Virchows Archiv [Pathol Anat] (1981) 394:1–29

Virchows Archiv A

Review Article

Iatrogenic Disease in the Newborn

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Summary. The role of intrapartum asphyxia and cerebral birth trauma as an important cause of perinatal mortality is well known and its contribution to perinatal morbidity as a cause of cerebral palsy is widely appreciated. This has led to more careful monitoring of pregnancy and labour, although monitoring techniques are not without hazard. The widespread availability of intensive care facilities for the newborn has resulted in the survival of many infants, particularly those of low birth weight, who might previously have died. Efficacious modes of treatment may, unfortunately, bring in their wake serious problems in the form of iatrogenic disease which may cause or contribute to rapid demise or whose effects may not be fully apparent for many years. Ante natal investigations have also become frequently used and have their own hazards.

Key words: Iatrogenic disease – Intensive care – Neonate.

Introduction

It is important that the pathologist play his part in the recognition of and recording of iatrogenic lesions in the newborn, in doing so he makes an important contribution to safe and effective management of the sick neonate. Over the past two decades, practices in neonatal intensive care have undergone considerable modification and revision as a result of the recognition of the potentially damaging side effects of some forms of treatment. The need for more effective, non-invasive monitoring techniques has provided the stimulus for the evaluation and incorporation of recent advances in science and engineering into the nursery and to more critical and continuous appraisal of neonatal management by the clinician.

Although this review is largely concerned with iatrogenic disease produced in neonatal intensive care, it also examines abnormalities occurring as a result of new forms of ante-natal and obstetric monitoring which may give rise to problems in the

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0340-1227/81/0394/0001/$06.00

perinatal period. I shall also review some of the hazards of breech delivary but for accounts of classical cerebral birth injury refer the reader to Fedrick and Butler (1971) and Pape and Wigglesworth (1979).

Amniocentesis

Amniocentesis is a method of investigation which has become widely used in recent years, performed for cytogenetic, metabolic and α feto-protein studies, in the management of pregnancies of Rhesus negative women with antibodies and, near to term, to examine lecithin/sphyngomyelin ratios to determine foetal lung maturity. During the second trimester this procedure may be complicated by fetomaternal haemorrhage, retroplacental bleeding or chorioamnionitis provoking abortion (Robinson et al. 1973), although one large study suggests that these problems occur with similar frequency in women not so investigated (NICHD Study Group 1976). Leakage of amniotic fluid may persist for many weeks following amniocentesis and may be followed by the premature onset of labour, perhaps provoked by chorio-amnionitis developing some weeks after the procedure. The pregnancy may also proceed towards term and the resulting fetus, subject for many weeks to intra-uterine compression from iatrogenic oligohydramnios may have many of the stigmata of the Potter syndrome, including squashed facies and flexion deformities of limbs, despite adequately functioning kidneys. It may succumb to respiratory insufficiency due to pulmonary hypoplasia induced by this oligohydramnios.

Direct injury to the fetus complicating amniocentesis in the second trimester is uncommen but is more frequently seen following intra-uterine transfusion or following amniocentesis closer to term. A variety of injuries have been described including bowel obstruction and fistulae, laceration of organs, cardiac tamponade or pneumothorax, occular injury, injection of radio-opaque dye into the fetus and porencephaly (Creasman et al. 1968; Youroukos et al. 1980).

Monitoring

Fetal cardiotocographic monitoring during labour is now used extensively and monitoring frequently done by means of a clip attached to the fetal scalp. These may produce perforation of the periosteum and subperiostial haemorrhage. These injuries are a site of potentially serious neonatal infection, which may be acquired intra partum.

The potential of breech delivery for producing cerebral anoxic damage is well known, however, there are other hazards of this manoeuvre which should be borne in mind. The increasing efforts made to salvage infants born prematurely results in more survwors of breech delivery, which is commoner in the premature. Spinal cord injury may follow breech delivery if the neck is over-extended, either as the result of direct injury to the spinal cord or anoxic damage mediated by injury to the cervical portions of the vertebral arteries (Yates 1959). Occipital osteodiastesis may occur during breech delivery, the lower part of the occipital bone being dislocated inwards, resulting in catastrophic haemorrhage from damage to venous sinuses overlying the suture line (Wigglesworth and Husemeyer 1977). Bruising of skin and

muscles of the trunk and lower limbs during breech delivery may be so extensive as to produce anaemia or jaundice.

Other hazards of breech delivery which are not immediately apparent but may produce problems later are interstitial testicular haemorrhage and pituitary ischaemic damage. Dunn (1975) drew attention to the extensive interstitial haemorrhage in the testis following breech delivery and suggested that infertility might result. Rona and Tanner (1977) describe a higher incidence of breech presentation and forceps delivery amongst infants with growth hormone deficiency when compared with the frequency of these events in the 1958 British Perinatal Mortality Survey. These authors consider breech delivery to be an indication of previous abnormality rather than the direct cause of growth hormone deficit, but Piccolo et al. (1979) reviewed the perinatal histories of their patients with growth hormone deficiency and found a much higher incidence (19.6%) of breech presentation when compared with a control group (1.6%) and postulated a causal relationship between perinatal anoxic damage to the pituitary and subsequent growth hormone deficiency.

Damage Produced in Ensuring Adequate Respiratory Functions

Many iatrogenic lesions in the neonate are related to the importance of maintaining adequate tissue oxygenation and, following the realisation that a persistently high pO_2 may produce retrolental fibroplasia and blindness (Conference on Retrolental Fibroplasia 1955), the necessity to maintain the infants pO_2 within the narrow limits of adequacy and safety. Ventilation of the premature infant with severe respiratory distress is a life-saving manoeuvre which may be required for some days or even weeks. It is at present the accepted method of management, although the prospect of surfactant replacement may curtail the need for long term ventilation in the future (Morley et al. 1981). The hazards of ventilation may be conveniently considered in three groups; those directly attributable to contact with the apparatus by which ventilation is effected, those resulting from the pressure of the gases used and those related to the gas mixture itself.

The skin of the preterm infant is not as well keratinised as that of the term infant or adult and is thus very sensitive to damage by pressure or friction and unsightly excoriation may be produced around the nose or mouth by contact with endotracheal tubes or face mask. Although injury of this sort is not lifethreatening it may induce considerable parental anxiety. More serious is the damage which may be produced in the larynx or trachea. In the larynx acute ulceration of the vocal cords and subglottic region is a frequent complication of long term ventilation. In cases where the damage is superficial, healing occurs without sequelae, but where there is extensive fibrosis, subglottic stenosis may result from shrinkage of fibrous tissue and may necessitate tracheostomy or plastic repair of the larynx. Further down the airways shallow ulcers healing by squamous metaplasia of the columnar epithelium, may occur in the anterior wall of the trachea where there has been contact with an endotracheal tube. Sometimes the anterior half of the trachea has its normal ciliated, mucus producing columnar epithelium completely replaced by squamous epithelium (Fig. 1) which may interfer with bronchial toilet and thus predispose to pulmonary infection. Perforation of the trachea (Reynolds and

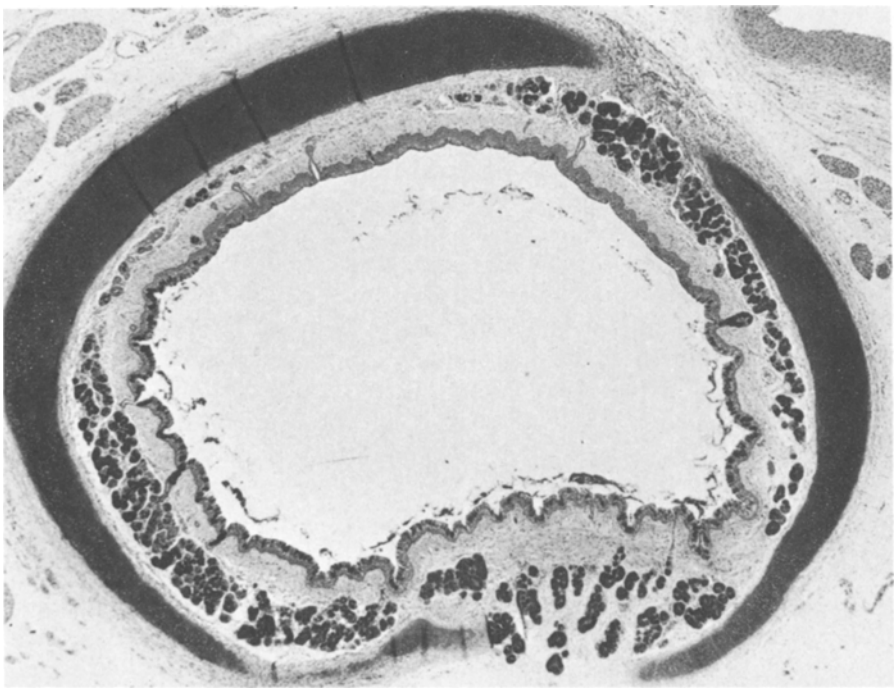

Fig. 1. Cross section of trachea. Anterior part of the epithelial lining shows squamous metaplasia with loss of goblet cells. H.E. ×25

Taghigadeh 1974) and oesophagus (Clarke et al. 1980) are infrequent complications of endotracheal intubation.

The second group of problems associated with ventilation are those resulting from the pressure of the gases necessary to permit adequate gas exchange which increases with decreasing lung compliance. Immature lungs are fragile and interstitial leakage occurs readily. Gas accumulates along the interlobular septa and beneath the pleura (Figs. 2, 3) and can be seen on inspection as small bubbles beneath pleura at necropsy. Larger amounts of gas may accumulate in the interlobar fissures or track into the anterior mediastinum and the subcutaneous tissues of the neck, or may extend downwards accumulate in the retroperitoneal tissues. Occasionally, large amounts of gas may accumulate in the interstitial tissues of one lobe (Figs. 4, 5) producing mediastinal shift and further embarrassment of ventilation; large accumulations of gas may fail to undergo resorption and thus necessitate lobectomy (Drew et al. 1978).

