PARANATAL ANOXIA AND ITS RESIDUAL ENCEPHALIC LESIONS*†

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And a certain man lame from his mother's womb was carried, whom they laid daily in the gate of the temple which is called beautiful, to ask alms of them that entered into the temple.

ACTS 3 : 2

THIS BRIEF MENTION of a man crippled in his lower extremities who, according to St. Luke, the physician, was "lame from (his) mother's womb", constitutes a historical introduction to the concept of the serious effects of abnormal birth. The specific cause of such disabilities seems to be echoed in a statement made centuries later by one William Little[2] who wrote: "In two cases, the birth occurred at the full period of gestation, but owing to the difficulty and slowness of parturition, the individuals were born in a state of asphyxia (asphyxia neonatorum), resuscitation having been obtained at the expiration of two and four hours through persevering efforts of the accoucheurs." Over the long period which has elapsed between the pronouncements of Saint Luke and "Saint" Little, it has come to be recognized that children who have been crippled "from their mother's womb" may develop "permanent spastic contractions in various parts of the body."§ Moreover, from the time that such deformities were first painted on the walls of Egyptian sepulchres, depicted on the canvasses of mediaeval masters, and described by medical writers since the Renaissance, the clinical picture of these deformed individuals has become indelibly impressed upon the hearts and minds of laymen and physicians alike.

The reason for this tardiness on the part of medical historians in connecting the occurrence of paranatal asphyxia and the development of the several forms of paralytic phenomena results from a failure to comprehend the complex mechanism of anoxia. It is true that Little's contemporaries were willing to designate spastic paraplegia as "Little's disease," but the precise relationship

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between the anoxic cause and deforming motor effect was overlooked. The entire problem was subsequently thrown into a turmoil by the variable picture of the cerebral lesions found at autopsy in these cases. Moreover, the convincing pronouncements of such authorities as Osler[3] and Freud[4] were misleading to their contemporaries. Although they were not certain as to the precise cause of this brain damage, they had decided that it was not due to asphyxia. Living in 1960, we cannot so readily be excused for our ignorance; a quarter of a century has now elapsed since the effects of anoxia of the human brain have become known. In the light of present-day knowledge, it is therefore fair to ask why medical writers still persist in designating these natal episodes as "birth injuries." Because the motor and intellectual residuals of the anaesthetic anoxias, for example, are so definitely recognized, why are we so slow to acknowledge their clinical counterparts in children who have experienced a severe degree of anoxia at the time of birth? Now that we can readily identify post-anoxic changes in the brain of adults, why are neuropathologists in particular so reluctant to admit the same lesion in the brain of a child, damage which obviously dates back to the birth process?

In this brief presentation, the writer hopes to make clear to anaesthetists, so vitally concerned with the effects on the brain of oxygen deficiency, the true status of this problem. If it is true, as Beecher and Todd[5] have suggested, that the most common complication of anaesthesia is still cerebral anoxia, every well-trained anaesthetist is without excuse on this point.

IMPORTANCE OF PARANATAL ANOXIA TO PRESENT-DAY MEDICINE

It is legitimate to inquire "Just how important are the residuals of paranatal anoxia to present-day medicine? Does it have a possible answer to some questions as to the still unsolved etiology of certain neurological or psychiatric disorders, or is the entire matter 'much ado about nothing'?" The most direct approach to the answer of this question is to evaluate briefly the three major symptoms of anoxia that occur in our post-anaesthetic hypoxic patients.

These symptoms are (i) the hyperkinetic phenomena such as muscle tremors, jerkings, and most of all true convulsive seizures, (ii) paralytic manifestations in the more severely affected individuals, and (iii) the intellectual obtuseness, emotional aberrations, and behaviour disorders.*

In the first place, the problem of *epilepsy* assumes medical importance if for no other reason than its frequency. If the group of convulsive disorders that date back to the time of early infancy or to birth itself are investigated, it will be found that these phenomena include a variety of disorders which are usually associated with a generalized cerebral dysrhythmia as noted on the electro-encephalogram. Do these "spells" have any causal relationship to an anoxic process occurring during birth? When such convulsive attacks occur in cases of cerebral palsy in association with characteristic anoxic lesions in the brain,

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*If indeed these are the acute and subacute effects of post-anaesthetic anoxia, why should we be surprised that epilepsy, palsy, or intellectual deficits can be consequences of the chronic post-anoxic state?

there can be but little question. In such instances, it is logical to assume that both the palsied state and the convulsive seizures are due to the single etiological factor of anoxia.

