# 7 · Respiratory System

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## Development and Structure

Our knowledge of the development of the respiratory system has unfolded rapidly in recent years following the application of modern techniques in molecular biology and genetics. Some of these, together with highly specific immunocytochemistry, are now readily applied to material obtained for diagnostic purposes, with great practical medical benefit.

The respiratory system comprises the nose, nasopharynx, larynx, trachea, bronchi and lungs. In considering the pathology, it can be divided into two parts: the upper respiratory system, comprising the nose, nasopharynx, larynx and trachea; and the lower respiratory system, comprising the bronchi and lungs.

### Face and Nasopharynx

The development of the face and nasopharynx is dealt with on pp. 210–214.

### Larynx

Between the 3rd and 4th weeks of gestation (about 3 mm) the respiratory primordia, including the tracheobronchial groove, make their appearance caudal to the hypobronchial eminence. At the end of the 4th week the epithelial component of the larynx develops rapidly with the appearance of the hypopharyngeal eminences on either side, indicating the site of the right and left arytenoid swellings, forming the primitive laryngeal aditus.

Towards the end of the 5th week and during the 6th week, the *epiglottis* makes its appearance as a midventral prominence at the base of the third and fourth arches, cephalic to the glottis. The arytenoid swellings continue to grow towards the base of the tongue, enfolding the epiglottis during the process. At this stage of development, actively proliferating epithelium temporarily obliterates the entrance to the larynx. In the ensuing weeks, the growth of the larynx proceeds rapidly, and the lumen is re-established. However, the entrance becomes ovoid, and there is a persistent interarytenoid notch in the sagittal plane. By the 10th week, the essential elements of the larynx are established, and the vocal cords appear on either side of the laryngeal lumen.

The larynx now grows much more slowly, and it is not until the last trimester of intrauterine life that it attains its definitive form, but it remains high in the neck. The laryngeal cartilages make their appearance at about the 10th week from the 4th and 6th pairs of the brancheal arches.

### Trachea

The tracheobronchial groove appears early during the 4th week of gestation. At this stage, it has a blunted caudal end but an extensive communication with the ventrocaudal part of the pharynx. The future trachea, represented by the distal portion of the groove, lies ventral to and parallel with the oesophagus from which it is separated by the tracheo-oesophageal septum. The blunted end forms the *primary bronchial (lung) buds*. Tracheo-oesophageal separation occurs during the 4th and 5th weeks.

The endodermal outgrowth from the pharynx gives rise to the epithelial lining and glands of the trachea; the cartilage, muscle and connective tissue investing the organ are derived from the surrounding mesenchyme.

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Cartilage rings are identifiable during the 10th week. The epithelial glands are not apparent until about the 4th month, and during subsequent weeks they assume their final characteristics. By the 5th month, the main anatomical features of the trachea are established.

## Lungs

The *pulmonary primordia* or *lung buds* appear towards the end of the 3rd and beginning of the 4th week of gestation at the caudal end of the tracheobronchial groove. They are generally asymmetrical, inclining to the right, and made up of two lobes, a large right and a smaller left lobe, separated by a shallow sulcus. During the following weeks and up to the 7th week, by a series of monopidial and irregular dichotomous branchings, the principal bronchi appear, establishing the basic organization of the mature lung into lobar and segmental units. At this stage there are ten principal branches on the right and eight on the left. Between the 10th and 14th weeks, there is active division and ramification of the bronchi, producing about 70% of the bronchial generations. By the 16th week, the bronchial tree is fully developed and the lung has a glandular appearance. Capillaries rapidly penetrate the epithelium, and the glandular appearance becomes canalicular. The number of bronchial generations is now complete and is actually in excess of the final number found in adults; by a process of alveolarization some of the non-respiratory bronchioles are transformed into respiratory bronchioles, finally leaving some 27 generations.

In experimental animals many growth factors and cytokines have been shown to play an essential role in growth, differentiation and maturation of various organs, including the lower respiratory system. In the human fetus, as in various animal species, *epidermal growth factor*, a growth-promoting polypeptide, seems to be among the principal polypeptides in stimulating epithelial proliferation, differentiation and/or chloride and fluid exchange of the developing airway which finally leads to maturation. Its action is through the activation of *epidermal growth factor receptors*, which are already present on the epithelium of the conducting airways during the first trimester (12–13 weeks) of gestation. Activation of these receptors catalyses phosphorylation of many intracellar substances, chief among them *lipocortin–1*, which has many actions (such as binding of calcium, acidic phospholipids and actin filaments), but inhibits phospholipase A2 activity, which may affect local prostaglandin synthesis. *Transforming growth factor* $\alpha$, which also appears early during the first trimester of gestation, may function as the predominant ligand for epidermal growth factor receptor during early fetal lung development. *Insulin-like growth factors I and II*, regulatory peptides which are present early in the fetal lung during development, also play an important role in the control of cell proliferation, differentiation and exchange between the cell surface and extracellular fluids. Through the specific *insulin growth factor binding proteins*, by various complex mechanisms, they are involved in the regulation of cell growth, as well as the control of response to substances or factors that may alter lung growth, differentiation and proliferation. These various elements, controlled by specific genes, may have a paracrine/autocrine effect on the normal developing lung. The cell adhesive glycoprotein, *fibronectin*, a promotor of cell migration and differentiation during early lung development, may also be under the control of these growth factors. The entire process from the beginning is constantly under the genetic control of a programmed sequence of events during lung development. Certain gene(s) regulate the positional identity of the organ in early embryogenesis, while others control the various phases of proliferation and differentiation (pseudoglandular, canalicular and saccular) by way of the epithelial–mesenchymal interactions and cell–cell contacts through specific cellular receptors.

The bronchial tree is now represented by the two main bronchi; these are subdivided into lobar bronchi, segmental bronchi, lobular bronchi and alveolar ducts. The first 19 of these form the conducting airway, whose main role is to convey air to and from the lungs, and which do not take part in gas exchange. The first seven divisions are cartilaginous in type; the remaining twelve are membranous non-respiratory bronchioles and terminal bronchioles. The following four (generations 20–23) are respiratory bronchioles and, like the remaining four (generations 24–27), which form the alveolar ducts, participate in gas exchange.

At birth, the respiratory unit is the primitive alveolus or "saccule", of which there are about 25 million; further development continues, increasing in rate at about 2 months after birth, resulting in the maximum number of alveoli (about 300 million) at the age of 8 years (see pp. 14–18 for illustrations). The results of recent studies suggest that alveolar formation begins in utero by the 30th week of gestation; however, alveolar formation remains principally a postnatal event. Thus, from these data, five stages of intrauterine lung development have been proposed:

1. *Embryonic*, 26th day to 6th week
2. *Pseudoglandular*, 6th to 16th week
3. *Canalicular*, 17th to 28th week

4. *Saccular*, 28th to 36th week
5. *Alveolar*, after the 36th week

The postnatal period can be divided into two phases: birth to the 18th month, during which there are major shifts in the volumetric proportions of the parenchymal compartments, more intense during the first 6 months of life; and from 18 months to adulthood, when there is proportionate growth of all components in a linear fashion. Epithelial keratin expression in the developing lung may be of value in better defining the various stages of lung development and maturity.

As the pulmonary primordia appear, and subsequently divide and proliferate, the bronchi invade the mass of mesenchymal tissue along the midline and thus create the future mediastinum. Growth continues into the developing pleural cavities, and eventually the surface becomes covered by mesothelial cells which are continuous with those of the pleura.

The mesenchymal tissues encircling the bronchi give rise to the cartilaginous elements, smooth muscle layers, and the supporting connective tissue. This connective tissue becomes very scanty as one approaches the periphery of the bronchial tree. The cartilaginous elements make their appearance about the 7th week, and are fully established by the 25th week. Discountinuous elastin microfibrils first appear around primitive bronchioles at about week 10 of gestation and at about week 20 they can also be observed at the primordium of secondary crests as amorphous material. By week 28 they make their appearance in the saccular walls as thin bundles and are more prominent around the terminal bronchioles. At term, they are present in the primitive alveolar septae.

Mucus-secreting structures are recognizable by the 13th week of intrauterine life, when goblet cells are observed in the epithelium of the trachea and the proximal and intrasegmental bronchi. They seem to grow most rapidly between weeks 14 and 28; at birth they are not found distal to the bronchi. Recently, it has been shown that human bronchi express, like other mucus-secreting organs, a single or two closely related mucin genes, which may be useful in the regulation of mucin gene expression in certain disease states.

The blood supply to the respiratory primordium appears at about week 5 (5 mm) as a capillary network arising from the sixth arch. These vessels take up position next to the branches of the bronchial system, and remain interrelated throughout development. These are the pulmonary artery branches, which are referred to as conventional branches. Besides these arteries, there are additional vessels – supernumerary or accessory arteries – which appear about the 12th week and arise from the hilus. Both systems are complete by the 16th week. Vascular growth and proliferation are under a variety of external factors which may stimulate the growth of vascular endothelial cells. Signals mediated by polypeptide growth factors and physical interactions may take their origin from the endothelial cells themselves in conjunction with specific cell surface molecules.

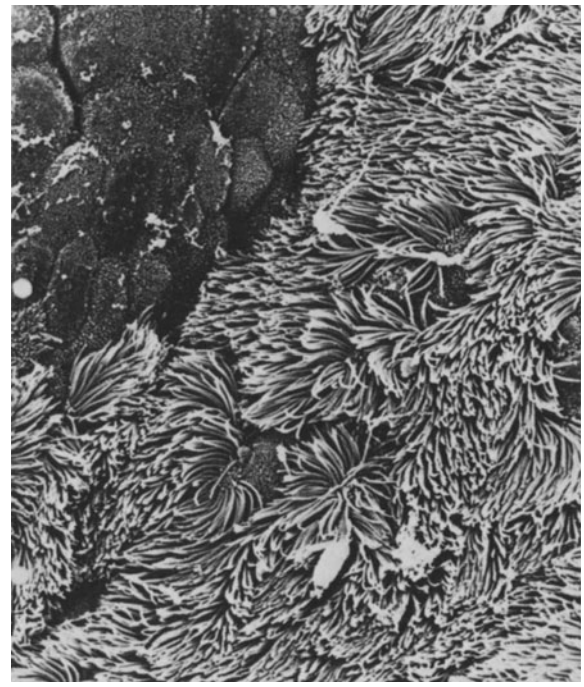
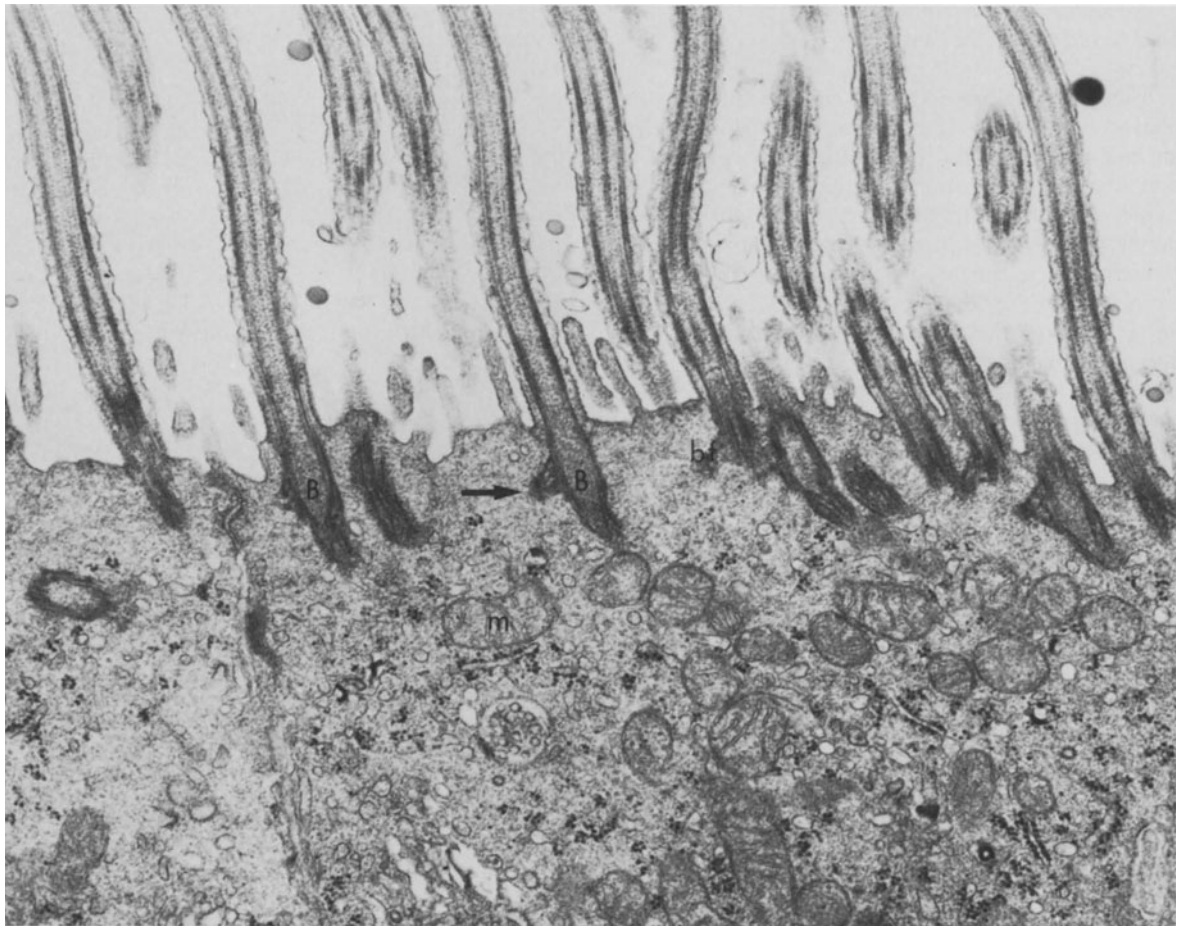


**Fig. 7.1.** Scanning electron micrograph showing cilia of bronchiolar epithelial surface. Clara cell surface, upper left-hand corner. (× 2500) (Courtesy of Dr Y. Kapanci)

The blood supply to the developing lungs drains into a venous plexus, forming a single pulmonary vein that empties into the heart. This vein finally becomes incorporated into the future left atrium, and its main branches on each side form the superior and inferior pulmonary veins.

The pseudostratified columnar epithelium of the large airways is made up of various types of cell. The most common is the ciliated cell, which continues into the respiratory bronchioles, where it is somewhat flatter or cuboidal. These cells are covered by cilia (Fig. 7.1), which are partly anchored by dynein arms and contractile elements to the apical portion of the cell (Fig. 7.2). Contractile elements are also present within cilia. Ciliary movements play an important role in the defence mechanism of the respiratory system, and its absence is associated with certain disease entities.

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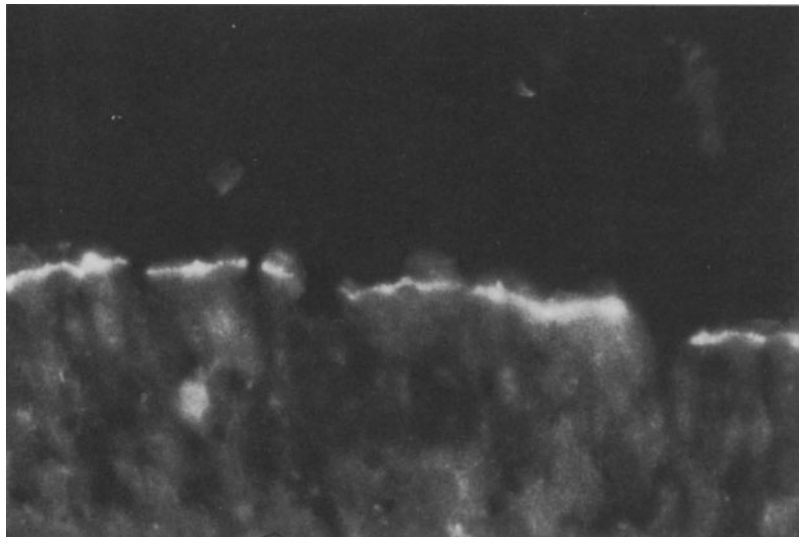


b

**Fig. 7.2.** **a** Electron micrograph showing basal bodies (*B*) and basal feet (*bf*) of cilia. Microfilaments and microtubules (*arrow*) can be seen radiating from the basal feet. Mitochondria (*m*) are also present. **b** Immunofluorescent staining of human bronchial epithelium with AAA serum showing a subciliary fluorescent band of actin. (× 400) (Courtesy of Dr Y. Kapanci)

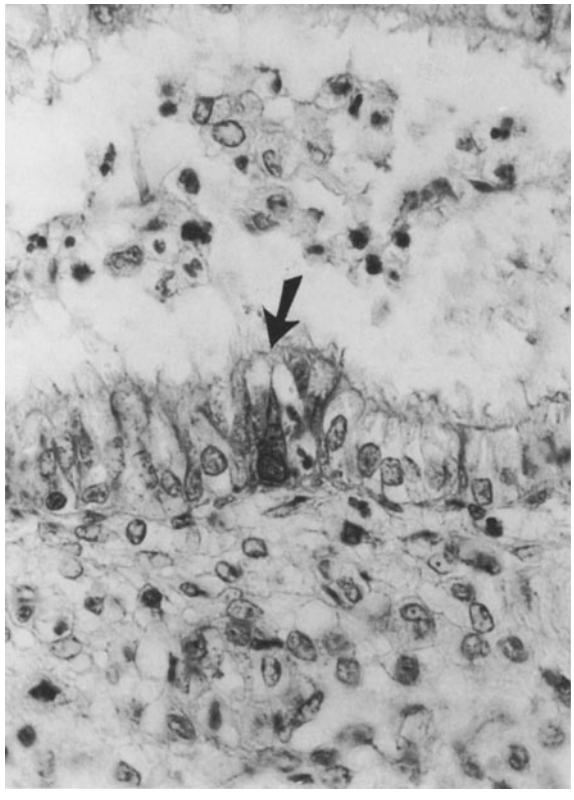
Between isolated or small groups of ciliated cells are the goblet cells, which empty their secretion on the epithelial surface. Against the basal membrane and between the basal portions of the two previous cell types mentioned are the basal cells, which are reserve cells capable of replacing either the ciliated or the goblet cells as necessary.

Three other cell types are also encountered within the respiratory epithelium throughout the tracheobronchial tree. The first is the *Kulchitsky-like* (argyrophil) *cell*, which may occur singly or in groups of two or three. These cells are more prevalent in fetuses and newborns than in the adult, are more commonly referred to as *neuroendocrine cells*, and form part of the dispersed neuroendocrine (APUD) system.

Cell clusters of similar cells are better known as *neuroendocrine bodies*, and together they form the pulmonary neuroendocrine system exerting local paracrine influence by way of synaptic (neurocrine) controls with possible complex responses to nervous influences (Fig. 7.3). They first appear between the 8th and 10th weeks of gestation and attain their maximum density just before term. They contain secretory granules containing monoamines and/or serotonin as well as bombesin, calcitonin and leuenkephalin, the latter mainly within the neuroendocrine cells. They have a sensory innervation with both afferent and efferent terminals. Although their role is not clearly understood, they seem to react as chemoreceptors in response to hypoxia, hyperoxia and hypercapnia therefore regulating ventilation–perfusion ratios in the lung by action on the bronchiolar or bronchial smooth muscle. These cells are considered to be precursors of bronchial carcinoids and have been associated with oat-cell carcinomas.

*Clara cells* are the second type and are found in greater numbers in the bronchioles. They are nonciliated dome-shaped cells containing granules (Fig. 7.4). Recent studies have shown that these cells synthesize, stock and secrete proteinaceous substances identical to those of type II epithelial cells and thus may contribute to the surfactant layer. They also act as stem cells in the process of bronchiolar repair.

The third type is the *brush cell* (type III cell), characterized by its pronounced microvillous covering. This cell type, though rare, has been described at all levels of the airway including the acinus. Its precise function is unknown.



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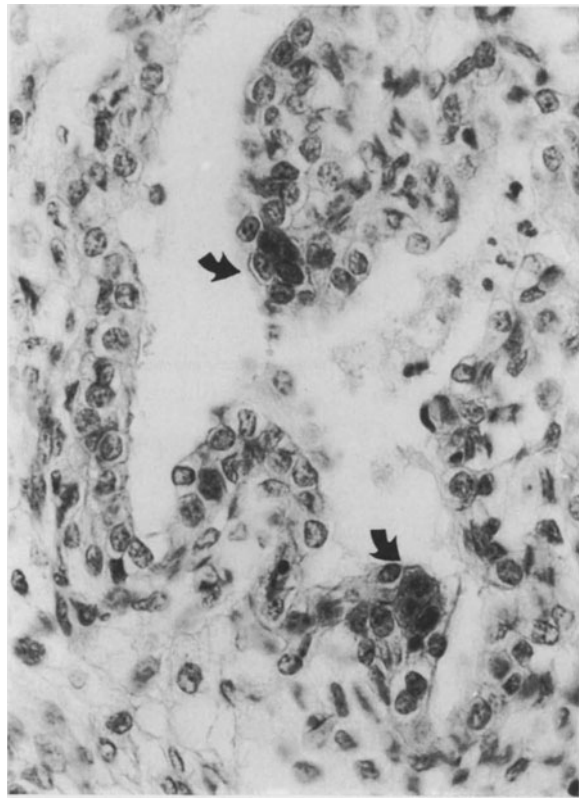
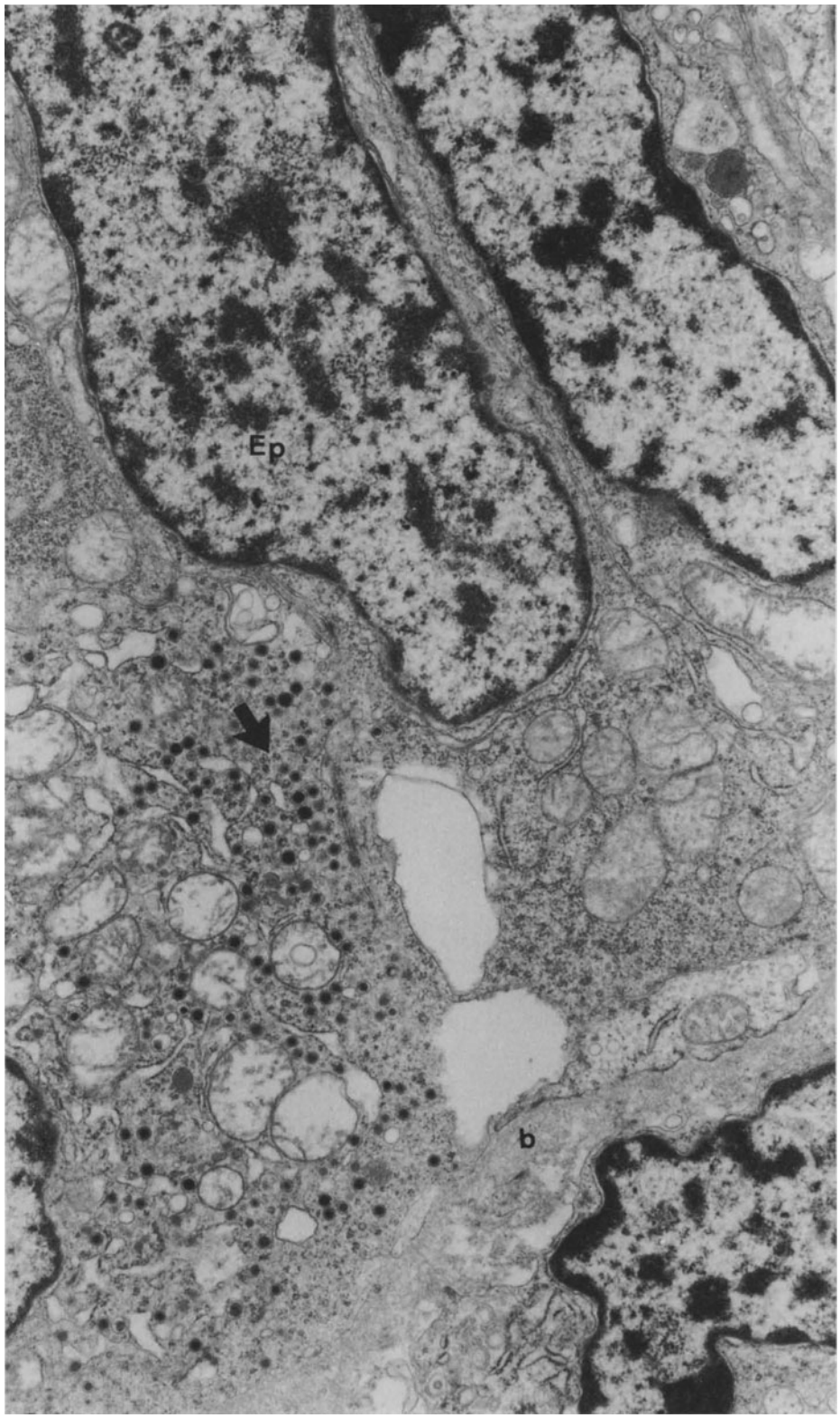


b

**Fig. 7.3.** Fetal lung at 32 weeks' gestation. **a** Neuroendocrine cell (*arrow*). (Grimelius, × 600) **b** Neuroepithelial body stained for bombesin (*arrow continued overleaf*).