A common sequel of interstitial emphysema is pneumothorax (Fig. 6). The frequency of pneumothorax differs between units and is related to the type and pressure of ventilation and probably to the admissions policy of that particular unit. It complicated the course of 13.4% of 209 consecutive admissions to one unit (Moessinger et al. 1978) and is reported in 28% of infants receiving intermittent positive pressure ventilation (I.P.P.V.) for hyaline membrane disease reviewed by Lindroth et al. (1980). The development of pneumothorax is a life-threatening complication in the infant with hyaline membrane disease and requires immediate percutaneous drainage. The use of chest drains is not without hazard however and

Fig. 2. Interstitial emphysema involving both lobes of left lung. Multiple air bubbles can be seen beneath the pleura. There is a larger accumulation of gas at the hilum on the right. The tip of the chest drain protrudes through the lower edge of the left upper lobe

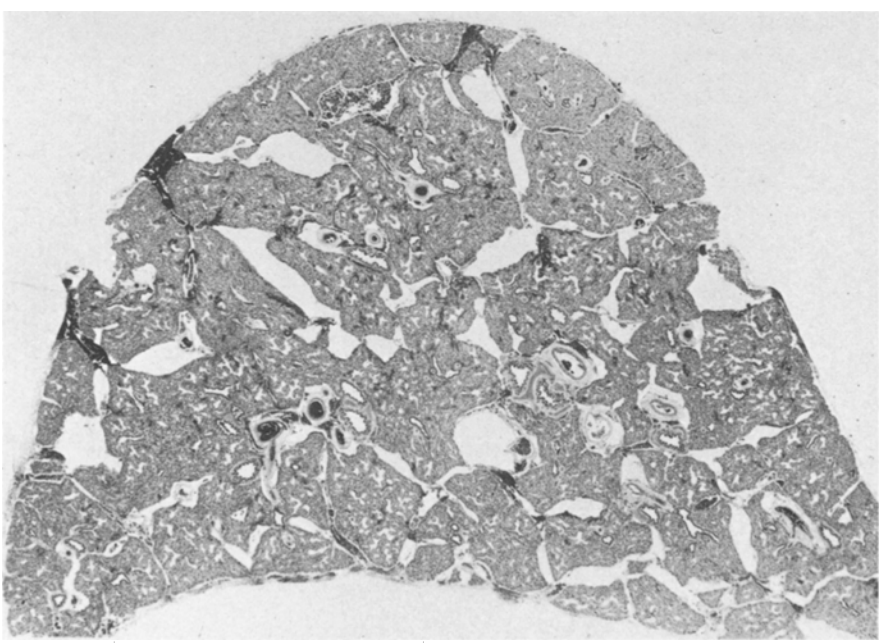

Fig. 3. Complete section through lobe of lung shows accumulation of gas round vessels and airways and along interlobular septa. Tear in pleura is an artefact. H.E. $\times 10$

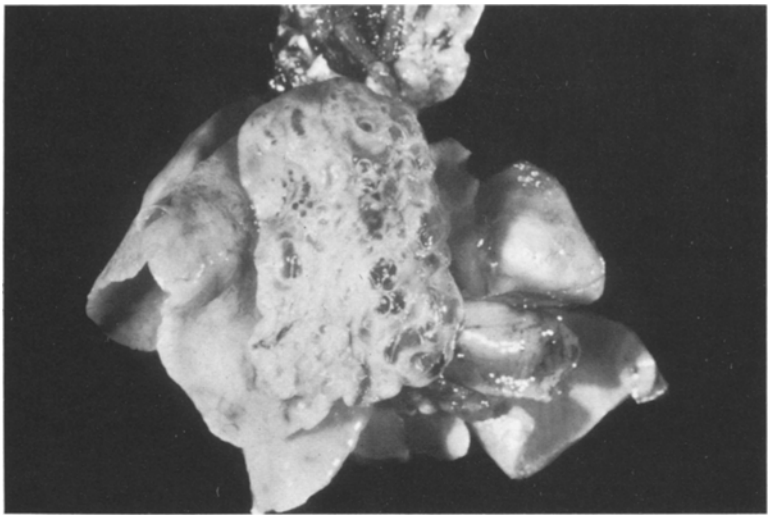

Fig. 4. Large accumulations of gas are seen beneath the pleura of the upper lobe. Lower lobe is not affected

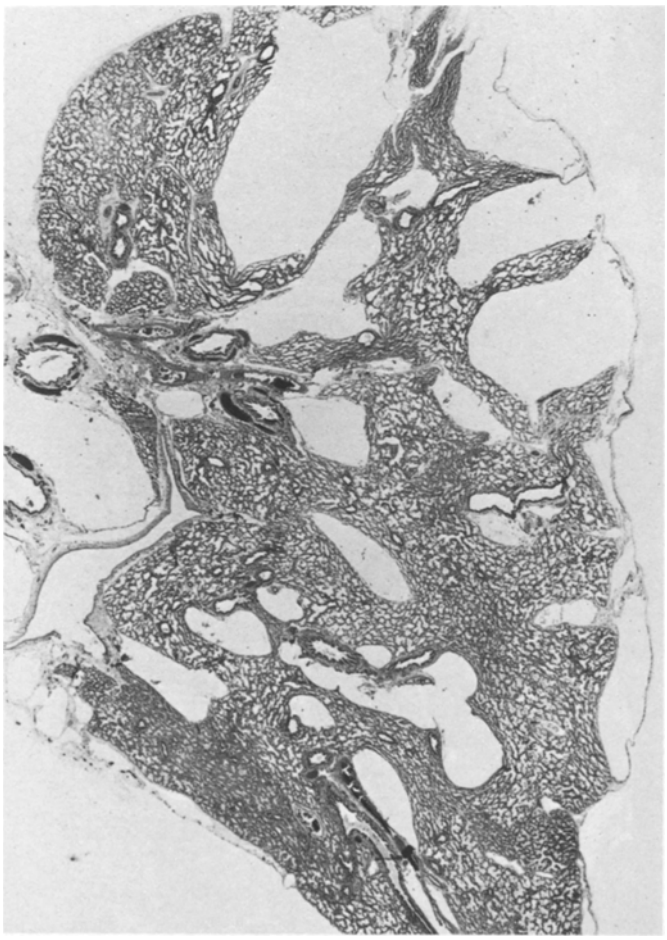

Fig. 5. Section through that lobe shows distortion of the lung architecture by large accumulations of gas in interlobular septa and beneath the pleura with compression of surrounding lung. H.E. $\times 10$

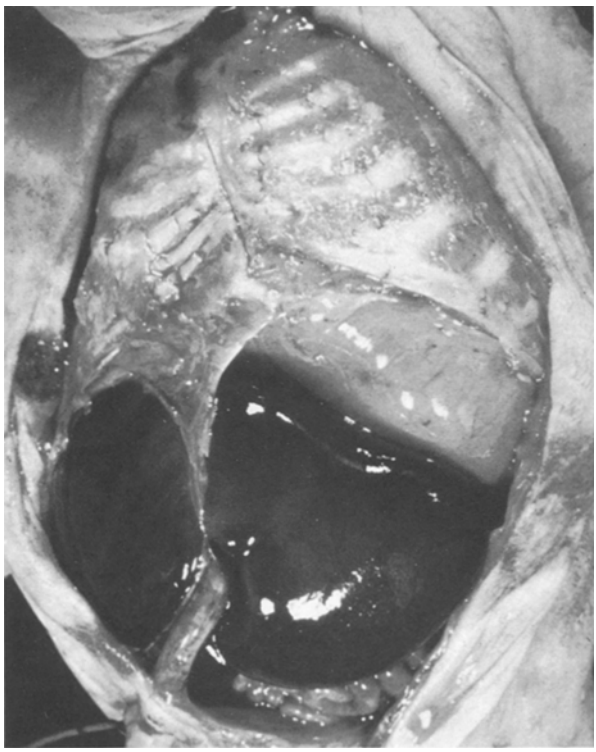

Fig. 6. A large left sided pneumothorax had pushed the diaphragm down on that side. Note the marked asymmetry of the chest which may be apparent on inspection before commencing dissection

the lung may be perforated by the drain (Fig. 7). The frequency of perforation depends on the type of drain used, the use of a metal trocar during siting of the drain and the experience of the operator. One paper reports a frequency of lung perforation of at least 25% in infants whose hyaline membrane disease was complicated by pneumothorax (Moessinger et al. 1978).

Premature infants who develop severe hyaline membrane disease requiring continuous ventilation with high concentrations of oxygen at high pressures and who survive longer than one week are very likely to develop bronchopulmonary dysplasia (B.P.D.). This was first described by Northway et al. (1967) in infants following ventilator therapy for hyaline membrane disease. A spectrum of morphological and histological appearances is seen in the lung depending on the length of survival. The effect of these changes on pulmonary physiology is a progressive loss of compliance, an increase in the pO_2 required to maintain tissue oxygenation and pulmonary hypertension. In the early stages the naked-eye appearance of the lungs differs little from that of classic hyaline membrane disease except that the lungs are slightly bulkier and interstitial oedema makes interlobular septa prominent. The histological appearance at this time is one of widespread necrosis of small airways epithelium followed by healing with loss of ciliated epithelium, pseudostratification and squamous metaplasia (Fig. 8) together with an

Fig. 7. Unexpanded lung of hyaline membrane disease. A perforation made by the chest drain is seen close to the lower border of the right lower lobe

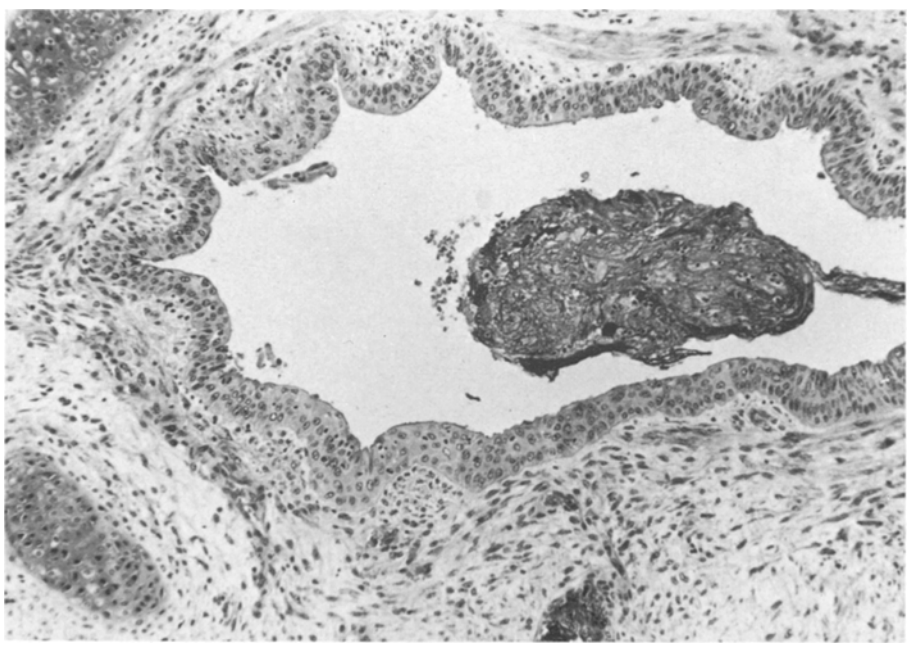

Fig. 8. Squamous metaplasia of bronchial epithelium. Lumen contains mucus. H.E. ×195

increase in thickness in alveolar walls with increased cellular infiltration, macrophages being particularly prominent. Shreds of organising hyaline membrane are seen lining airways. There is interstitial oedema and small lymphatics are often dilated. Later, the lungs increase in volume and come to fill the chest so that there may be linear identations from contact with the chest wall, particularly

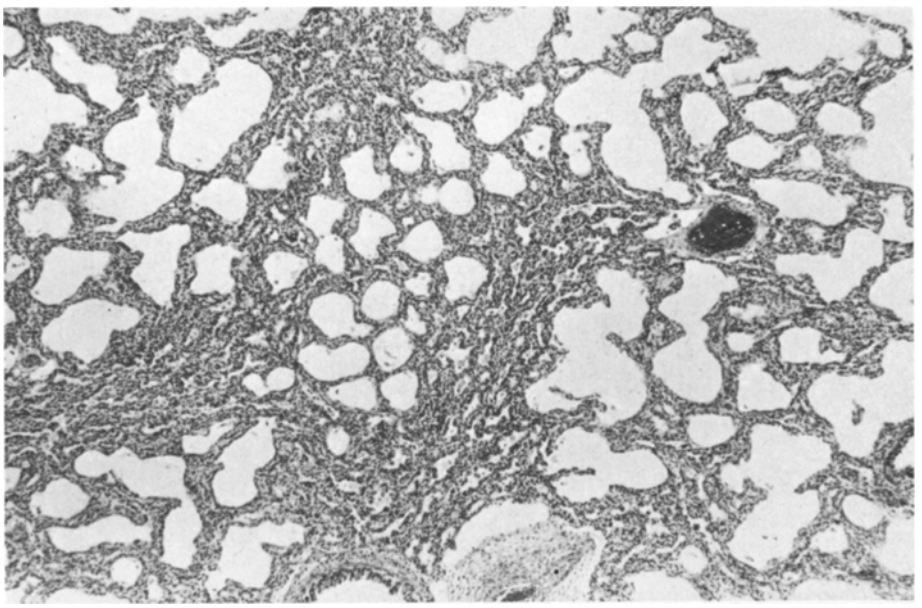

Fig. 9. Areas of overdistention of terminal airways alternate with patchy collapse. Interlobular septa are diffusely thickened. H.E. × 80

noticable on the upper lobes posteriorly. Interlobular septa may retain prominence but by this time the striking macroscopic abnormality is one of a lobular distribution of over-distension (Fig. 9), gas filled air spaces being visible as small bubbles through the pleura alternating with lobules which are collapsed (Fig. 10). Microscopically, fibroblasts are prominent in the alveolar walls and reticulin and later collagen fibres are laid down. The alveolar lining cells are prominent and cuboidal with strikingly eosinophilic cytoplasm (Fig. 11) electron microscopic examination shows these cells to be granular pneumocytes (Bonikos et al. 1976). The microscopic appearance of over-distended lobules with rounded air spaces contrasts with collapse of surrounding lung (Fig. 9). Muscular hypertrophy and fibrosis develops in the walls of small airways. There may be pooling of secretions in alveoli which predisposes to infection. Pulmonary hypertension with right ventricular hypertrophy and patency of the ductus arteriosus are seen in long survivors.

