EFFECTS OF FOETAL HYPOXIA

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Foetal hypoxia may result in stillbirth or morbidity and mortality in the first days of life, with the possibility of sequelae due to damage to the central nervous system in survivors.

The exact percentage of deaths attributable to foetal hypoxia is not known, while the extent to which it is responsible for mental deficiency and cerebral palsy in later life is even more uncertain. This is due mainly to difficulty in the diagnosis of hypoxia. Although the history of pregnancy and labour may reveal a condition likely to have impaired foetal oxygen supply, the inaccessibility of the foetus until birth means that we are ignorant of the degree or duration of any intra-uterine hypoxia. Diagnostic difficulties persist even after birth, because clinical syndromes in newborn babies are often common to several pathological lesions. To some extent these difficulties are now being met by studies of blood oxygen saturation in the first hours after birth. When sequelae are considered, a further difficulty is that respiratory troubles at birth and impaired neurological function subsequently may both be the result of some handicap to intra-uterine development and not cause and effect.

Before describing the effects of foetal hypoxia it will be useful to recall the main groups of causes. Intra-uterine hypoxia may result from hypoxia of the mother, interference with the function of the placenta or umbilical vessels, or haemolytic disease of the foetus. Hypoxia may develop at birth or afterwards because of intracranial birth trauma, depression of respiration by analgesics or anaesthetics given to the mother in labour, or congenital anomalies of the foetus. The last-mentioned will not be considered further here, but it is usually impossible to separate the effects of hypoxia and birth trauma clinically.

Stillbirths

Among ante-partum stillbirths is a group of cases with pathological evidence of asphyxia in the form of petechiae or ecchymoses on visceral surfaces and, often, massive inhalation of amniotic contents. In about half of these cases, premature

placental separation with severe ante-partum haemorrhage has occurred and it is clear that there was a sudden cessation of the foetal oxygen supply. In the rest of the group the cause of the oxygen deprivation is usually obscure, but there seems very little reason to doubt that death has been due to sudden asphyxia.

In the largest group of ante-partum stillbirths autopsy shows maceration of the foetus only. It has been suggested that the majority of these deaths, many of which are associated with maternal toxæmia, are due to placental insufficiency. This hypothesis implies an inadequate supply of oxygen, as the foetal needs increase as one factor leading to the death of the foetus.

When babies dying during labour or within one hour of birth are considered, another large group is found in which signs of asphyxia are the only pathological findings. With present knowledge it seems justifiable to attribute death to intra-partum asphyxia, because the history usually reveals a condition liable to cause foetal hypoxia, for example, post-maturity (Walker, 1954), labour lasting more than 24 hours, or complications such as intra-partum haemorrhage or prolapsed cord.

The two groups, ante-partum and intra-partum asphyxia, comprise approximately 40 per cent. of all stillbirths.

Neonatal morbidity and mortality

Respiration is not initiated normally when an infant is born in a state of hypoxia. Barcroft's (1946) work showed that hypoxia of the brain altered the respiratory response to peripheral stimuli which initiate respiration under optimal conditions. However, in the past insufficient attention has been paid to the effect of hypoxia on cardiovascular function at birth, and certainly, once the respiratory centre has responded, the cause of persistent respiratory difficulty should be sought in the lungs or circulatory system.

The mildly hypoxic infant is cyanosed after birth and its first gasp usually delayed for one or two minutes; rhythmical respiration may not be established for five or 10 minutes. With more

severe hypoxia the baby may show skin pallor as well as cyanosis (asphyxia pallida) and the muscles are flaccid. A very small number of these infants die without making any respiratory effort, but the rest begin to give irregular gasps, usually delayed for more than 30 seconds after birth. It must be emphasized that infants suffering primarily from intracranial birth trauma show a similar picture.

Clinical progress takes several courses in infants whose symptoms are due primarily to hypoxia. Some babies die after a period of gasping. In others, irregular gasps gradually give place to rhythmical breathing. This often takes 15 to 20 minutes and may be achieved after an hour or more by infants who are kept alive meanwhile with oxygen therapy, for which the intra-gastric route is frequently used at the present time. Once rhythmical breathing is established there may be no further trouble in the neonatal period, but in some cases respiratory difficulty returns, usually within 12 hours of birth. A third group of babies develop rhythmic breathing, but with evidence of persistent respiratory difficulty in the form of grunting expiration and inspiratory recession of the lower ribs and sternum. Other signs are an impaired percussion note over the lungs, diminished air entry and sometimes inspiratory rales. Cyanotic attacks may occur.