There can also be little uncertainty in cases in which the seizures have occurred since early infancy but are either purely jacksonian in nature or are generalized with constant localizing manifestations associated with corresponding focal electroencephalographic dysrhythmias. So often, a surgical exploration results in the disclosure of focal cortical scars or cysts. Such lesions have been described by Ford[6] and Penfield and Erickson.[7] Microscopically, their structural characteristics indicate an identity with more recent anoxic alterations of later life.

The greatest degree of uncertainty exists as to whether there is any causal relationship between paranatal anoxia and the so-called "idiopathic" convulsions. In these instances, it is not often that one can elicit a clear-cut history of a paranatal anoxic state. Even the occurrence of an apnoeic state is frequently not recalled by the mother. There is some indirect evidence, however, that may have a significant bearing on this point. Nielsen[8] and subsequently Nielsen and Butler[9] pointed out that the first child born to a given family has a much greater likelihood of developing convulsive seizures. This correlates with the well-known fact that it is the first born child which is most apt to have difficulty in the birth process. In a subsequent study, Nielsen and Courville[10] reviewed the evidence favouring the possibility that many cases of epilepsy do have their genesis in anoxia at birth. It is also likely that in many such instances, any clinical evidence of anoxia may not have been observed, but it is now known that this state may exist in a cryptic form as a circulatory disorder. There is a strong suspicion on the part of the present writer that oversedation of the mother may play an important role in this process.[11] This point will be considered further in a subsequent section.

There is certainly much need for careful clinical studies of the total birth picture in idiopathic epilepsy, particularly with respect to evidence of foetal distress *in utero* and the amount of sedation given in relation to the period of apnoea together with the determination of the oxygen content of the blood in the umbilical vessels during the process of delivery.

The matter of *deficiencies in the intellectual field* should also be given critical scrutiny from this viewpoint. A review of a series of cases of cerebral palsy has shown that in from 30 to 40 per cent some degree of impaired mentation occurs.[12] It is not difficult in such cases with serious brain lesions to understand this association. It is easy to overlook more subtle signs of intellectual deficits in patients with less marked degrees of cerebral palsy. Perhaps of even greater importance is the observation that in about two-thirds of the cases of the so-called behaviour problems without well defined causes, disturbances in the brain wave pattern are to be noted. While paranatal anoxia is by no means the sole, or perhaps not even the most common, cause of these mental variations, there can be little doubt but that a large number of them do have their genesis in this situation.

The high incidence of paranatal anoxia is perhaps the most striking evidence

of its importance in the causation of *cerebral palsy*. Actual percentages vary from one series to another. As the result of study of the group of 160 cases of verified brain lesions in cerebral palsied children, the present writer concluded that about two-thirds were incident to some circulatory disturbance before or during the birth process, with anoxia as the chief pathogenetic factor. Fuldner[11] studied the possible etiological factors in 106 clinical cases of cerebral palsy and found a history of asphyxia at birth in about 90 per cent. Even if one accepts the lower of these two estimates, it is evident that paranatal anoxia is by far the most common factor in the causation of this clinical state, more than all other causes combined. This conclusion would indicate that if any material lowering of the incidence of cerebral palsy is to be expected a more critical analysis of paranatal anoxia must be made by both obstetricians and anaesthetists. This particular field of anaesthesia offers an excellent opportunity for further investigation of the possible factors involved.

RESIDUAL PARANATAL BRAIN LESIONS FROM FATAL CASES OCCURRING IN LATER LIFE

It is evident that our understanding of the pathogenesis and nature of the cerebral lesions found at autopsy in cerebral palsied individuals has been greatly delayed because of an incomplete knowledge of what can happen to the brain as a result of the anoxic states occurring in later life. This is not too surprising when it is realized that the disclosure of the ultimate lesions upon which an analysis must be made is delayed for months or years. By this time any interest in the causative factors may have been entirely dissipated. Moreover, in a community hospital, very few if any such lesions will be encountered in a lifetime. It is perhaps on this precise point that the present writer has been so fortunate, for he has had the opportunity to investigate the unusual lesions of the brain in a series of well over 65,000 autopsies in a large general hospital as well as an additional number (2,800) of coroner's autopsies. The collection of such cases that show the ultimate effects of anoxaemic states in general has been to him not only an opportunity but an obligation to the larger field of clinical medicine. This brief section, then, may be considered as a crystallization of the essential points characterizing the ultimate residual lesions of the anoxic state. Brief reference will also be made to the results of anoxia on experimental animals which fill in some important gaps in our knowledge. The experimental studies may be appropriately cited first.

