CEREBRAL MANIFESTATIONS OF ANOXIA

A Review of the Literature
Part II

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Unlike anesthesia for surgical procedures, where only one patient is involved, anesthesia for obstetrics may involve two persons, the mother and the child. Asphyxia that may occur during labor, whatever may be the cause, subjects the fetus to harmful effects.

The process of birth imposes a series of insults on the child. These include prolonged labor, instrumentation, pressure upon the head with subsequent hemorrhage, prematurity, and asphyxia. These last two, in the opinion of many authorities, constitute the greatest hazards.

Although the anesthetist may not be able to control all of the factors that may endanger the child, asphyxia, which is intimately associated with anesthesia, may be of great and serious import.

That asphyxia is a serious consequence of birth has been recognized since long before the discovery of modern anesthesia, but the added assault of asphyxia during anesthesia has increased the interest in the prevention of this hazard.

The exact role of asphyxia in the immediate and late sequelae of birth is difficult to evaluate. Many physicians accept a degree of asphyxia as an almost normal consequence of labor. Since there is no way of anticipating the intelligence of any individual, there may always be a doubt as to the role played by asphyxia in the subsequent development of the mental state. As studies progress, however, there begins to develop a body of evidence that gives weight to the hypothesis that cerebral damage with its varying manifestations can be the result of asphyxia associated with birth.

In this, as in part I of this review, a chronologic arrangement of some of the references from the literature has been made.

In 1836-37, Kennedy reported nineteen cases of spinal apoplexy, paralysis, and convulsions of newborn infants. He attributed some of these complications to the delay attendant on the first establishment of respiration and expressed astonishment that “cerebral affections in the infant should not be more numerous than they are.”

Lassere (1846) reported on apoplexy in the fetus and newborn child and pointed out that this disease was not the same functional disorder as that which occurs in the adult.

Browne (1860) attributed the psychic diseases of early life to the effects of pressure on the head during birth.

Little (1862) recognized the role of asphyxia on the mental and physical condition of the child. He summarized his opinion by saying: “Asphyxia neonatorum, through resulting injury to nervous centres, is the cause of the commonest contractions which originate at the moment of birth, namely, more or

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less general spastic rigidity, and sometimes of paralytic contractions." He reported forty-seven cases in which he emphasized that general spasticity is preceded by some abnormal act connected with the mode of birth. "Convulsions at birth, or subsequently to it, are but a symptom of lesion of the nervous centre." He further developed the subject with the opinion that "It is impossible not to connect the persistent affection of the intellect, of volition, and of organic life, with the injury the several nervous centres suffered in some instances before the foetus has reached the maternal pelvis, in others whilst in transit through it; and in a third set of cases, where the foetus was exposed to... asphyxia neonatorum, suspended animation and its concomitant congestion, effusion, capillary apoplexies of brain, medulla oblongata, and spinal cord... The greater or smaller impairment of intellect may safely be attributed to the greater or less mischief inflicted upon the cerebrum." He further contended that the severe lesions caused by mechanical compression and laceration with extended hemorrhage within the skull may give rise to deformity of the cranium, or to atrophy of the injured portions of the brain, and "are the cause of many cases erroneously described as congenital idiocy." Sixty-three cases to demonstrate this contention were presented. Anesthesia was not mentioned in this discussion.

Low\(^2\) (1893), in discussing asphyxia in relation to anesthesia, rationalized that fatalities resulted in only one of 7,000,000 administrations.

Salmon\(^3\) (1910) indicted alcohol and syphilis as the two causes of insanity. Alcoholic parents produced 26 per cent of epileptic children in his experience.

Barr\(^2\) (1911) included asphyxia as one of the causes of the increase of feeblemindedness.