Ever since Northway et al. (1967) described the chronic lung damage which could complicate hyaline membrane disease, iatrogenic factors have been freely implicated in the aetiology of this condition, although there is still dispute about the relative importance of various factors and their inter-relationships. Edwards et al. (1977) drew attention to the differences in history and clinical signs between infants with hyaline membrane disease who survived without B.P.D., those infants whose hyaline membrane disease was complicated by B.P.D. and those who died, usually shortly after birth, without developing B.P.D. He noted that the cases formed a continuum.

The aetiological factors implicated in B.P.D. are the use of endotracheal tubes, ventilation at high frequency and pressures, and the use of oxygen in high

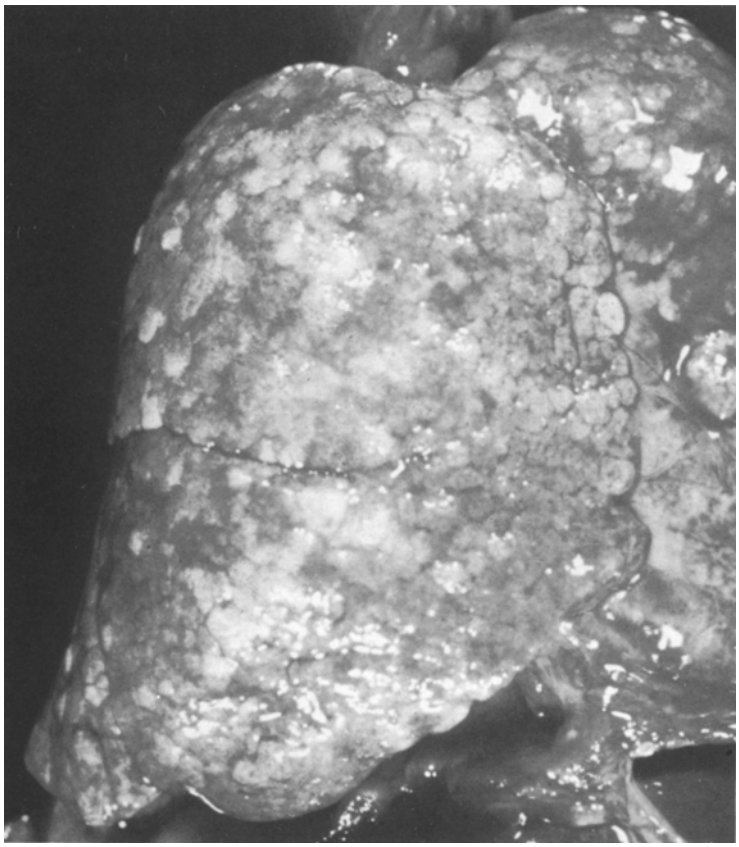

Fig. 10. Bronchopulmonary dysplasia. The lungs are bulky and fill the chest. Overdistended airways are seen as small bubbles through the pleura

concentration. Taghizadeh and Reynolds (1976) described a reduction in the number of cases of B.P.D. when ventilation with high peak airways pressure was replaced by ventilation at lower pressures and a slower rate. These authors could not demonstrate any relationship between pulmonary pathology and the use of high concentrations of oxygen for lung ventilation. Others (Bonikos et al. 1976; Edwards et al. 1977) contend that high oxygen concentrations are important in the aetiology of B.P.D. Whilst admitting that intubation and the mechanics of ventilation may paly a part in the development of B.P.D. Edwards (1977) suggests that the association with mechanical factors may be in a purely facilitatory role. The administration of high oxygen concentrations to animals for long periods can produce changes in pneumocytes similar to those seen in infants with B.P.D. (Bonikos et al. 1975) and the damage produced in the lungs of lambs ventilated with oxygen did not occur in similar animals ventilated with air (de Lemos et al. 1969). Pulmonary interstitial oedema with spectacular lymphatic dilatation is particularly prominent in the early stages of B.P.D. and congestive cardiac failure with shunting through a patent ductus arteriosus has been implicated in the development of this type of lung pathology. Brown et al. (1978) suggest that the lung damage may be

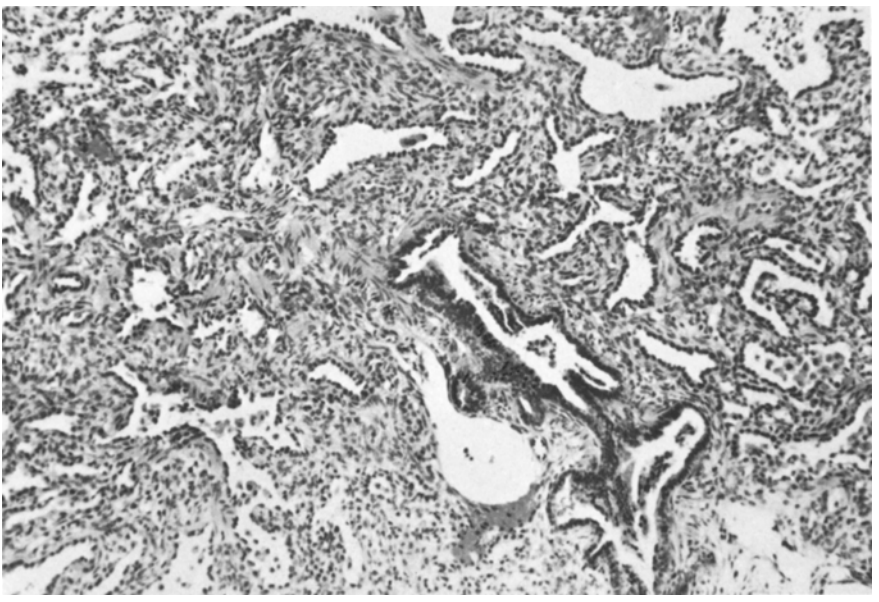

Fig. 11. Bronchopulmonary dysplasia. The alveolar lining cells are cuboidal and very prominent. Larger airways epithelium is irregular. H.E. ×195

mediated by interstitial oedema irrespective of its cause and found a higher mean fluid intake in the first five days of life of infants developing B.P.D. when compared with a control group, which they felt to be a significant risk factor.

Umbilical Catheterisation

Catheterisation of the umbilical vessels is commonly performed in the sick neonate because of the ready accessibility of relatively large vessels. Catheterisation was originally performed for purposes of exchange transfusion but now it is more frequently done for classical blood transfusion, infusion of nutrients and for investigative procedures.

Umbilical venous catheterisation was popular because of the ease of insertion of the catheter when compared with umbilical arterial catheterisation, but is now rarely performed because of the high incidence of complications, particularly umbilical vein thrombosis. This is very likely to follow the infusion of hypertonic solutions (Kitterman et al. 1970). Other factors which apparently increase the risk of umbilical vein thrombosis are failure to ensure that the catheter tip is in the inferior vena cava, and leaving the catheter *in situ* for longer than two days (Larroche 1970). Patchy hepatic necrosis and pulmonary thrombo-embolism (Fig. 12) are frequent early complications of umbilical venous catheterisation (Scott 1975). Massive hepatic necrosis may accompany portal vein thrombosis (Larroche 1970). Necrotising enterocolitis is reported following umbilical venous catheterisation for exchange transfusion (Corkery et al. 1968; Orme and Eades 1968). An infrequent late complication of umbilical venous catheterisation is portal hypertension presenting with splenomegaly or haematemesis (Junker et al. 1976; Lauridsen et al. 1978).

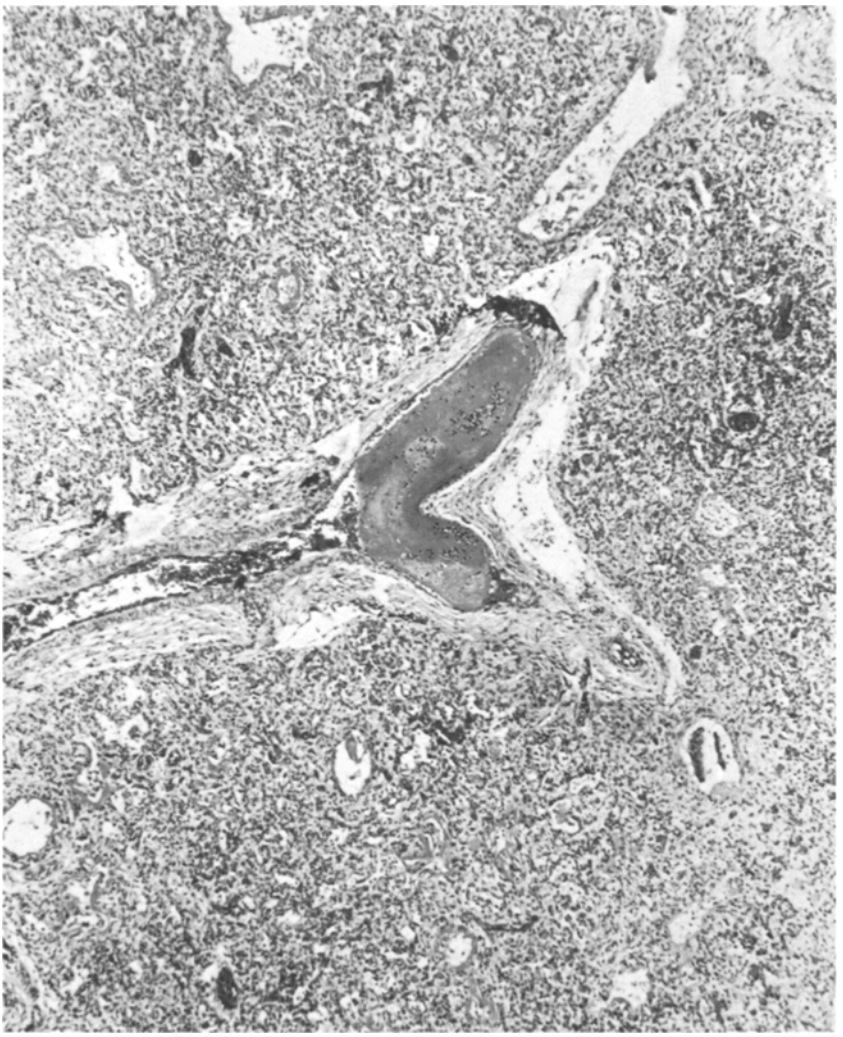

Fig. 12. Thrombo-embolus straddles the bifurcation of a pulmonary artery. Hyaline membranes line terminal airways. H.E. ×80