The ultimate effects on the brain of experimental neonatal anoxia have been carefully investigated by Windle, Becker, and Weil.[14] By an ingenious method of impairment of the uterine blood supply of pregnant guinea pigs just prior to birth of their young, a state simulating paranatal anoxia could be produced. By following a group of these animals for a number of months, some of the ultimate effects of anoxia on the brain were demonstrated. It was observed that atrophy of the entire brain was one of the consequences of this procedure, as would ordinarily be expected. What was not anticipated, however, was that atrophy could also involve only a hemisphere or even a single lobe of the brain.

Their work therefore demonstrates that comparable situations of lobar or hemispheral atrophy as well as total atrophy of the brain could occur as a result of neonatal anoxia. This potential of the anoxic state in the newborn is important, for it is just this group of residual lesions which have been particularly difficult to evaluate in man.

In the writer's series of cases, there were several examples in which lobar and hemispheral atrophy, as well as total atrophy of the brain, had taken place. This change seemed to be the only demonstrable alteration responsible for cerebral palsy and reduced mental acuity.

What has been learned from a study of so many examples of cerebral anoxia of later life that has proven to be of help in the evaluation of the cerebral lesions dating back to birth? In the first place, it becomes clear that certain fundamental alterations, obviously due to anoxia and ischaemia, are observed in the brains of older individuals and these seem to have their counterpart in brain damaged children.[15] This group of lesions constitutes a series of alterations progressing in their simplest form from a mild degree of atrophy of a given group of cerebral convolutions to a widespread nodular cortical change. Next to this lesion, there occurs a more severe degree of cortical atrophy such as is seen in the residuals of occlusive vascular lesions which may result in actual porencephalic defects in the brain.

In the second place, the characteristic cortical change histologically constitutes a second and parallel series, existing in its mildest form in a patchy or laminar loss of nerve cells and progressing with increasing degrees of damage to the intermediate cellular lamina until either a laminar vascular scar (in less severe degree of damage) or a grossly evident laminar cortical necrosis results.

A third observation, one which parallels the cortical alterations, but which does not follow a typical pattern, is a progressive degeneration or actual softening of the lenticular nucleus. The index lesion in this respect is the softening of globus pallidus such as occurs in consequence to a severe exposure to carbon monoxide or other asphyxiant gases.[16]

The fourth observation, one that seems not to have attracted the attention which it deserves, is the tendency for certain types of anoxic disorders to result in regressive changes in the underlying white matter. Following the more severe degrees of anoxia, there results the quite rapid formation of cysts in the cerebral centrum. In a slower evolution of this process, demyelination with gliosis constitutes the ultimate lesion. These lesions can develop only under certain circumstances in which prolonged survival after an anoxic insult is the chief etiological factor. It is observed most often after carbon monoxide and nitrous oxide, and less so after exposure to other asphyxiant gases.

The fifth observation involves the cerebellum more or less diffusely, resulting in a generalized atrophy of this organ, although a few examples of focal atrophy have also been seen. This is not so commonly found after anoxias of adult life, although its basic histological lesion, a diffuse loss of the Purkinje and granule cells, occurs in a wide variety of conditions associated with a circulatory disturbance if not an obvious anoxic state. This particular feature is now under

study in the Cajal Laboratory, and a full report will be forthcoming within the next year or so.