Ford\(^1\) (1928) investigated the effects of asphyxia on the brain, with special reference to asphyxia neonatorum. "Asphyxia neonatorum may be caused by any accident which prevents the initiation of pulmonary respiration immediately after the placental circulation has been interrupted. ... Intracranial hemorrhage from birth trauma is a common reason for failure to breathe. This condition is the so-called 'pallid asphyxia' and is the result not the cause of intracranial hemorrhage. ... If we exclude intracranial hemorrhages as a result of asphyxia, we must, nevertheless, admit that multiple petechial hemorrhages in the brain and meninges are found in all forms of asphyxia, not only in infants but also in adults. ... Clinical studies ... have afforded no support to the theory that asphyxia alone is an important factor in cerebral birth injury. ... A large number of cats and kittens were asphyxiated in various ways. ... In the first series of experiments the animal was asphyxiated rapidly by washing out the air from a bell jar with nitrogen. ... After respiration had failed there was an interval of three to five minutes during which artificial respiration was found to be effective, but after this period the heart stopped and could not be started in most cases, although epinephrine and other cardiac stimulants were injected directly into it. If the animal were revived, it always recovered promptly and completely. ... Seven animals were killed after asphyxiation, the time varying from immediately after the conclusion of
the experiment to two weeks later. In no case could any gross or microscopic hemorrhage be found, but extreme congestion was detected in cats killed soon after asphyxiation. . . . It was concluded that anoxemia brought the heart to a standstill before any lasting damage was inflicted on the nervous system. This experiment was designed to duplicate the sudden more or less complete type of asphyxia which might occur during birth. . . . In the second series of experiments kittens were placed in a bell jar and a constant stream of low oxygen mixture was run through. In this way kittens could be kept for as long as 12 hours in an atmosphere of 5.5 to 6 per cent oxygen. . . . The brains of five kittens were studied. No gross or microscopic lesions were found."

Doll, Phelps and Melcher (1932), in discussing the etiology of mental deficiency following birth injury, included asphyxiation. They grouped the sequelae into three categories: (1) those that caused death; (2) those that caused immediate signs; and (3) those in which evidence was delayed. They found that the role of asphyxia was difficult to interpret.

Riley (1933) reviewed the subject of asphyxia neonatorum.

Lewis (1936) and Clifford and Irving (1937) stressed the role of analgesics in the production of asphyxia neonatorum.

Schreiber and Gates (1938) reported seven cases of cerebral injury due to anoxia at birth. Amytal, scopolamine and morphine, nitrous oxide-oxygen-ether, nitrous oxide and oxygen, and ether were the analgesics and anesthetics involved in the episodes. In one of the incidents the mother and the baby suffered the effects of anoxia. The authors concluded that "Complete anoxemia maintained even for 10 minutes, or less acute for a longer time, may lead to irreparable damage to the nervous system. . . . The mother as well as the child may show evidence of brain damage associated with birth analgesia, both being equally exposed to cerebral anoxia if present. . . . Encephalography has been employed in a considerable number of cases in this series of 'birth injuries' associated with deep analgesia. Brain atrophy, either generalized or unilateral, is a frequent finding."

Cole et al (1939), in discussing the etiologic factors in neonatal asphyxia, reported that "Asphyxia of the newborn infant has assumed an entirely new significance in recent years for two reasons: A greatly modified conception of the inauguration of respiration and the demonstration of the various pathologic changes that may be produced in the central nervous system by anoxia. . . . Extensive areas of 'devastation necrosis' have been observed in the brains of infants dying a few days after severe asphyxia at birth which are apparently identical with those observed in death from known anoxic states, such as nitrous oxide anesthesia, acute alcoholic intoxication and hyperpyrexia. . . . [In the records of 5,000 mothers and babies] . . . the most important single factor in the etiology of neonatal asphyxia is prematurity. The next most important factor is the trauma of labor. . . . Sedatives in any amount definitely increase the incidence of asphyxia in the baby in direct proportion to the amounts given. General anesthesia in any amount definitely increases the incidence of asphyxia in the baby in direct proportion to the duration of the anesthesia."
Schreiber (1939) studied a group of mentally deficient children. In reporting the series he said: "Considerable clinical evidence supports the conclusion that the brain tissue of an infant can sustain much less oxygen deprivation than can the adult organ and, therefore, is more readily damaged from this particular cause than is adult cerebral tissue. The clinical diagnosis of such tissue damage is more difficult with the infant, since there is no yardstick of previous mentality in evaluation, and the infant (or young child) cannot adequately describe his deficiency. . . . It appears significant that in our group of 252 children, whose mental deficiency was thought to be related to conditions at birth and for whom reliable birth data were obtainable, 176 (70 per cent) were found to have a history of asphyxia, regardless either of the manner of delivery or whether the baby was full term, premature, or a twin. This group of children included all those born in the years 1928 through 1938, seen with mental deficiency as a symptom and about whom the respiratory situation at birth was known. Any child for whom an inherited defect was suspected or for whom there was a history of postnatal cerebral trauma or infection was excluded from the group. Most of these children, observed at the Children's Hospital of Michigan and in private practice, were referred with convulsions or spasticity by pediatricians or psychiatrists for an opinion as to the advisability of neurosurgical measures or encephalography. . . . In a careful review of the maternal, prenatal and birth histories of these mentally deficient children, it was evident that single or combined anoxic factors contributed to the mechanism responsible for the production of asphyxia. In some cases, a carefully recorded history disclosed events occurring during pregnancy which may have been responsible for cerebral cell damage in the fetus; in other cases, the clinical syndrome of the neurological findings suggested that the devastating cerebral asphyxia came on some time after the baby was born. . . . Damaging cerebral anoxia may result from increased but unfulfilled oxygen demand due to intrinsic or extrinsic causes. . . . None of the instances of mental deficiency in this group of defective children were considered solely due to the action of pleonectic agents. However, the possibility of such occurrences must be kept in mind if therapeutic adjuncts are used which form methemoglobin and thus deprive the blood of some of its oxygen-carrying capacity. A deficiency in carbon dioxide in the blood causes the hemoglobin to combine more tightly with oxygen, so that it is not available to the cerebral cells. This is of clinical significance in the resuscitation of the newborn and has been an effective argument for the employment of the carbon dioxide-oxygen mixture as advocated by Yandell Henderson. . . . The habit of consigning defective children in the early years of their existence into groups, largely for disposition of their physical welfare, should have as a basis a more extensive inquiry into the etiological factors responsible for the subnormal organism. The thesis of cerebral anoxia from asphyxia in the newborn cannot be unequivocally rejected as a positive factor in brain deterioration merely on the time-worn basis of developmental central nervous system defects. Many of the anomalous degenerative and atrophic changes have a biochemical
explanation which determines their organic departure from the normal. 'Birth asphyxia' is a term loosely applied in private and hospital practice."