**c**

**Fig. 7.3.** (continued). **c** Electron micrograph (× 600) of a neuroendocrine cell (*bottom left*) showing numerous spherical granules (*arrow*) of variable densities. *Ep*, epithelial cell; *b*, basement membrane. (TEM, × 21 716)

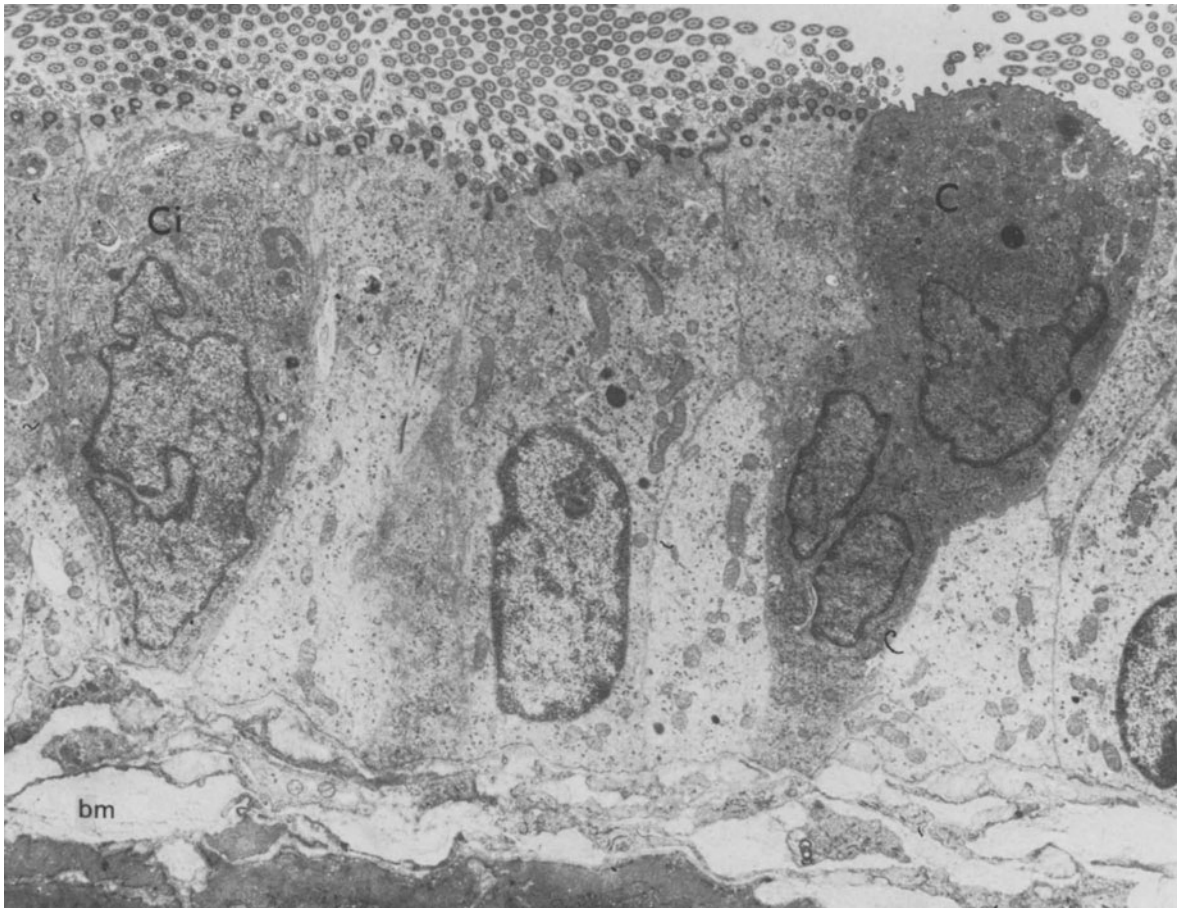



**Fig. 7.4.** Electron micrograph of normal bronchiolar epithelium with its ciliated cells (*Ci*) and a Clara cell (*C*) on the right. Note the basal membrane (*bm*). (× 6300) (Courtesy of Dr Y. Kapanci)

At this point, it is necessary to describe briefly the terminal respiratory unit and the interalveolar septum. The terminal respiratory unit consists of the structures that are distal to the terminal bronchiole. Each terminal bronchiole gives off two to five orders of respiratory bronchiole. The last respiratory bronchiole leads into the first alveolar ducts, which vary in number between two and five. Each alveolar duct opens into as many as 10–16 alveoli. The aveoli are separated by an interalveolar septum made up of three parts: the alveolar epithelium, capillary and interstitial tissue.

Alveolar epithelium is made up of two cell types. Type I cells or squamous pneumocytes have a broad thin cytoplasmic sheet and nuclei that often protrude above the epithelial surface. These cells cover about 90% of the alveolar surface. Type II cells, or granular pneumocytes, are more numerous than type I cells, but because of their configuration – round or cuboidal – they occupy only about 5% of the alveolar surface. They are characterized by surface microvilli and the presence of cytoplasmic osmiophilic lamellar bodies, suggesting a secretory function. These bodies, which appear in the cells at about the 25th week of gestation, are associated with the production of surface-active material (surfactant), a substance that plays an important role in lung expression. Type II pneumocytes are also considered to play an important role in epithelial regeneration. Both cell types are attached to a continuous basement membrane.

The alveolar septa are provided with a single capillary network. The capillary has a basement membrane, which is covered by a single layer of endothelial cells; pericytes are present in the capillary wall (Fig. 7.5).

The interstitial tissue contains some collagen and elastic fibres, among which are found contractile interstitial cells or myofibroblasts. There are also some macrophages in varying numbers within the interstitium (see General References).

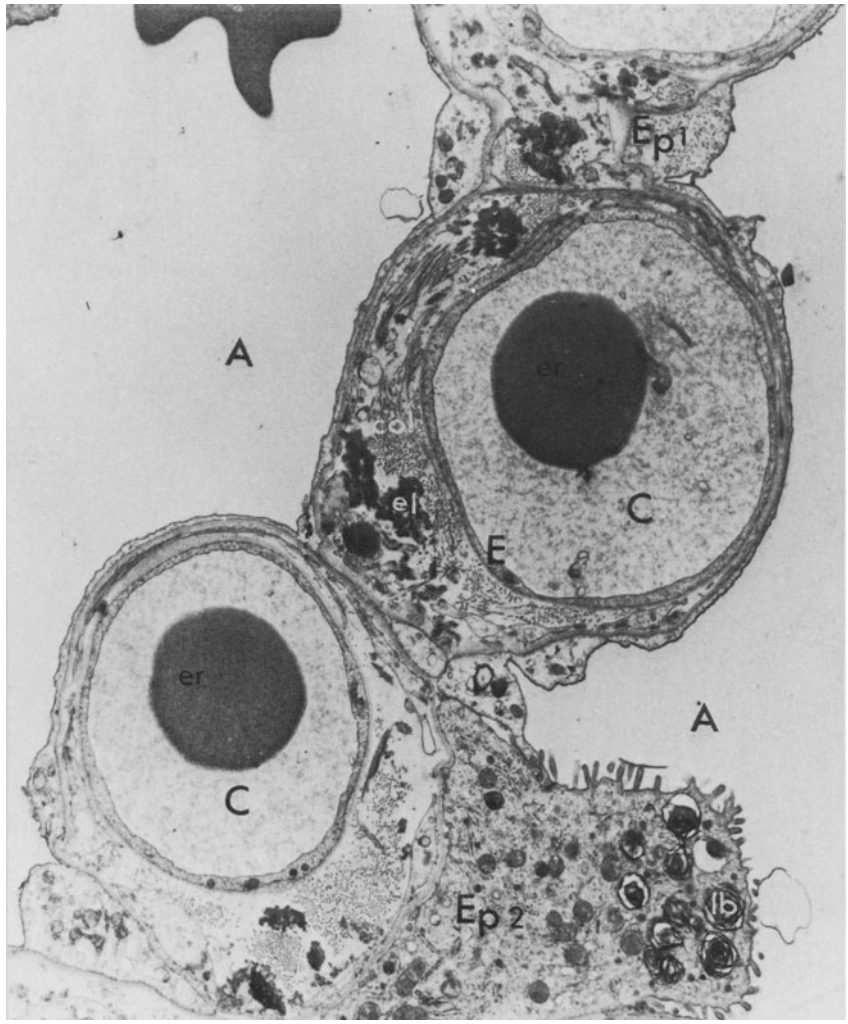
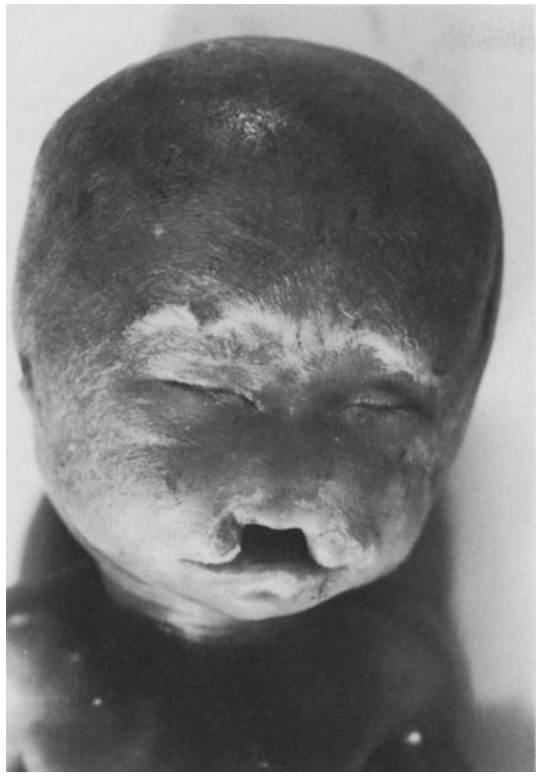



**Fig. 7.5.** Electron micrograph of human alveolar septum. The alveolar spaces (*A*) are lined with type I (*Ep I*) and type II (*Ep 2*) epithelial cells, the latter containing lamellated bodies (*lb*). Capillaries (*C*) contain erythrocytes (*er*) and are lined with endothelial cells (*E*). Collagen fibres (*col*) and elastic fibres (*el*) are conspicuous. (× 5700) (Courtesy of Dr Y. Kapanci)

# Nose and Nasopharynx

## Congenital Abnormalities of the Nose

Illustrations of various malformations of the nose have been documented by Patten (1968) and Potter (1962) (Fig. 7.6). *Congenital absence* of the nose and anterior nasopharynx is a rare condition. Gifford et al. (1972) described two cases and reviewed the literature on the subject. In *cyclopia*, another rare condition, in which there is fusion of the eyes, there is a proboscis-like cylindrical fleshy mass hanging from the nasal region or the forehead in place of the nose. Sometimes this bears a single central orifice representing a nostril, but in other instances there is no external opening. In most cases there is no communication with the nasopharynx (Landing 1957; Potter 1962). Rontal and Duritz (1977) described a case in which a lateral proboscis replaced one of the nostrils. Cyclops have also been described in association with chromosomal abnormalities, and principally with trisomies (Arakaki and Waxman 1969). In a somewhat milder form of cyclopia, *cebocephaly*, there is hypoplasia of the maxillary bones and nose associated with a lissencephalic brain with fusion of the cerebral hemispheres and internal hydrocephaly. *Frontonasal dysplasia*, another relatively rare condition, may or may not be associated with cleft lip and cleft palate. The condition appears to be a developmental defect not necessarily related to chromosomal



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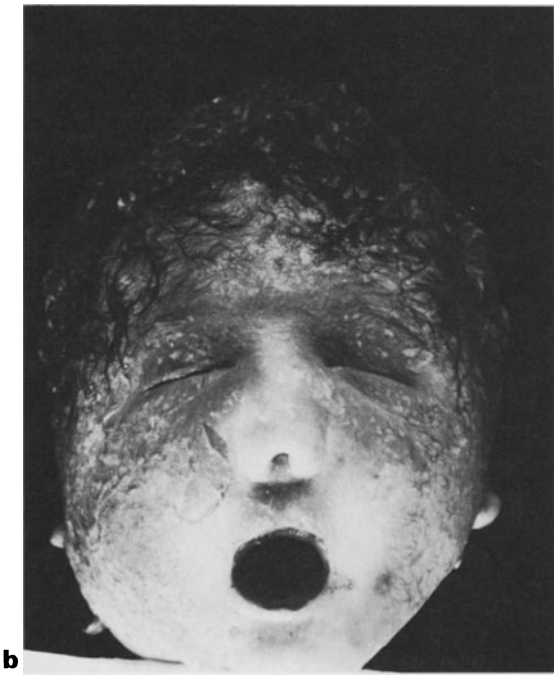


b

**Fig. 7.6.** **a** Absence of the nose of a polymalformed female fetus of 22 weeks' gestation with trisomy 13. **b** Male fetus of 36 weeks' gestation with malformed nose and a central dimple but no nasal openings.

abnormalities (Sedano et al. 1970). *Aplasia* (hypoplasia) of the alae nasi is rare and often associated with other abnormalities, including deafness and abnormal endocrine function (Johanson and Blizzard 1971) and cardiac anomalies with situs inversus and severe hypoproteinaemia (Helin and Jodal 1981). *Craniofrontonasal dysplasia* (craniosynostosis, ocular hypertelorism, broad nasal root, with a bifid nasal tip or median nasal groove) is another rare syndrome which does not seem to follow a Mendelian mode of inheritance (Sax and Flannery 1986). Cleft lip and palate are discussed on pp. 51).

*Choanal atresia* can be divided into two main types. Anterior atresias are found when the epithelial plugs between the developing medial and lateral nasal placodes are not absorbed in the embryo. Posterior (choanal) atresia, by far the most common form although still a rare anomaly, is usually situated at the level of the sphenoid, vertical vomer and palatine bones adjacent to the nasopharynx. Choanal atresia is often found in association with certain syndromes or chromosomal abnormalities such as the CHARGE association or the trichorhinophalangeal syndrome type 1 (Langer–Giedion syndrome) (Marchau et al. 1993; Morgan et al. 1993). It is an important cause of neonatal asphyxia; it can be relieved by a simple surgical procedure or by prompt medical management (Winther 1978; Stahl and Jurkiewicz 1985; Ferguson and Neel 1989).

The anomaly occurs as a result of bony overgrowth, an excess of hyperplastic cartilage, or membranous proliferations, or results from combinations of these factors. It is most commonly unilateral, with a right-sided predominance, but may be bilateral, complete or incomplete. It has been known to be inherited as a dominant trait in certain families. Choanal atresia has a female predominance (estimated at 2 : 1), and is often associated with other congenital anomalies, mainly of the cardiovascular system, face and, in rare instances, the kidney (Qazi et al. 1982; Stahl and Jurkiewicz 1985; Ferguson and Neel 1989).

*Dermoid cysts* of the nose are rare. They may be the cause of a widened nasal septum, septal deviation or duplication (Taylor and Erich 1967; Hoshaw and Walike 1971; Szalay and Bledsoe 1972), and are classified according to location into: *superficial*, found mainly in the perpendicular plate of the ethmoid bone or the quadrangular cartilage; and *deep* or *septal*, found within the columella and the vomer. They may also be observed in Jacobson's organ or the nasopalatine region of the floor of the nose (Pratt 1965; Sing and Pahor 1977). Some communicate with the dermis by a fistulous tract opening in the midline of the nasal bridge or by a small dimple in the skin (MacGregor and Geddes 1993; Cauchois et al. 1994). Macroscopically, they are round or oval,

**Fig. 7.7.** Fistulous tract of nasal dermoid cyst lined with stratified squamous epithelium in an 8-year-old boy. (H&E, × 35)

firm or rubbery masses which, on histological examination, show a cavity lined with stratified squamous epithelium (Fig. 7.7).

## Acquired Disease

Nasal deformities in the neonatal period are generally associated with mechanical ventilation and are the direct complications of nasal endotracheal tubes (Gowdar et al. 1980). In infants and children, the majority of acquired pathological conditions are associated with infections or trauma. Chemical irritants or obstructions of the nares by foreign bodies are also important in this age group. In infections, bacterial or virological studies of secretions or scrapings will often indicate the pathogenic agent responsible, but many pathogens (bacterial or viral) can now be detected by the indirect immunofluorescence and/or the enzyme-linked immunosorbent assay (ELISA) technique (Popow-Kraupp et al. 1986). Both tuberculosis and congenital syphilis of the nose have become rare entities, at least in industrialized countries. The nasal lesions formerly encountered in yaws in the developing countries have been almost completely eliminated; however, leprosy still remains a problem, and the diagnosis can often be established from nasal scrapings (Barton and Davey 1976; Olson et al. 1979).

### *Hypertrophic or "Hyperplastic" Rhinitis*

Hypertrophic or "hyperplastic" rhinitis is a relatively common condition among adolescents, and has been considered to be associated with chronic infection of the nose or the paranasal sinuses. However, there is evidence that it might be related to a hypersensitivity reaction and that hormonal factors may be important. New radiological techniques and especially computed tomography are valuable in arriving at a correct diagnosis (Williams and Williams 1969; Nguyen et al. 1993).

Excised mucosa shows squamous metaplasia of the epithelium together with glandular atrophy. There is marked submucosal oedema with some fibrosis and a varying degree of chronic inflammation.

### *Rhinoscleroma*

Rhinoscleroma is a slowly progressive chronic granulomatous disease often beginning as a bilateral lesion in the nose with nasopharyngeal extension. The larynx and trachea are also often involved. Though endemic in Eastern Europe, Central and South America, Africa and the Far East, it can be encountered in any part of the globe and can affect either sex of any race at any age. There is a slight female preponderance. The condition is encountered most frequently among those living in poor socioeconomic conditions or with impaired immune function. The disease affects the mucous membranes, causing hyperplasia and hypertrophy of the surface epithelium. As it progresses, an atrophic rhinitis develops, with the formation of nodular granulation tissue, which, in most cases, obstructs and destroys the nares.

Histologically, the lesions are divided into three stages, which depend on the clinical phase of the disease. The first is the catarrhal–atrophic stage, in which there is squamous epithelial metaplasia accompanied by a mixed subepithelial inflammatory reaction including polymorphonuclears and some granulation tissue. Second is the granulomatous stage, characterized by a pseudoepitheliomatous hyperplasia and a mixed chronic inflammatory reaction associated with numerous large histiocytes or

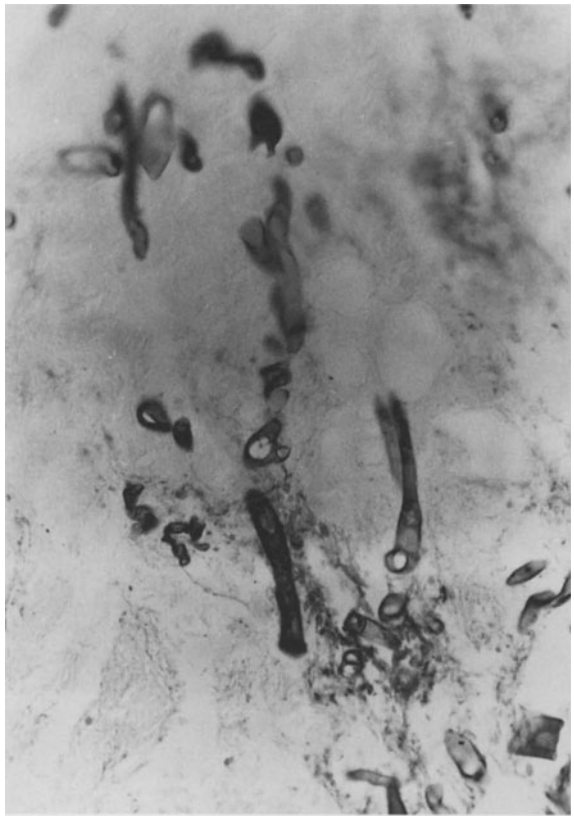


**Fig. 7.8.** Mucomycosis. The fungus may go unnoticed unless special stains (PAS, Grocott) are employed. (Grocott, × 310) (Courtesy of Dr J. Briner).

foam cells (Mikulicz cells) with a central nucleus and a clear vacuolated cytoplasm. Some of these histiocytes contain several gram-negative encapsulated bacilli (*Klebsiella rhinoscleromatis*), which are considered to be the cause of the disease. The bacilli, although apparent in gram-stained tissue, are distinct in sections stained by silver impregnation techniques or by the periodic acid–Schiff (PAS) stain. Specific immunohistological techniques are useful, and the organisms are readily observed on electron microscopy. Thirdly, there is sclerotic stage, resembling the granulomatous stage, leading to nasal deformity or destruction may ensue with extension into the adjacent structures, including the bony skeleton, and eventually leading to severe disabilities or stenosis in the late fibrotic stages (Andraca et al. 1993).

*Mucomycosis* by its presentation (a purulent brownish nasal discharge, sometimes with bleeding) may resemble clinically the first stage of rhinoscleroma. However, special stains (PAS, Grocott) will illustrate the fungus (Fig. 7.8). It may be the cause of nasal obstruction, septal nasal perforation or cerebral involvement.

## *Sinus Histiocytosis with Massive Lymphadenopathy*

*Sinus histiocytosis with massive lymphadenopathy* or Rosai–Dorfman disease is a benign condition that sometimes involves the nasal cavities and paranasal sinuses with extension into the maxillary sinus, retro-orbital space and even the brain. It is usually accompanied by massive lymphadenopathy, principally in the cervical region. The condition has a worldwide distribution, but appears to be more common in developing countries or in patients with an immunodeficiency state or condition and in autoimmune disorders. Although all ages may be affected, there is a predilection for infants and children. Both sexes are about equally involved. Histologically, the tissue crossed by fibrous bands is infiltrated by large histiocytes mixed with lymphocytes and occasional lymphoid aggregates without germinal centres. The histiocytes, isolated, in groups or sheets, have a clear cytoplasm containing a large indented nuclei with a prominent nucleoli (Fig. 7.9). The cytoplasm is PAS positive and stained with S100 protein and occasionally with CDI. Emperipolesis is a common feature, with lymphocytes and plasma cells present in the cytoplasm. These lymphocytes are CD4 and CD8 positive, indicating their T-cell nature. An occasional atypical histiocyte resembling the Reed–Sternberg cell has been described. The aetiology of the condition is unknown, but some authors have incriminated the Epstein–Barr virus, while others favour the association of a dysimmunity state with an inflammatory state (Foucar et al. 1990; Paulli et al. 1992). Involvement of the subglottis and trachea have also been documented in a 17-year-old boy (Leighton and Gallimore 1994).

## *Lethal Midline Granuloma or Non-healing Midline Granuloma*

A mixed group of conditions (inflammatory, neoplastic and vasculitic) have been described under this non-specific title, but using detailed immunohistochemical studies it has been shown that in the majority of cases non-Hodgkin's lymphomas (B- or T-cell types) or malignant histiocytosis is the most frequent underlying pathological condition (Fu and Perzin 1979; Aozasa and Inoue 1982; Ishii et al. 1982; Weis et al. 1986). Fu and Perzin have emphasized the need to take many sections from outside the necrotic area to arrive at a correct diagnosis. However, it is necessary in all cases to exclude the possibility of *Wegener's granuloma*, which often presents clin-

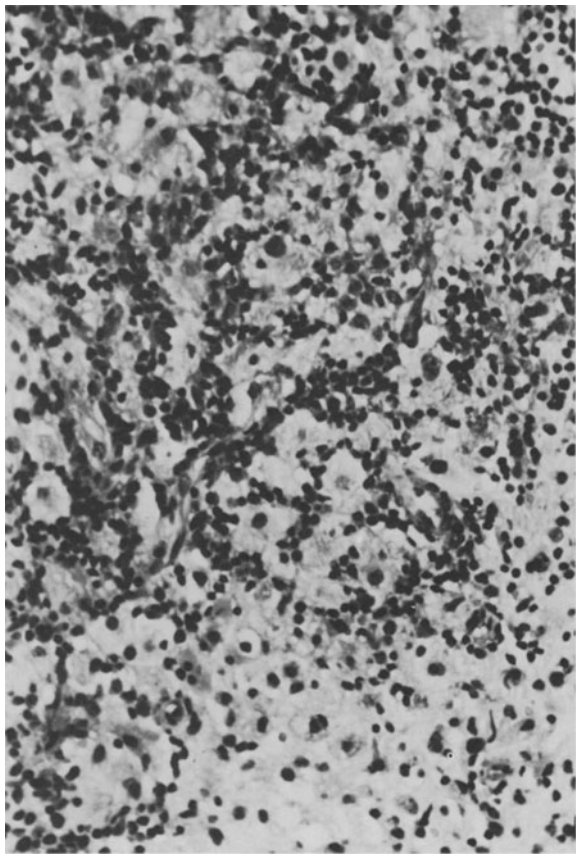


**Fig. 7.9.** Sinus histiocytosis in a 9-year-old boy, presenting as polypoid nasal masses with extensive involvement of the surrounding tissues and destruction of the adjacent bony structures. (H&E, × 160)

ically in this way. Baliga et al. (1978) collected eight childhood cases of Wegener's granuloma from the literature, and three of these were of the generalized type. Moorthy et al. (1977) were able to collect seven cases of the generalized type and added two of their own. Recently, Nespoli et al. (1979) described another case in a 27-month-old girl, the youngest on record. Histologically, the condition is characterized by angiocentric angiodestructive aseptic necrosis, which likewise involves the kidneys and in many instances the lungs (Crissman et al. 1982).

## Tumours

Neoplasms of the nose and nasopharynx in infancy and childhood are rare; however, tumours of the surrounding tissue (brain, meninges, bony skeleton) may protrude into the nasal cavity or nasopharynx, producing symptoms, mainly obstructive.

### *Nasal Polyps*

Nasal polyps are not true neoplasms but are associated with chronic nasal inflammation or repeated allergic reactions within the nasal cavity. They may also be associated with vascular disturbances in the mucosa or be the result of mechanical obstruction. They are frequently encountered in certain systemic diseases, the principal of which is fibrocystic disease of the pancreas (mucoviscidosis) (Berman and Colman 1977). These last authors, among others, have suggested that one should always look for cystic fibrosis in children presenting with nasal polyps. Although their aetiology in this condition is not fully understood, it has been stated to be associated with iodide therapy; however, this has not been supported in all series (Finn et al. 1981; David 1986). Tos et al. (1977) could not find differences between nasal polyps from cases of cystic fibrosis and those of other origins; however, Oppenheimer and Rosenstein (1979) have shown histochemical differences between polyps in cystic fibrosis and those of atopic patients.

Polyposis forms an integral part of *Kartagener's syndrome* (Siewert–Kartagener), a hereditary condition with autosomal recessive inheritance involving different genetic determinants and affecting equally both sexes without racial predisposition. Patients present with situs inversus, chronic bronchitis with bronchiectasis (bilateral), rhinosinusitis, nasal polyposis and chronic recurrent otitis media, with absence or underdevelopment of the frontal sinuses and a high percentage of infertility in males due to spermatozoal immotility. In this syndrome, there is partial or complete lack of ciliary motility of the epithelial cells lining the upper and lower respiratory system and the middle ear as well as the tails of spermatozoa. Ciliary dysfunction is considered to be the cause of the disease, and is due to the absence of, or abnormalities in, the ciliary dynein arms (outer, inner or both) normally rich in ATPase (Fig. 7.10), the radial spokes and an abnormal internal structural arrangement of the microtubular doublets within the cilia. This condition has also been reported in dogs (Afzelius et al. 1984; Pysher and Neustein 1984; Sturgess and Turner 1984; Popper et al. 1985; Eavey et al. 1986; Sturgess et al. 1986). Kartagener's syndrome is now considered to be part of the more general "immotile cilia syndrome", also referred to as the "dyskinetic cilia syndrome" or "ciliary dyskinesis", comprising a heterogeneous group of disorders exhibiting a spectrum of ciliary structural anomalies associated with a range of abnormalities in ciliary motility and defects in the granulocyte locomotory system. There is absence of, or diminished, cilial motility; various structural abnormalities of cilia associated with chronic infec-

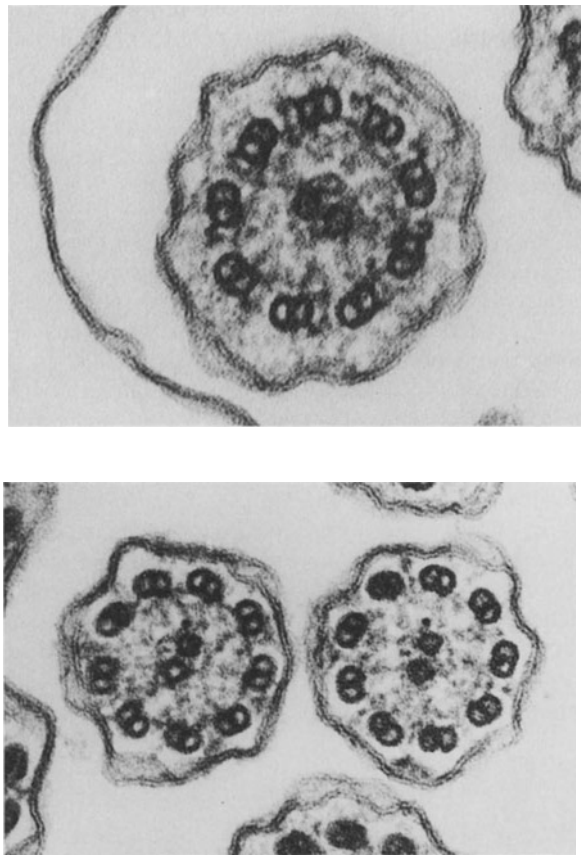


**Fig. 7.10.** **a** Normal cilium showing 9 + 2 doublets and presence of all the dynein arms. **b** Case of Kartagener's syndrome showing total absence of all the dynein arms, both inner and outer. (× 82 800)

tion of the upper and lower respiratory system with bronchiectasis; and male infertility, irrespective of situs inversus, associated with headache and some sensory disturbances. Genetic factors may play a role in some of the various ultrastructural variations observed (Eavey et al. 1986; Sturgess et al. 1986; Torikata et al. 1991; Verra et al. 1993; Rayner et al. 1995).