Following the appreciation of the frequency and seriousness of the complications of umbilical venous catheterisation umbilical arterial catheterisation is now more usual. This procedure has its complications but these are not as frequent as with venous catheterisation. The most common is thrombosis in the abdominal aorta or iliac arteries. The frequency of this complication varies between 24 and 95% of infants investigated by angiography and from 3.5–48% of cases subjected to necropsy examination (see Wesstrom et al. 1979). Personal experience supports a high incidence of aortic thrombosis following catheterisation (Fig. 13) but in most cases this is of a minor degree and would probably have resolved had the infant survived. Major aortic thrombosis (Fig. 14) is infrequent. Wesstrom et al. (1979) found a positive correlation between frequency of thrombosis and duration of catheterisation and with the use of side hole catheters (implicating the dead space at

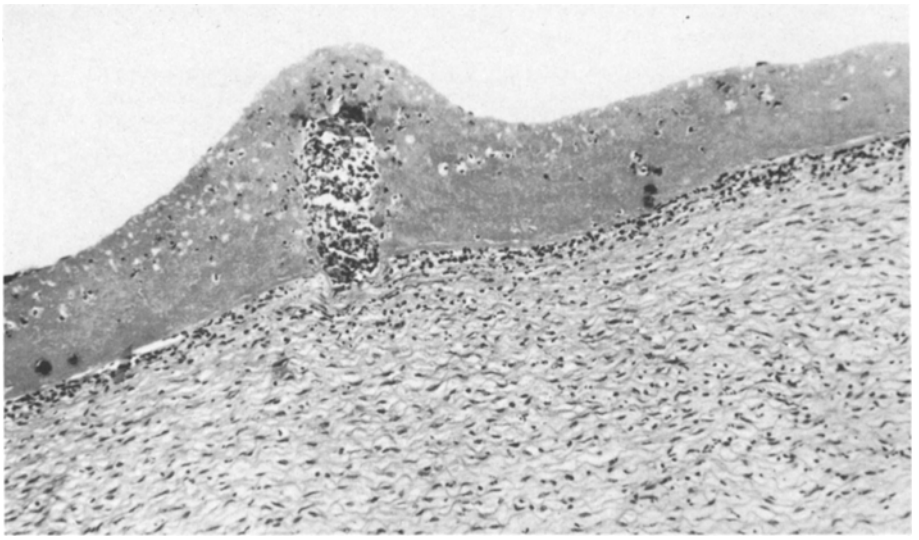

Fig. 13. Thrombus adherent to the wall of the aorta following umbilical arterial catheterisation. H.E. ×195

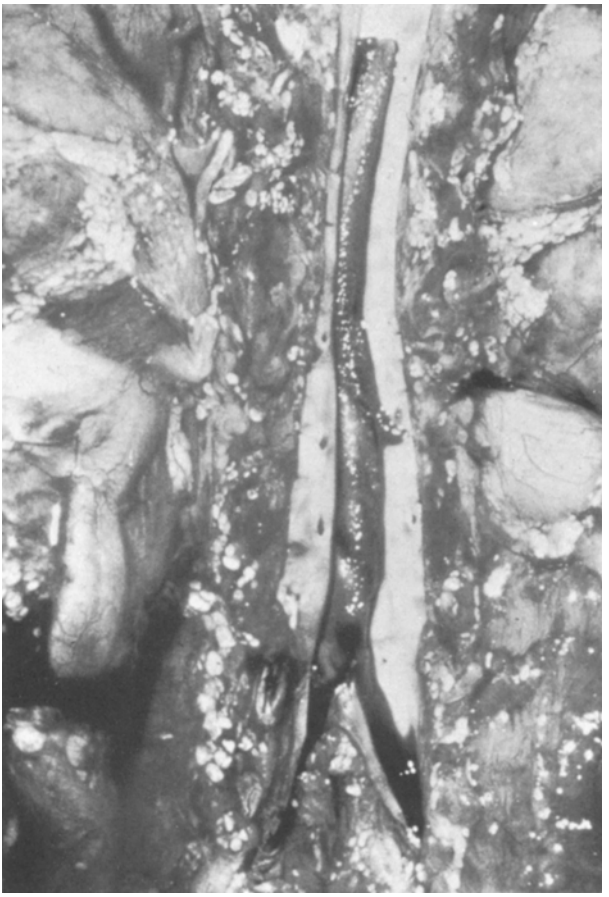

Fig. 14. Massive aortic thrombosis following umbilical arterial catheterisation

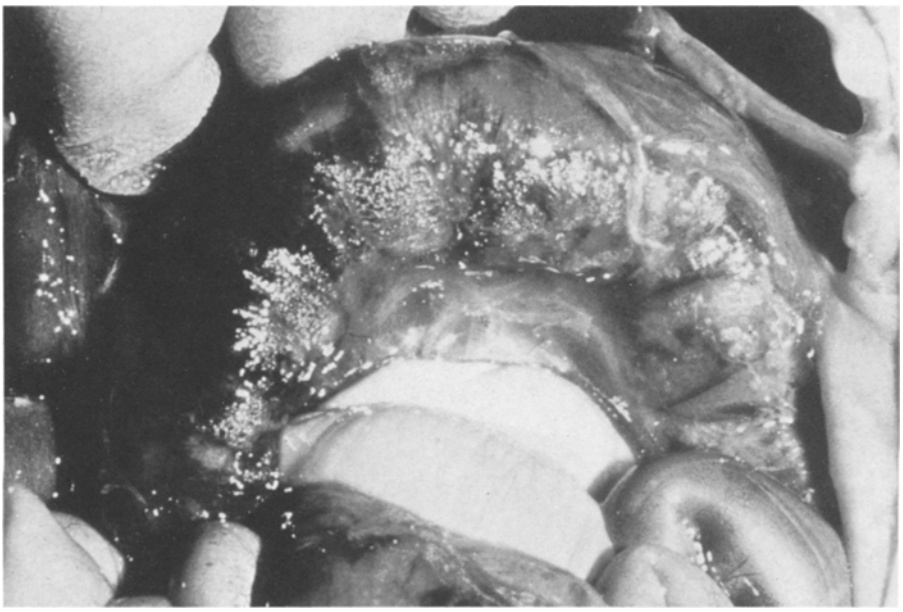

Fig. 15. Infarction of the colon complicating the massive aortic thrombosis seen in the previous illustration

the tip of such catheters as the site of initiation of thrombosis), low siting of the catheter tip and use for parenteral nutrition. Massive aortic thrombosis may be accompanied by infarction of viscera (Fig. 15) and gangrene of limbs, although not all cases are fatal and follow-up studies show remarkably few sequelae in survivors (Wesstrom 1980).

Not all cases of neonatal aortic thrombosis are associated with arterial catheterisation. Knowlson and Marsden (1978) draw attention to massive aortic thromosis resulting from propagation of thrombus arising within the ductus arteriosus. Examination of this vessel should be part of every perinatal necropsy and it should be examined with particular care in the presence of large vessel thrombosis even when there is a history of catheterisation.

An aneurysm of the aorta is described following umbilical arterial catheterisation of preterm neonate (Rajs et al. 1976). The aneurysm communicated with the oesophagus and resulted in fatal haematemesis. The authors suggest that the aneurysm resulted from a combination of local damage from the tip of the catheter and anoxic damage of the aortic wall. Damage to the intima may occur in cases where the catheter remains in situ for some days (Bunton et al. 1977) and also when undertaken to enable pressure studies to be performed in the management of the term neonate with congenital heart disease (Cooke et al. 1980) (Fig. 16).

Other complications of aortic catheterisation include haemorrhage from the umbilicus following displacement of the catheter and interstitial haemorrhage around the umbilical arteries. This may result in blood stained ascites or peri-aortic haemorrhage perhaps resulting from anoxic damage caused by spasm of small vessels during the insertion of the catheter. Gluteal skin necrosis has been described as a complication of umbilical arterial catheterisation (Mann 1980), but others have

Fig. 16. Intimal damage in the aota following aortic catheterisation for investigation of congenital heart disease in a term infant

found similar skin damage associated with the excessive use of as a skin antiseptic (Wilkinson et al. 1981).

Because of the serious complications of major vessel catheterisation some units have tried alternative approaches such as of indwelling cannulation or puncture of peripheral arteries. Serious sequelae have been reported following temporal artery catheterisation, namely slow development of contra-lateral hemiplegia over a period of five or six months (Simmons et al. 1978) and these authors have suggested that the practice is discontinued. Radial artery sampling may be complicated by gangrene of the hand (Fig. 17) and carpal tunnel syndrome resulting from local haematoma (Koenigsberger and Mersinger 1977) although Adams and Rudolph

Fig. 17. Amputation of the forearm following radial artery puncture complicated by gangrene

(1975) reported only minor complications, such as bruising. Even though the radial pulse was lost in four of their cases there were no subsequent ischaemic problems.

Septic arthritis of the hip has been described as a complication of femoral venepuncture in the neonate (Asnes and Arendar 1966) which emphasises the need for scrupulous aseptic technique when performing any large vessel puncture.

Hypertension is a serious complication of umbilical arterial catheterisation in infancy. Plumer et al. (1976) describe ten infants with hypertension of whom eitht had umbilical arterial catheterisation in the neonatal period, in seven of these thrombus was demonstrated in one or both renal arteries. Five of these infants died and the authors recommend an aggressive approach to the management of this complication, with early nephrectomy, as response to medical treatment is poor. All five fatal cases had undergone umbilical arterial catheterisation.

Catheterisation of the posterior tibial artery is suggested as an alternative to catheterisation of the temporal and radial arteries in view of the serious sequelae of sampling from those sites. Complications are minor, being confined to cyanosis of toes, which responds to removal of the catheter (Spahr et al. 1979).

Necrotising enterocolitis has been recognised with increasing frequency in infants over the last two decades. There seems to be a real increase in the number of cases seen during this time (Goldman 1980) and a variety of iatrogenic factors seem to play a part in the development of this disorder. Abdominal distension with or without vomiting is followed by the appearance of blood in the stools, resulting from mucosal damage. Abdominal x-ray at this time may reveal pneumatosis intestinalis. Intestinal perforation, peritonitis, septicaemia and shock and the rapid demise of the infant may supervene as the layers of the intestinal wall are progressively damaged. Since the adoption of conservative management of this condition in the form of gastric suction and intravenous feeding, surgery may be avoided in many cases in the acute stages and mortality has fallen, although intestinal obstruction caused by mural fibrosis as part of the healing process may precipitate surgical intervention at a later stage.

