Pathology of perinatal hypoxia

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At birth the newborn infant is required to make an abrupt adjustment to a new environment. The most immediate changes required to support extrauterine life are concerned with respiration and the circulation. The infant must be able to expand its lungs fully and at the same time the pulmonary circulation must be adequate for gaseous exchange to occur between the air spaces and the pulmonary capillaries. Even the mature infant may have some difficulty in making the adjustment and this becomes an even greater problem in the case of the premature baby. In many instances there may be no apparent cause for the interruption of the pregnancy and the infant is inherently healthy but is under 2500g birthweight. In some pregnancies, however, maternal factors such as preeclampsia or antepartum haemorrhage may be the cause of premature delivery and the infant, as well as being premature, may also be hypoxic at birth.

Severe accidental haemorrhage may result not only in premature delivery but also in stillbirth or intrauterine death (Claireaux, 1954). Interruption of the placental circulation for any reason is a potent cause of intrauterine hypoxia and its effect on the fetus may vary from distress to intrauterine asphyxia. The im-

portance of hypoxia as a factor in perinatal mortality is shown in the table (Chamberlain *et al*, 1976). The figures indicate that the main cause of perinatal loss is still intrauterine hypoxia resulting in stillbirth and this factor is also responsible for a considerable number of deaths in the first week of life. The respiratory distress syndrome and intraventricular haemorrhage are also prominent features in perinatal mortality and both are associated with hypoxia in the newborn infant.

Stillbirths

The fetus may be fresh or macerated in accordance with the time at which interruption of the placental circulation took place. The pathological changes are more easily demonstrated in the fresh than in the macerated fetus but examination of the latter should not be omitted on this account. Both macroscopic and histological lesions can be found in the macerated fetus as well as in the fresh stillbirth.

Abnormalities such as a short cord or a cord wound round the neck should not in themselves be taken for evidence that the fetus was suffering from hypoxia. A prolapsed cord at the time of delivery is

Order 1970	Major Anatomical Findings	Singletons and Twins 1970			Singletons and Twins 1958			Order 1958
		No. of Cases	% All Deaths	Incidence Per 1000 Deliveries	No. of Cases	% All Deaths	Incidence Per 1000 Deliveries	
1	Stillbirths with IU asphyxia	104	26.3	6.1	709	29.9	10.0	1
2	Congenital malformation	85	21.5	5.0	357	15.1	5.0	3
3	Stillbirths without anatomical lesions	59	14.9	3.4	364	15.4	5.1	2
4	Respiratory distress syndrome	54	13.7	3.1	216	9.1	3.1	4
5	1st week deaths with IU asphyxia	30	7.6	1.7	101	4.3	1.4	6
6	Immaturity	27	6.8	1.6	—	—	—	—
7	Blood group incompatibility	11	2.8	0.6	95	4.0	1.3	7
8	Intracranial birth trauma	7	1.8	0.4	210	8.9	3.0	5
9	Intraventricular haemorrhage	7	1.8	0.4	57	2.4	0.7	11
10	Massive pulmonary haemorrhage	3	0.8	0.2	63	2.7	0.9	10
11	Pneumonia	2	0.5	0.1	95	4.0	1.3	8
12	Extrapulmonary haemorrhage	2	0.5	0.1	7	0.3	0.1	12
	1st week deaths	—	—	—	—	—	—	—
	No anatomical lesions	—	—	—	65	2.7	0.9	9
13	Miscellaneous	4	1.0	0.2	29	1.2	0.3	13
	Total	395	100.0	23.0	2368	100.0	33.1	

Table Major anatomical findings in perinatal deaths according to a British births survey in 1970 and a perinatal mortality survey in 1958

another matter. If such a cord becomes nipped between the fetal head and the maternal pelvis the blood flow to the fetus may suddenly and completely cease and the latter dies. Unfortunately, there is often a lack of any obvious pathological lesion demonstrable at necropsy.

The single catastrophe which will result in pathological changes being found in the fetus is severe accidental haemorrhage—abruptio placentae. At necropsy widespread petechial haemorrhages are found in both the visceral and parietal pleura. The whole lining of the chest and the upper surface of the diaphragm may be studded with these haemorrhages. The lungs are also covered by petechiae or even small ecchymoses. At histological examination the haemorrhages are largely subpleural and interstitial but in some instances focal intraalveolar haemorrhage is also seen (fig 1).

