely. The writer knows of no possible biological alchemy by which focal hemorrhages can be transformed into bundles of myelinated nerve fibers.

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DR. JAN CAMMERMEYER, Bethesda, Md.: Dr. Windle regrets that he could not attend this Symposium and report the recent results of two years' work on experimental anoxia in newborn guinea pigs and monkeys. Some of the results were briefly discussed elsewhere (Anat. Rec., 130: 389 and 470, 1958). I don't feel competent to discuss any papers presented today because my experience with this type of material is limited. Furthermore, after I have heard the comments by people with many years of experience in this particular field, I am wondering how much can be gained by a discussion of the neuropathological changes related to a period of anoxia around childbirth. In my opinion such a discussion can be started only when we are assured of a perfect autopsy, preferably in front of all of us, so that we may check what the skull looks like, the appearance of leptomeninges, the vascular system, the brain, the visceral organs, and so forth. After the careful assembly of all material I doubt very much that we would still accept the classification hitherto used for neuropathological changes observed in such material. It seems rather surprising that the same type of lesions are evaluated so differently by two or more investigators. Because of this diagnostic insecurity I believe we ought to reconsider our entire procedure.

Another subject which is often neglected is the development of cerebral damage. Discussion of this must be preceded by a careful timing of the onset of cerebral damage and must include a careful consideration of the metabolic characteristic of the brain and spinal cord. All through embryonic life, fetal life, and early childhood, there is a continuous change in the intensity of metabolism going on in different parts of the nervous system, as demonstrated by Himwich and associates. These metabolic peculiarities of different regions vary, not only with age but also among species. Therefore, we can hardly expect to obtain the same results in experiments on different species.

The lantern slides which Dr. Windle asked me to present are from a study to be published by Drs. Ranck and Windle (Physiol., 1(4): 63, 1958). They show a monkey brain with a multitude of changes resulting from experimental neonatal asphyxia. At term, after 158 days of gestation, delivery of the fetus in the intact placenta was performed by cesarean section. The placenta was opened after 15 min. 30 sec. The distribution of pathological changes was most remarkable; they were confined to the brain stem and spinal cord, sparing the cerebral cortex. This is, of course, rather similar to the localization of Kernicterus with erythroblastosis foetalis, but differs entirely from the sites of greatest damage after anoxia in adults.

The paper entitled “Perinatal Infections of the Nervous System” by Drs. Abner Wolf and David Cowen, which was the second paper of the second part of the Symposium, will be published in the April, 1959 issue of this Journal.