The next observation, one within the fairly characteristic pattern of cerebral responses to lowered oxygen tension, indicates that a considerable variety of lesions may result in a single case, depending upon the mechanism and degree of oxygen deprivation. It is also possible that these changes are owing in part to the length of time the impairment of oxygen supply persists. This fact can be seen by reviewing the possible lesions in the brain which may occur after carbon monoxide "poisoning," one type of anoxia with which most of us are familiar. As the writer has pointed out in an earlier study,[17] it is possible to find (i) diffuse cortical changes with spotty and laminar necrosis, so characteristic of anoxia incident to nitrous oxide, (ii) focal haemorrhage, softening and/or formation in the lenticular nucleus (especially the globus pallidus) which, of course, is the type-lesion of carbon monoxide "poisoning," (iii) selective damage to the Purkinje and granule cells of the cerebellar cortex, (iv) the formation of gross cortical-subcortical softenings, particularly in the parieto-occipital region, (v) the formation of local cortical-subcortical cysts with longer periods of survival, (vi) multiple cyst formation in the cerebral white matter, and finally, (vii) a diffuse demyelination of the cerebral centrum. The important conclusion from this fact is that anoxia *per se* can result in a wide variety of lesions, some which may not be appreciated at all as a residual of this state.

Our seventh observation is a corollary to this fundamental fact, namely that more than one of these lesions may be present in any one case producing thereby a *lesion-complex*. Such a situation can be interpreted properly only by recognizing the individual types of cerebral changes and appreciating that all of them must have an impaired oxygen supply as their genesis. It is also possible that such a complex may result from a combination of the various forms of anoxia (anoxic, anaemic, and histotoxic forms).

ANOXIA INCIDENT TO THE BIRTH PROCESS AS A POSSIBLE CAUSE OF BRAIN DAMAGE IN INFANCY

The misunderstanding of the complex nature of the brain lesions found in crippled children has been due to a failure to see in these well-defined patterns of tissue change the classical hallmarks of anoxia. The first impression of the average investigator is that such lesions must be the result of some unusually complex pathogenetic process and, by inference, must be of congenital, degenerative, or infectious etiology. By applying such etiological labels to this kind of lesion, we excuse ourselves from the necessity of looking further into their causation. But to put the proposed thesis of their anoxic etiology to the test, these various lesion-complexes must be broken down and each of the lesions composing them must be examined with critical scrutiny. It will be logical to start from the more simple lesions and proceed to those which are more complex.

(a) *Widespread cerebral softening in infancy.* This group of lesions is relatively rare, even though the several subvarieties are grouped together. They are

usually, exposed at autopsy in infants who have presented a progressive down-hill course to death from within, the first few months to a year or two of life. The clinical course is characterized by the early onset of convulsive seizures, followed by evidence of defective mentation, and finally by the development of quadriplegias and decorticate rigidities. The less severe lesions consist of a diffuse softening of the cerebral gray matter (Alper's disease). At times, these lesions of the gray matter are associated with subcortical or central cyst forma-tion. In more severe cases, the softening involves both the cortex and sub-cortex.[18] The very localization of the physical alterations in the brain suggests an anoxic etiology. In addition, the author's recent investigation of the problem suggests that their genesis lies in some circulatory disorder occurring at the time of birth.*[19]

(b) *General cerebral atrophies.* The chronic counterpart of this group of lesions may be included under this term of general cerebral atrophies. This term implies that either the cerebrum as a whole, or one hemisphere, is dif-fusely atrophic. The convolutions individually seem to be fairly uniform in diameter but are simply smaller than normal in size. In the cases of the hemi-atrophies, sections from comparative areas in the cerebral hemispheres indicate that the smaller hemisphere is marked by a patchy loss of cortical nerve cells. Even in these presumed hemiatrophies, the larger hemisphere is smaller than that in the average child of corresponding age. This is suggested even during life, for the head of the affected child is inclined to be smaller than average. Roentgenograms of the skull often show a smaller cranial vault on the side of the smaller hemisphere. As a basis for consideration of etiology, the experi-mental work of Windle and his associates[14] gives us the clue in an anoxic episode either just before or at the time of birth. This factor may be of the nature of a lessened circulatory irrigation, although a straight anoxic episode at the time of birth may have taken place. As Windle et al. have demonstrated, it was not unusual to find in their animals what appeared to be a generalized anoxic process, could cause an atrophy of one hemisphere or even a solitary lobe of the brain.

(c) *Focal cortical scars or cysts.* Ford[6] and Penfield and Erickson[7] have pointed out that focal cortical scars or cysts may be the cause of epileptiform convulsions, often characterized by localizing phenomena. When these small lesions are examined microscopically, they prove to have the identical struc-ture of nodular cortical atrophy (or sclerosis), with their characteristic anoxic changes in the cerebral gray matter. These findings suggest that such lesions have their genesis in a mild form of paranatal anoxia, but one in which the secondary and perhaps more obvious ischaemic changes have produced the essential epileptogenic lesions. This aspect of the problem will be considered in greater detail in a subsequent section.