If the hypoxia develops in utero before the draining of the liquor amnii the infant will tend to aspirate large quantities of fluid and amniotic debris into the lungs. At necropsy this can be expelled from the cut

Fig 1 Lung of stillborn fetus showing subpleural haemorrhage.

Fig 2 Lung of stillborn fetus showing aspiration of liquor amnii.

Fig 3 Lung of stillborn fetus showing aspiration of meconium.

surface like a grey-white milk. On histological examination squames and other debris are found in the alveoli (fig 2). In other instances the anal sphincter will have relaxed and meconium released into the amniotic sac. This also may be aspirated, either as a viscid paste which blocks the bronchial tree completely or as an emulsion with liquor amnii which is sucked down into the respiratory bronchioles and air sacs (fig 3). Occasionally this form of aspiration has occurred sufficiently long before delivery for a pneumonia to develop (fig 4). This is the so-called intrauterine type of pneumonia. It is not always possible to culture organisms from the lungs in these cases.

Other organs affected by intrauterine hypoxia are the brain, the liver and the thymus. In the brain in the mature fetus small perivascular haemorrhages may be found in the white matter and cerebral nuclei (fig 5). Subcapsular haemorrhages may be found over the surface of the liver, particularly in the premature infant. Occasionally a large, single, subcapsular haemorrhage is found over one or other lobe (fig 6). These may rupture at the time of delivery, particularly if the fetus presents by the breech and a haemorrhage occurs in the interstitial and subcapsular connective tissue of the thymus.

Birth trauma

Severe birth trauma at delivery resulting from pronounced cephalo-pelvic disproportion is now exceedingly rare. Birth trauma as a cause of perinatal death has declined markedly in recent years (table). The main necropsy finding in cases classified under this heading is subdural haemorrhage with or without tears of the falx cerebri or tentorium cerebelli. In most instances nowadays the death should be classified as 'birth trauma—hypoxia' rather than simply as birth trauma. The fetus or infant concerned has almost invariably suffered from pronounced fetal distress before delivery. Forceps have been applied and delivery effected with the minimum of trauma. At necropsy a subdural haemorrhage is found. The hypoxia which occurred during the time when the fetus was distressed resulted in engorgement of the cerebral venous system. The cerebral veins and venous sinuses are distended and are liable to rupture in response to relatively minor injury. This is particularly the case in respect of the great cerebral vein of Galen. This vein is 1 cm long and is entirely unsupported throughout its length. When it ruptures blood is found in the subdural space over the posterior half of the cerebral hemispheres and also in the posterior fossa beneath the tentorium. Injury to this vein and resultant severe haemorrhage may be the only necropsy findings. Tears of the falx or tentorium

which may also rupture venous sinuses are not usually found in these circumstances.

Neonatal deaths

Whether the distressed infant dies some time before delivery, at delivery, or a few minutes or hours after delivery does not greatly affect the postmortem findings except for the additional complication of maceration in the earlier intrauterine deaths. Thus the lesions already described in the fresh stillbirths are those likely to be found in the infant who dies as a result of hypoxia shortly after delivery.

The infant, particularly the mature infant who survives for a day or two, may show additional lesions at necropsy. Aspiration of meconium or liquor may be uneven and some parts of the lung may be able to expand at birth while others have blocked airways. Expandable lung may overexpand, either as a result of the infant's own efforts or the resuscitative zeal of the attendants. Interstitial and subpleural bullae may form (fig 7). The latter may rupture with the formation of a pneumothorax which may be unilateral or bilateral. The presence of meconium or liquor in the lungs facilitates the growth of microorganisms and a pneumonia may develop.

The premature infant poses special problems. The cause of the prematurity may have been the result of maternal preeclampsia or placental separation, in which case the pathological changes may be similar to those already described. In the majority of instances, however, no specific cause of premature delivery can be found. In these patients hypoxia results not from inadequacy of the fetal blood supply before delivery but from a failure to achieve adequate respiratory performance after birth. These infants are unable to promote gaseous exchange between the air in their alveoli and the blood in the pulmonary capillary bed. In the case of the very premature infant (under 1000 g birthweight), sometimes called the 'immature', the lungs are not yet ready to support extrauterine life, the potential air spaces are still lined by cuboidal epithelium and separated from one another by a primitive mesenchyme (fig 8). According to Morison (1970), oedema fluid may escape from the lung capillaries and displace air from adjacent air spaces. This tends to increase hypoxia and progressive pulmonary oedema may develop into a vicious circle.