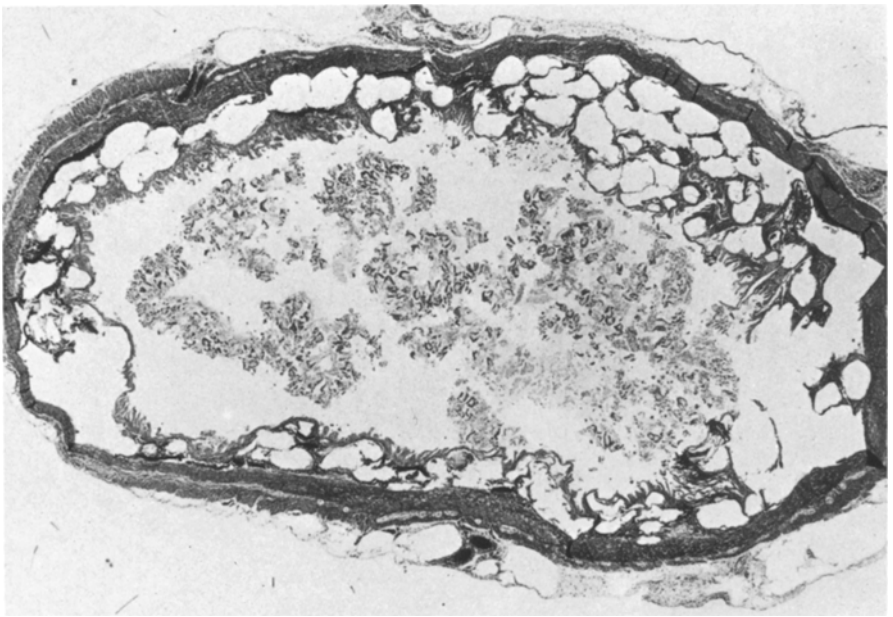

Fig. 18. Necrotising enterocolitis. Transverse section of bowel. Gas accumulation is seen in the submucosa and serosa. Van Gieson's method ×17

Examination of the intestine in these infants reveals areas of necrosis and haemorrhage which are frequently multiple. They may affect any part of the gastrointestinal tract from the stomach to the rectum but are particularly frequent in the small intestine. The necrotic process appears to start in the mucosa and may be confined to the inner part of the wall as a shallow, ill-defined haemorrhagic ulcer in the mucosa which may be seen from the serosal aspect of the intestine as a red or plum coloured area with an indistinct border. With the loss of mucosal integrity, the gas diffuses into the wall and becomes trapped in the loose tissues of the submucosa (Fig. 18) and occasional gas bubbles are seen between muscle bundles.

Necrosis may extend to involve the muscle coat of the bowel. Patchy thinning of the wall occurs with bulging of the necrotic parts of the wall which are first dark purple and then cream or tan and opaque in colour with a hyperaemic border. Perforation and peritonitis may occur. In some cases gas may be present in mesenteric veins and in the liver, often accompanied by infarction or necrosis.

There are no specific histological features. Large vessel thrombosis or embolism is not seen although thrombosis of veins in the vicinity of more extensive lesions may occur and is presumed to be secondary. Organisms may be demonstrated in the wall by Gram's stain. Healing of necrotising enterocolitis is by fibrous replacement of damaged tissue and subsequent shrinkage may lead to stricture formation. The luminal surface becomes re-epithelialised but the normal mucosal pattern of the intestine and continuity of muscle layers may be lost (Fig. 19).

The earliest cases of necrotising enterocolitis were described as complications of exchange transfusion. Intestinal lesions were attributed to ischaemic damage resulting from rapid changes in blood flow and blood pressure which may occur in the splanchnic circulation during such procedures (Waldausen 1963; Corkery et al.

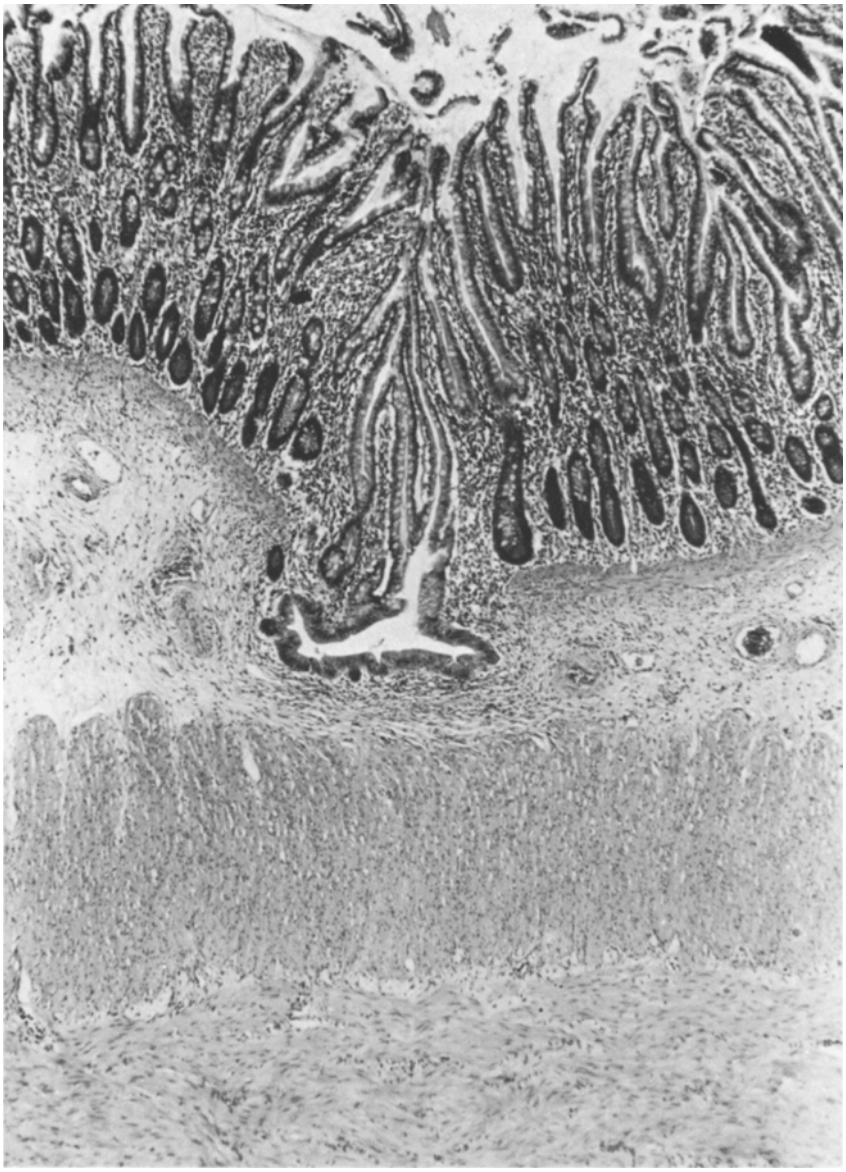

Fig. 19. Necrotising enterocolitis. The intestinal mucosa has almost returned to normal but continuity of the muscularis mucosae is lost. H.E. ×80

1968; Orme and Eades 1968). With a decline in the number of exchange transfusions performed since the introduction of anti-D therapy in the prevention of Rhesus haemolytic disease of the newborn, the commonest victim of necrotising enterocolitis is now the small preterm neonate, subject to episodes of hypoxia as a result of apnoeic attacks, birth asphyxia or hyaline membrane disease. In these infants, intestinal ischaemia is thought to result from episodic splanchic shutdown in response to systemic hypotension (Lloyd 1969), although a common factor in

their management may be the use of an indwelling umbilical arterial catheter (Bunton et al. 1977). Necrotising enterocolitis has been described following cardiac catheterisation and angiography (Cooke et al. 1980) and although the catheterisation and injection of contrast medium may induce vascular spasm, it is possible that in this situation the ischaemia is secondary to reduced blood flow in the splanchnic circulation as a result of hyperviscosity of the blood following the use of contrast medium of high osmolality and having a diuretic action. The association of hyperviscosity of the blood and necrotising enterocolitis was described in a prospective study of newborn infants of low birth weight by Hakanson and Oh (1977) and a causal relationship inferred.

In some cases, intestinal obstruction seems to be a contributory factor (Cook and Rickham 1963; Dunn 1963), local mucosal ischaemia being produced by a rise in intraluminal pressure. In one unit a correlation was found between the incidence of necrotising enterocolitis and the frequency of the practice of rapidly increasing the volume of the feed (Goldman 1980) and it is suggested that the bradycardia and hypoxia which may result from large volume feeds may contribute to the development of intestinal ischaemia.

There seems to be no doubt that the initiating factor in necrotising enterocolitis is intestinal mucosal ischaemia, irrespective of its aetiology. Ischaemia may not however be the only factor involved. It has been suggested that intestinal infection may play a part and both Salmonellae (Stein et al. 1972) and Clostridium butyricum (Howard et al. 1977) have been implicated in "epidemics" of necrotising enterocolitis in neonatal units. The protective effect of breast milk may be mediated by enhancement of growth of lactobacilli inthe intestine which in turn deters colonisation by pathogenic organisms (Barlow et al. 1974). Whether the next step is a straightforward infection of compromised tissue by intestinal pathogens or normal bowel flora, or whether a Schwartzman reaction occurs involving localisation of bacterial antigens within the mucosa following bacterial invasion of the wall as a sensitising episode, the necrosis occurring subsequently following bacteraemia (McKay and Wahle 1955; Fraser and Berry 1967), is not entirely resolved. The finding by Wilson and Woolley (1969) of thrombocytopenia in infants with necrotising enterocolitis perhaps supports the second hypothesis.

A common factor of the management of the groups of infants likely to develop necrotising enterocolitis is the use of catheters and giving sets and doubts have been expressed concerning the safety of polyvinychloride (PVC) (Rogers and Dunn 1969).

Cerebellar Haemorrhage

Cerebellar haemorrhage is reported in preterm infants, particularly those being ventilated by face mask which was held in position by a 1″ Velcro band (Pape et al. 1976). To ensure good fit the band must be tightly applied to the head and resulted in deformity of the skull. The haemorrhagic lesions in the cerebellum have the histological features of venous infarcts.

Intraventricular Haemorrhage

The aetiology of intraventricular haemorrhage in the newborn is poorly understood and different combinations of factors may operate in different individuals. It is

generally accepted that in most cases the haemorrhage occurs after birth and preterm infants are more likely to be affected than mature ones. Some of the manipulations used in the management of hyaline membrane disease have been implicated as factors in the aetiology of intraventricular haemorrhage. These include external pressure to the soft skull of the preterm infant in attaching apparatus and the use of a tight neck seal in positive pressure ventilation which again can produce a rise in intracranial pressure. The use of I.P.P.V. also increases central venous pressure; thus all these manoeuvres tend to decrease cerebral blood flow and perhaps produce cerebral ischaemia. Alkali therapy has been implicated in the aetiology of I.V.H. by some authors (Anderson et al. 1976; Wigglesworth et al. 1976), but this is discounted by others (Roberton and Howat 1977). Rapid administration of hyperosmolar sodium bicarbonate will tend to increase cerebral blood flow by increasing blood volume, perhaps inducing a rise in blood pressure and will also produce rapid changes in C.S.F. pressure. A relationship between hyperosmolality and intraventricular haemorrhage is found by Thomas et al. (1976) but the hyperosmolality was not related to hypernatraemia. However, protein intake was found to be much reduced in babies with intraventricular haemorrhage compared with controls because of a smaller milk intake and it was suggested that hyperosmolality could have resulted from tissue break-down following protein starvation.

Drugs and Nutrients

Unwanted side effects may accompany the use of drugs and nutrients in the management of the low birth weight preterm infant.