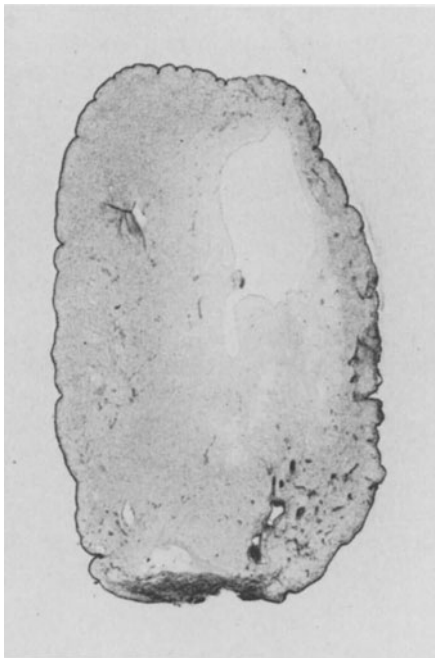
Most nasal polyps arise from the mucosa of the ethmoidal cells at the level of the middle meatus or in the paranasal sinuses. They may be single or multiple, unilateral or bilateral, and either sessile or pedunculated. They are often the source of nasal bleeding or obstruction, and may cause displacement and even destruction of the bones limiting the nasal cavity (Winestock et al. 1978). On gross inspection, they present as smooth round or oval myxomatous masses, yellowish in colour. Histologically there is hypertrophy of the mucous membrane covered by columnar ciliated epithelium, sometimes with squamous metaplasia. The stroma is very loose, fibrillar and oedematous. There is stromal atypia in some cases, which may be falsely interpreted as sarcoma (Compagno et al. 1976). The vessels are dilated, and there are scattered aggregates of lymphocytes and plasma cells with eosinophils (Fig. 7.11). The submucosal glands are generally hyperplastic, but may be atrophic in some areas.

*Choanal polyps* are a different clinical entity. They generally arise from the mucosa of the maxillary sinuses and project towards the posterior choanae. Their histology is very similar to that of other nasal polyps.

In tropical and subtropical countries, many mycotic infections of the nose in children can present as nasal polyps (Engzell and Jones 1973). Histological examination often reveals granulation tissue, sometimes with granulomas and/or foci of necrosis. Special staining techniques (silver impregnation or PAS) are often necessary for identifying the particular fungus (Fig. 7.11c). Cultures may be necessary in establishing the diagnosis (see Chapter 14, pp. 729).

## *Epithelial Tumours*

Epithelial tumours of the nasal cavity are rare in the paediatric age group. *Papillomas* are occasionally observed in childhood with a marked preponderance for male subjects. The lesions have been known by many synonyms, but currently they are commonly referred to as *inverted papillomas*. In most of the older literature, this term was applied to lesions presenting an inverted growth pattern and situated principally on the lateral walls of the nasal cavity, while those having a fungating exophytic growth pattern and located on the septum were referred to as septal papillomas. The pathological features, clinical presentations and behaviour, apart from their growth pattern, are similar and therefore do not warrant different names. The tumour is usually unilateral, can be localized or diffused, papillary or lobulated, or occasionally pedunculated. Histologically, there is marked proliferation of basal cells, which may partially or completely replace the ciliated cells by a stratified squamous epithelium. This hyperplastic epithelium produces invaginations within the fibrous stroma, and intercellular "microcysts" are not an uncommon feature (Fig. 7.12). Mitotic figures are relatively few and nuclei atypia rare. There are sometimes varying degrees of dyskeratosis and some hyperkeratotic areas. Many of these tumours appear to be histologically benign but are locally aggressive. Clinically they behave as malignant tumours, and aggressive surgery is indicated because inadequate removal is followed by local recurrences and squamous cell carcinoma is known to develop from these lesions. There is increasing evidence that these types of

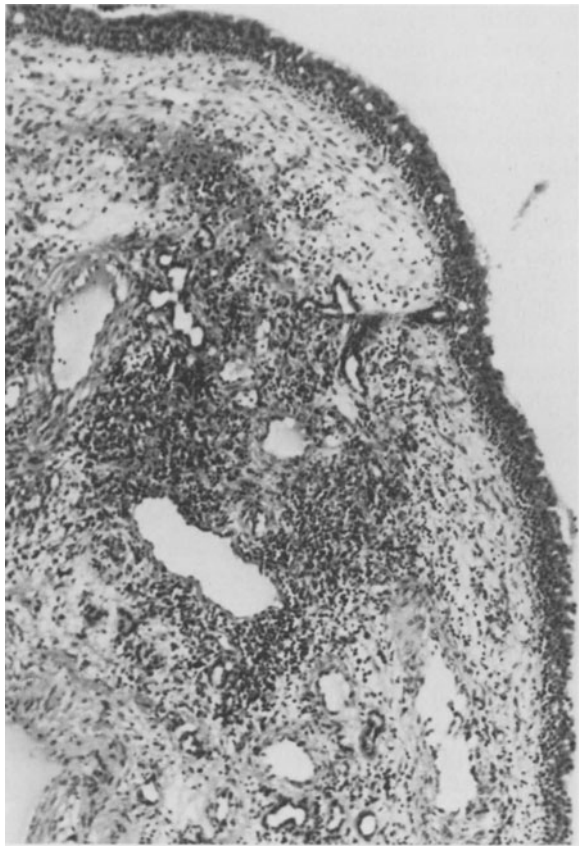


a

lesions may be associated with one or more specific types of human papillomaviruses (Kelly et al. 1980; Perzin et al. 1981; Eavey 1985; de Villiers et al. 1986; Kahn et al. 1986).

*Squamous cell carcinoma* of the nasal cavity is very rare in childhood. We have observed a case in a 9-year-old boy who presented with a large polypoid necrotic mass obstructing the right nostril and causing extensive destruction of the corresponding maxilla (Fig. 7.13). Carcinoma of the nasopharynx, however, is more prevalent, even though Jaffé (1973a) recorded only three cases in his review of 178 tumours of the head and neck in children.

In childhood *carcinomas of the nasopharynx* are more common in the Far and Middle East, and especially in Africa, where they may represent about 15% of all nasopharyngeal carcinomas. These tumours do occur in other areas but are rare. They cause nasal obstruction, deafness, cranial nerve palsy, and protosis. There is a male predominance and a high incidence of distant metastases. Patients with these tumours have high antibody titres to Epstein–Barr



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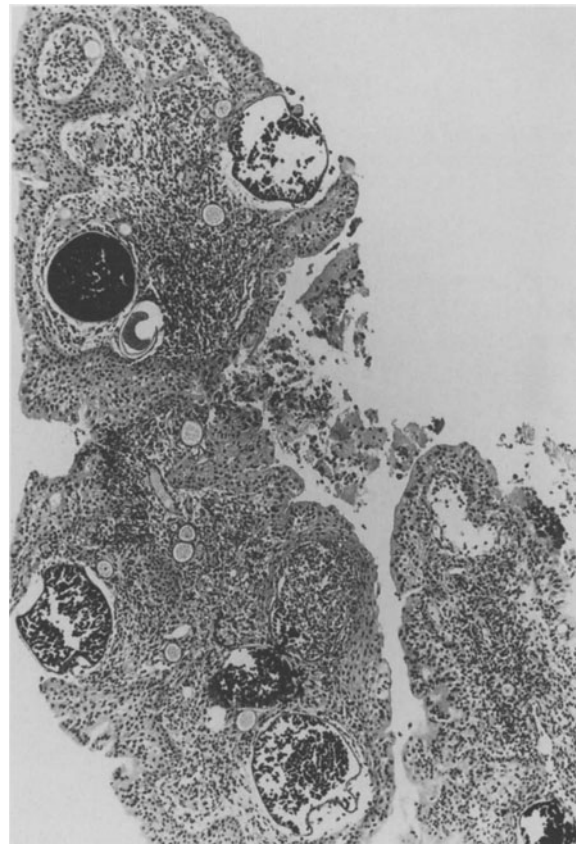


c

**Fig. 7.11.** **a** Nasal polyp from a 12-year-old boy with cystic fibrosis. **b** Nasal polyp in a child with chronic sinusitis. **c** Rhinosporidosis in a male patient from Sri Lanka (HCE, × 50) (Courtesy of Dr J. Briner)

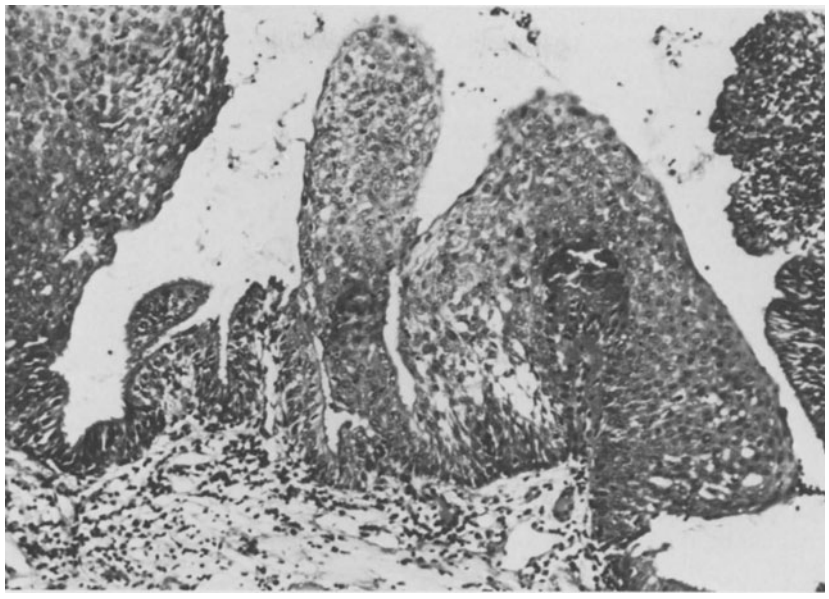
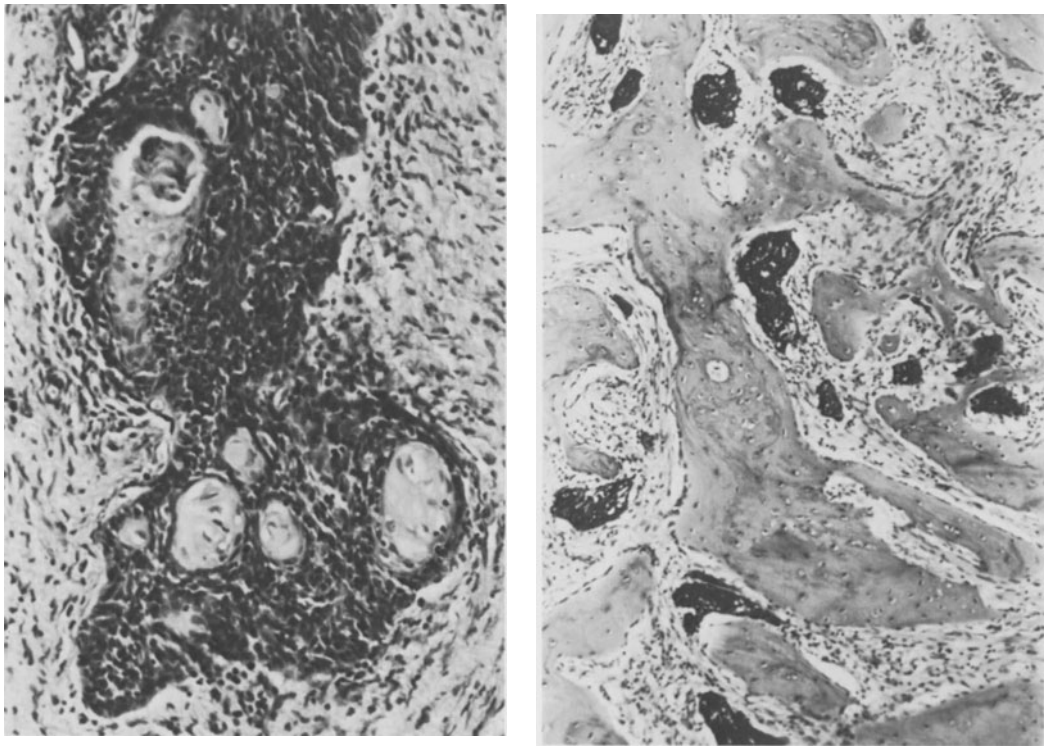


**Fig. 7.12.** Nasal papilloma in a 14 year-old girl with papillomatosis of the laryngotracheal tree discovered at age 3. Note the numerous "microcysts". (H&E, × 160)



**a** **b**

**Fig. 7.13.** **a** Squamous-cell carcinoma of the nasal cavity in an 11-year-old boy. (H&E, × 225); **b** Infiltration and destruction of the adjacent bones. (H&E, × 60)

virus, and the virus can also be identified in the tumour and other cells (Niedobitek and Young 1994).

Carcinomas of the nasopharynx vary in histological appearance. The well differentiated epidermoid carcinoma is more often encountered in the adult, whereas in childhood the tumours are generally poorly differentiated, resembling transitional cell carcinoma. The cells are large with an almost inconspicuous cytoplasm, and sometimes they have a syncytial appearance. Their nuclei are quite large, round or oval with prominent nucleoli. Some cases may have the appearance of a lymphoepithelial carcinoma of the *Schmincke–Regaud* type; others may be anaplastic in character (Pick et al. 1974). By the use of antibodies (keratin antibodies, leucocyte common antigen, desmin, myoglobin, etc.), it is now possible to arrive at a precise diagnosis of this often undifferentiated carcinoma (Miettinen et al. 1982; Shi et al. 1984; Ziegels-Weissman et al. 1984; Frierson et al. 1986; Micheau 1986).

*Intranasal mixed tumours* (*pleomorphic adenomas*) have also been reported in children. The histology is similar to that of pleomorphic tumours of the major salivary glands, but they have a relatively lower rate of recurrence (Compagno and Wong 1977).

The majority of nasopharyngeal tumours (benign or malignant) in childhood are derived from the supporting tissues and from neighbouring structures – for example, the nasopharyngeal papillary adenocarcinoma (Wenig et al. 1988).

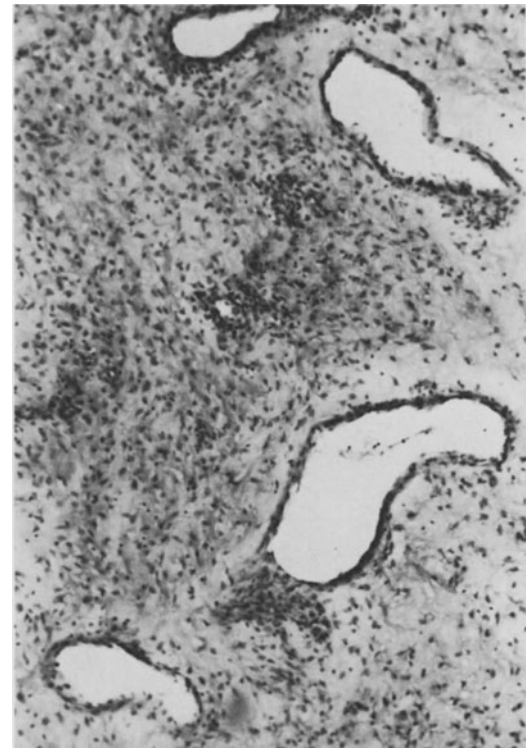


**Fig. 7.14.** Juvenile nasopharyngeal angiofibroma in a 13-year-old boy. Note the fibrocytic stroma with the stellate cells and the scattered vessels devoid of muscular layers. (H&E, × 160)

## *Vascular Tumours*

*Haemangiomas* of the nose and nasopharynx are occasionally encountered in infancy and childhood. They can arise anywhere in the nasal cavity but have a predilection for the anterior nasal septum, and are a frequent cause of bleeding. They may present as extremely vascular sessile or pedunculated polyps causing obstruction and are sometimes associated with cutaneous haemangiomas (Strauss et al. 1981) *Benign haemangioendothelioma* has also been described in children. In these highly cellular tumours the capillaries are lined with prominent but uniform endothelial cells (Fu and Perzin 1974a).

*Juvenile nasopharyngeal angiofibroma* is a rare haemangiomatous tumour occurring principally in adolescent males and is more common in fair-skinned and red-headed individuals. Although benign, it is often locally aggressive and may displace and distort adjacent structures and even erode bone. It occasionally appears before puberty, but grows rapidly during this period and may regress in later years, undergoing hyalinization, fibrosis and or myxomatous changes. These clinical features have suggested hormonal dependence, even though the tumour has been reported in adults and in females. Bilateral carotid angiography is one of the most useful diagnostic aids (Conley et al. 1968; Hicks and Nelson 1973; Fu and Perzin 1974a; Sessions et al. 1981).

The pathology of this lesion has been described in detail (Taxy 1977; Arnold and Huth 1978). It generally develops as a solitary, sessile, somewhat lobulated mass in the region of the sphenoethmoidal recess or the choana, from where it may protrude into the nasal cavity, producing obstruction. It can extend into neighbouring structures. Histologically, the angiofibroma is covered by normal nasopharyngeal epithelium and is composed of numerous distended vessels lined with a flattened endothelium in a relatively dense fibrous stroma. The vessel walls are devoid of elastic fibres, and their muscular coats are irregular, incomplete or even absent in smaller vessels, as demonstrated by specific immunohistochemistry. The stroma is fibrocytic in appearance, with a varying amount of collagen fibres but little or no elastic fibres and numerous S100 positive nerve fibres. The stromal cells are myofibroblasts staining positive with Vimentin and smooth muscle actin (Beham et al. 1993) (Fig. 7.14). Taxy (1977) and

Arnold and Huth (1978) have recently described the ultrastructure of these tumours. Angiofibromas create many therapeutic problems due to bleeding, local extension and a high rate of local recurrence (Sessions et al. 1981; Chandler et al. 1984; Jones et al. 1986). Androgen receptors have been demonstrated in these tumours (Lee et al. 1980), suggesting that they may be androgen dependent. Recently, Kumagami (1991) has demonstrated oestradiol in the stromal cells and Schiff et al. (1992) have localized an angiogenic growth factor in the endothelial cells by immunohistochemical techniques. This benign lesion may undergo sarcomatous transformation into a malignant fibrous histiocytoma after irradiation or combined therapy (Spagnolo et al. 1984). Nasopharyngeal angiofibroma must be distinguished from fibromatosis of the region usually encountered in younger children and more so in infancy. The lesion may mimic haemangioma, which must be considered in the differential diagnosis.

*Angiofollicular lymph node hyperplasia* (Castleman's disease) of the nasopharynx is rare and could easily be mistaken for juvenile nasopharyngeal angiofibroma clinically. The tumour, however, is composed of lymphoid tissue covered by respiratory epithelium. Within this tissue are numerous variably sized germinal centres with hyalinized central zones (Fig. 7.15). The germinal centres are surrounded by concentric rings of lymphocytes (B-cells), and the interfollicular zones are made up mainly of T-lymphocytes. Among these are groups of plasmacytoid monocytes. The tissue is richly vascularized and some of these vessels may have hyalinized walls (Chen and Kuo 1993).

*Lymphangioma* of the nasal cavity is extremely rare but may sometimes be seen in adolescents and has been reported in infancy (Beneck et al. 1985). It presents as a polypoid mass covered by normal respiratory epithelium; in a fibrous stroma there are numerous dilated lymphatic vessels lined with flattened endothelial cells (Fig. 7.16).

*Haemangiopericytoma* has also ben recorded in the nasal cavity (Fu and Perzin 1974a). Benveniste and Harris (1973) reviewed the literature and found ten cases, one of which was in a 4-year-old girl. They added one case of their own, which occurred in a newborn. Compagno (1978) has reviewed the subject of haemangiopericytomas of the nasal cavity, and found that although they do occur in childhood they are more common among adults.

## *Fibrous Tumours*

Fibrous tumours are exceedingly rare in children. Fu and Perzin (1976b) did not find any cases of *fibroma* in the paediatric age group in their material, but observed three cases of *fibromatosis*. Townsend et al. (1973) described a case of what they referred to as a histocytoma in a 3-year-old boy and Rice et al. (1974) recorded a case in a 13-year-old girl. Jaffé (1973a) has reported a case of *malignant histiocytoma* of the nose in an infant. The histological picture usually shows fibroblast-like cells with a histiocytic component presenting a wide range of morphologic changes (Perzin and Fu 1980).

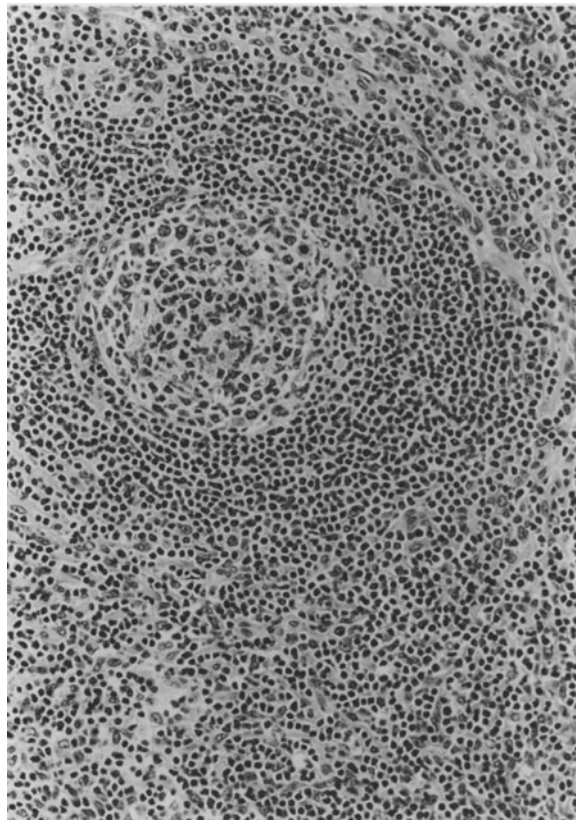


**Fig. 7.15.** Castleman disease showing hyalinization of the follicular zone surrounded by rows of mononuclear cells in an "onion skin" fashion. (H&E, × 50)(Courtesy of Dr J. Briner)

*Fibrosarcoma* is also very rare. Fu and Perzin (1976b) found only one case below 15 years of age among their 13 patients, and made reference to two others in children (Fig. 7.17).

## *Muscular Tumours*

Smooth-muscle tumours (*leiomyoma* and *leiomyosarcoma*) of the nasal cavity are rare. There were no cases in children in the series of Fu and Perzin (1975). Striated-muscle tumours are more common. Fu and Perzin (1976a) described one case of *rhabdomyoma* and found another in the literature; Canalis

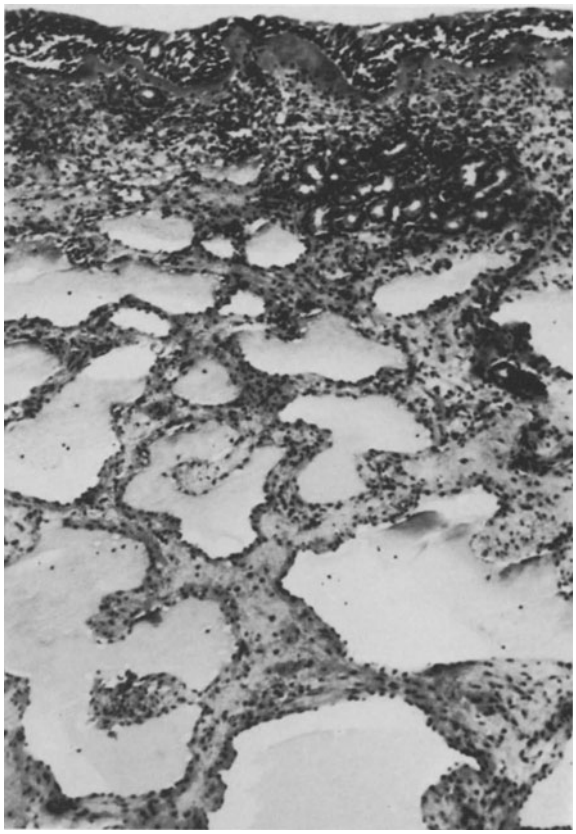


**Fig. 7.16.** Lymphangioma in a 15-year-old. (H&E, × 60)

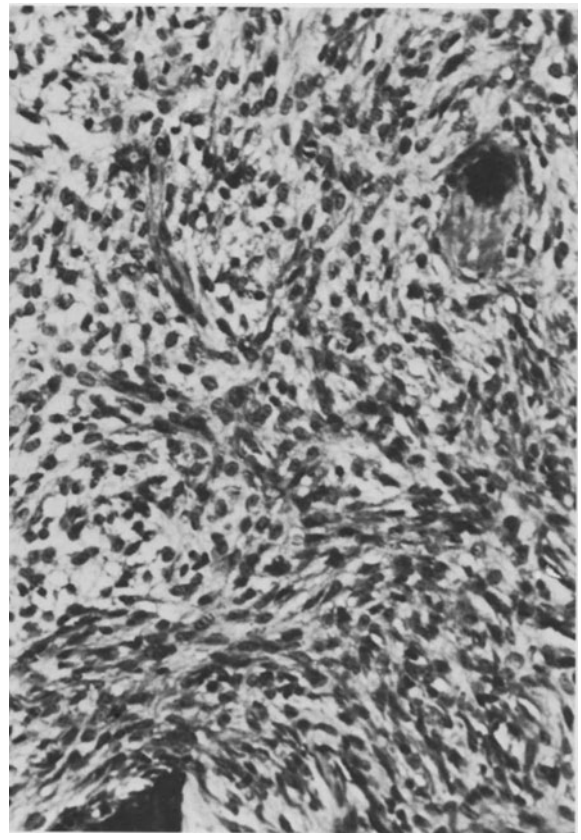


**Fig. 7.17.** Slow-growing fibrosarcoma of the nasal cavity in a 13-year-old boy. (H&E, × 225)

et al. (1978) have reviewed the literature on *rhabdomyosarcoma* in this region and found 96 recorded cases, 56 of which were well documented, and added four of their own. Rhabdomyosarcomas can occur in the nose or nasopharynx, and often present as polypoid masses (Jaffé 1973a; Fu and Perzin 1976a; Kuruvilla et al. 1990), often with a history of repeated local resection. The predominant histological pattern encountered is of the embryonal type and could easily be mistaken for a chronic inflammatory reaction. Immunohistochemistry could be a valuable asset in arriving at the correct diagnosis, and the use of suitable markers (myoglobin, desmin, skeletal muscle actin, and fetal, slow and fast myosins) for one or more of the striated myofibrilar proteins would indicate the degree of differentiation of the neoplastic rhabdomyoblastic cells. Ultrastructural studies will also help to confirm the diagnosis. The tumours infiltrate the surrounding structures extensively, making resection difficult, if not impossible, in most cases (Donaldson et al. 1973; Liebner 1976; Bale et al. 1983; Eusebi et al. 1986; Bussolati et al. 1987).