In the less immature but still premature infant (1200-2500 g birthweight) respiration may be established with some difficulty but the infant throughout its short life suffers from severe respiratory distress. At necropsy the lungs show widespread atelectasis with overdistension of respiratory bronchioles and collapse of distal air spaces. The respiratory bron-

Fig 4 Lung of macerated fetus with pneumonia.

Fig 5 Brain showing focal haemorrhage.

Fig 6 Liver showing subcapsular haemorrhage.

Fig 7

Fig 7 Lung of newborn infant with emphysema.

Fig 8 Lung of premature infant with atelectasis.

Fig 9 Lung of premature infant with hyaline membrane formation.

Fig 8

Fig 9

chioles are often lined by a thick, acidophil, hyaline membrane (fig 9). Membrane formation is to some extent related to the time which has elapsed between delivery and death of the affected infant. It is excessively rare if death occurs within one hour of delivery but is quite common in infants dying between six hours and 36 hours after birth.

Infants with severe respiratory distress may die as a

result of poor pulmonary function but quite a high proportion succumb on account of severe intraventricular and subarachnoid haemorrhage. At necropsy the ventricular system contains a large amount of blood clot and fresh blood (fig 10). Blood is also found in the cisterna magna and subarachnoid space over the cerebral hemispheres and cerebellum. When the blood clot is removed from the lateral ventricle

Fig 10 Brain of premature infant showing intraventricular haemorrhage.

the source of the haemorrhage is seen to be caused by bleeding into the germinal layers of the subependyma over the caudate nucleus. These subependymal lesions eventually rupture into the cavity of the lateral ventricle and cause the massive intraventricular haemorrhage. At one time it was believed that the vessels involved belong to the *venae terminales* of the vein of Galen system (Claireaux, 1963). More recently Hambleton and Wigglesworth (1976), using injection techniques, have suggested that the capillaries in the germinal layer supplied mainly by Heubner's artery, a branch of the anterior cerebral artery, may rupture as a sequel to hypercapnia and hypoxia in the patient. In addition to haemorrhage, venous thrombosis has been reported (Larroche, 1964). This finding, however, tends to be inconstant and is not the prime cause of intraventricular haemorrhage.

Severe intraventricular haemorrhage is a spectacular lesion, occurring mainly in the premature infant which is likely to cause almost instantaneous death. Less obvious lesions caused by hypoxia and affecting the cerebral hemispheres or brain stem have been reported (Smith *et al*, 1974). Their 11 patients were all in the 750 to 2000 g birthweight range, ie, were delivered prematurely. In seven of these infants no maternal cause was found. There was one example each of preeclamptic toxemia, rhesus isoimmunization, concealed accidental haemorrhage and abruptio placentae among the remaining four patients. In all but one patient there were focal lesions in the grey and white matter which were hypoxic or ischaemic in origin. Their extent and severity was variable. In some, neuronal karyorrhexis in the grey matter of the

brain stem suggested that the hypoxic damage had occurred in the last few days of life. Other lesions included subependymal haemorrhage, periventricular leucomalacia, periventricular haemorrhage and cystic encephalomalacia.

Hypoxic damage to the brain, if severe, is likely to cause death in the perinatal period. Less severe damage may be consistent with survival for a few weeks or even months after delivery. Necropsy findings in these older infants will include changes which have become superimposed on those present shortly after birth. Thus periventricular leucomalacia may be followed by gliosis (Banker and Larroche, 1962) and milder forms of intraventricular haemorrhage may lead to hydrocephalus as a result of organization of blood in the meninges (Smith *et al*, 1974). The later clinical effects of severe hypoxia at birth have been studied by Scott (1976) who showed that neurological abnormality was associated with prolonged intrapartum hypoxia while short periods of more complete asphyxia were not necessarily damaging.

The intracranial lesions associated with hypoxia which are liable to result in perinatal death are now well documented. Less severe lesions which are consistent with survival into childhood have been studied less fully and are worthy of further investigation.

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