Hexachlorophene was been used as a topical bacteriostatic agent in the newborn, both for local application to the umbilical cord area and as a whole body application for cleansing purposes. Its administration to rats produced neurological abnormalities progressing to spasticity of the hind limbs and spongy degeneration was demonstrated in the brain and spinal cord at necropsy (Kimbrough and Gaines 1971). Hart (cited by Lockhardt 1972) applied 3% hexachlorophene emulsion to the skin of infant monkeys daily for 90 days. Percutaneous absorption of hexachlorophene was demonstrated and all treated monkeys had focal spongy lesions throughout the central nervous system whilst control animals showed no abnormality. Powell et al. (1973) described spongiform changes in the brain stem of six preterm infants who had at least four whole body exposures to hexachlorophene. Cerebral abnormalities were symmetrical and consisted of "bubbly" change in myelinated fibres in the medial longitudinal fasciculus, the medial lemniscus and cerebellar peduncles. The authors implicated prematurity, low birth weight and the presence of skin lesions as predisposing factors. Shuman et al. (1974) found similar cerebral changes in 17 of 248 brains from infants and children. All were of low birth weight and all had been subjected to repeated whole body applications of 3% hexachlorophene. They speculate that the relatively large surface ara of the low birth weight infant and the poorly keratinised skin of the preterm baby might more readily permit transcutaneous absorption of drugs than that of the mature infant.

It is well known that virus infection may be transmitted by the use of blood or blood products. The transmission of hepatitis is usually a complication of the treatment of patients requiring multiple transfusion or the use of products made by pooling the serum from many donors. Transmission of cytomegalovirus (C.M.V.) infection may complicate the transfusion of very small amounts of blood. The infection is usually asymptomatic but more serious infection may occur in individuals whose immunological responses are compromised in some way. The preterm neonate may fall into this group and fatal illness may follow transfusion in the neonatal period (Benson et al. 1979). This knowledge has provoked studies to determine the frequency with which infection might be transmitted in these circumstances, Yeager (1974) followed up infants who had been nursed in an intensive care nursery and found that 25 % of 77 infants treated with blood products were excreting C.M.V. at 7 months of age, compared with 11 % of 74 infants from the same nursery who had not been so treated. In a smaller study, Benson et al. (1979) found that 4 of 11 infants became infected with C.M.V. following blood transfusion and that C.M.V. infection following blood transfusion was abolished in that unit by the exclusive use of C.M.V. antibody-free blood for transfusion in the neonatal period.

That intravenous alimentation using a mixture of amnio-acids and sugar was capable of maintaining normal neonatal growth rate was reported by Wilmore and Dudrick in 1968 and was welcomed by those caring for infants undergoing surgery in the neonatal period. The availability of Intralipid emulsion, a mixture of fats and fatty acids suitable for intravenous administration which provided a concentrated source of calories, was a further advance as fluid overload was a limiting factor when sugars and amnio-acids were used alone. Several reports of cholestasis in infants receiving parental alimentation have appeared since that of Peden et al. 1971. Bernstein et al. (1977) investigated five infants who became jaundiced whilst receiving amnio-acids and hyperosmolar sugar solution by an intravenous route by means of liver biopsy. They found cholestasis with evidence of hepatocellular damage, giant cell transformation of hepatocytes and prominence of Kupffer cells with contained P.A.S. positive material and bile pigment (Fig. 20). There was no fatty change. Koga et al. (1975) demonstrated fat and pigment in Kupffer cells and hepatocytes following parental nutrition which involved the use of lipid emulsions (Figs. 21, 22). Whitington and Black (1980) described cholelithiasis in preterm infants treated with intravenous amnio-acids and fat emulsions and frusemide. They suggested that the cholestasis which complicated parental nutrition in their patients was important in the formation of the gall stones and speculated that frusemide might have contributed to their formation by reducing bile salts, independent of bile flow, or by enhancing the secretion of calcium into the bile.

Pulmonary fat embolism was described in infants following the administration of "Intralipid" by Barson et al. (1978) in both preterm and mature neonates. They considered that associated factors were severe acidaemia resulting from respiratory distress or sepsis and excessive peak flow rates during the administration of lipid emulsions. Levene et al. (1980) described fat accumulation in pulmonary capillaries following intralipid infusion in preterm infants when the infusion rate was below the recommended maximum and plasma lipaemia was not observed. Extensive

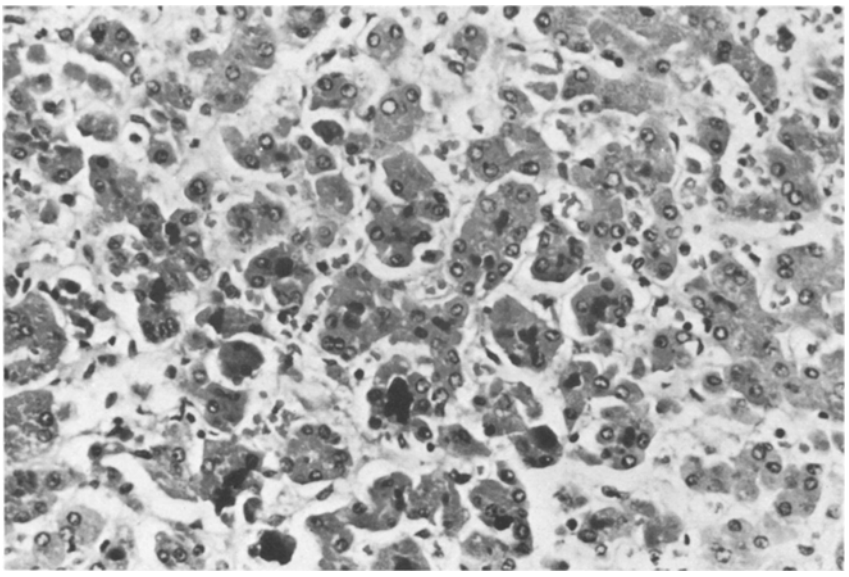

Fig. 20. There is marked bile plugging, sinusoidal dilatation and prominence of Kupffer cells. H.E. × 500

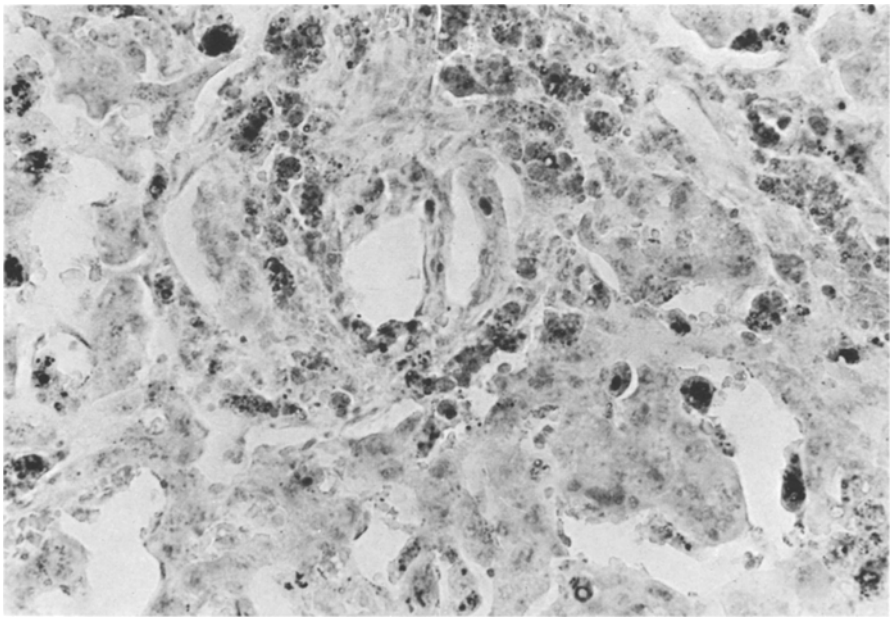

Fig. 21. Liver following intralipid infusion. Fat is seen in Kupffer cells. Oil red O × 360

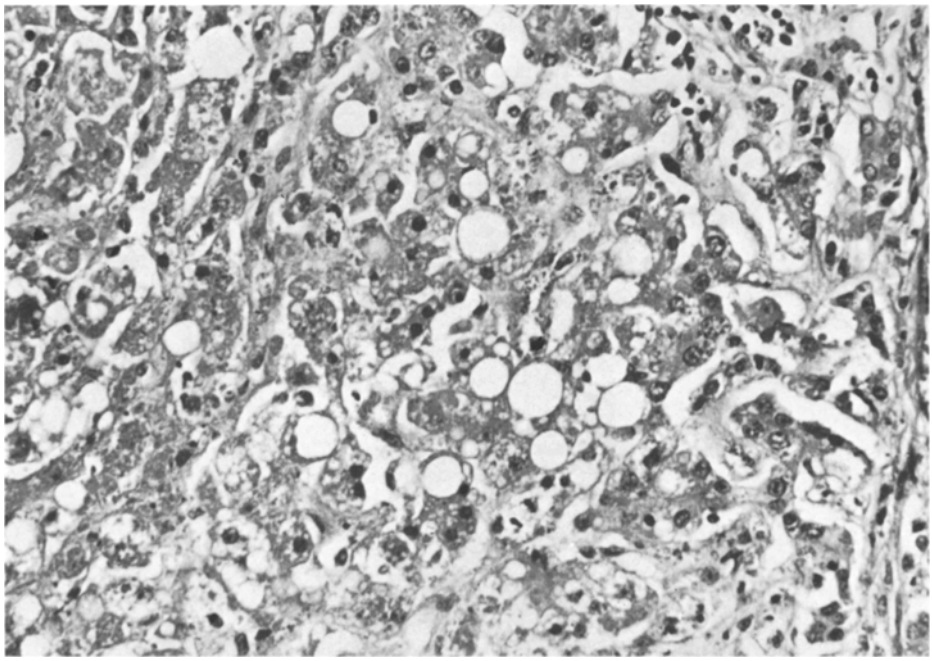

Fig. 22. Fatty change of hepatocytes together with a foamy appearance of Kupffer cells in distended sinusoids. There is patchy round cell infiltration. H.E. $\times 360$

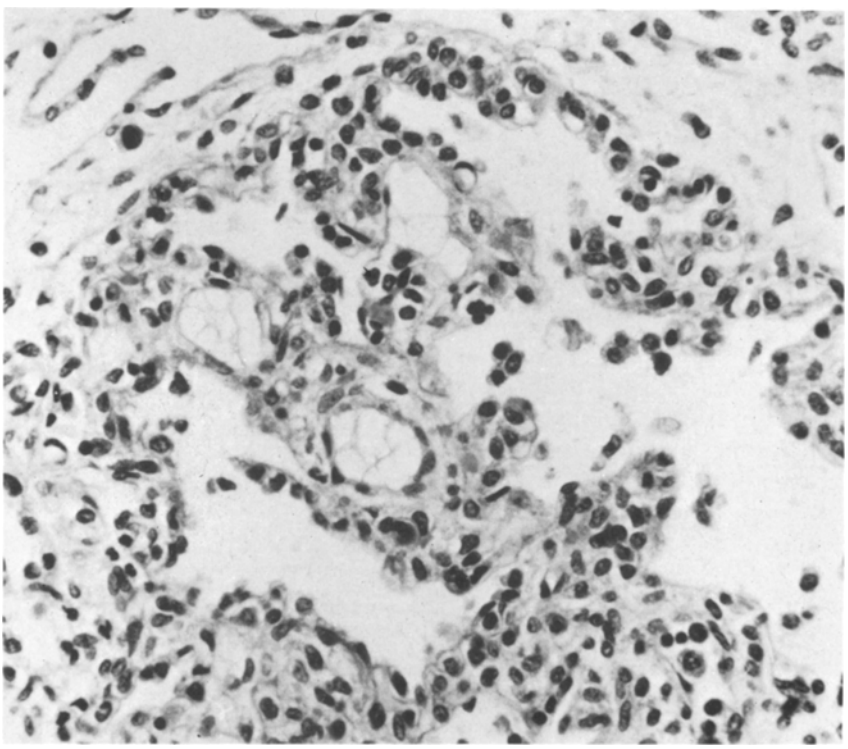

Fig. 23. Lung following administration of Intralipid. Globules are seen in several capillaries. H.E. $\times 500$