### *Tumours of Cartilaginous and Osseous Nature*

Tumours of cartilaginous and osseous nature are uncommon in the nasal cavity in children. *Chondromas* have been mentioned in the literature (Fu and Perzin 1974c) and are usually found in the nasal septum as a polypoid mass. Histologically, it is difficult to determine whether these lesions are neoplasms or merely hypertrophic areas of the cartilaginous septum or heterotopic islets of cartilage. *Chondrosarcoma* was observed in four children by Fu and Perzin (1974c), who collected 25 documented cases from the literature, including some children. *Chordomas* are uncommon in the nasopharynx, and even more so in childhood. Although the histology is characteristic in most cases (Fig. 7.18), it can present difficulty, especially when mixed with other tissue components, mainly cartilaginous foci (Heffelfinger et al. 1973).

Both *fibrous dysplasia* and *ossifying fibroma* are extremely rare. Fu and Perzin (1974b) reported eight cases of these two conditions presenting in the first

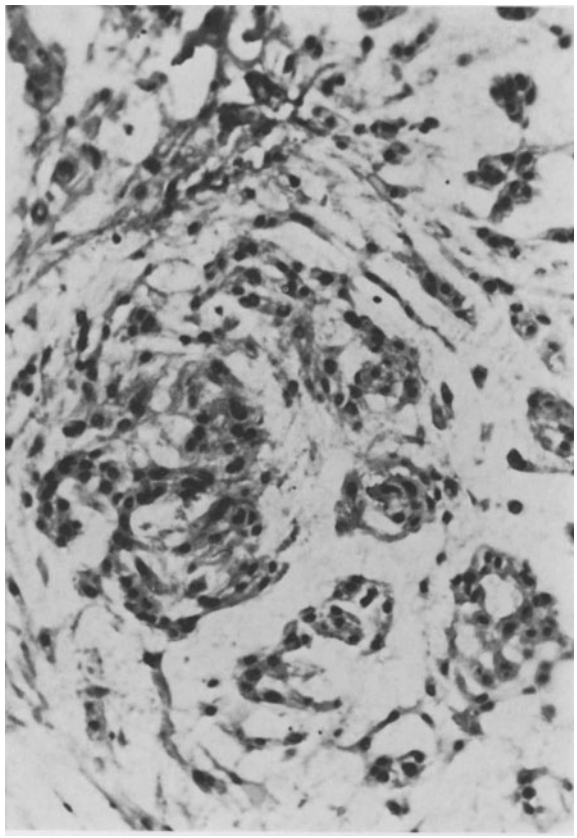


**Fig. 7.18.** Chordoma of the paranasal sinuses (Courtesy of Dr C. Bozic) (H&E, × 225)

two decades. Ossifying fibroma, although a benign tumour, provokes extensive local bone destruction. The tumour is made up of bony trabeculae separated by abundant fibrous tissue (Dehner 1973). This tissue is quite cellular, containing numerous spindle-shaped fibroblasts, sometimes arranged in whorls.

There are occasional rare mitotic figures. Other types of benign osseous tumours, and *osteosarcomas* and *myxomas*, have been encountered in childhood (Fu and Perzin 1974b, 1977).

## *Other Tumours*

*Heterotopic nervous tissue* or so-called "nasal glioma", can be found in the nasopharyngeal region. It is a rare congenital abnormality of mature neural tissue and can be found intranasally or extranasally or both and may be multiple. Heterotopic nervous tissue can also be observed in other regions of the head and neck, and when located in the nasopharynx are often associated with malformations of the head and face. Histologically, the tissue is composed of various components including glial tissue, neuronal cells, ependyma, choroid plexus (Fig. 7.19a), retinal-like elements, oligodendroglia and even calcification (Fig. 7.19b). These tumours are usually polypoid, pale, soft or rubbery and are often received in fragments. In older patients they may be firm and somewhat fibrous. Most cases are observed in children with a high percentage of cases arising in and around the nasal cavity.

Heterotopic nervous tissue must be distinguished from encephalocele. However, although the malformation may be distinguished from the heterotopia by the presence of meninges or tissue organization, there remain intermediate forms where the decision remains a problem (Patterson et al. 1986; Yeoh et al. 1989).

Primary meningiomata of the nasal cavities and sinuses are rare. Ho (1980) found seven cases described in children and Taxy (1990) found two other cases. Although glomus tumour of the region is very rare it must be taken into consideration among the differential diagnoses of these various lesions (Hayes et al. 1993).

*Olfactory neuroblastoma* or aesthesioneuroblastoma, has also been described in children. Bailey and Barton (1975) presented a case in a 6-year-old boy and reviewed the literature. They found 25 cases occurring before the age of 20 years, three in the first decade and 22 in the second. These tumours appear to arise from the basal layer of the olfactory sensory epithelium in the upper nasal cavity above the middle turbinate and are of neural crest origin. Even though they may be related to the childhood neuroblastoma of other regions, they are quite distinct biologically, although arginine vasopressin has recently been recovered from such a tumour (Chaudhry et al. 1979; Elkon et al. 1979; Singh et al. 1980). Histologically the tumour consists of groups or nests of neuroblasts, which have a lymphocytoid appearance. The cells have a round or oval nucleus with coarse or thin chromatin; the cytoplasm is scanty, the stroma is fibrillary, and there may be pseudo-rosettes around some fibrillar elements (Fig. 7.20). Immunohistochemistry and electron microscopic studies are now mandatory to differentiate this entity from undifferentiated carcinomas, lymphomas, embryonal rhabdomyosarcomas and other small-cell tumours of the region. These tumours may extend into the adjacent paranasal sinuses but rarely metastasize (Levine et al, 1986; Taxy et al. 1986; Lloreta et al. 1992; Kleinclaus et al. 1993). Siwersson and Kindblom (1984) have recently described an *oncocytic carcinoid* of the nasal cavity, another rare tumour, associated with a bronchial carcinoid in a 13-year-old girl.

Teratomas of the nasopharynx are rare and can be the cause of neonatal asphyxia and hygroma coli;

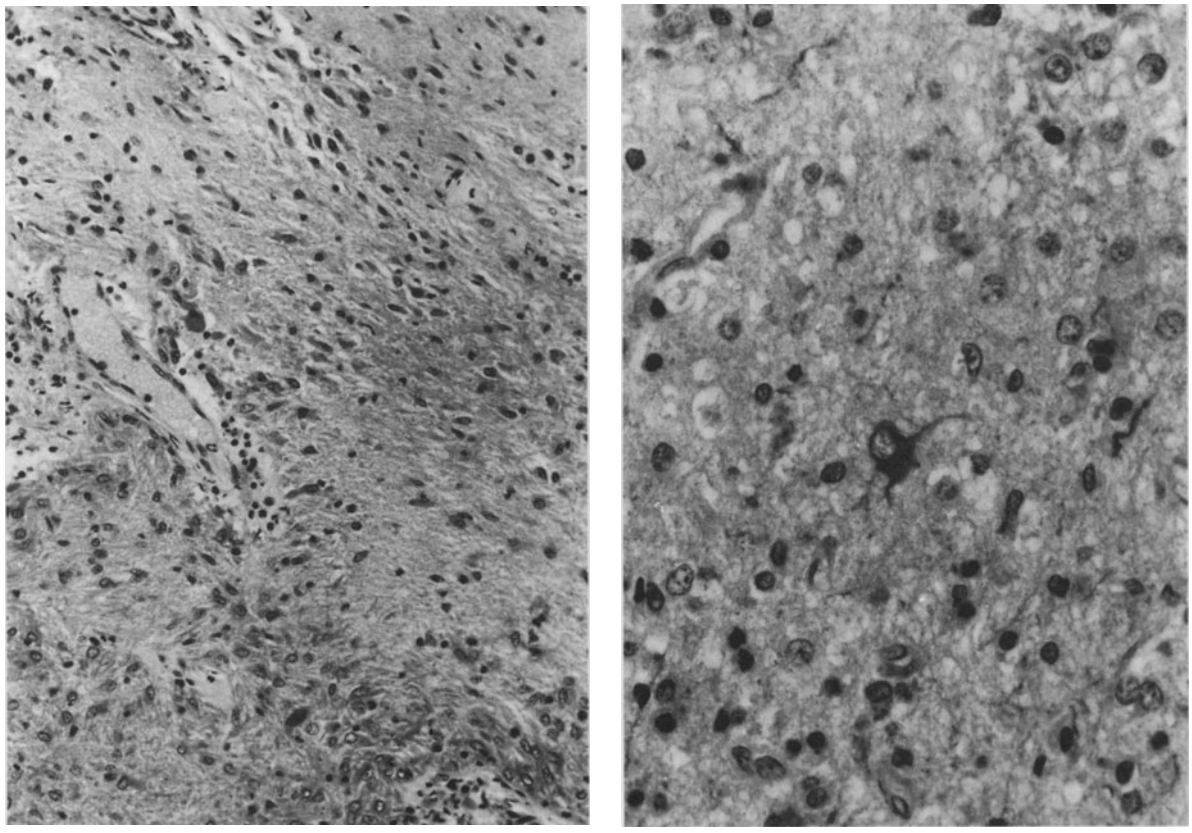


**Fig. 7.19.** **a** So-called nasal glioma of the nasal cavity of a 14-week-old male infant. There are many calcified areas. (H&E, × 50) **b** Ganglion cell with neurofilaments. (S-100 protein, × 78)

they may go unnoticed and present symptoms only during childhood. These tumours are generally of the adult or mature type, but other types have also been described (Zerella and Finberg 1990; Tharrington and Bossen 1992; Jaarsma et al. 1994; Rothschild et al. 1994).

*Malignant lymphomas* (non-Hodgkin's) are not uncommon in childhood and occasionally affect the nasopharynx, presenting in either a nodular or a diffuse form (Wollner et al. 1976). The introduction of monoclonal antibodies has helped in identifying the B- and T-cell variants and in separating this group of tumours from plasma cell granuloma (a benign condition) and the undifferentiated carcinomas (Fellbaum et al. 1989; Ratech et al. 1989; Seider et al. 1991; Arber et al. 1993; Niedobitek and Young 1994).

In Africa, however, lymphoblastic lymphoma (*Burkitt's lymphoma*) is prevalent in the paediatric age group, and may first present as a simple isolated mass or multiple tumours in the jaw, maxilla, nasal cavity or nasopharynx, with distortion and destruction of the bones (Burkitt 1970). The histological, cytological and ultrastructural features of this fascinating tumour, together with the environmental factor(s) that may play a role in its aetiology, have all been fully documented (Epstein and Achong 1970; Wright 1970). The histology is characteristic, with sheets of immature lymphoblasts among which are scattered large histiocytes, giving the tumour the characteristic "starry sky" appearance. The histocytes have an abundant clear vesicular cytoplasm containing phagocytosed cellular elements (Fig. 7.21).

# Larynx and Trachea

## Congenital Malformations

### *Congenital Laryngeal Atresia*

Congenital laryngeal atresia is an extremely rare condition; few cases have been recorded in the literature,

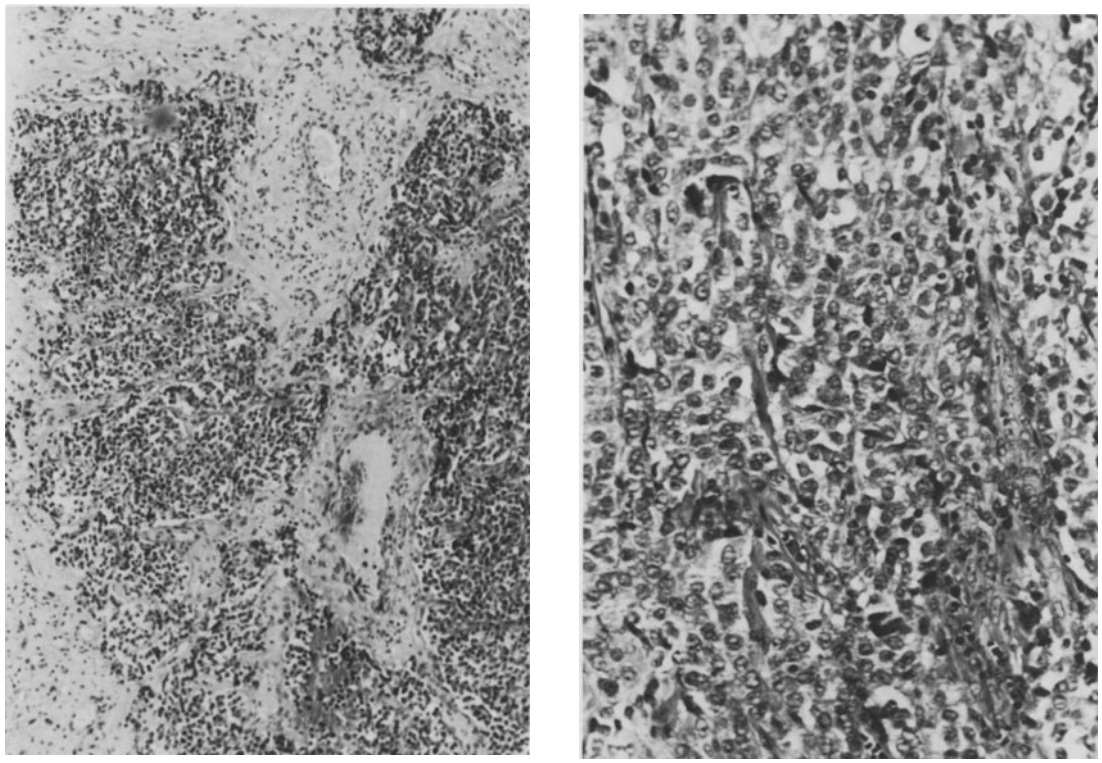



**Fig. 7.20.** Olfactory neuroblastoma (aesthesioneuroblastoma) in an 11-year-old boy. (H&E, **a** × 40, **b** × 120) (Courtesy of Dr C. Bozic)

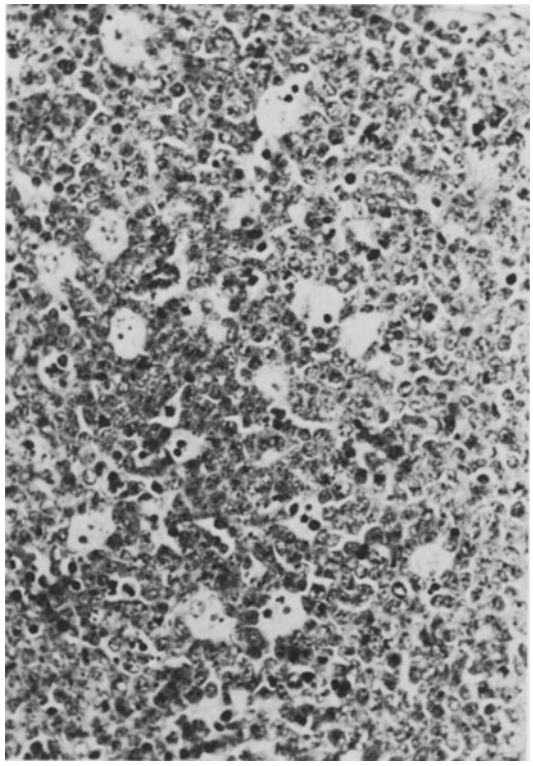


**Fig. 7.21.** Burkitt's lymphoma, with its "starry-sky" appearance, in a 9-year-old African boy. (H&E, × 120)

and these have often presented in association with other congenital anomalies (Fox and Cocker 1964; Morimitsu et al. 1981; Schlesinger and Tucker 1986). The atretic zone can be localized in the glottic, supraglottic or subglottic region, or it can affect the entire larynx. The cricoid cartilage may form a diaphragm across the stenosed larynx. We have seen a case in which this diaphragm was pierced by a small hole. The condition results from the failure of resorption of epithelium during the 7th and beginning of the 8th week of intrauterine life. Partial resorption of the lamina may lead to *stenosis*, which usually occurs in the subglottic region with narrowing of the inferior margin of the cricoid cartilage. Two main histological variants can be observed: cartilaginous and soft-tissue anomalies. This abnormality is more frequently encountered than atresia. Both conditions are often associated with other anomalies (Landing and Dixon 1979; Walton et al. 1985; Wigglesworth et al. 1987). Malformation of the epiglottis (bifid, anomalous accessory cartilages) may be associated with these

and other anomalies (Healy et al. 1976; Templer et al. 1981).

*Laryngomalacia* (flabby larynx) is one of the main causes of stridor in the perinatal period. It is associated with three well defined anatomical abnormalities characterized by: a flaccid epiglottis, which may be hypoplastic, long and with cartilage deficiency; poorly supported arytenoids; and short aryepiglottic folds. All of these are responsible for narrowing of the larynx during inspiration. Two distinct groups have been recognized: a congenital form in neonates with symptoms shortly after birth and another observed in older infants and children. The condition is associated with other respiratory disorders and certain syndromes (Landing and Dixon 1979; Nussbaum and Maggi 1990). Hypercellularity with staining abnormalities of the cartilaginous matrix have been noted in a familial case of laryngomalacia.

### *Laryngeal Webs*

Laryngeal webs are much more common than atresias, but may be considered to be lesser degrees of the same lesion. They, like atresia and stenosis, are causes of cyanosis, stridor or other signs of respiratory distress in the newborn. Webs are usually thin bands situated at the anterior portion of the vocal cords, partially obstructing the laryngeal orifice. They result from failure of normal separation of the two vocal cords. Occasionally they are observed on the posterior portion. They have been reported in families and in association with various congenital anomalies (Gay et al. 1981) Histologically these webs are made up of dense connective tissue, sometimes containing skeletal muscle and numerous capillaries. The proximal surface is covered with squamous epithelium, and the distal surface with respiratory epithelium.

There have been occasional case reports or reviews of the relatively rare condition of *cleft larynx*, but the abnormality may be more prevalent than the literature suggests. The length of the cleft varies widely. In some cases it presents as a slit in the posterior midline of the cricoid cartilage, resulting in a communication between the larynx and the superior portion of the (often atretic) oesophagus. In other cases, it extends to the level of the trachea as far as the carina, resulting in an oesophagotrachea. This abnormality is known to run in families; it affects mostly girls and has been reported in siblings and occasionally associated with hamartoma, tracheo-oesophageal fistula, congenital heart anomalies or part of a clinical syndrome. The clinical symptoms (stridor, feeding difficulties, recurrent aspiration) generally appear shortly after birth, but can go unnoticed until childhood. In severe cases, prompt treatment is needed. Surgical repairs have been attempted with some success (Novak 1981; Holinger et al. 1985; Tyler 1985; Corbally 1993).

### *Laryngeal Cysts and Laryngoceles*

Laryngeal cysts (mucocele), like laryngoceles (aerocele), are generally located at the level of the laryngeal ventricle, and there is often some confusion between the two conditions. Cysts are closed cavities and do not have an outlet into the laryngeal lumen, in contrast to laryngoceles. These abnormalities can protrude into the lumen or be situated within the wall of the larynx. Less commonly they are found at any level in the neck; they attain a considerable size, displacing adjacent organs, Stell and Maran (1975) reviewed the literature on laryngocele and found some 139 cases described in both children and adults. Cysts may increase in diameter as their mucus content increases, and laryngoceles can also vary in size, depending on the quantity of air trapped inside them. Most cysts are supraglottic, whereas subglottic (retention) cysts have been documented principally among premature infants as a complication of prolonged intubation with subglottic stenosis (Miller et al. 1989; Smith et al. 1990a; Civantos and Holinger 1992; Chu et al. 1994). Histologically both cysts and laryngoceles are lined with respiratory epithelium.

### *Tracheal Agenesis*

Total or partial absence of the trachea is a rare abnormality with just over 60 cases reported in the literature. Tracheal atresia can be divided into three anatomical types based on the chronology of the development and separation of the trachea from the oesophagus during intrauterine life. In type I the upper trachea is atretic but the normal lower trachea, with the bronchi and lungs, connects to the oesophagus; in type II, the whole trachea is absent and the bronchi join in the midline forming a unique trunk which opens into the oesophagus (the majority of cases fall into this category); in type III, the trachea is absent and the bronchi arise separately from the oesophagus. Tracheal agenesis may occur in association with a number of malformations, including laryngeal anomalies or atresia, ventricular septal defects or other congenital cardiac malformations, aberrant lung lobation, abnormalities of the upper gastrointestinal tract and pancreas, and central nervous system malformations, and especially in association with the Pallister–Hall, VATER and VACTERL syndromes. Tracheal hypoplasia has also

been described in patients with chromosomal abnormalities (Holinger et al. 1987; Downing 1992; Wells et al. 1992; Davis et al. 1992; Aboussouan et al. 1993).

### *Tracheal Stenosis*

Tracheal stenosis occurs in several forms and is often associated with abnormalities of the main stem bronchi or other major or minor congenital malformations (Smith et al. 1984; Chambran et al. 1988; Hoffer et al. 1994). The condition may present as one or several continuous complete or solid tracheal rings at any level of the tracheal tree, with narrowing of the segment involved. In rare instances the trachea is completely cartilaginous, and the lungs have been found to be abnormal in some cases (Fig. 7.22). Associated anomalies are not uncommon and the condition can be observed in association with many syndromes. Tracheal stenosis may also be the result of compression by an abnormal adjacent vessel (displaced aorta, vascular rings and anomalous left pulmonary artery).

### *Tracheomalcia and Bronchomalacia*

Tracheomalacia and bronchomalacia are conditions in which the tracheobronchial tree shows abnormal flaccidity and softness of the cartilaginous framework (defective calcium deposits), with a tendency to collapse during respiration. Tracheomalacia may be divided into two main groups: *primary* (affecting normal infants, premature babies and the dyschondroplasias) and *secondary* (associated with tracheo-oesophageal fistula, arterial compression or vascular rings or other compression) (Grundfast et al. 1981; Cogbill et al. 1983; Benjamin 1984; Denneny 1985; Sotomayor et al. 1986). When the anomaly affects the larynx it is known as *laryngomalacia*. Hypercellularity with staining abnormalities of the cartilage matrix have been noted in a familial case of laryngomalacia. *Congenital tracheal diverticulum*, although rare, must be considered among the differential diagnoses. The lesion is composed of smooth muscle and cartilage, and may occur alone or in association with other congenital anomalies of the tracheobronchial tree.

### *Tracheo-oesophageal Fistula*

Tracheo-oesophageal fistula is a relatively common congenital malformation, with various anatomical presentations that may or may not be associated with oesophageal atresia. Tracheal abnormalities are not uncommon and include cartilage deficiency with an increase in the extent of the muscle in the membranous part of the tracheal ring. The condition has been reported in twins (Holden and Wooler 1970; Sundar et al. 1975; La Salle et al. 1979; Wailoo and Emery 1979; Sankaran et al. 1983; Whalen et al. 1987). Emery and Haddadin (1971) and Maeta et al. (1977) have shown that there is extensive squamous metaplasia of the tracheal epithelium, especially in cases with associated oesophageal atresia (see also p. 217). This condition is often associated with other malformations involving various systems, thus giving rise to complex patterns.

## Acquired Lesions

### *Traumatic*

Various *foreign bodies* can lodge in the larynx or trachea in children and provoke symptoms of obstruction.

Lesions induced by *endotracheal intubation* (Fig. 7.23) are common in infants treated in intensive care units for the respiratory distress syndrome or for other neonatal respiratory difficulty. The lesions may be localized in the larynx at the level of the vocal cords, but are more often observed in the subglottic region or in the trachea. Less severe lesions consist of erosion of the mucosa; in the more severe forms the submucosa is ulcerated and infiltrated by inflammatory cells. The cartilage may be severely eroded in areas, and perforation can occur. These lesions are becoming less frequent because of better techniques and modifications of the materials used in tube manufacture; however, healed lesions may cause severe scarring and subglottic or tracheal stenosis and/or deformation. Histologically, there are various degrees of destruction of the cartilage plates with extensive scar tissue covered by a hyperplastic squamous epithelium. These lesions are more common and appear to be more severe in premature babies, especially when ventilated over long periods (Hwang et al. 1988; Wiswell et al. 1989; Weber et al. 1991).

High-frequency jet ventilation may also cause severe damage to the trachea and main stem bronchi with extensive necrosis leading to tracheobronchi obstruction by a mixed basophilic membrane (Fig. 7.23c) made up of mucus, fibrin, damaged necrotic tissue and blood. The distal airways show extensive squamous cell metaplasia (Delafosse et al. 1988; Wiswell et al. 1988; Polak et al. 1989; Davis et al. 1990; Keszler et al. 1991).

*Corrosive agents* (acids and alkalis) ingested accidentally and vomited may subsequently be aspirated,

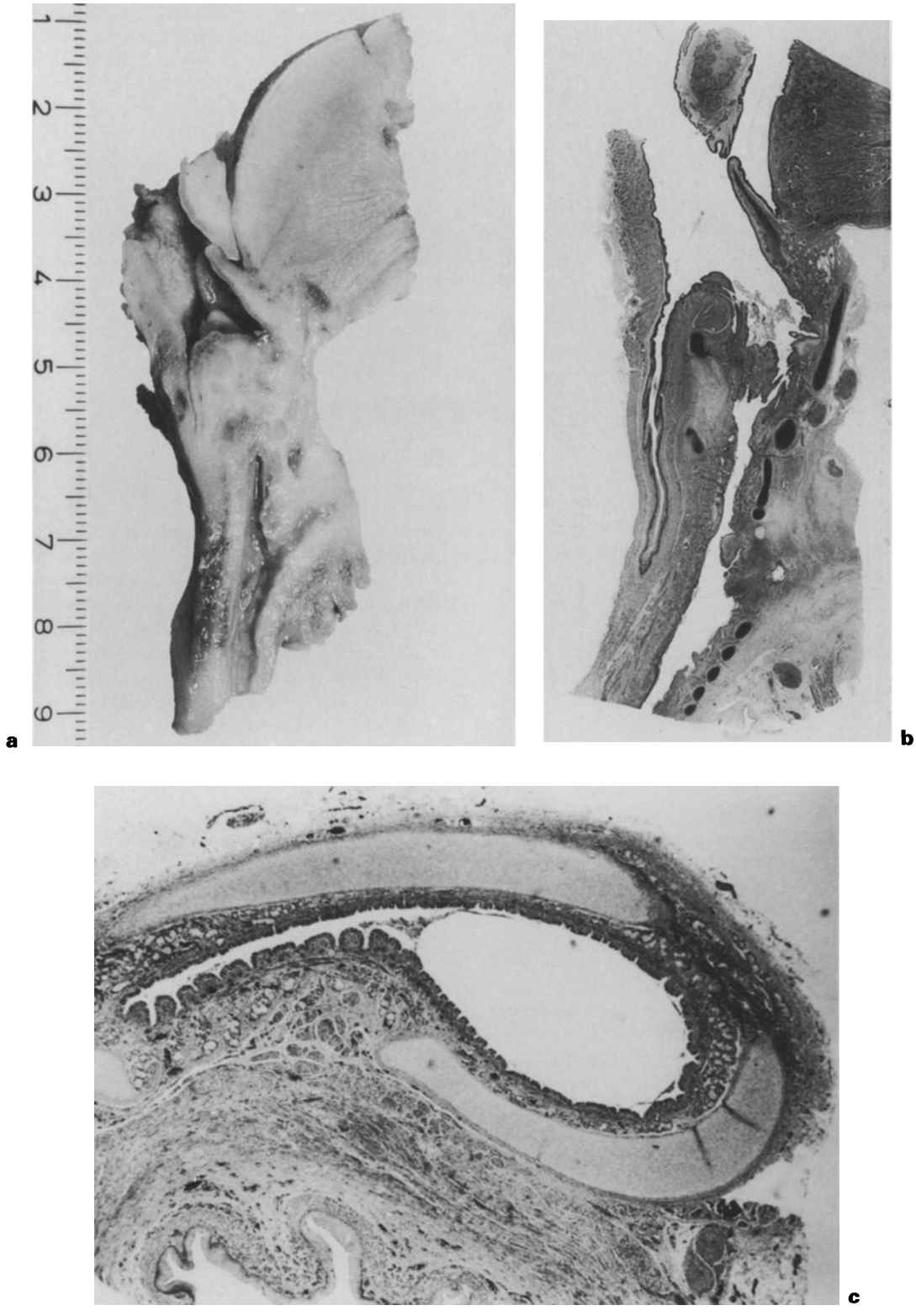
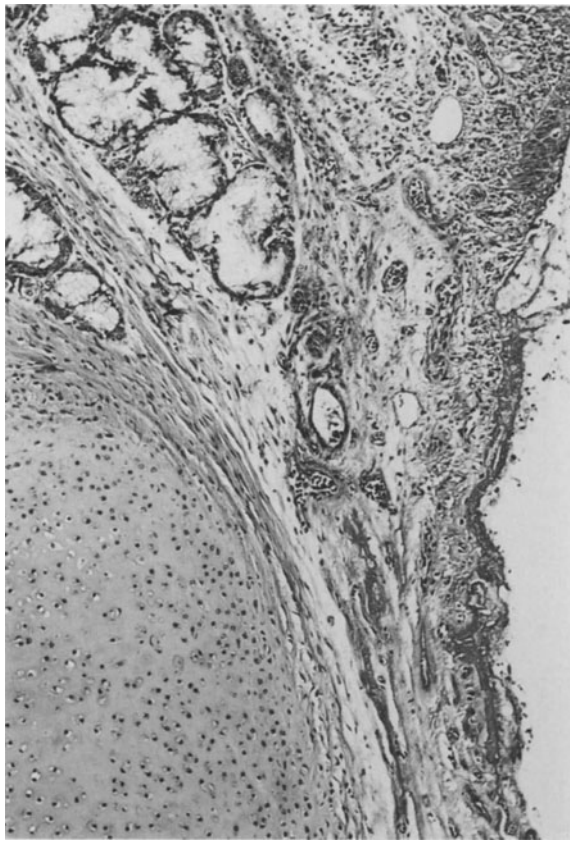



**Fig. 7.22.** **a** Gross specimen showing marked stenosis of the upper deformed portion of the trachea. **b** Histological section showing the abnormal cartilage rings, absent in places. (**a, b** Courtesy of Professor C.L. Berry) **c** Stenosis and malformation of the trachea in a case of VATER complex.