The newborn infant has considerable powers of withstanding hypoxia. Cross and Tizard (1956) have shown that there is a marked fall of oxygen consumption in infants breathing 15 per cent. oxygen. There was evidence that some anaerobic metabolism occurred, but this was far from compensating for the fall in aerobic metabolism. These findings explain the clinical fact that the body temperature of hypoxic infants often falls several degrees, even though the environmental temperature is kept at a level which normally maintains a constant body temperature. It appears that this is part of a protective mechanism and attempts to combat the fall of body temperature are contra-indicated.

Premature infants are commonly oedematous. Morison (1952) has pointed out that intra-uterine hypoxia, by impairing circulatory efficiency in the foetus, may lead to oedema which is reflected very imperfectly in the plasma, since water and electrolytes which pass to the extra-vascular space can be replaced from the relatively great reserves in the maternal tissues. Loss of the oedema fluid after birth is difficult, because it does not represent a loss from the infant's blood with associated osmotic pressure disturbance. Further, removal of fluid from the air spaces in the lungs by the pulmonary circulation will be impaired.

Approximately one-third of infants with respiratory difficulty in the first few days of life develop

one or more cerebral signs. These include convulsions, excessive wakefulness, restlessness, irritability when disturbed, shrill high-pitched cry, tense anterior fontanelle and alterations of muscle tone. They are attributable to the effects of hypoxia and carbon dioxide retention on the brain and cerebral vessels, and there is evidence that a raised venous pressure, which can increase cerebrospinal fluid pressure, plays a part in some cases (Bonham Carter, Bound and Smellie, 1956). The occurrence of cerebral signs in hypoxic infants again illustrates the difficulty in distinguishing between intracranial birth trauma and effects of hypoxia clinically.

Many babies survive a period of respiratory difficulty in the early days of life. They are usually the less severe cases and, in general, the greater the birth weight the better the chance of survival. Improvement is gradual over several days and it is true to say that the baby is likely to survive if it has reached the age of four days.

In fatal cases cyanotic attacks increase in frequency and severity with apnoeic periods. Cyanosis becomes persistent and terminally the gasping respirations of severe hypoxia are seen. Death usually occurs before the end of the third day. At autopsy three lesions are found commonly: the pulmonary syndrome of the newborn (Bound Butler and Spector, 1956), intraventricular haemorrhage or pneumonia.

The pulmonary syndrome, which is found much more frequently in premature infants and is particularly liable to follow delivery by caesarean section, is the commonest finding. It is recognized by microscopical examination of the lungs, which shows resorption atelectasis with one or more of the following: hyaline membrane, intra-alveolar haemorrhage and pulmonary oedema. The mode of production of these lesions is not yet clear, but disturbance of cardiovascular function is probably of major importance. Bonham Carter (1957) has reviewed recent research, which suggests that, firstly, alveoli are expanded initially by distension of pulmonary capillaries with blood as well as by the respiratory effort and, secondly, where the peripheral pulmonary vascular resistance is very high, probably due to asphyxia, a high cardiac output, dependent on a high venous pressure, is necessary to overcome it so that the pulmonary capillaries are adequately filled with blood. He suggests that in the pulmonary syndrome peripheral vascular resistance in the lungs rises with increasing asphyxia until the cardiac output cannot overcome it, and so the alveoli are never properly expanded. Patency of the ductus arteriosus, which persists or recurs with hypoxia, may play a part if the direction of blood flow is from pulmonary artery to aorta, so that blood normally used to

distend pulmonary capillaries is diverted. A diminished blood volume is probably another important factor, as suggested by Gunther (1957). She confirmed that usually substantial amounts of blood are transferred to the baby from the placenta if the cord is left untied, but showed that babies born by caesarean section, for example, often gain little due to the baby being held higher than the placenta and other factors.

Intraventricular haemorrhage is confined to premature babies and often accompanied by evidence of the pulmonary syndrome, in which case the bleeding may be due to hypoxia secondary to the lesion in the lungs.