(d) *Cerebellar atrophies.* A great deal of work has been done on atrophy of the cerebellum in the recent past. This work certainly proves that a reduction

*Rarely these widespread cortical lesions undergo a slower process of deterioration with a generalized loss of the parenchymatous elements and with a replacement gliosis; under these circumstances a cortical change designated as a "walnut kernel" brain results

in size of the individual cerebellar folia in many, if not most, cases cannot be laid at the door of cerebral anoxia. But in some cases, cerebral anoxia is indeed the actual cause, This has already been suggested clinically by the group of the so-called cerebral palsied children whose predominant symptom-complex is that of ataxia-atonia. This is also implied by the disclosure by specific examination of the cerebellar tissues in cases whose other lesions are characteristically of anoxic etiology.[19] It would therefore appear that these structural alterations in the cerebellum are present in minor degrees in many instances of cerebral palsy, but in these the suggestive cerebellar manifestations are obscured by the predominant cortical or ganglionic symptoms. Much more study of the accompanying cerebellar changes is necessary to evaluate more completely the unequivocal examples of the ataxic-atonic group.

(e) *The nodular atrophies* (*or scleroses*). The most common basic lesion of the brain in cerebral palsied children is this irregular atrophic and sclerotic change in portions of the cerebral cortex. In fact, a variety of distributions of this change may be found in any large series of cases.[20] Such examples can be compared in all their detail to ischaemic lesions of the cortex in older individuals with arteriosclerosis.[21] This seems to establish without question the pathogenesis of the lesion. But it is also necessary to recognize from other experiences with the anoxic state that oxygen lack may set in motion a degree of vasomotor dysfunction which produces this secondary or ischaemic type of lesion. This may occur either in the form of the epileptic lesions of Ford[6] and Penfield and Erickson,[7] the so-called lobar sclerosis of Bresler,[22] or finally as the diffuse lesions seen in severe cases of nodular sclerosis.[20] This lesion is commonly associated with porencephalic cysts (which are but an advanced degree of the same process), alterations in the basal ganglia, or even cystic formations in the central white matter. These combinations further demonstrate the truth of one of the postulates already set forth to the effect that multiple lesions, all of anoxic etiology, may be found in a single case.

(f) *The ganglionic-cortical lesions.* Still another group of lesion-complexes are those which involve the basal ganglia and, to a lesser extent, the cerebral cortex. The predominant lesion affects various ganglionic structures or sub-ganglionic nuclei so that the outstanding clinical symptom is that of various hyperkinetic states, most commonly that of choreoathetosis. This group of cerebral palsied children are recognized as a separate clinical entity on this basis. The most common lesion seems to be that of status marmoratus, a peculiar change characterized by the presence of an increased number of bundles of myelinated nerve fibers, occurring chiefly within or near the ganglionic masses but involving the cerebral cortex at times. Status dysmyelinisatus (degeneration of the myelinated nerve fibers) is much more rare. Cysts or atrophy affecting the lenticular nucleus are also described. Although the pathogenesis of status marmoratus is still a subject of much conjecture, but possibly due to secondary destruction of cortex in embryonic life,[23] most students of the problem agree that this lesion is a consequence of "birth injury".[24] Because this lesion is so often associated with other changes in the brain characteristic of cerebral anoxia, it seems logical to assume that it also is of an anoxic

(g) *Lesions of the central white matter.* The structural alterations in this group of lesions involving the cerebral white matter have divided the investigators studying these lesions into several camps. As for *gliosis*, the least important of the three, there is perhaps little to say other than its association with so many other lesions of the group here considered speaks strongly in favour of its origin in some diffuse circulatory process such as anoxia. The second lesion described as *chronic infantile cystic degeneration of the cerebral white matter* is believed by a larger portion of investigators to be the result of multiple haemorrhages incident to occlusion of the internal venous system of Galen. The present writer cannot accept this thesis for reasons brought out in a recent publication.[24] Moreover, he has had the opportunity to study a series of three recently born infants whose fatal lesion appeared to consist of a widespread condensation of multiple petechial haemorrhages occupying most of the cerebral white matter.[25] Since multiple haemorrhages into the cerebral centrum are characteristic of acute anoxia under other circumstances, and since in the cases studied there was evidence of an anoxic episode at birth, it seems reasonable to believe that neonatal anoxia may well have been its cause.