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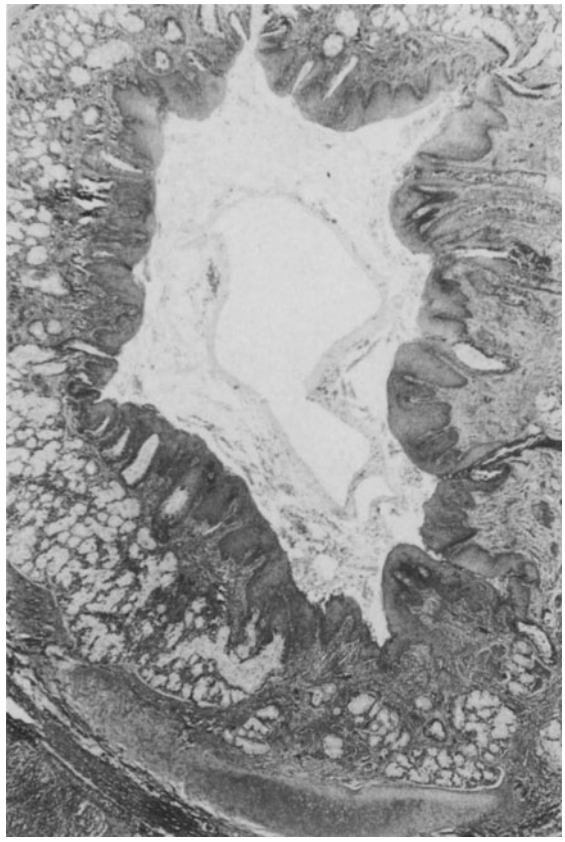

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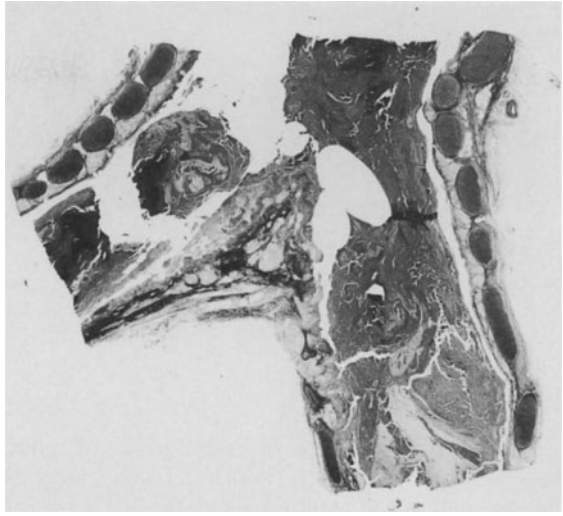


c

**Fig 7.23.** **a** Severe ulceration of the tracheal mucosa covered by fibrin and infiltrated by chronic inflammatory cells. Ten days' endotracheal intubation. (H&E, × 60) **b** Twenty-seven days' intubation leading to tracheal stenosis and severe and extensive squamous metaplasia of the epithelium. (H&E, × 25) **c** Extensive destruction of the tracheal and bronchial walls in a case of high jet ventilation.

causing oedema and necrosis of the laryngeal and tracheal mucosa. Lysol and kerosene cause similar lesions, the latter especially in developing countries. In rare instances, toxic gases may be the cause of irritation of the mucosa with oedema, congestion and a secondary inflammatory reaction (Greene and Stark 1978). Various foreign bodies when aspirated can cause severe damage to the treachea, larynx and main bronchi, sometimes resulting in perforation, but more often in secondary aspiration pneumonia (Van Asperen et al. 1986; Esclamado and Richardson 1987).

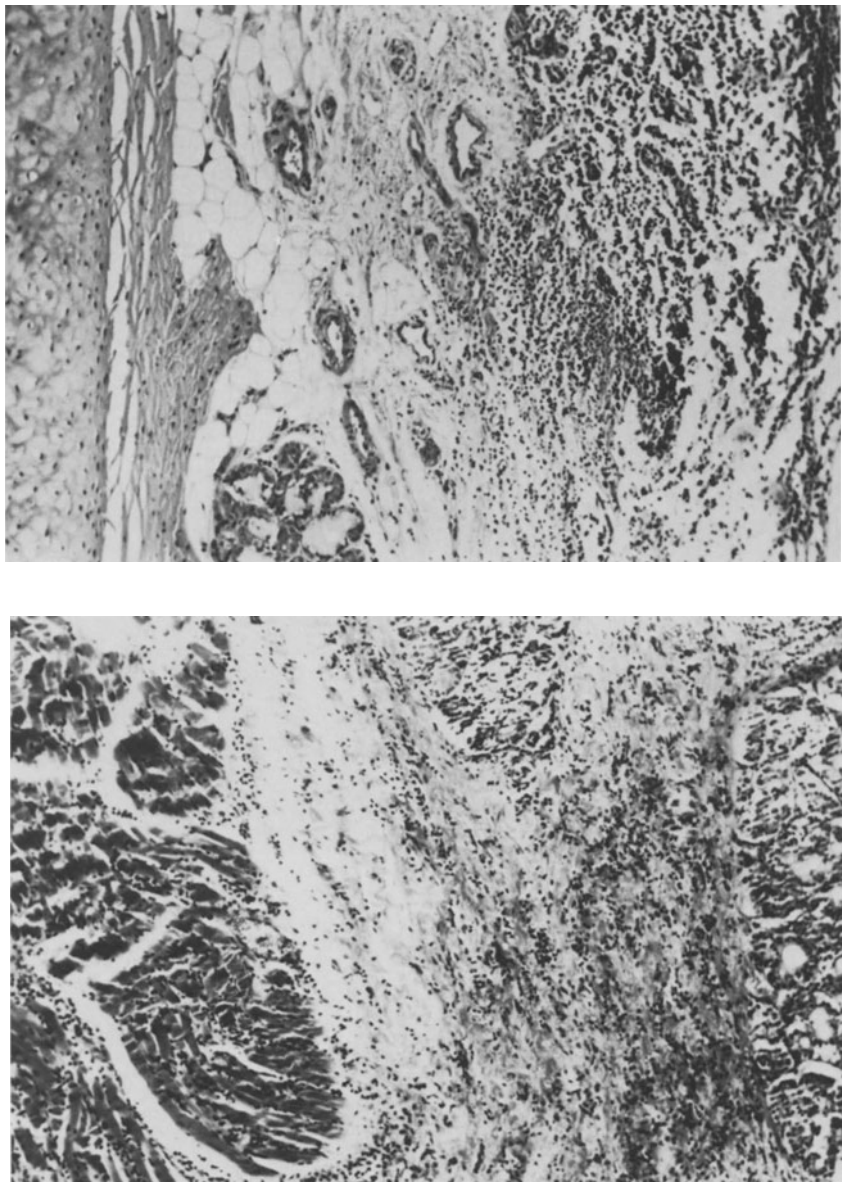


**Fig. 7.24.** Acute epiglottis in an 8-month-old boy. (H&E, × 90) **a** Acute inflammation with ulceration and oedema of the epiglottic mucosa. **b** Inflammation of the subglottic region with extension into the deep muscle layers.

## *Infections*

Acute infections of the larynx and trachea, including the epiglottis (*laryngotracheo-bronchitis*), may be life-threatening and require prompt medical or surgical attention (Bass et al. 1974; Scheidemandel and Page 1975; Cantrell et al. 1978; Cohen and Chai 1978; Liston et al. 1983; Diaz 1985). Various microorganisms have been recovered, the most common being *Haemophilus influenzae*, $\alpha$-haemolytic streptococci, $\beta$-haemolytic streptococci group A, *Staphylococcus aureus*, pneumococci and Neisseria. Vaccine against *Haemophilus influenzae* type b, among others, has considerably diminished the frequency of these agents as potential pathogens. In many developing countries, *Corynebacterium diphtheriae* still plays an important role in infections of this region.

Anatomically, changes in the epiglottis are the most striking; however, both the larynx and the trachea are also usually involved. The epiglottis is markedly swollen, oedematous and congested. Its edges are rounded, and there is partial stenosis of the laryngeal orifice as a result. The larynx is also oedematous, and the vocal cords may touch in the middle. Histologically there is marked oedema of the submu-

cosal tissues of the epiglottis and larynx, extending into the trachea. A diffuse polymorphonuclear infiltration extending into the deeper layers may be seen, usually sparing the cartilaginous structures. The lesions are non-specific (Fig. 7.24). With *C. diphtheriae* infection there is necrosis of the mucosa, and a pseudomembrane, composed of a fibrin network in which there are leucocytes and numerous bacteria is present.

Virus infections usually affect the subglottic region and are characterized by oedema with marked congestion and some round-cell infiltration; associated bacterial infection is common.

The larynx and trachea may be the site of non-specific granulomas in cases of acute and chronic infections. In the developing world tuberculosis of the region may be encountered, and the lesions usually present as mucosal ulcerations with the characteristic appearance. Cohen et al. (1978c) have described a case of Wegener's granulomatosis of the larynx in a 12-year-old girl with the diffuse systemic form of the disease. Mycotic lesions of the larynx and trachea may present as ulcerations (Vitale et al. 1993) or pseudocarcinomatous hyperplasia of the mucosa especially in patients with AIDS or those with some other immunodeficiency state. Viral infections, mainly herpes and cytomegalovirus, may also be observed in such patients.

## *Tumours*

Tumours of the larynx and trachea are quite uncommon among infants and children.

*Epidermoid cysts* of the vocal cords are occasionally observed in children, and may cause dysphonia. They may be unilateral or bilateral, and are often associated with glottic sulcus and/or mucosal bridges. Although there is still debate concerning their origin, some consider them congenital anomalies. Histologically, they resemble epidermoid cysts elsewhere (Monday et al. 1983; Bouchayer et al. 1985).

*Epithelial Tumours. Papilloma* is by far the most common tumour of this area and is more appropriately referred to as *juvenile laryngotracheal papillomatosis*, because multiple lesions are the rule. These tumours occur more frequently among children whose mothers present with condyloma acuminata during pregnancy and in recent years evidence has accumulated that one or more types of papillomaviruses (HPV6, HPV7, HPV16, HPV18, HPV30, HPV33) may be associated with these lesions. The viruses can often be demonstrated in the apparently normal adjacent epithelium, explaining the possible repeated recurrences. Papillomatosis often begins as a single wart on the vocal cords and spreads along the mucosa of the larynx to reach the trachea and even the main stem bronchi. The warts may disappear spontaneously at puberty, but are frequently recurrent despite repeated excisions. Squamous cell carcinomas are known to develop from these lesions, especially after irradiation. In such instances it is not always easy to identify the area of carcinomatous transformation, in spite of widespread metastases (Crissman et al. 1988; Chaput et al. 1989; Basheda et al. 1991; Dickens et al. 1991; Simon et al. 1994).

Histologically there is marked hyperplasia of the squamous epithelium with some degree of keratosis and parakeratosis associated with koilocytosis but no hyperkeratosis. The hyperplastic epithelium is thrown into folds about a thin stalk of connective tissue containing few capillaries and a few chronic inflammatory cells. Focal dysplastic areas can be observed in cases followed over several years (Fig. 7.25).

*Squamous cell carcinoma* of the larynx in children is extremely rare. Large national surveys of tumours in children have failed to find this tumour; however, there are some cases in the literature (Orton 1947; Jones and Gabriel 1969; Jaffé 1973b; Askin 1975). In a review of the recorded cases, Gindhart et al. (1980) collected 54 cases and added one of their own. The origin is often in the vocal cords and there is a male predominance (3 : 2), usually with advanced disease at diagnosis (Shvero et al. 1987; Ohlms et al. 1994). X-ray irradiation for juvenile papillomas may be a predisposing factor. There have also been reports indicating that carcinomas in the supraglottic area in adults have developed in laryngoceles (Micheau et al. 1975). The histological appearance of this tumour is similar to that of other squamous cell carcinomas. Weber and Grillo (1978) treated a case of squamous cell carcinoma of the trachea in a 13-year-old girl, and Olmedo et al. (1982) an adenoid cystic carcinoma in a 16-year-old girl.

Briselli et al. (1978), in a review of the literature on tracheal *carcinoids*, found one reported case in a 13-year-old adolescent girl.

*Vascular Tumours. Haemangiomas* of the larynx and trachea, although uncommon, are important lesions because of the diagnostic problems they present and the high mortality rate among infants with these lesions. They may be observed at birth or shortly thereafter, grow progressively with age, and usually present some months after birth. They are occasionally associated with haemangiomas in other sites including the skin, head and neck. They are most often localized in the subglottis, but may also involve the supraglottic region. The lesion may be confined to the submucosa, or appear as sessile, flat, pinkish or bluish masses in the mucosa, and may be the cause of

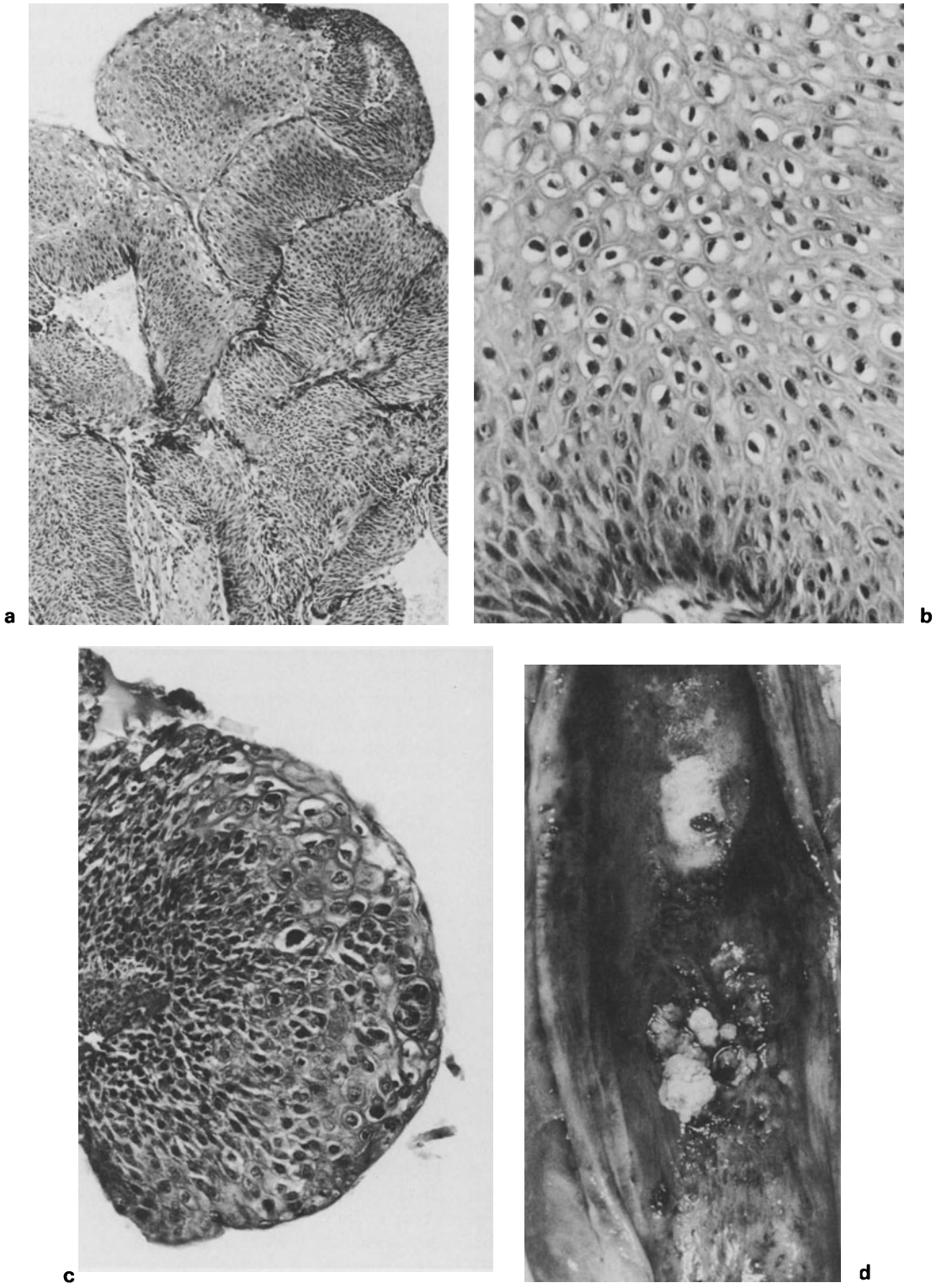



**Fig. 7.25.** Laryngeal papilloma. The lesions were discovered at the age of $2\frac{1}{2}$ years and led to the patient's death at 25 years from extensive metastatic squamous cell carcinoma. **a** Papillomas extending from the larynx into the main stem bronchi at age 12 years. (H&E, × 35) **b** Note severe koilocytosis in biopsy at age 16 years. (H&E, × 225) **c** Severe dysplastic changes with intraepithelial neoplasia. (H&E, × 225) **d** Bouquet of multiple tracheal papillomas at the time of death, with marked scarring above and below the lesions as a result of repeated biopsies.

airway obstruction. In tracheal lesions there may be extension into the perichondrium and/or beyond the tracheal rings. Spontaneous or partial regressions have been observed between the ages of 1 and 8 years, with slow resolution in others by 12–15 years of age. There is a marked female predominance. Biopsy is not recommended because of the haemorrhage that may result. Recently, various new treatements have been introduced in the management of these lesions. The histology is that of haemongiomas elsewhere (Ezekowitz et al. 1992; Ohlms et al. 1994; Sie et al. 1994).

*Lymphangiomas* of the larynx in infancy and childhood are rare and are usually associated with cystic hygroma or cavernous lymphangioma of the head and neck region. They can occasionally be found as isolated tumours, or present as a laryngocele or a saccular cyst (Jaffé 1973b; Moore and Cobo 1985; Cohen and Thompson 1986; Donegan et al. 1986). Jaffé (1973b) had also observed a *haemangiopericytoma* in a 3-month-old boy.

*Tumours of Nervous Origin. Neurofibromas* of the larynx may occur and are sometimes associated with neurofibromatosis (von Recklinghausen's disease). In recent reviews of this subject (Jafek and Stern 1973; Maisel and Ogura 1974) there were four recorded cases in the paediatric age group, one of which occurred in a 3-month-old boy, and Stanley et al. (1987) added two more cases from their series. Neurilemmoma is also extremely rare in this age group: Horovitz et al. (1983) in a review of the literature could only find one recorded case in a 6-year-old girl, and Stanley et al. (1987) reported three more occurring in the second decade of life.

*Tumours of Muscular Origin. Granular cell myoblastoma* of the larynx has been reported in children by Booth and Osborn (1970), Nasser et al. (1970) and Thawley and Osborn (1974). The tumour has also been documented in the trachea in children. These tumours appear to have a familial occurrence, and all races seem to be affected. Several tissues or organs may be simultaneously involved. Immunohistochemistry has shown that these tumours are probably of Schwann cell origin rather than muscular (Thaller et al. 1985; Muthuswamy et al. 1986; Nathrath and Remberger 1986; Rifkin et al. 1986, Stanley et al. 1987)

*Leiomyoma* of the trachea is extremely rare (Bouros et al. 1987) and Kitamura et al. (1969) could find only nine published cases, one of which was in a 15-year-old patient presented by Unger (1952). *Rhabdomyosarcoma*, although an uncommon tumour, is perhaps more prevalent than most other soft-tissue tumours of these parts. There have been reports of this tumour occurring in the larynx of children (Wayoff and Labaeye 1973; Frugoni and Ferlito 1976; Fu and Perzin 1976a; Canalis et al. 1978), as well as in the trachea (Ho and Rassekh 1980).

*Cartilaginous Tumours*. Chondroma and chondrosarcoma tumours of the larynx and trachea have been recorded in adults but are exceptional in childhood (Simpson et al. 1979).

*Chemodectomas*. Non-chromaffin paraganglia of possible Kultschitzky cell origin sometimes occur in the larynx. Hohbach and Mootz (1978) found 23 recorded cases in the literature, one of which occurred in a 14-year-old boy, and added one of their own.

*Other Tumours*. In their review of tracheal tumours Gilbert et al. (1953) found nine cases of *fibroma* among children. Cohen et al. (1978a) described a case of *fibrous histiocytoma* in the trachea of a $2\frac{1}{2}$ year old girl, and Sandstrom et al. (1978), in their review, found one case in a 15-year-old girl. Rosenberg et al. (1981) described two cases of *fibromatosis* of the larynx in neonates and retrieved six from the literature, some of which had been previously reported as either fibroma or fibrosarcoma. The difficulty in the histological diagnosis, especially when some lesions show evidence of local invasion or malignant changes, indicates the importance of immunohistochemistry and electron microscopy in the study of these lesions (Pollak et al. 1985; Tan-Liu et al. 1989). Witwer and Tampas (1973) described a case of tracheal *fibroxanthoma* in a 5-year-old boy, and discovered a second case in the literature. *Pleomorphic adenoma*, a benign mixed tumour, has been described in both the larynx and the trachea in children (Som et al. 1979; Heifetz et al. 1992). Sarcomas, including rhabdomyosarcomas of the larynx and trachea have been documented in this age group (Gorenstein et al. 1980a; Olmedo et al. 1982; Abramowsky and Witt 1983; Dodd-O et al. 1987), and one cannot over-emphasize the importance of immunohistochemistry and ultrastructural examinations as aids to a correct diagnosis. *Liposarcoma*, an extremely rare tumour of the region, has not been described in children (Esclamado et al. 1994).

Cohen et al. (1978d) described a case of a primary *lymphosarcoma* of the larynx in a girl aged 4 years 7 months, and also reported on a *solitary plasmacytoma* affecting the larynx and upper trachea in a 15-year-old girl treated for systemic lupus erythematosus (Cohen et al. 1978b).

# Lungs

## Congenital Abnormalities

Congenital abnormalities of the lungs are varied and often complex. They may be isolated to the lungs but it is not uncommon to find such abnormalities associated with other organ or system malformation.

There is no general agreement on the classification of pulmonary agenesis. Schneider (1912) first attempted to divide the abnormality into three groups:

1. Agenesis, in which there is complete absence of bronchi, alveolar tissue and their blood supply
2. A group in which a rudimentary bronchus arose from the trachea with no pulmonary tissue investing its tips
3. A group with a poorly developed main bronchus invested by a fleshy mass of ill-developed pulmonary tissue

This classification was subsequently modified by Boyden (1955), who recommended a system based on the degree of developmental arrest. There were also three categories:

1. Complete absence of one or both lungs (agenesis)
2. Suppression of all but a rudimentary bronchus (aplasia)
3. Abortive growth (hypoplasia)

Spencer (1977a, b) proposed yet another classification, based on the categories of anomalies:

1. Bilateral complete agenesis
2. Unilateral agenesis, which is further subdivided into three groups, which are identical with Schneider's three groups
3. Lobar agenesis and other lesser forms of congenital abnormality

We shall follow this last general classification.

*Bilateral* or *complete pulmonary agenesis* is a very rare condition, and there are few recorded cases. The laryngotracheal tree may terminate blindly at the level of the larynx or trachea, or even at the main stem bronchi. The pulmonary artery normally takes its origin from the right ventricle, but terminates in the thoracic aorta by way of the ductus arteriosus. The bronchial arteries and pulmonary veins are usually absent, and there are other associated abnormalities affecting the cardiovascular system, upper gastrointestinal system, anus, urogenital system, musculoskeletal system and spleen. It may also be observed in association with some syndromes (VACTERL), and polyhydramnios has been documented in two cases, one of which presented with hydrops fetalis (Engellenner et al. 1989). There are now 12 cases on record and they all seem to be part of the same developmental field defect (Toriello and Bauserman 1985; Toriello et al. 1985).

*Unilateral pulmonary agenesis* is much more common than complete agenesis, and is not compatible with normal life. This condition has been referred to by several names in the numerous case reports or reviews on the subject. According to Spencer's (1977a, b) classification there are three subgroups, each of which corresponds to one of Schneider's (1912) three groups, described above. There may be other associated abnormalities involving the cardiovascular system, gastrointestional tract, ipsilateral facial bones, vertebral column and upper limbs and their associated muscles, and urogenital system, as well as diaphragmatic agenesis or hernia. Over 260 cases of this condition are described in the literature (Say et al. 1980; Mardini and Nyhan 1985; Toriello et al. 1985). Agenesis of one lobe with abnormality of the bronchial tree has also been described (Maesen et al. 1993). The life expectancy of these patients depends on the severity of the associated malformations and the problem of infections in the existing lung. Ryland and Reid (1971) and Hislop et al. (1979) have further shown that in existing lung tissue there is bronchial reduction with an increase in alveolar density. The pulmonary artery in their case also showed a reduction in both the conventional and the supernumerary branches, which was more marked for the former group of vessels.