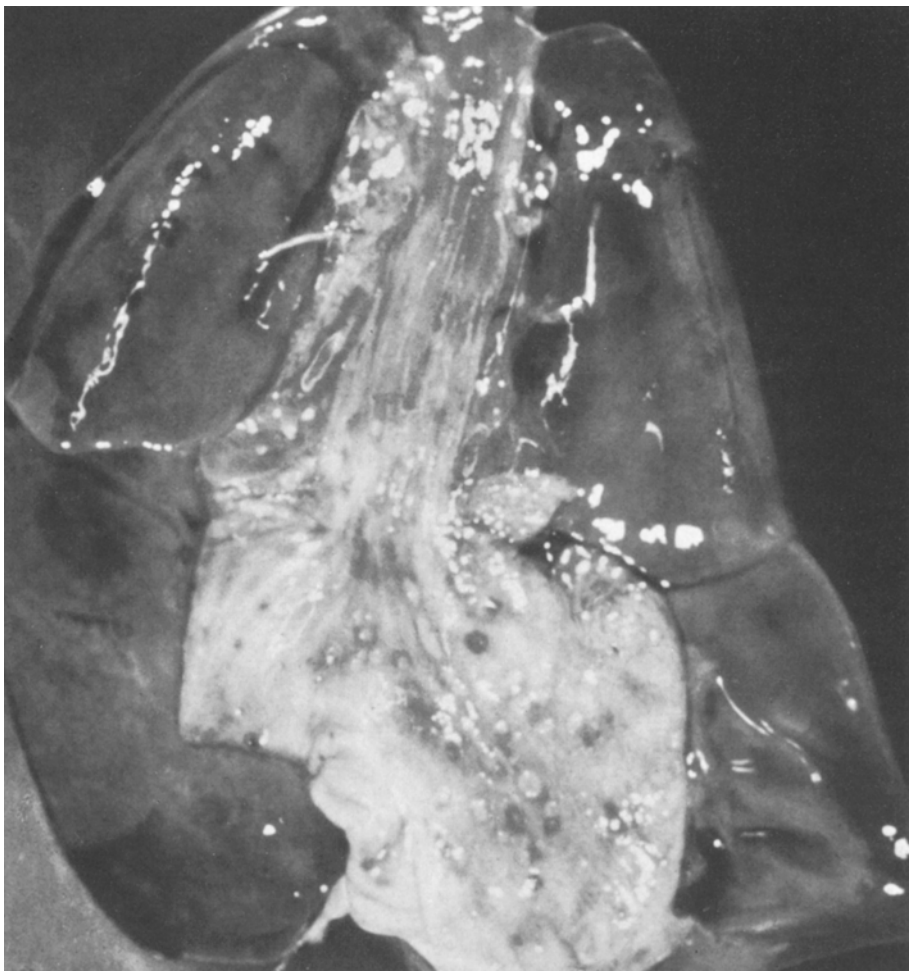

Fig. 24. Multiple punched out ulcers are seen in the gastric mucosa. At necropsy the stomach and upper small intestine were filled with blood

accumulation of lipid in pulmonary capillaries will seriously interfere with lung function. Histological examination of routinely stained sections will reveal empty capillaries or refractile material within small vessels (Fig. 23). Oil red O staining of frozen sections will demonstrate lipid globules within vessels and within histiocytes. Multiple infarcts of the lung are seen in some cases (Levene et al. 1980).

Dahms and Halpin (1980) described lipid accumulation in pulmonary arteries, particularly in the intimal layer, although the media and occasionally the adventitia are involved. The vessels also showed changes of pulmonary hypertension which were expected from the clinical course of the patients. They speculate that lipid accumulates in the walls of previously damaged vessels and were unable to demonstrate these changes in a retrospective study unless both intralipid administration and pulmonary hypertension were present.

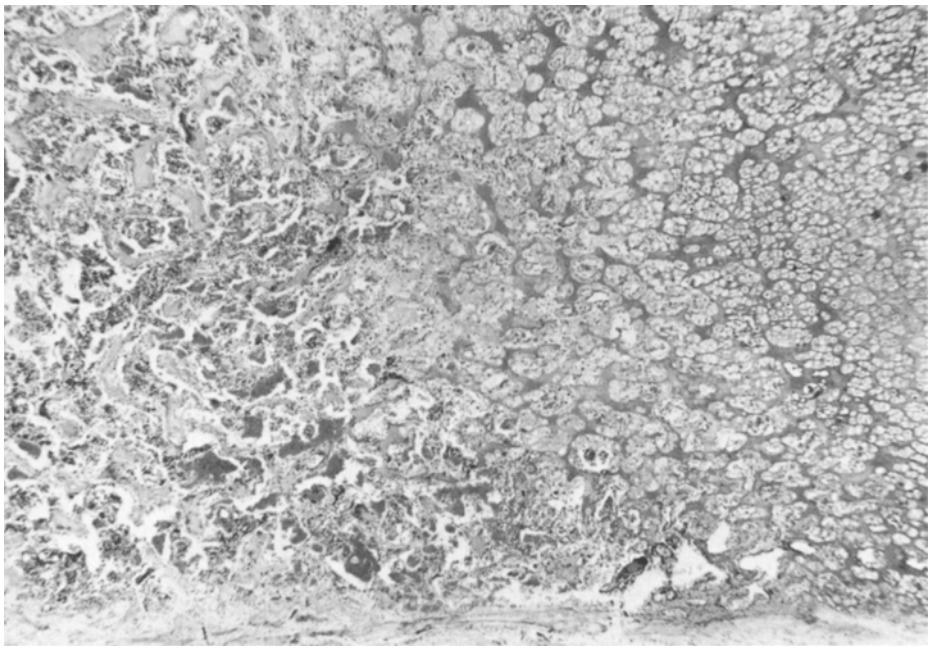

Fig. 25. Costo-chondral junction. Chondrocytes columns have disappeared and the junction line is quite irregular. Bony trabeculae are very thin and poorly mineralised. H.E. $\times 50$

Following the administration of Intralipid to neonates, fat may be demonstrated by histochemical methods in tissues obtained at necropsy and is seen in histiocytes throughout the reticulo-endothelial system. Fischer et al. (1980) have demonstrated that the administration of fat emulsions to mice results in deterioration of neutrophil and macrophage function and postulate that its administration to humans may compromise handling of bacteria which in some situations may contribute to development of infection. Administration of Intralipid to the preterm neonate may thus be contra-indicated.

Tolazoline, an alpha adrenergic blocking agent, is related chemically to both histamine and the sympathomimetic amines. It is used in the management of the neonate with pulmonary hypertension either complicating hyaline membrane disease or meconium aspiration or without co-existing lung disease. Gastrointestinal haemorrhage might be predicted as a side effect in view of its histamine-like structure. This was reported in six of twenty one infants treated with Tolazoline by Goetzman et al. (1978) who described a variety of complications in 14 or their patients including haematuria, renal failure, hypotension, hypertension, thrombocytopaenia and pulmonary haemorrhage. Multiple discrete ulcers measuring up to 3 mm diameter may be found scattered through the gastric mucosa (Fig. 24). Haemorrhage may be life threatening.

Nutritional rickets occurs in preterm infants with respiratory problems resulting from a combination of low calcium and vitamin D intakes compounded by the administration of sodium bicarbonate and perhaps frusemide (Chudley et al. 1980; Oppenheimer and Snodgrass 1980). Typical findings are expansion of the

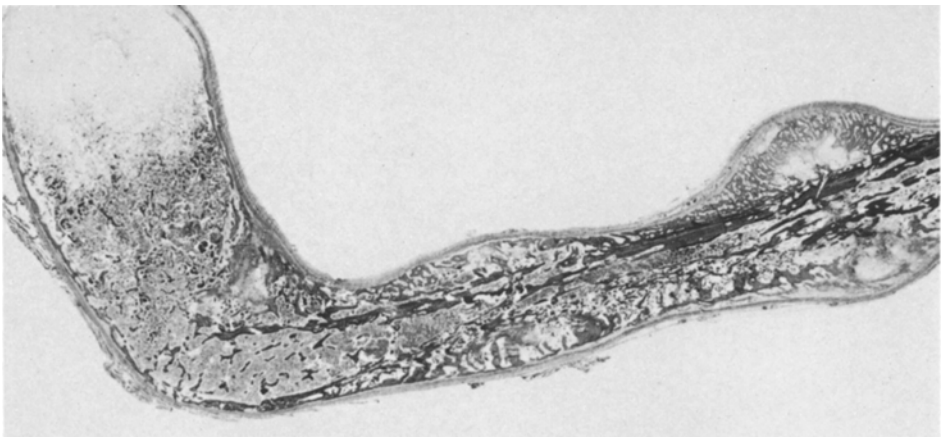

Fig. 26. Rib showing irregularity of the costo-chondral junction. Bizzare angulation resulting from fracture and elevation of the periosteum by callus where healing of the fracture has occurred. H.E. × 5

ends of ribs (Fig. 25) and long bones with poor mineralisation of the bones. Rib fractures may occur in the absence of history of trauma and result in bizarre angulation of ribs (Fig. 26). Administration of calcium supplements and vitamin D is recommended in such infants with chronic respiratory problems.

Conclusions

This review is intended to assist the pathologist in his interpretation of abnormalities encountered during the neonatal necropsy or in surgical specimens. It illustrates the necessity for close co-operation between clinician and pathologist and the need for each to understand to problems of the other if they wish to identify changes which may have arisen as a result of treatment.