Kabat (1940) studied newborn dogs and concluded that young animals have 400 per cent greater resistance to arrest of brain circulation than adult animals. He concluded that "There seems to be good reason to believe . . . that the brain of the human infant is more resistant to anoxia than the adult organ."

Clifford (1937) (1940) presented the subject of asphyxia of the fetus and the newborn infant.

Peterman (1941) also presented the subject and reported that "Among the less well-known cerebral birth injuries are those neurologic sequelae of apnea and anoxia. . . . The severity of the symptoms depends upon the location and amount of cerebral tissue injured. This is, of course, dependent upon the duration of the anoxemia. . . . Another type of cerebral injury is edema of the brain . . . the edema usually produces lethargy and hypotonicity which last for twenty-four to forty-eight hours. If it is extensive or severe, it impairs cerebral circulation and leaves the same sequelae as does anoxemia."

Rodgers (1941): "The exact relationship of atelectasis to asphyxia is difficult to determine. Obviously, asphyxia may be caused by atelectasis in which insufficient aeration prevents hemoglobin from picking up sufficient oxygen in the lungs, but, on the other hand, asphyxia may prevent the lungs from expanding because of the anoxemic effect of the blood on the respiratory center, which in turn prevents the deep initial inspiratory movement required to initiate rhythmic breathing. . . . The barbiturates function by depressing the respiratory center, and obviously the fetal respiratory center is more susceptible to these drugs than that of the mother. Thus, a dose which merely quiets the mother may lead to a markedly lethargic and dangerously apneic infant at birth. . . . Anesthetics, particularly nitrous oxide, lower the oxygen saturation of the fetal blood. . . . Late neurological symptoms often found in infants who have had difficult operative deliveries may result from prolonged deep anesthesia and not from the actual operative procedures."

Windle and Becker (1942) studied the effects of anoxia on the central nervous systems of guinea pigs, using litter mates as controls. Anoxia produced in 103 animals invariably resulted in symptoms of neural damage. Transient shock, tremors, ataxia, and inco-ordination were not associated with impaired behavior or brain pathology. More than eight minutes of anoxia produced decerebrate states, evidenced by atonia, convulsions, paralysis, hyperesthesia and hyposthesia, and somnolence. These signs were correlated in some animals with behavioral changes. Examination of the tissues showed devastation of the brain and cord, hemorrhage, and general atrophy.

The same authors (1943) reported that 65 per cent of guinea pigs showed central nervous system damage following asphyxia. Unlike the litter mates, the animals showed errors in maze and alternation problems. Weight loss was greater than that of the litter mates; weakness, tremors, paralysis, and delayed, inco-ordinated 'righting' followed asphyxiation of fetuses. The animals developed spastic paralyses, convulsions, and weakness of ex-
traocular, facial, tongue, and pharyngeal muscles. Hearing and vision were probably less acute in the asphyxiated group. The brains of the affected animals showed necrosis, edema, chromatolysis, petechial hemorrhage, and destruction of the cerebral cortex pyramidal cells.