### *Minor Abnormalities*

Abnormal lobulation is not an uncommon finding in post-mortem material, and is often the result of lobar fusions or accessory fissures. It is generally associated with other congenital malformations, usually cardiovascular, e.g. Ivemark's syndrome, Fallot's tetralogy, polysplenia and situs inversus (Landing and Wells 1973). The bronchial tree of these abnormal lungs also shows variations from the normal bronchial pattern, and it must be emphasized that many accessory lobes (azygos, cardiac, left middle) are variations of normal lobulation.

There is an uncommon condition in which the lungs are fused in the midline behind the apex of the heart, giving them a *horseshoe* appearance. The condition (25 cases) is described in association with dextrocardia and other cardiac anomalies, as well as bronchial, parenchymal and pleural anomalies and the VATER association (Hawass et al. 1990; Hassberg et al. 1992; Ersoz et al. 1992; Figa et al.

1993). The condition is also often associated with the *Scimitar syndrome* (anomalous drainage of the right pulmonary vein to the inferior vena cava, often subdiaphragmatic, right lung hypoplasia and other cardiac and vascular anomalies), another rare condition which may present with symptoms in early infancy or childhood or may be completely asymptomatic. It has been described in families (Cabrera et al. 1989; Redington et al. 1990; Yamaguchi et al. 1990; Dupuis et al. 1993; Trinca et al. 1993).

*Accessory supernumerary bronchus (bronchus cardiacus superior dexter* or *sinister*) is a rare anomaly in which the accessory bronchus takes its origin directly across from the orifice of the right (left) upper lobe bronchus. The condition must be distinguished from the much commoner *displaced bronchi* in which the bronchi take off from unusual sites (Maesen et al. 1983). Congenital bronchial atresia is not altogether uncommon, but is most often discovered in adults. The atretic bronchus often appears as a series of cystic dilatations reminiscent of bronchiectasis (Jederling et al. 1986).

### *Pulmonary Hypoplasia*

A decrease in lung volume and weight is generally referred to as pulmonary hypoplasia due to a developmental abnormality resulting in a reduction in numbers and/or size of the acini. Both lungs may be involved (oligohydramnios), or the lesion may be unilateral (diaphragmatic hernia) in which case the lesion is usually apparent, whereas, in the former, the lungs may appear normal on gross inspection although there is a marked reduction in volume and weight when compared with those of other fetuses of comparable gestational age. There are many ways of assessing pulmonary hypoplasia. Lung weight is still the simplest, but this is subject to variations depending on the pathological lesions. Wet lung weight to body weight ratio is widely accepted as a simple method, available to all in spite of the variations that may occur in cases with lung pathology or in hydrops fetalis. The normal values range between 0.018 and 0.025 with wide variations.

Other methods include alveolar radial count or its modified versions which are easily reproducible, lung tissue maturity (quantitative biochemical assays of desaturated phosphatidylcholine, ultrastructural studies of acinar cellular lining), morphometric evaluation of the acini, DNA estimation of cell number and elastic tissue distribution. A significant number of cases, unilateral, or bilateral, are associated with malformations forming a heterogeneous group of abnormalities including cases associated with syndromes, with or without chromosomal anomalies.

Hypoplasia with oligohydramnios from prolonged leaks of amnotic fluids, renal agenesis, renal polycystic disease, renal dysplasia or congenital urinary tract abnormalities with obstruction is perhaps the best documented form. Hypoplasia in oligohydramnios is associated with markedly diminished lung volume, and small acinar size and surface area for gestational age. The lungs are structurally and biochemically immature with a lag in the appearance of several elements making up the developing pulmonary parenchyma. As in other cases of pulmonary hypoplasia, there is extension of the muscular arteries into the intra-acinar level together with an increase of medial arterial thickness.

Reduction in the intrathoracic space may be the consequence of congential diaphragmatic hernia (unilateral), polycystic kidney and liver disease, immune and non-immune hyrops with polyhydramnios, pleural effusions, the chondrodysplasias, neonatal hypophosphatasia, intrathoracic tumours and abdominal wall defects. In this group, hypoplasia in diaphragmatic hernia (Fig. 7.26) is the best documented. There is delay in pulmonary maturity with a diminished number of airways, blood vessels and acinar numbers in the ipsilateral lung, although the contralateral may be within normal limits with an increase in alveolar numbers (Fig. 7.27).

The condition is also observed with anencephaly and other neuromuscular conditions, in which cases there is pulmonary immaturity and acinar developmental delay. However, there are cases in which no apparent cause is evident. In Down's syndrome, pulmonary hypoplasia is associated with a reduction in number and size of the acini, which is responsible for the postnatal development of subpleural emphysema or cysts. Recent studies suggest that loss of lung fluid and decrease in fetal breathing movements are important factors in the genesis of pulmonary hypoplasia, but other factors (genetic programme disturbances, hormonal cell-mesenchymal interactions) may be important contributing factors (Cooney and Thurlbeck 1982; Page and Stocker 1982; Cooney and Thurlbeck 1985; George et al. 1987; Wigglesworth et al. 1987; Silver et al. 1988; Argyle 1989; Nicolini et al. 1989; Nakamura et al. 1990; Haidar et al. 1991; Rosenak et al. 1991; Wigglesworth et al. 1991; Barth and Rüschoff 1992; Husain and Hessel 1993; Foster et al. 1994; Di Fiore and Wilson 1995).

## Accessory Lungs and Pulmonary Sequestration

Müller (1918) defined *accessory lung* as an organ-like mass of pulmonary tissue with its own pleura, separated from the rest of the lung. The accessory

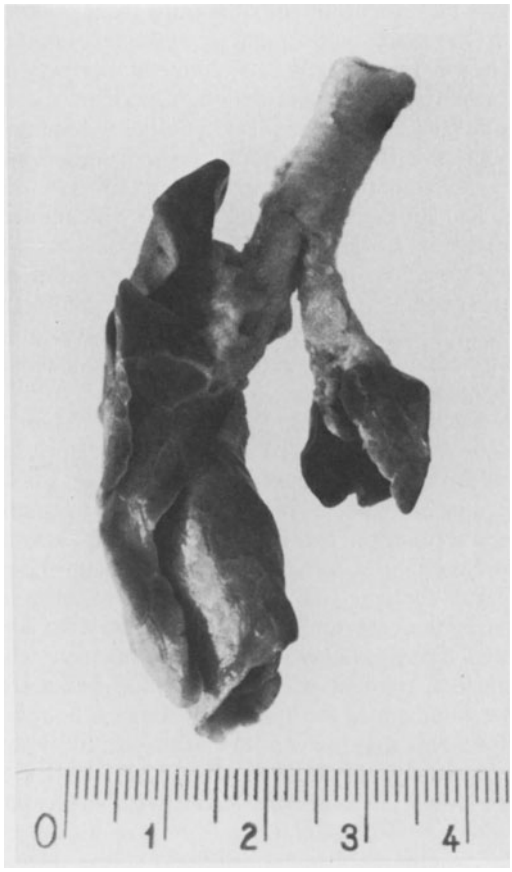



**Fig. 7.26.** Pulmonary hypoplasia of the left lung in a patient presenting with a large left diaphragmatic hernia. (Courtesy of Dr C. Bozic)

lung may connect with either the tracheobronchial tree or the fore-gut. *Pulmonary sequestration*, on the other hand, describes a piece of lung which, although lying within the same pleura as the normal lung, is not connected to its bronchial system or derivatives. The sequestrated tissue receives its blood supply from a systemic artery. This condition must be distinguished from *ectopic* or *herniation lung tissue*, which has been described in the neck and thoracic regions in association with iniencephaly and certain syndromes (Landing and Dixon 1979; Bridger et al. 1992). Sequestered lung may be located within the main lung (*intralobar sequestration*) or separate from it (*extralobar sequestration*). It is possible, from these broad definitions, to separate four main pathological entities without considering minor variations or combined abnormalities. These are:

1. Accessory lung with connections to the tracheobronchial tree
2. Accessory lung with bronchi arising from fore-gut derivatives
3. Extralobar pulmonary sequestration
4. Intralobar pulmonary sequestration

These various lesions used to be considered rare abnormalities, and were usually accidental findings at autopsy. They were sometimes discovered during treatment of a repeated pulmonary infection or during the course of certain radiographic procedures. As radiographic procedures and techniques improve, the lesions are discovered more frequently, and have been reported at all ages. Pulmonary sequestration is sometimes associated with funnel-chest deformity and other anomalies (Gerle et al. 1968; Accard et al. 1970; Felson 1972; Dutau et al. 1973; Jaubert de Beaujeu et al. 1973; Iwa and Watanabe 1979; Savic et al. 1979).

### *Accessory Lung with Connections to the Tracheobronchial Tree*

The accessory bronchus takes its origin from the normal tracheobronchial tree and terminates in a mass of poorly defined pulmonary tissue. The latter may be cystic or may resemble a hamartoma. Examples of this type of abnormality have been described by Cotton et al. (1956) and Herxheimer (1901).

### *Accessory Lung with Bronchi Arising from Fore-gut Derivatives*

The accessory bronchus originates from fore-gut derivatives, usually the lower (occasionally the upper) portion of the oesophagus or the stomach. The tissue lies outside and separate from the lung proper. Histologically it is made up of tubular structures lined by ciliated respiratory-type epithelium. The bronchus leading to the accessory lung may be lined by squamous epithelium similar to that of the oesophagus or by gastric-type mucosa, depending on its origin. The artery supplying the accessory lung generally arises from the aorta (Grans and Potts 1951; Boyden et al. 1962; Gerle et al, 1968; Pai et al. 1971; Kobler and Ammann 1977; Stocker et al. 1978).

### *Extralobar Pulmonary Sequestration*

These masses consist of bronchial and alveolar structures, often lying behind the lung. They may be located at any level from the neck to the diaphragm.

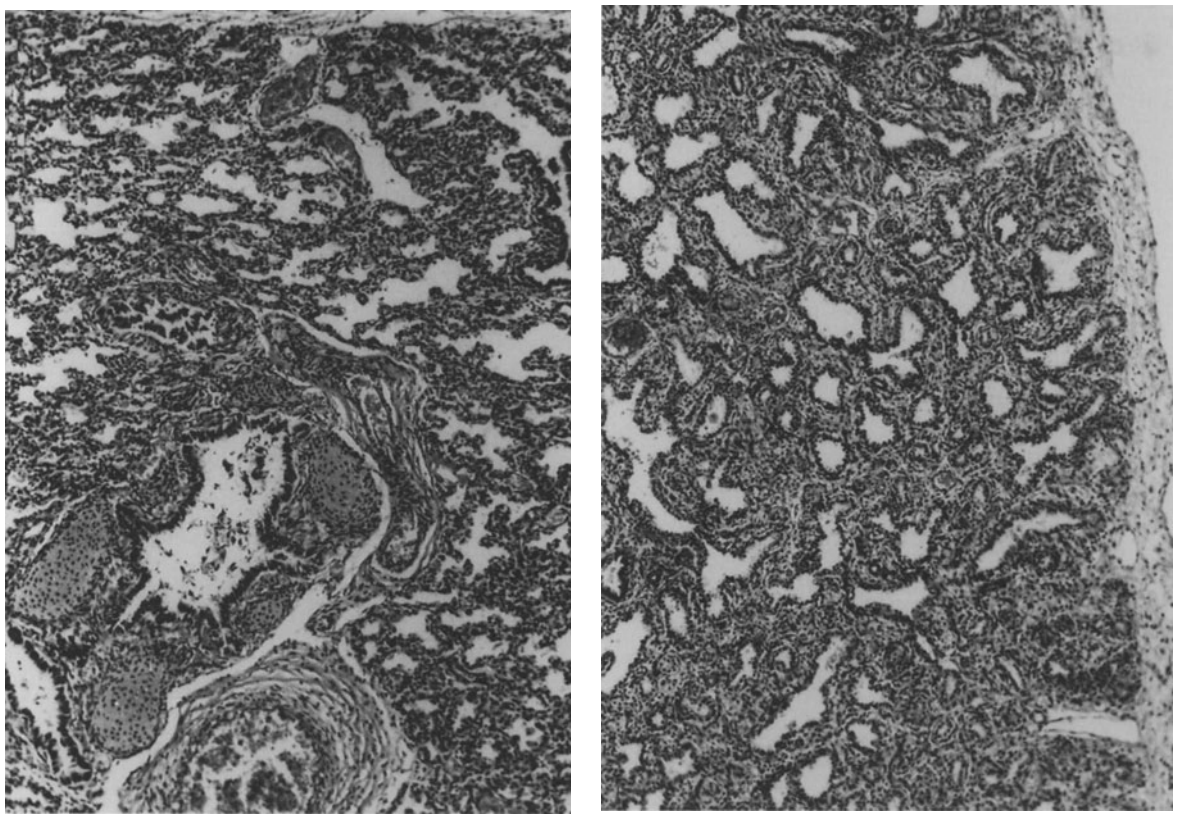


**Fig. 7.27.** **a** Pulmonary hypoplasia (diaphragmatic hernia) showing abnormal peripherial bronchial cartilage plates with grouping of reduced bronchial and bronchiolar branches. (H&E, × 20) **b** Pulmonary hypoplasia (Down's syndrome, 20 weeks' gestation) showing marked reduction in number and size of acini together with delay in maturation. (H&E, × 20)

The majority have been found on the left, and they are frequently associated with diaphragmatic hernia or some other congenital malformation. The arterial supply to the sequestrated tissue is usually by a number of small branches from the thoracic or abdominal aorta, but occasionally from the subclavian or intercostal arteries. The venous drainage is by way of the azygos system (Accard et al. 1970; Jaubert de Beaujeu et al. 1970; Merlier et al. 1970; Bliek and Mulholland 1971; Stocker and Kagan-Hallet 1979).

### *Intralobar Pulmonary Sequestration*

This is a relatively common abnormality. The sequestrated pulmonary tissue does not communicate with the tracheobronchial tree and is contained within the pleura of the normal lung. It is usually situated in the lower lobes and mostly on the left, although other lobes may contain the lesions. The posterior basal segment is most frequently involved. This abnormality is rarely associated with other malformations.

The sequestrated tissue frequently consists of a single cystic cavity or a group of interconnecting cysts. Less commonly, a solid mass of tissue is found, which is not separable from the surrounding normal lung. This mass contains dilated bronchus-like spaces lined with respiratory-type epithelium whose walls sometimes contain cartilage plates. Alveolus-like structures are also observed.

The artery supplying the sequestrated tissue is usually prominent, taking its origin from the thoracic or abdominal aorta, or occasionally from the intercostal arteries. The supplying artery is generally short, of large diameter, and has an elastic structure similar to that of the pulmonary artery. The venous drainage is by way of the pulmonary venous system (Pryce 1946; Pryce et al. 1947; Buchanan 1959; Zelefsky et al. 1971; Dutau et al. 1973).

The embryogenesis and pathogenesis of these abnormalities are still a matter of debate, and there

are many theories on their formation. With the advent of routine ultrasound examinations during pregnancy, the diagnosis of this condition is now often made during intrauterine life (Pryce et al. 1947; Delarue et al. 1959; Gebauer and Mason 1959; Kyllonen 1964; Gerle et al. 1968; Lebrun et al. 1985; Mendoza et al. 1986b).

## Cysts

Lung cysts remain a controversial subject with no satisfactory classification available, although several have been proposed. They can be divided into two main groups, congenital and acquired, the latter being by far the most common. There is still some difficulty in deciding whether a cyst is congenital or acquired, especially when it is discovered after the neonatal period. One can only be sure that a cyst is congenital if it is discovered in a fetus or newborn, as acquired cysts can occur in the first months of life after pulmonary infection, particularly staphylococcal or viral infections, pulmonary infarctions, or maldevelopment of the distal airways, especially in association with cardiovascular malformations in Down's syndrome. In older children the distinction between the two becomes almost impossible. They can affect only a portion of the lung or of a lobe, and can be single or multiple. Either sex may be affected (Bâle 1979; Stocker 1987; Gonzalez et al. 1991).

Spencer (1977b) has presented a temporary classification based on pathology. His groups are:

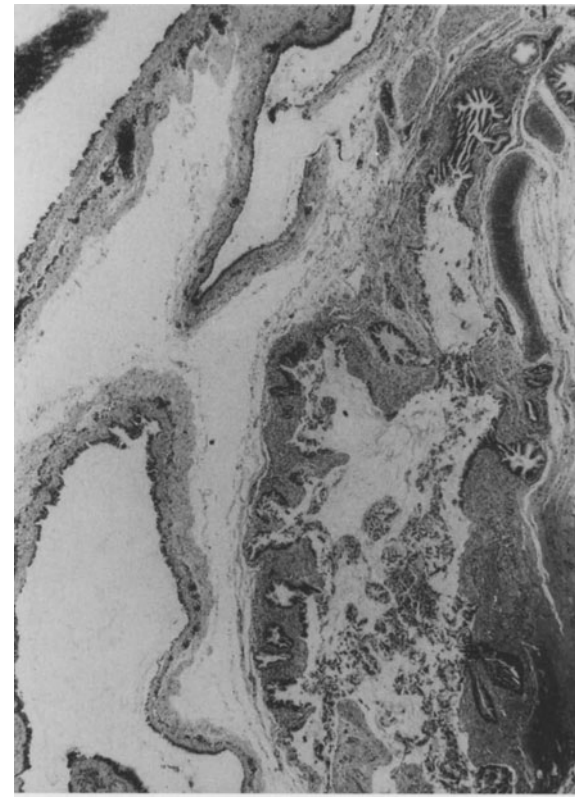
A. Congenital, further subdivided into four types:
   1. Central and peripheral
   2. Lymphangiomatous
   3. Cystic change in an intralobular sequestrated or accessory lung, and enterogenous cysts
   4. Congenital cystic adenomatoid malformation

B. Acquired cysts.

There are also four large subgroups of this class, which will not be discussed further here.

*Central cysts* are often referred to as bronchogenic. They are usually observed in the mediastinum near the hilus or a main bronchus, and appear to have been derived from a large bronchus. Less commonly they occur in the wall of the oesophagus or in the subcutaneous tissue of the chest wall or neck. They are most often single cysts, variable in size, and do not necessarily communicate with the tracheobronchial tree but may simply be attached by a fibrous band. Histologically the cysts are lined by a pseudostratified columnar epithelium, the wall consisting of smooth muscle bundles, cartilage plates and abundant

a



b

**Fig. 7.28.** **a** Central bronchogenic cyst from a newborn presenting with symptoms of respiratory distress. (H&E, × 4) **b** The cysts resemble normal bronchial wall in places. Note the cartilage plates and normal appearing bronchial mucosa. (H&E, × 20)

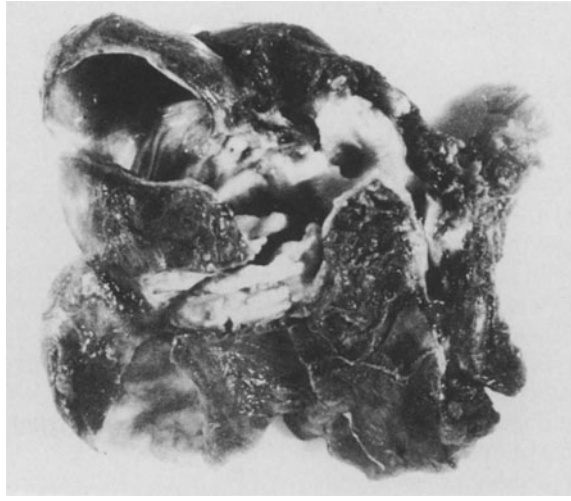
elastic fibres. There are also numerous subepithelial glands, which explain the presence of mucus in the lumen (Fig. 7.28). The changes caused by infection may be superadded.

*Peripheral cysts* probably develop as a result of disturbance in the growth of the bronchial tree at a late stage of intrauterine life or even after birth. They are usually multiple, and may affect both lungs, a lobe or part of a lobe, or even an entire lung (Fig. 7.29a). Microscopically they may communicate with a parent bronchus, and they are a form of honeycomb lung of infancy. Histologically, they are lined with ciliated or cuboidal respiratory epithelium. Their wall consists of connective tissue in which there are many elastic fibres and a few small cartilage plates but practically no smooth muscle fibres. Subepithelial mucus glands are usually absent (Fig. 7.29b).

## *Cystic Adenomatoid Malformation*

Cystic adenomatoid malformation is a relatively rare condition, and has often been included with congenital cystic disease of the lung or pulmonary sequestration. It is now considered a hamartoma and in some instances may be associated with dysplastic or neoplastic tissues and other congenital malformations such as extralobar sequestration, renal agenesis, malformation of the urogenital tract and cardiac anomalies. The diagnosis is now made in utero by ultrasound as the condition is known to be associated with anasarca and maternal polyhydramnios. The abnormality is usually unilateral, affecting one or more lobes, usually the lower lobe (Stocker et al. 1987; Carles et al. 1992a; Heydanus et al. 1993; Zangwill and Stocker 1993; Thorpe-Beeston and Nicolaides 1994), but more than one lobe may be involved. The lesions may be bilateral and occupy variable proportions of the lobes, as in a case we have seen recently. The condition has also been described in adults (Pulpeiro et al. 1987). Tumours are known to develop in or in association with this malformation (Stephanopoulos and Catsaras 1963; Ueda et al. 1977).

Kwittken and Reiner (1962) were among the first to attempt to define the condition histologically, and included an increase of terminal respiratory structures with intercommunicating cysts of various sizes lined with respiratory-type or cuboidal epithelium, polypoid formation of the mucosa and an increased



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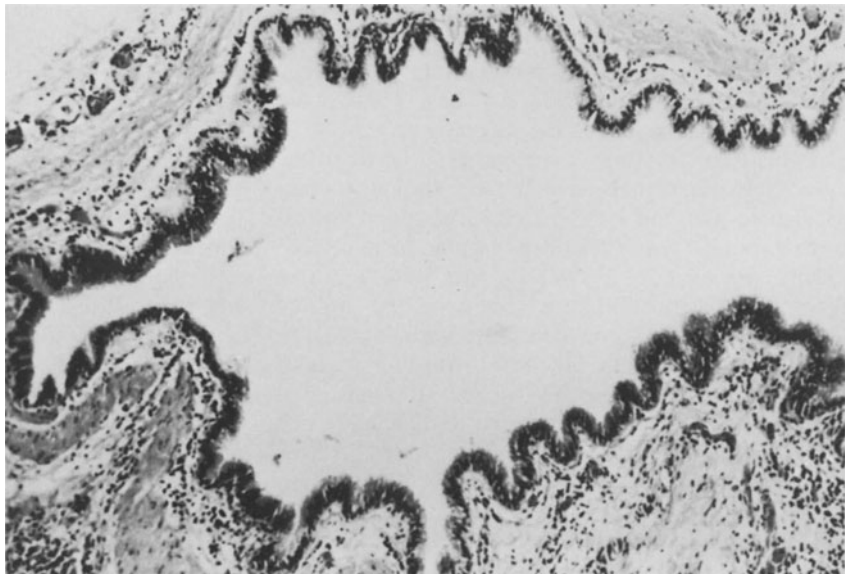


**b**

**Fig. 7.29.** **a** Peripheral bronchial cysts in a 3-month-old child. **b** Wall of peripheral bronchogenic cyst from a 4-year-old boy. (H&E, × 35) (Courtesy of Dr.C. Bozic)

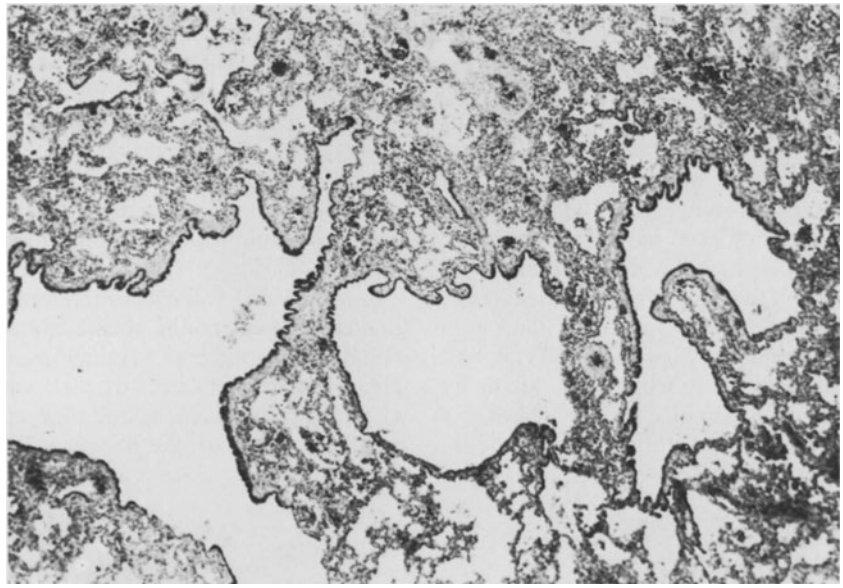


**Fig. 7.30.** Congenital cystic adenomatoid malformation, corresponding to type II lesions of Stocker et al. (1977), from a 3-day-old baby girl. (H&E, × 25) (Courtesy of Dr C. Bozic)

amount of elastic fibres in the wall beneath the epithelium. There was usually absence of cartilage and there were no inflammatory cells.

In 1973, Van Dijk and Wagenvoort described three cases of this condition and proposed a new classification into cystic, intermediate and solid types. Stocker et al. (1977) reviewed 38 cases and proposed a different classification. These authors also grouped their cases into three distinct categories, based on clinical, gross and histological criteria. *Type I* lesions presented only a few large thick-walled cysts containing air or fluid. These cysts were lined with ciliated pseudostratified columnar epithelium with numerous polypoid projections in the lumen. The wall contained smooth-muscle fibres and elastic tissue, but very few cartilage plates. There were smaller cysts adjacent to the larger ones, and large alveolus-like structures were observed between the cysts. Sometimes these alveolus-like structures communicated with the smaller cysts. The blood vessels were normal. *Type II* lesions presented as numerous evenly spaced cysts, generally less than 1 cm in diameter. They communicated with the normal bronchial tree. The cysts were lined with cuboidal or tall columnar ciliated epithelium, with rare areas of pseudostratification (Fig. 7.30). The wall consisted of a thin layer of loose fibromuscular tissue, and in this there were dense concentrations of elastic tissue beneath the epithelium. The cysts appeared to communicate with structures resembling respiratory bronchioles and alveolar ducts. Cartilage was not observed as a part of the lesion but rather as a normal component of the bronchi. There is a subgroup of the type II lesion containing bands of striated muscle fibres throughout the lesion, lying close to the bronchiole-like cysts and blood vessels from which may develop the rhabdomyosarcomas described in association with this lesion. *Type III* lesions were less numerous and presented as bulky and firm masses of pulmonary tissue occupying almost the entire lobe or lobes and containing very small visible cysts (less than 0.5 cm). The cysts were similar to bronchioles in size and distribution, and were lined in areas with ciliated cuboidal epithelium or, in most places, with non-ciliated cuboidal epithelium (Fig. 7.31). Electron microscopic studies of these cells (Olson and Mendelsohn 1978) have shown that they are composed primarily of granular pneumocytes (type II) and few type I pneumocytes. They resembled the glandular structure of the developing lung and were separated by a loose connective-tissue stroma with a few elastic fibres and occasional smooth-muscle fibres. Cartilage was absent.