Pneumonia occurs in full-time or premature babies and is an important sequel of hypoxia to note, because it should be preventable. It is wise to give wide-spectrum antibiotics for three days to infants who have shown distress during delivery or have been slow to establish normal respiration and needed resuscitation after birth. It has been shown that such a policy reduces the number of neonatal deaths attributable to pneumonia.

It must be understood that the three pathological lesions mentioned may arise from causes other than hypoxia. However, at the present time it appears that hypoxia is responsible for about 50 per cent. of deaths in the first week of life.

Sequelae

Studies of the effects of foetal hypoxia on later cerebral function have not given consistent results and some possible reasons for this have been mentioned already. A few examples will illustrate the difficulty of making definite statements about prognosis with our present knowledge.

Lilienfeld and his associates (1951, 1954, 1955) have used the retrospective method of selecting groups of abnormal children and tracing the history of the pregnancy and delivery in those cases. The first study showed that mothers of children with cerebral palsy had significantly more complications of pregnancy and labour and prematurity than the population of births from which they were derived. In two further studies similar results were obtained for cases of epilepsy and mental deficiency, using for a control series the next birth to that of an abnormal child from the same place matched for race and maternal age group. In the last two investigations the history of the infant's neonatal condition was also considered and a significant increase of abnormalities (convulsions, cyanosis and asphyxia) was found. In viewing the specific maternal complications, it was noted that those more prone to produce foetal anoxia, such as toxæmia and bleeding in pregnancy, were more important than difficulties in delivery. In this connection it is interesting that MacKay (1957)

has shown that in pre-eclampsia the cord oxygen levels are lower than those found in normal pregnancies and that the order of the reduction was related to the duration and severity of the disease. On the other hand, as far as premature children are concerned, Douglas (1956) found that those resulting from uncomplicated pregnancies had considerably greater handicaps in mental ability than those from pregnancies in which there was a history of toxæmia, ante-partum haemorrhage or induction of labour.

Other investigations have been concerned with the follow-up of groups of infants who were asphyxiated at birth. For example, Darke (1944) found that infants who had shown asphyxia pallida or been apnoeic for three minutes or longer after birth, with no physical evidence of injury then or following, had significantly lower intelligence quotients than a control group consisting of their siblings or parents. On the other hand, Campbell, Cheeseman and Kilpatrick (1950) found no evidence that asphyxia neonatorum was a common cause of later mental or physical retardation. They studied cases of asphyxia pallida or asphyxia livida lasting more than two minutes and used infants whose births were recorded immediately before and after each case as controls.

Recent investigations have used blood oxygen saturation as an objective measure of the infant's condition at birth. Aggar and her colleagues (1955) found no significant relation between blood oxygen levels in the first three hours of life and intelligence as tested in early childhood. Other studies are in progress.

Thus at the present time it is not possible to make a dogmatic statement about the prognosis of foetal hypoxia. However, while severe or prolonged hypoxia may damage the central nervous system, it is probably true to say that, in general, the outlook for infants who have undergone a period of hypoxia during or shortly after delivery is much better than was thought at one time.

In practice the clinician needs guidance on the prognosis of the particular infant who has established normal respiration only with difficulty. Craig (1950), considering cases of 'intracranial irritation,' found that it was rare for survivors who showed no signs of residual disability in the neonatal period to develop sequelae. The following features justify an optimistic view of babies who have required resuscitation at birth, or shown respiratory difficulty with or without cerebral signs in the first days of life. The baby sucks well and sleeps unbrokenly between feeds, there is no twitching, the tension of the anterior fontanelle is normal, the muscles are neither hypertonic nor hypotonic, and the infant lazily stretches his limbs at times; the Moro reflex is normal.

Conclusion

Foetal hypoxia is responsible for a large proportion of stillbirths and neonatal deaths and considerable morbidity in the neonatal period.

Prevention of the conditions which cause hypoxia must be the ultimate aim and progress is being made. In the meantime, much work is needed on the mechanisms by which hypoxia leads to neonatal morbidity and death, so that better treatment for infants with respiratory difficulty after birth can be devised.

The prognosis of foetal hypoxia is not yet clear, but it appears likely that the risk of impaired neurological function in later life is small in most cases.

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