Biggs\(^2\) (1944) outlined the treatment of severe asphyxia of the newborn as dictated by the “consensus of the best opinions” in the literature.

Darke\(^8\) (1944) selected twenty-six cases of the most severely asphyxiated newborn infants who survived birth and the hospital period following, out of a total series of 25,261 births. Twenty-three similar cases from the records of a different hospital were also secured. Of these, fourteen children of the first group and five of the second were located and used for the study. The author concluded that “a statistically significant difference in mental status exists between a group of children severely asphyxiated and apneic at birth and a control group consisting of their siblings or parents.”

Preston\(^28\) (1945) reported 132 cases in which anoxia had occurred. “The nervous system of every child so classified was found damaged enough seriously to affect his subsequent behavior. . . . The lesser degree of anoxia caused abnormal, hyperactive behavior; the greater caused apathetic behavior incompatible with normal living. . . . Arrest of physical, mental, nervous, and emotional, as well as personality development took place throughout the series.”

Beck\(^2\) (1946) cautioned against the dangers of anoxia “when the mother’s respirations are slowed and made more shallow by the use of sedative drugs and anesthetics, the oxygen supply to the placental lake is diminished, and the danger of intrauterine anoxia and asphyxiation is increased to such an extent that most of the methods which have been recommended for the relief of pain during labor may cause the death of the child if they are not given with caution. . . . While artificial respiration may sustain life until the respiratory center has recovered from the action of these drugs and the child is able to breathe naturally, the effect of the anoxia on other parts of the brain may lead to serious consequences.”

Fletcher\(^11\) (1945) studied twenty-nine cases of personality disintegration following the use of nitrous oxide. He proffered a suggestion that, in addition to its interest to the medical profession, the question of anoxia is also “directly related to many problems of education. Our institutions of learning, from the primary school to the university, are filled with problem students. Tonsils, adenoids and teeth are routinely removed from children of all ages. General anesthetics are usually employed for these operations. Many perplexing problems of the school room may possibly be explained on this basis.”

In 1946 Fender et al\(^10\) studied dogs and reported the results. “Pregnant bitches within the last week of pregnancy were subjected to atmospheres containing as low as 4% oxygen from 20 to 30 minutes. Carbon dioxide was removed. One bitch aborted the evening of the experiment and ate her young. Twenty-five pups born 24 to 72 hours after the experiment died during their first few weeks; 3 survived without apparent neurologic involvement. Of the 5 surviving animals, two developed status epi-
lepticus at 5 and 6 weeks; the first was killed after 24 hours, the second survived three days during which seizures were almost constant. Microscopic studies of the brain revealed no significant departure from normal. . . . We believe a significant percentage of patients who suffer from convulsions for which no obvious cause can be ascribed have histories of complicated fetal life or birth."

Russ and Strong\textsuperscript{31} (1946) stressed the importance of immaturity in the production of asphyxia.

Halstead\textsuperscript{17} (1947) proposed a correlated study of brain injured persons and anoxia in normal humans.

Gruenwald\textsuperscript{16} (1947), among other causes of mental deficiency of prenatal origin, included oxygen deficiency. "Fetal oxygen deficiency as a cause of brain damage and subsequent mental defect has been studied by several investigators in infants and in experimental animals. It occurs most commonly during labor, but it may also happen earlier. . . . In guinea pigs, controlled periods of anoxia at birth produce morphologic changes in the brain, and abnormalities of behavior which, if not severe, are comparable with human mental deficiency. In human cases it is difficult to decide whether brain damage is the cause or the sequel of anoxia, but there are good indications that in some cases the cerebral changes are produced by anoxia. Proper prenatal and obstetrical care should reduce anoxia of the fetus to a low minimum. In certain cases, maternal and consecutive fetal anoxia should be combated by the administration of oxygen to the mother. . . . The obstetrician's difficulties are increased by the fact that procedures which diminish the duration of anoxia during labor, tend to increase the danger of mechanical trauma, and vice versa."