References

Adams JM, Rudolph AJ (1975) The use of indwelling radial artery catheters in neonates. Pediatrics 55:261–265

Anderson JM, Bain AD, Brown JK, Cockburn F, Forfar JO, Madin GA, Turner TL (1976) Hyaline membrane disease, alkaline buffer treatment and cerebral intraventricular haemorrhage. Lancet 1:117–119

Asnes RS, Arendar GM (1966) Septic arthritis of the hip: a complication of femoral venepuncture. Pediatrics 38:837

Barlow B, Santulli TV, Heird WC, Pitt J, Blanc WA, Schullinger JN (1974) An experimental study of acute neonatal enterocolitis – the importance of breast milk. J Ped Surg 9:587–595

Barson AJ, Chiswick ML, Doig CM (1978) Fat embolism in infancy after intravenous fat infusions. Arch Dis Child 53:218–223

Benson JWT, Bodden SJ, Tobin JO'H (1979) Cytomegalovirus and blood transfusion in neonates. Arch Dis Child 54:538–541

Bernstein J, Chang CH, Brough AJ, Heidelberger KP (1977) Conjugated hypoerbilirubinaemia in infancy associated with parenteral alimentation. J Pediatr 90:361–370

Bonikos DS, Bensch KG, Northway WH, Edwards DK (1976) Bronchopulmonary dysplasia: the pulmonary pathologic sequel of necrotising bronchiolitis and pulmonary fibrosis. Human Pathol 7:643–666

Brown ER, Stark A, Sosenko I, Lawson EE, Avery ME (1978) Bronchopulmonary dysplasia: possible relationship to pulmonary edema. J Pediatr 92:982–984
Bunton GL, Durbin GM, McIntosh N, Shaw DG, Taghizadeh A, Reynolds EOR, Rivers RPA, Urman G (1977) Necrotising enterocolitis. Arch Dis Child 52:722–777
Chudley AE, Brown DR, Holzman IR, Oh KS (1980) Nutritional rickets in 2 very low birthweight infants with chronic lung disease. Arch Dis Child 55:687–690
Clarke TA, Coen RW, Feldman B, Papile L (1980) Esophageal perforations in premature infants and comments on the diagnosis. Am J Dis Child 134:367–368
Conference on Retrolental Fibroplasia (1955) Retrolental fibroplasia in the United Kingdom. BMJ, iii:78–82
Cook RCM, Rickham PP (1969) Neonatal intestinal obstruction due to milk curds. J Ped Surg 4:599–605
Cooke RWI, Meradji M, de Villeneuve VH (1980) Necrotising enterocolitis after cardiac catheterisation in infants. Arch Dis Child 55:66–68
Corkery JJ, Dubowitz V, Lister J, Moosa A (1968) Colonic perforation after exchange transfusion. BMJ 4:345–349
Creasman WT, Lawrence RA, Thiede HA (1968) Fetal complications of amniocentesis. JAMA 204:91–94
Dahms BB, Halpin TC (1980) Pulmonary arterial lipid deposit in newborn infants receiving intravenous lipid infusion. J Pediatrics 97:800–805
DeLemos R, Wolfdorf J, Nachman R., Block AJ, Leiby G, Wilkinson HA, Allen T, Haller JA, Morgan W, Avery ME (1969) Lung injury from oxygen in lambs: the role of artificial ventilation. Anesthesiology 30:609–618
Drew JH, Landau LI, Acton CM, Kent M, Campbell PE (1978) Pulmonary interstitial emphysema requiring lobectomy. Arch Dis Child 53:424–426
Dunn PM (1963) Intestinal obstruction in the newborn with special reference to transient functional ileus associated with respiratory distress syndrome. Arch Dis Child 38:459–467
Dunn PM (1975) Testicular birth trauma. Arch Dis Child 50:744–745 (Abstr)
Edwards DK, Dyer WM, Northway WH (1977) Twelve years' experience with bronchopulmonary dysplasia. Pediatrics 59:839–846
Fedrick J, Butler NR (1971) Certain causes of neonatal death V. cerebral birth trauma. Biol Neonate 18:321–329
Fischer GW, Wilson SR, Hunger KW, Mease AD (1980) Diminished bacterial defences with intralipid. Lancet II:819–820
Fraser GC, Berry C (1967) Mortality in neonatal Hirschsprung's disease: with particular reference to enterocolitis. J Ped Surg 2:205–211
Goetzman BW, Sunshine P, Johnson JD, Wennberg RP, Hackel A, Merten DF, Bartoletti AL, Silverman NH (1976) Neonatal hypoxia and pulmonary vasospasm: response to tolazoline. J Pediatrics 89:617–621
Goldman HI (1980) Feeding and necrotising enterocolitis. Am J Dis Child 134:553–555
Hakanson DO, Oh W (1977) Necrotising enterocolitis and hyperviscosity in the newborn infant. J Pediatrics 90:458–461
Howard FM, Bradley JM, Flynn DM, Noone P, Szawathowski M (1977) Outbreak of necrotising enterocolitis caused by clostridium butyricum. Lancet II:1099–1102
Junker P, Egeblad M, Nielsen O, Kamper J (1976) Case Report: Umbilical vein catheterisation and portal hypertension. Acta Paediatr Scand 65:499–504
Kimbrough RD, Gaines TB (1971) Hexachlorophene effects on the rat brain. Arch Environ Health 23:114
Kitterman JA, Phibbs RH, Tooley WH (1970) Catheterisation of umbilical vessels in newborn infants. Pediatr Clin North Am 17:895
Knowlson GT, Marsden HB (1978) Aortic thrombosis in the newborn period. Arch Dis Child 53:164–166
Koenigsberger MR, Moessinger AC (1977) Iatrogenic carpal tunnel syndrome in the newborn. J Pediatrics 91:443–445
Koga Y, Swanson VL, Hayes DM (1975) Hepatic "intravenous fat pigment" in infants and children receiving lipid emulsions. J Pediat Surg 10:641–648
Larroche JCl (1970) Umbilical catheterization: its complications. Anatomical study. Biol Neonate 16:101–116

Lauridsen UB, Enk B, Gammeltoft A (1978) Oesophageal varices as a late complication to neonatal umbilical vein catheterization. Acta Paediatr Scand 67:633–636
Levene MI, Wigglesworth JS, Desai R (1980) Pulmonary fat accumulation after intralipid infusion in the preterm infant. Lancet II:815–818
Lindroth M, Svenningsen NW, Ahlstrom H, Jonson B (1980) Evaluation of mechanical ventilation in newborn infants. Acta Paediatr Scand 69:143–149
Lloyd JR (1969) Etiology of gastrointestinal perforations in the newborn. J Ped Surg 4:77–84
Lockhardt JD (1972) How toxic is hexachlorophene? Pediatrics 50:229–235
McKay DG, Wahle GH (1955) Epidemic gastroententeritis due to escherichia coli 0111 B_4. Arch Pathol 60:679–693
Mann NP (1980) Gluteal skin necrosis after umbilical artery catheterisation. Arch Dis Child 55:815–817
Moessinger AC, Driscoll JM, Wigger H (1978) High incidence of lung perforation by chest tube in neonatal pneumothorax. J Pediatrics 92:635–637
Morley CJ, Bangham AD, Miller N, Davis JA (1981) Dry artificial lung surfactant and its effect on very premature babies. Lancet :64–68
NICHD National Registry for Amniocentesis Study Group (1976) Midtrimester amniocentesis for prenatal diagnosis. Safety and Accuracy. JAMA 236:1471–1476
Northway WH, Rosan RC, Porter DY (1967) Pulmonary disease following respirator therapy of hyaline membrane disease. New Eng J Med 276:357–368
Oppenheimer SJ, Snodgrass GJAI (1980) Neonatal rickets. Histopathology and quantitative bone changes. Arch Dis Child 55:945–949
Orme R L'E, Eades SM (1968) Perforation of the bowel in the newborn as a complication of exchange transfusion. Br Med J iv:349–351
Pape KE, Armstrong DL, Fitzhardinge PM (1976) Central nervous system pathology associated with mask ventilation in the very low birth weight infant: a new aetiology for intracerebellar haemorrhages. Pediatrics 58:473–483
Pape KE, Wigglesworth JS (1979) Haemorrhage, ischaemia and the perinatal brain. Birth Trauma, Ch 5, Spastics International Medical Publication. Heinemann, London
Peden VH, Witzleben CL, Skelton MA (1971) Total parenteral nutrition. J Pediatr 78:180
Piccolo F, Pasquino AM, Boscherini B, Taggi F, Pasquini P (1979) Hypopituitary dwarfism and breech delivery. Arch Dis Child 54:485–486
Plumer LB, Kaplan GW, Mendoya SA (1976) Hypertension in infants – a complication of umbilical arterial catheterisation. J Pediatr 89:802–805
Powell H, Swarner O, Gluck L, Lampert P (1973) Hexachlorophene myelinopathy in preture infants. J Pediatr 82:976–981
Rajs J, Finnstrom O, Wesstrom G (1976) Case Report: Aortic aneurysm developing after umbilical artery catheterization. Acta Paediatr Scand 65:495–498
Reynolds EOR, Taghizadeh A (1974) Improved prognosis of infants mechanically ventilated for hyaline membrane disease. Arch Dis Child 49:505
Robertson NRC, Howat P (1977) Intraventricular haemorrhage and alkali therapy. Arch Dis Child 52:248–254
Robinson A, Bowes W, Droegemueller W, Goodman S, Shikes R, Greenshur A (1973) Intrauterine diagnosis: potential complications. Am J Obstet Gynecol 116:937–941
Rogers AG, Dunn PM (1969) Intestinal perforation, exchange transfusion, and P.V.C. Lancet II:1246
Rona RJ, Tanner JM (1977) Aetiology of idiopathic growth hormone deficiency in England and Wales. Arch Dis Child 52:197–208
Scott JM (1965) Iatrogenic lesions in babies following unbilical vein catheterization. Arch Dis Child 40:426–429
Shuman RM, Leech RW, Alvord EC (1974) Neurotoxicity of hexacholorphene in the human: 1. A clinicopathologic study of 248 children. Pediatrics 54:689–695
Simmons MA, Levine RV, Lubchenco LO, Guggenheim MA (1978) Warning: serious sequelae of temporal arterial catheterisation. J Pediatr 92:284
Sphar RC, MacDonald HM, Holzman IR (1979) Catheterization of the posterior tibial artery in the neonate. Am J Dis Child 133:945–946
Stein H, Beck J, Solomon A, Schmaman A (1972) Gastroenteritis with necrotising enterocolitis in premature babies. BMJ 2:616–619
Taghizadeh A, Reynolds EOR (1976) Pathogenesis of bronchopulmonary dysplasia following hyaline membrane disease. Am J Pathol 82:241–258

Thomas DB (1976) Hyperosmolality and intraventricular haemorrhage in premature babies. Acta Paediatr Scand 65:429–432

Waldhausen JA, Herenden T, King H (1963) Necrotising colitis of the newborn: common cause of perforation of the colon. Surgery 54:365–372

Wesstrom G, Finnstrom O, Stenport G (1979) Umbilical artery catheterization in newborns. 1. Thrombosis in relation to catheter type and position. Acta Paediatr Scand 68:575–581

Wesstrom G (1980) Umbilical artery catheterisation in newborns. V. A clinical follow-up study. Acta Paediatr Scand 69:371–376

Whitington PF, Black D (1980) Cholelithiasis in premature infants treated with parenteral nutrition and furosemide. J Pediatr 97:647–649

Wigglesworth JS, Keith IH, Girling DJ, Slade SA (1976) Hyline membrane disease, alkali, and intraventricular haemorrhage. Arch Dis Child 51:755–762

Wigglesworth JS, Husemeyer RP (1977) Intracranial birth trauma in vaginal breech delivery: the continued importance of injury to the occipital bone. Br J Obstet Gynaecol 84:684–691

Wilkinson A, Baum JD, Keeling JW (1981) Gluteal skin necrosis after umbilical arterial catheterisation (letter). Arch Dis Child 56:237–238

Wilmore DW, Dudrick SJ (1968) Growth and development of an infant receiving all nutients exclusively by vein. J Amer Med Ass 203:860

Wilson SE, Woolley MM (1969) Primary necrotising enterocolitis in infants. Arch Surg 99:563–566

Yates PO (1959) Birth trauma to the vertebral arteries. Arch Dis Child 34:436–441

Yeager AS (1974) Transfusion-acquired cytomegalovirus infection in newborn infants. Am J Dis Child 128:478–483

Youroukos S, Papadelis F, Matsaniotis N (1980) Porencephalic cysts after amniocentesis. Arch Dis Child 55:814–815

Accepted May 12, 1981