In their series, Stocker et al. (1977) found that type I and type II lesions were by far the most frequently observed. They also noted that type I lesions were larger, involving almost the entire lobe or lobes with no adjacent normal pulmonary tissue. Furthermore, type I lesions were more commonly associated with other congenital malformations.

Two additional types (0 and IV) have been added to the present classification (Stocker 1994). Type 0 affects the proximal tracheobronchial tree. The cysts are lined by a ciliated pseudostratified columnar epithe-

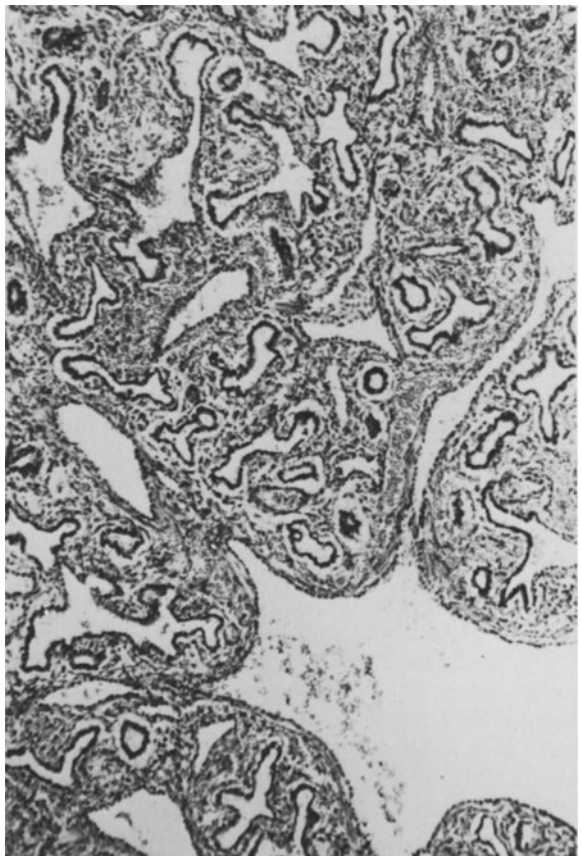


**Fig. 7.31.** Type III lesion of congenital cystic adenomatoid malformation (classification of Stocker et al. 1977) from a premature baby boy. (H&E, × 60)

lial lining with goblet cells. Mucus cells and cartilage are always present but there is absence of striated muscle. Type IV cysts are peripheric, lined by flattened type I pneumocytes and low cuboidal epithelial cells. The walls are variable in thickness with many vessels whose walls also vary in thickness.

### *Pulmonary Lymphangiectasis*

Pulmonary lymphangiectasis is not uncommon. Clinically it presents as respiratory distress in the neonate. Infants with this anomaly rarely survive beyond 24 h; however, cases have been recorded of survival for some weeks or even years. There is a net male predominance. The abnormality has been described in association with other congenital malformations (asplenia, cystic renal disease, anomalous pulmonary drainage) or restricted to the lung. This has led some authors to separate the condition into three categories: a generalized form, a form associated with obstructive cardiovascular anomalies with abnormal pulmonary venous connections, and an idiopathic form isolated to the lung. When unique and localized it is referred to as *lymphangioma* and, when diffuse, occupying one or more lobes, as *lymphangiectasis.*

The aetiology is obscure, and various theories are proposed as to its pathogenesis, including obstruction of the pulmonary venous flow, obstruction of the pulmonary lymphatics, and anomalous pulmonary development with failure or regression of the developing lymphatic network. It has been described in association with pulmonary hypertension in the neonate, pleural effusions or chylothorax, and it has been reported in siblings. The condition may be widespread involving bone, soft tissue and/or viscera and is then referred to as *lymphangiomatosis* (Stocker et al. 1978; Karmazin et al. 1989; Kelso et al. 1991; Stark and Mark 1992; Ramani and Shah 1993; Verlaat et al. 1994).

Macroscopically both lungs are generally involved, although there are a few reported cases in which only one lung has been involved. The lungs are large and firm, with a grossly lobulated or nodular surface. Between the lobules, one can observe the lymphatic network, with multiple round or ovoid cystic cavities lying beneath the pleura and containing fluid. The cut surface may appear relatively normal or show a honeycomb appearance with thickening of the intralobular septa, which may contain numerous cysts, resembling interstitial emphysema. Histologically the septa are thickened throughout the lung, and they contain a lace-like network of distended lymphatic vessels of variable sizes extending into the intrapleural space (Fig. 7.32). The lymphatics are thin-walled, lined with a single layer of endothelial cells, and do not have valves. Muscle fibres are absent from the thickened septa, and there is no lymphoid tissue present.

## Heterotopic Tissue in the Lungs

There are few recorded cases of ectopic tissue within the pulmonary parenchyma. Heterotopic brain tissue has been observed in the lungs in anencephaly and in other cerebral malformations. Heterotopic glial tissue may be multifocal, unilateral or bilateral (Okeda 1978; Kanbour et al. 1979; Gonzalez-Crussi et al. 1980). Striated muscle in the lung has been documented both in adults and in childhood. Of the 20 cases so far described, eight have been in the paediatric age group (Chi and Shong 1982). Congenital adrenal tissue in the lung has been reported, and two of the cases presented with adrenal cytomegaly in both the adrenals and the heterotopic tissue (Armin and Castelli 1984). Heterotopic liver in the lung is also rare (Mendoza et al. 1986a), as is heterotopic thyroid tissue (Bando et al. 1993).

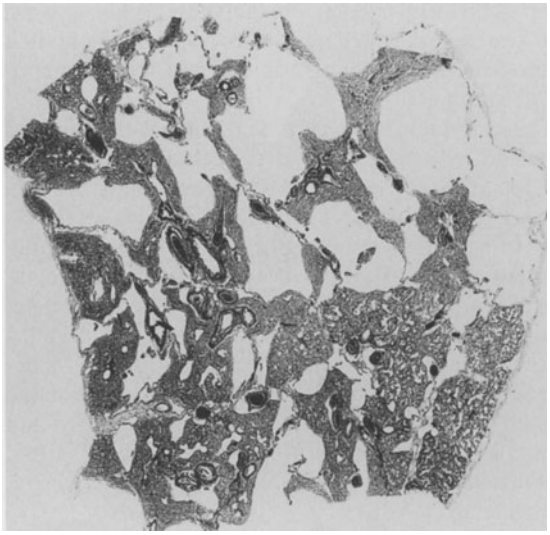


**Fig. 7.32.** Lymphangiectasis. There is diffuse dilatation of the lymphatics occupying the entire lobe, forming dilated cysts in many areas. (H&E, × 3)

## Lobar Emphysema

Lobar emphysema is also referred to in the literature as regional infantile emphysema or congenital obstructive emphysema, and the condition is due to air-trapping by a check-valve. The lesion can involve one or several segments, one or multiple lobes, or even an entire lung; the upper lobes are most often affected, with a slight predominance on the left. In rare cases both lungs have been involved. The condition is observed principally in neonates and infants. Clinically it manifests itself as a rapidly progressive respiratory distress syndrome, with dyspnoea and cyanosis leading to cardiorespiratory failure. On radiographs the affected area is hyperlucent, and there is compression atelectasis of the adjacent pulmonary parenchyma with displacement of the mediastinum toward the opposite side. A relatively high incidence of associated malformations, including cystic adenomatoid malformation, is recorded in these patients (Lincoln et al. 1971; Strunge 1972; Sulayman et al. 1975; Young et al. 1978; Moyland and Shannon 1979).

Although the underlying mechanism causing this condition is not always clear, obstruction of the bronchus leading to the involved segment, lobe or lung is an important cause. Extrinsic factors that can obstruct the bronchus include anomalous mediastinal blood vessels, enlarged lymph nodes, bronchogenic mediastinal cysts, and enteric duplications (Gerami et al. 1969; Schapiro and Evans 1972; Desvignes et al. 1974; Powell and Elliott 1977). Intrinsic causes include mucus plugs or redundant bronchial mucosal folds. More common, however, are structural defects in the bronchial wall, which may be overlooked unless careful histological studies of the main bronchus leading to the involved emphysematous zone are performed. The bronchus may be atretic or stenosed, or it may have abnormal cartilages, with cartilage present as hypoplastic or fragmented cartilage plates affecting either a localized area or several bronchi. The hypoplasia may be partial or total. Bronchomalacia may be included among the defects causing lobar emphysema as well as obstruction caused by secondary vascular disease. Emphysema in this age group has been recorded with Down's syndrome, in siblings and in a mother and daughter. Within recent years attempts at clearly defining the condition have been made in order to understand its physiopathology better. (Berlinger et al. 1987; Toran et al. 1989; Gonzalez et al. 1991).

By quantitative analyses of lungs with congenital lobar emphysema or "apparent" emphysema, Hislop and Reid (1970, 1971) and Henderson et al. (1971) were able to illustrate other causes. These various authors were able to separate combinations of anatomical lesions that may be associated with congenital lobar emphysema. They described the *"polyalveolar"* lobe (*acinus giantism*), in which there was an increase in alveolar number, and further showed that unilateral congenital emphysema can be present in a hypoplastic lung with contralateral compensatory emphysema. Silver et al. (1988) have described what they referred to as *perinatal pulmonary hyperplasia* associated with laryngeal atresia. Lung development was far advanced for the gestational age.

## Neonatal Pathological Conditions

It is impossible to over-emphasize the importance of radiographic examination of the body or the thorax before autopsy to enable the pathologist to exclude certain abnormalities within the thoracic cavity. The need to test the pleural spaces for pneumothorax is evident in view of the widespread use of assisted ventilation and, because useful information can be gained from bacteriological and virological studies, material from the trachea, bronchi and lungs and blood from the heart may be cultured. These examinations often supply valuable information and are often helpful in cases where the gross pathology is uninformative.

## *Amniotic Fluid and Meconium Aspiration*

It is well established that the fetal lung secretes a liquid that occupies the terminal air spaces and airways and whose composition and viscosity are different from those of the plasma and amniotic fluid (Adams 1966; Adamson et al. 1969a). There has been considerable controversy as to whether there are spontaneous fetal respiratory movements in utero, with mixing of the amniotic fluid with that of the fetal lung. Recent studies using various methods (mainly ultrasonic monitoring) have shown that fetal breathing movements in utero occur both in experiemental animals and in humans. These movements, which are associated with contractions of both the diaphragmatic and the intercostal muscles, have been detected early in gestation and they become more regular with advancing gestational age. Because of the high viscosity of lung fluid and the short duration of inspiration, normal breathing is insufficient to clear the tracheal dead space, and therefore the tidal volume is very small. It is mainly during gasping under various adverse conditions that relatively large volumes of anmiotic fluid may be inspired by the fetus (Benacerraf and Frigoletto 1986; Mortola 1987; Natale et al. 1988; Wiswell and Bent 1993). The amniotic fluid may sometimes be stained with meconium, suggesting fetal distress or acidosis. However, Miller et al. (1975) and Seppälä and Aho (1975) have suggested that the passage of meconium is not always a result of hypoxia or fetal distress, but may be a spontaneous or even a physiological phenomenon. Whatever the determining factors may be, the amount of meconium released and the quantity of meconium-stained amniotic fluid aspirated by the fetus depend largely on the duration and intensity of the stimulating factor.

Aspiration of amniotic fluid or meconium-stained fluid occurs mainly in mature or postmature infants, but can also be observed in the premature. It is generally associated with fetal anoxia, which may in turn be related to cerebral haemorrhage, vagal reflex, intrauterine pneumonia, congenital heart disease or other malformation, or drugs administered to the mother during pregnancy or at delivery. Aspiration may result in intrauterine death or the meconium aspiration syndrome of the newborn, which could be due to the inhibition of surfactant function by the aspirated meconium resulting in a decrease in lung–thorax compliance (Clark et al. 1987; Sun et al. 1993). The meconium aspiration syndrome is not infrequently associated with persistent pulmonary hypertension (persistent fetal circulation) (Reid 1986; Perlman et al. 1989; Swaminathan et al. 1989). The lung may show little on gross examination; however, the presence of meconium on the perianal region, within the external ear, or on other parts of the body and the placenta is an indication that intrauterine fetal distress or anoxia has occurred. The external ear should always be examined for meconium in a neonate; if the body has been washed postnatally, as often happens, traces can be discovered with a swab. The histological lesions are variable and include aspiration of amniotic fluid into the terminal airways, which are distended and contain fluid, a few squamous epithelial cells, and some cellular debris, and show congestion of surrounding capillaries. When meconium is aspirated, the distal airways are distended, containing masses of meconium with some squamous epithelial cells; the trachea and large bronchi may contain large meconium plugs; the bronchioles and terminal airways are also distended and are partly or completely filled with squamous epithelial cells and a little meconium (Fig. 7.33). In both instances there is congestion of the capillaries. Muscularization of the intra-acinar pulmonary arteries when present is consistent with persistant pulmonary hypertension.

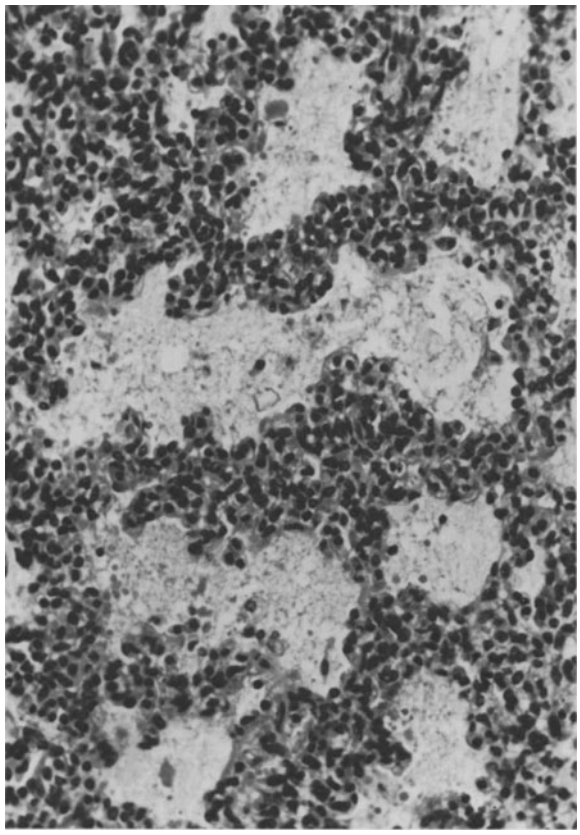
When squames are observed in the distal airways of infants several weeks after birth, it is, of course, possible that there might have been a period of intrauterine fetal distress with aspiration of amniotic fluid.

## *Perinatal Pneumonia*

Pneumonia in still born and newborn infants is a relatively common finding at autopsy. It is responsible for the deaths of 5%–20% of infants dying within the first 24–48 h of extrauterine life, and may be found in as many as 30% of stillbirths. Most authors refer to pneumonia occurring in those dying within 48 h of birth as intrauterine or congenital pneumonia, and associate it with aspiration of infected amniotic fluid in utero, maternal sepsis, or infection acquired during passage through the birth canal (intrapartal infection). The term *neonatal pneumonia* is reserved for pneumonia occurring during the first days or weeks after birth, but not after the first month of age. It is generally associated with infections acquired from the environment (delivery room and nursery).

In most infants dying in the immediate neonatal period, between 24 and 48 h of age, it is impossible to distinguish between the two groups.

Most intrauterine pneumonia is the result of infection ascending from the birth canal into the amniotic sac. It is associated with premature rupture of the membranes and prolonged labour, conditions that favour chorioamnionitis, the incidence of which



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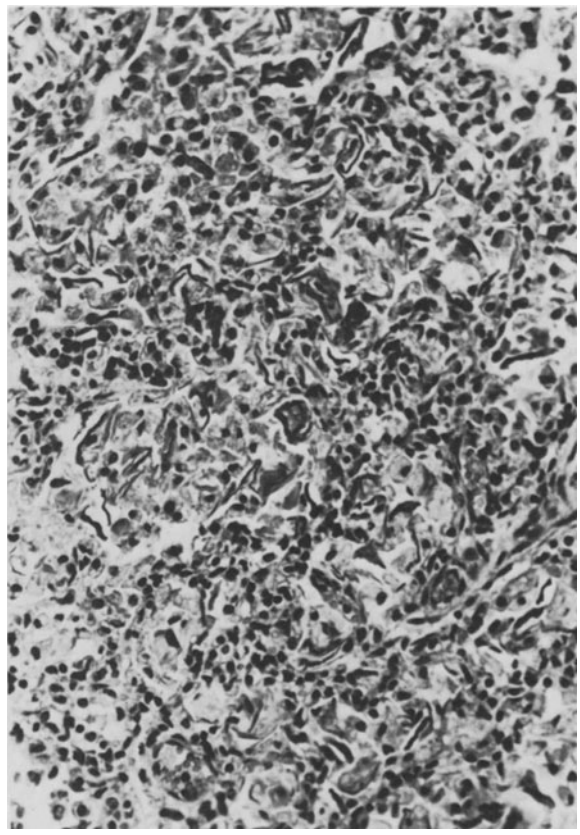

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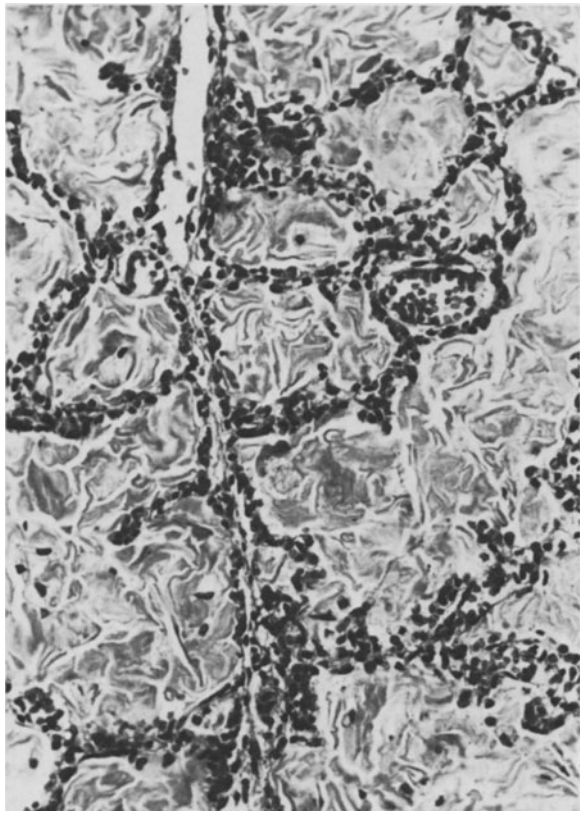

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**Fig. 7.33.** Lungs in neonatal asphyxia. (H&E, × 225) **a** Progressive respiratory distress in a full-term infant. Alveolar saccules are filled with amniotic fluid but contain little debris. **b** Severe respiratory distress with marked extension of alveolar saccules filled with squamous epithelial cells. **c** Prolonged respiratory distress. There is a giant cell reaction associated with secondary inflammation.

increases significantly after 24 h. Congenital pneumonia has also been observed in prolonged labour with intact membranes or where there have been obstetric manoeuvres during labour. In the remaining cases, infection is transplacental and is often associated with clinical symptoms in the mother, e.g. pyelonephritis.

Premature infants appear to be more susceptible to intrauterine pneumonia.

The commonest causative organisms are *Escherichia coli*, β-haemolytic streptococci group B, *Streptococcus faecalis*, *Staphylococcus aureus*, *Klebsiella–aerobacter*, *Pseudomonas aeruginosa* and, less frequently, *Haemophilus influenzae* and pneumococci. Numerous other pathogens have been isolated occasionally, including viruses, fungi, chlamydia and mycoplasmas (Alt et al. 1984; Campognone and Singer 1986; Tomashefski et al. 1989; Itoh et al. 1990; Webber et al. 1990; Bang et al.

1993; Eschenbach 1993; Primhak et al. 1993; Sanchez 1993; Wright and Butt 1994).

Gross inspection of the lungs reveals nothing apart from occasional localized pleurisy. Histologically, the distal airways are filled with a polymorphonuclear-rich inflammatory reaction, which may or may not contain squames. The most striking feature characterizing this type of pneumonia is the absence of fibrin, which has created doubt as to whether the histological picture is a true inflammatory response to infection or caused by aspiration of amniotic elements containing polymorphonuclear (maternal) leucocytes. Recent studies have now established that the inflammatory cells within the airspaces, as well in the interstitium, are of fetal origin and could be the fetal response to infection, toxins and/or chemotactic mediators or combinations, including meconium toxicity, inducing a pulmonary inflammatory reaction characteristic of intrauterine pneumonia. Peribronchial lymphoid hyperplasia may be an associated phenomenon, as well as an increase in the number of polymorphonuclear cells in the liver (Arnon et al. 1993; Grigg et al. 1993; Bohin and Field 1994; Scott et al. 1994; Stallmach and Karolyi 1994). The alevolar septa, bronchioles and bronchi are not involved. Bacteria are not usually observed in sections and, if present, are few (Fig. 7.34). In neonatal pneumonia the exudate contains fibrin, and interstitial inflammatory changes with monocytic cell infiltration can be seen. The bronchi and bronchioles may be surrounded by or infiltrated with mononuclear cells. Necrosis is common but may occur with the formation of microabscesses and/or pneumothorax, notably in staphylococcal infections

## *Pulmonary Haemorrhage*

The real incidence of massive pulmonary haemorrhage in the newborn is not known; there are wide variations in the individual series studied. It is sometimes found in stillborn infants, but is most common among those dying in the first 48 h of life. Premature infants and those small for gestational age are the most often affected. Symptoms may appear immediately after or within a few hours of birth and resemble a severe respiratory distress syndrome.

Although fluid escaping from the nose and mouth may resemble blood, chemical analyses have shown it to be a mixture of plasma filtrate and a small quantity of blood, comparable with haemorrhagic oedema fluid (Adamson et al. 1969b; Fedrick and Butler 1971b; Cole et al. 1973).

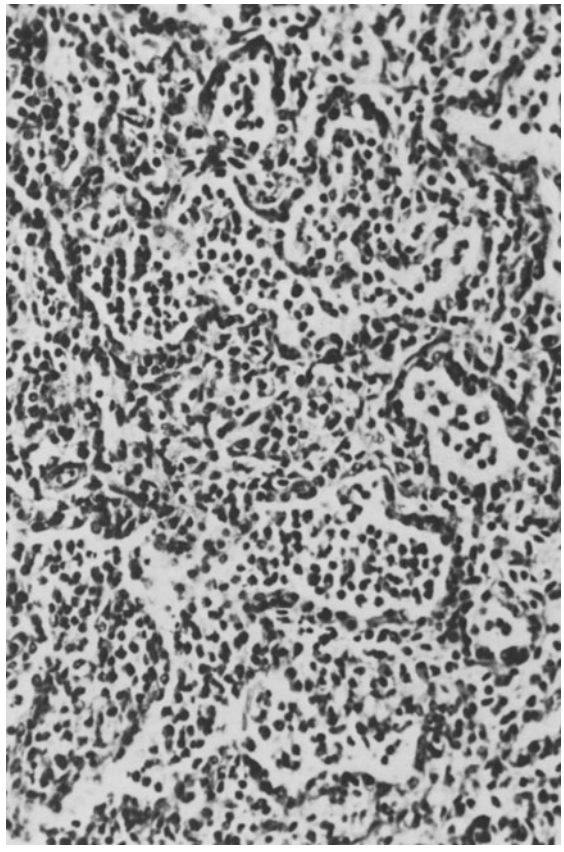
Several aetiologies have been proposed for this condition. It has been described in association with prenatal and perinatal asphyxia or anoxia, bacterial or viral infection, cerebral oedema and/or intraventricular haemorrhage, hypothermia, cardiac anomalies (patent ductus arteriosus or ventricular septal defect), haemorrhagic disease of the newborn, hyaline membrane disease and hyperammonaemia (Esterly and Oppenheimer 1966; Adamson et al. 1969b; Chessels and Wigglesworth 1971; Fedrick and Butler 1971b; Cole et al. 1973; Sheffield et al. 1976). The recent studies of Cole et al. (1973) and those of Trompeter et al. (1975) suggest that massive pulmonary haemorrhage in the neonate covers a spectrum of conditions that may rapidly lead to acute left ventricular failure owing to asphyxia. This is followed by an increase in pulmonary capillary pressure and pulmonary haemorrhage. It would appear that infants treated with synthetic surfactant therapy for idiopathic respiratory distress syndrome (IRDS) are more prone to develop pulmonary haemorrhage (Coffin et al. 1993; Pinar et al. 1993).

On gross examination the lungs are heavy, fleshy and of normal size. They may have one or several dark haemorrhagic areas; in most instances an entire lobe or several lobes may be involved. The trachea and large bronchi often contain blood-stained fluid. Histologically, the distended distal airways, bronchioles and some bronchi are filled with erythrocytes. The alveolar septa are markedly congested and show zones of interstitial haemorrhage (Fig. 7.35). Hyaline membranes, squames and mild inflammatory reactions have all been observed in association with this condition.

## *Idiopathic Respiratory Distress Syndrome (IRDS)/Hyaline Membrane Disease*

*Idiopathic respiratory distress syndrome*, with its well defined clinical presentation, was once the most frequent cause of death among neonates, especially the premature. The principal anatomic finding in these cases was hyaline membrane disease in the lung. Better understanding of some of the possible mechanisms of the condition and the enormous progress in perinatal intensive care units have reduced the death rate due to this disorder considerably, and in well equipped centres there are relatively few infants dying with hyaline membrane disease alone. Such deaths show a male preponderance, probably due to a slower lung maturation in male fetuses; in addition the second-born of twins appears to be at greater risk, as well as postmature infants. A familial predisposition has also been documented.