As for the third possibility, *diffuse demyelination of the cerebral white matter*, otherwise described as the infantile form of diffuse sclerosis (Schilder's disease), there is still room for uncertainty. Perhaps the greatest reason for doubt lies in the fact that in many cases there is a familial history of this disorder. There is a form which occurs in later childhood and another which develops in later life (Pelazeus-Merzbacher's disease)—still another argument against its genesis in a paranatal anoxic episode. Nevertheless, the fact remains that every detail of the histology of diffuse sclerosis has its exact counterpart in widespread degeneration of the cerebral white matter after serious exposure to carbon monoxide. Therefore, this etiology demands consideration for this possible cause, be it paranatal or otherwise. We are obliged to leave this problem at this point.

A survey of these lesion-complexes associated with, and presumably the cause of, cerebral palsy beginning in early life suggests that in from two-thirds to three-fourths of these patients a paranatal anoxic episode is their most common cause. This conclusion is based on the fact that when these complexes are analysed in the light of the cerebral changes incident to oxygen want of later life, their similarities argue in favour of an anoxic episode. Other changes (the general atrophies) resemble post-anoxic alterations in experimental animals. In still other lesions (status marmoratus) whose pathogenesis is difficult to evaluate, there is a clinical history of "birth injury" in the great majority of instances. As has already been pointed out, the presence of multiple lesions, each of which has been shown to have a possible anoxic etiology, constitutes still another argument in support of this conclusion.

RELATION OF THE ANAESTHETIST TO BIRTH PALSIES

It would be idle to discuss at length the problems of paranatal anoxia without condensing this material into some practical conclusions, for, while many anaesthetists may have an academic interest in the problem of cerebral palsy

because of the connection between anoxia at birth and its clinical consequences, any direct concern must lie in the more practical problems of the administration of anaesthesia to the mother-to-be at the time of delivery. What part, if any, is played by the anaesthetist in the production of anoxic damage to the brain of the newborn child? To the credit of the profession, the answer is "very little, if any." Nevertheless, it is well to review very briefly what the possibilities may be.

In the recent past, there has been an increasing demand on the part of women to be completely emancipated from the pain, if not the consciousness, of child-birth. It would appear as though the would-be-mothers were anxious, not only to be completely free of any discomfort in the process, but also to be completely oblivious to the entire proceedings. In view of this insistence, the obstetrician tends to put pressure on the anaesthetist to give the anaesthetic early, and to maintain it until the procedure is completed. But meanwhile, the evidence has accumulated that the more sedation and anaesthesia that has been administered, the more likely it will be that the infant will be born in a state of apnoea. Moreover, the length of this period of apnoea is proportional to the degree of narcosis produced.[11] It must be recognized that apnoea *per se* is probably not significant in the great majority of cases. But there are, nevertheless, two inherent dangers. The first danger lies in the possibility that, together with the increased depth of narcosis, the intercurrence of some other factor, such as a prolonged or difficult delivery or excessive haemorrhage, may superimpose two situations which add up to a serious degree of anoxia. The second danger lies in the fact that often this additional factor may be totally quiescent clinically so that the birth is presumed to be normal when it is not. This is evident in that in so many cases of cerebral palsy in which the cerebral lesion is unequivo-cally due to anoxia, there is nothing in the birth record to point to the exact causative factor. If the writer's long experience in the problem of paranatal anoxia has any meaning whatever, the most important contribution which he can make to the profession of Anaesthesia is this spectre of "silent anoxia," or hypoxia, if you please, which must reduce the mentality and cripple the limbs of so many of our children. How low the degree of narcosis that one can produce and still accomplish the legitimate purpose of anaesthesia, not how much anaesthesia can be produced and still be able to revive the infant, should be the studied objective. It is not any fear of what may happen to the mother, but a fear of what may happen to the brain of the newborn infant, whose very vulnerable nervous tissues are much more susceptible to the effects of oxygen want, that should be the guiding principle of practice of the art of anaesthesia under these circumstances.

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