Gesell and Amatruda\textsuperscript{15} (1947) included the following pertinent statements in their study of development: "Many defective infants react poorly to the birth process. . . . The methods and concepts of developmental diagnosis are of special importance in the interpretation of cerebral injuries. Most of these injuries occur prior to, during, or soon after birth. All told, they comprise perhaps one-fifth of all cases of amentia, and over one-third of the motor disabilities of crippled children. They also account for a considerable but undeterminable number of children who suffer from personality deviations, dullness, various forms of inadequacy, and subclinical defects and deficits. . . . The term injury as here used is equivalent to those destructive lesions which produce secondary types of mental defect and deviation, namely, traumata, hemorrhage, infections, toxic agents, anoxemia, irradiation. . . . Altho a neurone once destroyed cannot be regenerated, it can sometimes be replaced by the compensating development of an unharmed neuroblast. . . . Altho anoxemia may sometimes be present without apnea, apnea is the important clinical sign of anoxemia. . . . Cerebral anoxia, produced by obstetrical analgesics, oxytoxics, and anesthetics, may cause intracranial hemorrhages in utero. . . . A newborn amnion is likely to show cyanosis of severe grade on small provocation. . . . On the other hand an infant of superior endowment may escape some of the permanent effects which an inferior child would suffer."

The relationship of cerebral palsy and anoxia was presented by Perl-
stein (1947): "Of natal causes [of cerebral palsy], those which act
erate from the time the mother goes
into labor until the child is actually
delivered various examples might
be given. . . . The most important
of these is cerebral anoxia or as-
phyxia. The brain is very sensitive
to low oxygen intake and is easily
damaged by lack of this necessary
element. Thus a child who for any
reason does not breathe after birth
is likely to suffer brain damage
through anoxia. Among the causes
of such delayed breathing might be
delivery of the breech before the
head, blockage of the respiratory
passages by mucus, collapse of the
lungs (atelectasis), circulatory dis-
 turbances or the use during labor
of pain-relieving drugs such as
morphine which may inhibit respira-
tion in the child. Cerebral hemor-
rhage must be placed next in impor-
tance to anoxia as a natal cause
of cerebral palsy. In addition to
the obvious exogenous factors such
as obstetrical trauma, which may
cause brain hemorrhage, there are
many endogenous factors which
predispose to such bleeding. Of
these, one of the most important is
anoxia, which affects not only brain
tissue but also the blood vessels of
the brain making them more fragile
and frangible and thus more sus-
ceptible to rupture. Anoxia may
occur pre-natally also when the
placenta is infarcted or separates
prematurely. . . . Among the causes
of cerebral palsy which operate
after birth [is] . . . any form of
suffocation or anoxia."

Mengert (1948) placed the re-
sponsibility for anoxia directly on
the analgesic and anesthetic drugs.
"There is universal agreement that
anoxia, resulting in fetal asphyxia
is the principal cause of intrapartum
death. Moreover, many asphyxi-
ated infants are born alive, only to
die neonatally. . . . Asphyxia during
labor may result from direct inter-
ference with oxygen supply to the
child or through some mechanism
producing central depression. . . .
Almost half of the total fetal wast-
age occurs after birth, although the
genesis of most of these deaths
occurs during labor. . . . It is not
too far fetched to affirm that relief
of the pain of labor is numerically
and relatively the biggest single
cause of asphyxia of the newborn.
It is impossible to guess how many
subsequent deaths result from neo-
natal asphyxiation, but it may be
asserted that they are largely pre-
ventable. Subsequent atelectasis re-
mains a great problem . . . The
principal cause of anoxia during
and immediately following labor is
the analgesic and anesthetic drugs
administered to produce relief of
the pain of labor."

Little and Tovell (1949) made
an exhaustive review of the role of
analgesia and anesthesia in the pro-
duction of asphyxia neonatorum.

Anoxia in relation to cerebral
damage is increasingly being em-
phasized. Here, as with other med-
cal subjects, newspapers are be-
inning to publicize the problem.

Much has still to be learned of
the true relationship of causes and
effects. That analgesia and anes-
thetization are intimately involved in
the problem seems beyond doubt. By
constant awareness of the dangers
during delivery, the anesthetist will
help to prevent the sequelae that are
so devastating to the child.

Gellhorn and Ballin (1948)
studied rats between 4 weeks and
1½ years of age. They found that
the incidence and severity of con-
vulsions induced by electric current
declines as the age of the animal
increases.
SUMMARY

A review of the literature on cerebral manifestations of anoxia in the newborn has been presented. From these reports it seems that there are many and grave consequences of anoxia that may occur in the antenatal, natal, and neonatal periods. In addition to the immediate fatal effects of anoxia, the late sequelae include cerebral apoplexy, brain atrophy, spastic paralyses, convulsions, impaired intellect, personality defects, and others. The role of analgesics and anesthetics in the production of these effects has been presented.

BIBLIOGRAPHY


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