Prenatal identification of infants at risk, the better understanding of lung development and maturation have now made it possible to design new approaches in the treatment of this disorder, resulting in more favourable outcomes. The cases that now come to autopsy usually present with associated pathological conditions and/or complications (Farrell and Avery



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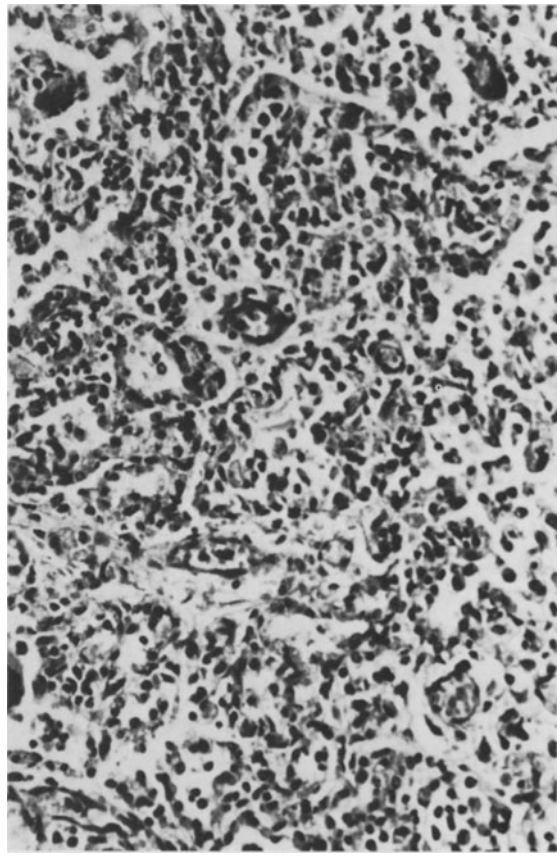

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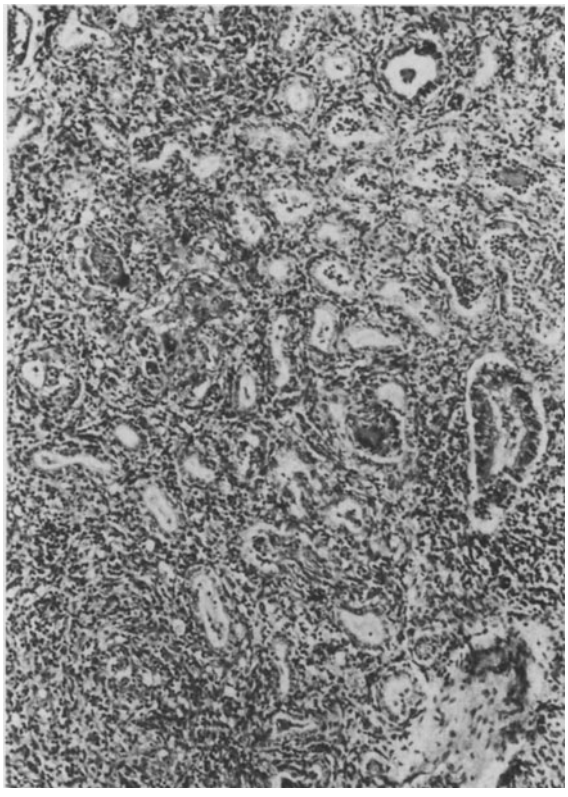

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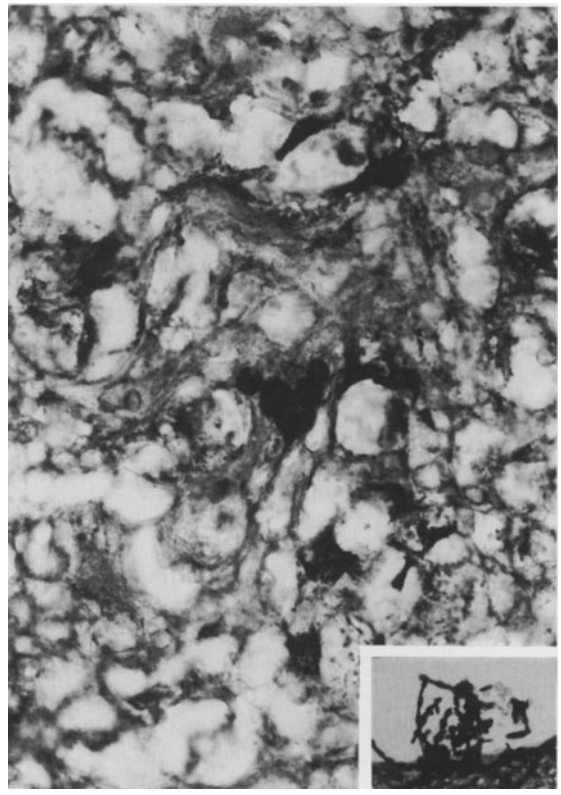

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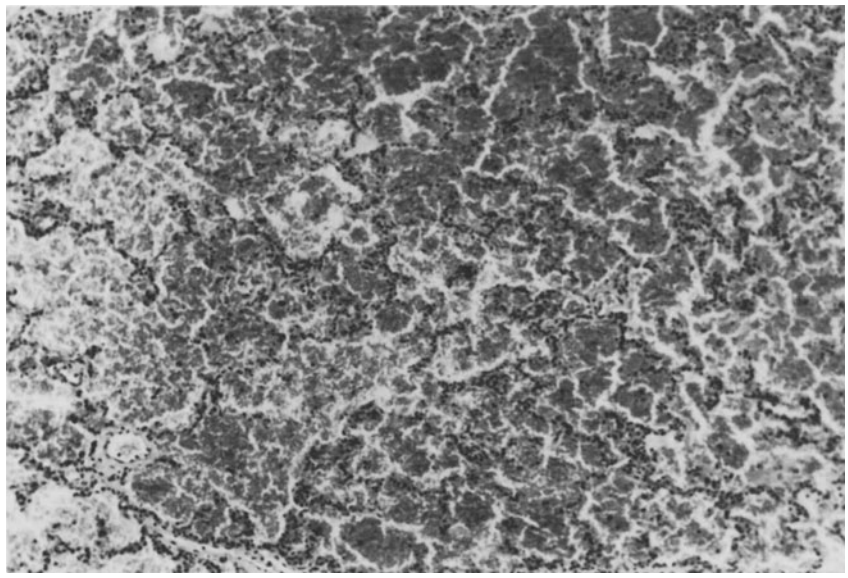


**Fig. 7.35.** Diffuse intra-alveolar haemorrhage of unknown origin in a newborn infant. (H&E, × 90)

1975; Bonikos et al. 1976; Northway et al. 1990; Seo et al. 1990; Van Lierde et al. 1991; Dobashi et al. 1993).

It is generally accepted that there are three main predisposing factors among infants who present with the respiratory distress syndrome:

1. *Prematurity* or *immaturity*. Infants of low birth weight (800–1500 g) appear to be more susceptible to this disorder than infants born at or near term. It should be noted that the condition has seldom been recorded in fetuses below 800 g and has not been seen in stillborn infants.
2. *Caesarean section*. There is still much controversy as to whether caesarean section per se predisposes to hyaline membrane disease; the evidence suggests that it does, and that this is more apparent following certain indications for section (fetal distress, maternal bleeding and placenta praevia). Catecholamines and other hormones that play an essential role in the preparation of the fetus for adaptation to extrauterine life are low or lacking and seem to be responsible, at least in part, for the incidence of the condition in this group.
3. *Maternal diabetes*. Here again, hyaline membrane disease may simply be the reflection of the high rate of premature delivery and caesarean section among this group. However, it is well established that these infants are both hyperglycaemic and hyperinsulinaemic due to the disturbance in glucose metabolism. Furthermore, there is growing evidence to suggest that insulin affects type II pneumocytes, causing a delay in their maturation and a diminution in desaturated phosphatidylcholine, phosphatidylglycerol and surfactant apoproteins (Farrell and Avery 1975; Rosan 1975; deMello et al. 1987; Nakamura et al. 1988; van Golde et al. 1988; Margraf et al. 1990).

*Histopathology*. Hyaline membranes apparently do not appear in stillborns, although some authors have interpreted necrotic cellular debris in such cases as the first changes leading to hyaline membrane disease. An infant must breathe for a short period before the clinical manifestations of the syndrome begins or hyaline membranes develop. Some authors have described their presence as early as 8 and 30 min (McAdams et al. 1973; de la Monte et al. 1986).

On gross inspection, the lungs are airless, reddish grey in colour, resembling liver and rubbery in consistency, but there is little or no change in weight and

**Fig. 7.34.** **a** Intrauterine pneumonia in a stillborn fetus. The alveolar saccules are distended and filled with polymorphonuclear leucocytes. Conspicuous absence of fibrin. **b** Intrauterine pneumonia with giant cells, probably of viral origin, in a 2-day-old infant whose mother presented with a temperature of unknown origin. No bacteria present. (H&E, × 225) **c** Intrauterine penumonia with granulomatous appearance and numerous giant cells. (H&E, × 160) **d** Grocott stain showing mycotic elements within the giant cells (× 650.) *Inset*, placental infection.

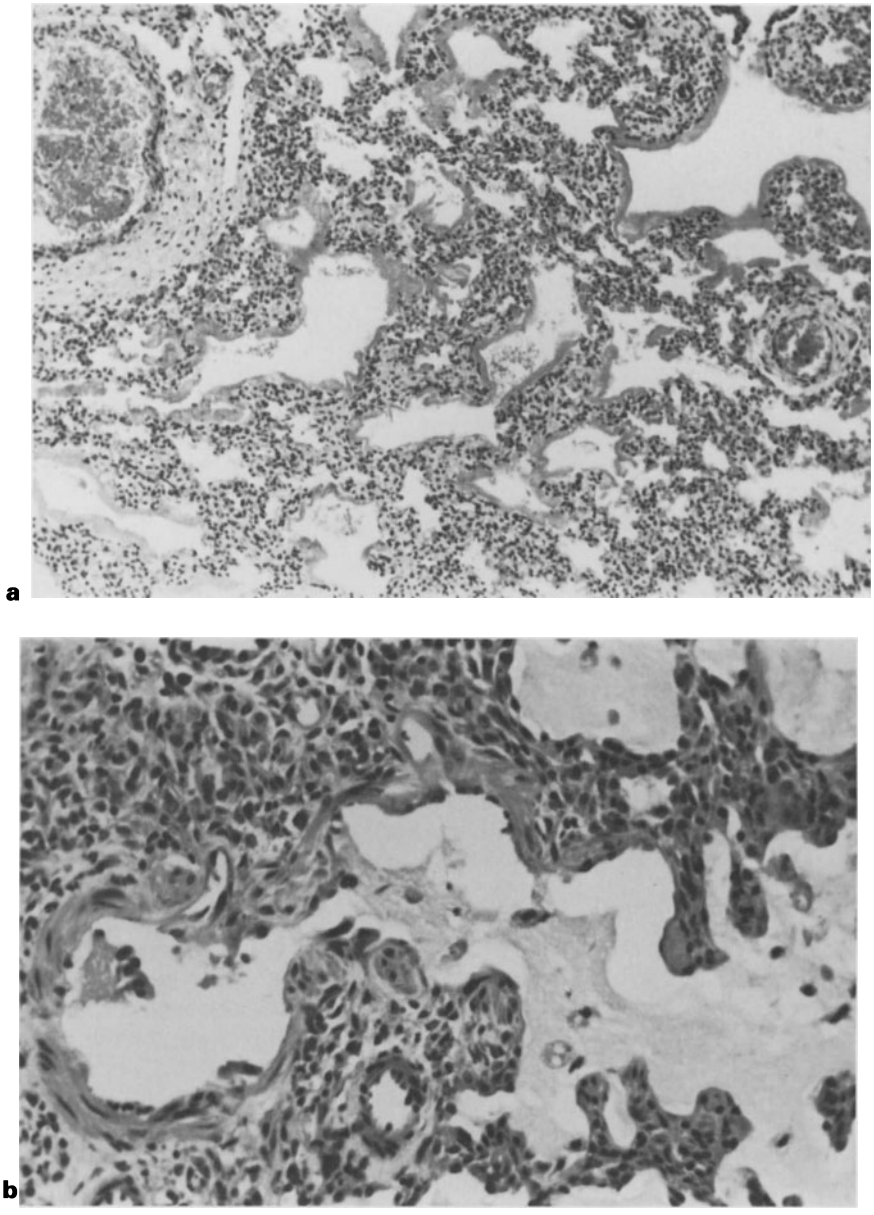


**Fig. 7.36.** Lungs in respiratory distress syndrome. **a** Some alveolar saccules are lined with hyaline membranes; other are collapsed. (H&E, × 90) **b** Organization of hyaline membranes invested by fibroblasts. (H&E, × 120)

size. Infants who succumb within the first 2 h after birth present diffuse bilateral atelectasis. The terminal airways are occasionally recognizable, distended and present necrosis of the respiratory epithelium and/or destruction and desquamation of their epithelial cells, taking on a basophilic appearance. Hyaline membranes may not be conspicuous at the early stages. Oedema fluid may be seen in some airspaces as well as in the interstitial tissues. The capillaries are usually dilated and there are often foci of haemorrhages. The lymphatics are generally dilated. One must be cautious, however, at this stage, to exclude an eventual intrauterine or perinatal infection (usually by group B streptococcus), which may present similar histological features, in which case a Gram stain could be useful. The airways may contain numerous polymorphonuclears.

After about 12 h the lesions are more extensive; dilated distal bronchioles and terminal airways are more conspicuous and alternate in an irregular fashion with atelectatic zones. The membranes are now quite conspicuous, extensive and confluent, and may be observed in atelectatic areas. They appear as homogeneous eosinophilic bands on the denuded thickened basal membrane, or epithelial cells of the distal bronchioles and terminal air spaces are seen

below, containing epithelial cellular debris and pyknotic nuclei (Fig. 7.36).

Interstitial and intraluminal haemorrhages are common findings. Arterioles appear contracted and the veins are congested. Lymphatics are usually dilated. In infants dying after 12 h the lesions are even more widespread, and the hyaline membranes are extensive, thicker and well defined.

Beyond 36 h of life the first signs of repair appear. Type II pneumocytes begin to regenerate at the margins of denuded areas and beneath the hyaline membranes; by day 3 these changes are well defined. The membranes become fragmented and resorption is in process (phagocytosis by macrophages). There is active interstitial fibroblastic proliferation, and this, with type II pneumocyte cell regeneration, seems to incorporate the membranes into the alveolar wall, leading to fibrosis of varying degree. Meanwhile, the oedema has diminished considerably. Tubular myelin and surfactant apoproteins are now prominent in the proliferating hyperplastic type II pneumocytes (Lauweryns 1969; Lauweryns et al. 1971; Finlay-Jones et al. 1973; Nilsson et al. 1978; Robertson 1987; deMello et al. 1987; Nakamura et al. 1988; Margraf et al. 1990).

The chemical composition of hyaline membranes has been extensively documented. They are weakly PAS-positive and rich in fibrin deposits, being most readily identified by fluorescent or electron microscopy. Conventional stains for fibrin (Mallory phosphotungstic acid haematoxylin) are often disappointing. Hyaline membranes have also been shown to contain high quantities of tyrosine, $\alpha_1$-antitrypsin and $C_3$ fractions of complement (Gitlin and Craig 1956; Berezin 1969; Lauweryns 1970; Demarquez et al. 1976; Singer et al. 1976).

In hyperbilirubinaemic premature infants with the respiratory distress syndrome, the hyaline membranes lining the distal airways may appear yellowish; hence the name *yellow pulmonary hyaline disease*. The condition is most often encountered among premature babies with a moderate bilirubinaemia who have been ventilated and received relatively high levels of oxygen for long periods. The membranes attain this colour as a result of increased permeability of the air–blood barrier in the lung to a serum protein–bilirubin complex. Yellow hyaline membranes stain positively for bile (Morgenstern et al. 1981; Turkel and Mapp 1983).

The pathogenesis of hyaline membrane disease is probably variable. Hyaline membranes have been described in association with or complicated by the aspiration of amniotic fluid, premature rupture of the membranes, neonatal asphyxia with acute anoxia and acidosis, hypothermia, intrauterine infection, congenital heart disease leading to rapid heart failure, pulmonary hypoperfusion, birth injury, erythroblastosis fetalis and deficient lung fibrinolytic activity (plasminogen activator). Immunological factors and neuroendocrine disorders have also been incriminated (Lieberman 1969; Fedrick and Butler 1970a; Ambrus et al. 1974; Farrell and Avery 1975; Kenny et al. 1976; Berkowitz et al. 1978).

However, the most important single contributory factor in the pathogenesis of the respiratory distress syndrome is the absence or low level of *surfactant (surface-active materials)*. The role of surfactant in the normal lung is well established. The terminal air spaces in the normal newborn infant, like the alveoli in adults, are lined with a surfactant (Fig. 7.37), which maintains their stability by lowering surface tension at the air–liquid interface, thus preventing alveolar collapse during pulmonary expansion. It has been noted that the lungs of newborn infants dying with hyaline membrane disease are consistently lacking or deficient in surfactant and surfactant apoproteins, which are normally secreted by the granular pneumocytes and Clara cells. Between 20 and 24 weeks' gestation, these cells make their appearance in the terminal spaces of the developing lung. Soon afterwards there is a marked decrease in the glycogen content of the type II cells, and osmiophilic lamellar inclusion bodies appear within the cytoplasm, representing the first morphological expression of the secretory activity of these cells. About the same period, surface-active materials, mainly phospholipids and surfactant apoproteins, can be recovered from the pulmonary fluid of the fetus or from the amniotic fluid in small quantities. They can also be identified in the fetal lung by immunohistochemistry. From then on the number of granular pneumocytes, and to a lesser degree Clara cells, increases rapidly, and by 30 weeks they are normally producing large quantities of surfactant, which attain their maximum levels at about the 35th week of gestation (Fig. 7.38).

*Apocrine epithelial antigen* (AEA) can be detected in type II cell membranes early in fetal lung before the occurrence of detectable surfactant. Anti-AEA also stains reactive material in hyaline membranes. Furthermore, the type II cells contain few intermediate keratin filaments; these vary in quality and quantity, depending on the development and maturation of the cells. The most active component of surfactant is dipalmitoyl phosphatidylcholine (saturated lecithin). This substance can already be detected in very small quantities between 18 and 20 weeks' gestation, and increases in amount with advancing gestational age. As a result, the determination of this phospholipid in amniotic fluid is now widely used to evaluate fetal lung maturity and predict which infants are at risk. Its value is expressed as a ratio of lecithin to sphingomyelin (L/S) (Rosenthal et al. 1974; Hallman et al.

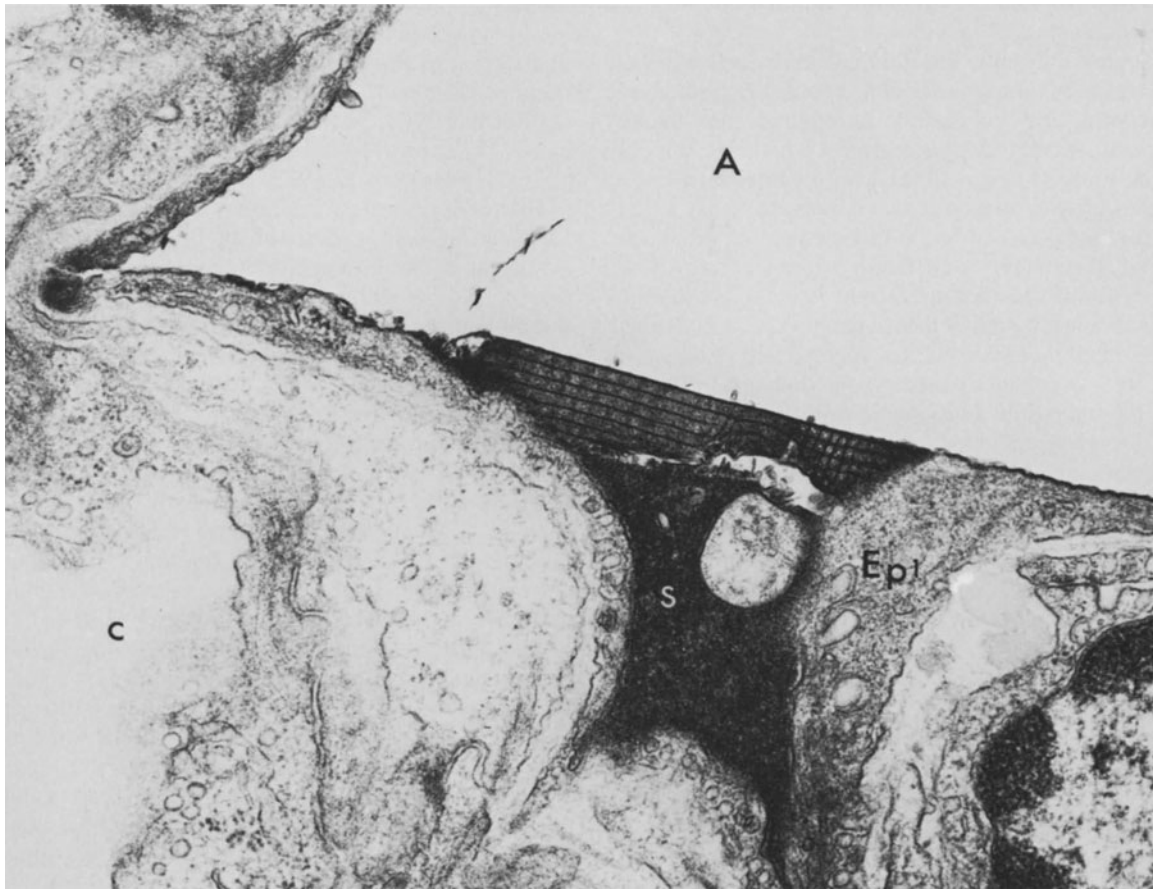



**Fig. 7.37.** Electron micrograph of surfactant (*S*) lining the alveolar surface. *A*, alveolus; *C*, capillary; $EP_1$, epithelial cell type 1. (× 41 000) (Courtesy of Dr Y. Kapanci)

1989; Bowie et al. 1991; Bender et al. 1994; Miyamura et al. 1994).

The regulation of lung phospholipid biosynthesis depends on certain enzymes, principally phosphatidic acid phosphohydrolase, within the granular pneumocytes. This enzyme can also be detected in the lung and amniotic fluids; its level increases with gestational age. Its concentration in amniotic fluid can also be used as an indicator of lung maturity as it rises in parallel with the L/S ratio. Phosphatidylglycerol is another good marker, as are amniotic fluid prolactin, surfactant apoproteins and lamellar body concentrations (Hallman et al. 1989; Dubin 1990; Bowie et al. 1991; van Kreel 1991; Fakhoury et al. 1994; Bender et al. 1994).

Surfactant contains variable amounts of phosphatidylethanolamines, phosphatidylglycerol and sphingomyelins (70%–80%) as well as neutral lipids (mainly cholesterol). Besides the active phospholipid component (dipalmitoyl phosphatidylcholine), surfactant also contains small amounts of carbohydrates and many proteins in varying quantities. It is now evident that the protein, which makes up about 10% of purified surfactant, is composed of two equal fractions, one of serum albumin, secretory IgA and IgG and the other of a species of associated apoproteins, four of which have so far been identified. These surfactant proteins (SP), designated SP-A, B, C and D, play an important role in the morphological structure and function of surfactant.

SP-A, a hydrophilic highly immunogenic family of glycoproteins, is cloned on chromosome 10(10q). It is synthesized and secreted by type II pneumocytes and bronchiolar Clara cells. The collagen-like sequences on its amino-terminal end make it structurally homologous to CIq and can thus enhance FcR and CRI mediating phagocytosis. Its non-collagenous terminal domain is responsible for its inhibitory effect on lipid secretion and binding to type II pneumocytes. Although it can be identified in fetal lung by 12 weeks' gestation, it is detected in substantial quantities only during the last trimester at about 34

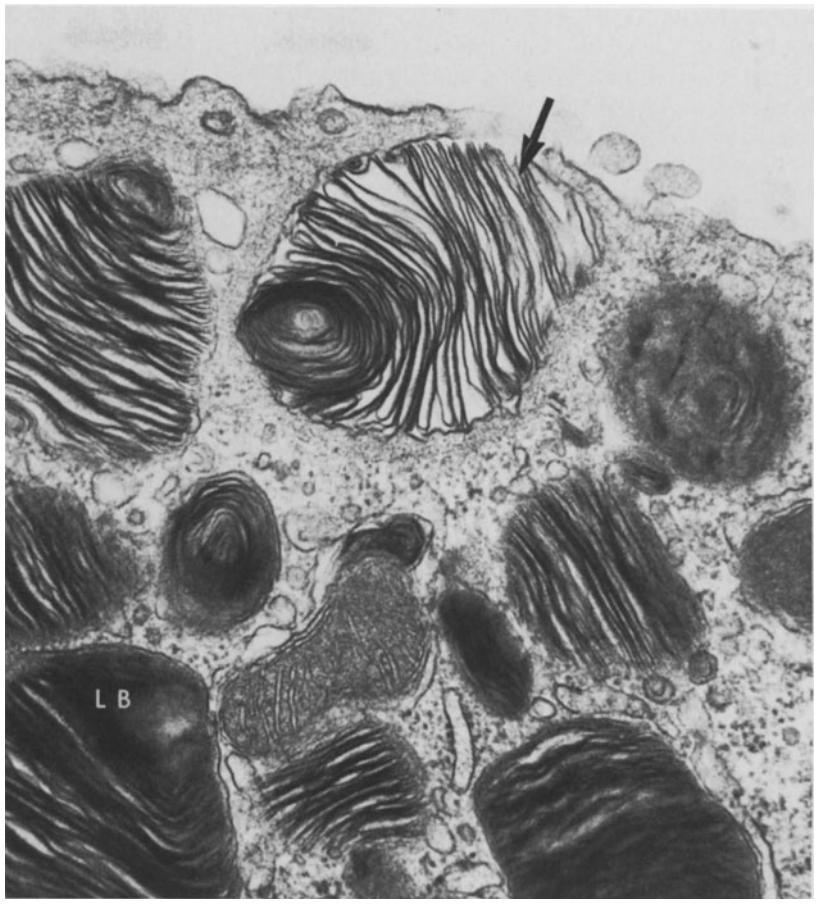



**Fig. 7.38.** Electron micrograph of granular pneumocyte (type II cell), showing numerous lamellated bodies (*LB*), one of which (*arrow*) is undergoing exocytosis. (× 68 000) (Courtesy of Dr Y. Kapanci)

weeks. It is regulated by a number of hormones and growth factors (glycocorticoids, cAMP, insulin, interferon $\gamma$, EGF and TGF $\beta$). It cooperatively enhances the activities of the hydrophobic apoproteins (SP-B and SP-C), but acts specifically as a regulator of function in surfactant metabolism and participates in the formation of tubular myelin and in the local defence mechanisms of the host. The type II pneumocytes express high-affinity receptors for SP-A in the surfactant recycling process.

SP-B, a highly immunogenic hydrophobic surfactant apoprotein, is associated with surfactant phospholipids. The genes for it are located on chromosome 2 and its mRNA is detectable early during the second trimester of gestation, well before its appearance as morphologically recognizable lamellar bodies and earlier than mRNA for SP-A, and is synthesized by both type II pneumocytes and bronchiolar Clara cells; its production is enhanced by glucocorticoids. Its biologically active form is derived from a much larger precursor protein and has the function of facilitating a reduction in surface tension. When associated with SP-A, it plays a major role in the transformation of the multilayered membranes of lamellar bodies into tubular myelin.

SP-C is a hydrophobic surfactant apoprotein synthesized by type II pneumocytes; genes for it are located on chromosome 8. mRNA is detectable early during the second trimester of gestation. It is markedly enhanced by glucocorticoids and is effective in facilitating phospholipid absorption.

SP-D, a hydrophilic collagenous glycoprotein, is encoded in chromosome 10 at the locus that also includes SP-A. It is secreted by both type II pneumocytes and Clara cells and is expressed during the canalicular phase of lung development. It is under the regulation of hormonal and growth factors and its mRNA can be upregulated by glycocorticoids. As a member of the C-type lectin family, which recognizes pathogens with carbohydrate-containing surfaces, it may have a prominent role in pulmonary defences against gram-negative bacteria and certain viruses. Furthermore, it interacts with macrophages through its carbohydrate binding domain and may have a significant clinical role in the respiratory distress syndrome both in the neonatal period and in

adults. (Kuroki et al. 1988; Possmayer 1988; Strunk et al. 1988; Van Golde et al. 1988; Ryan et al. 1989; Tenner et al. 1989; Hawgood and Clements 1990; Oomen et al. 1990; Otto-Verberne et al. 1990; Kuroki et al. 1991; Phelps and Floros 1991; Weaver 1991; Venkatesh et al. 1993; Deterding et al. 1994; Kuan et al. 1994; Crapo and Wright 1995).

Surfactant metabolism is complex and at present many aspects remain speculative. The intracellular phase takes place in the type II pneumocytes, where endoplasmic reticulum and the Golgi apparatus play an important role in the production of structured lamellar bodies. Intra-alveolar secretion of surfactant is under the stimulus of several agents, including adrenergic agonists, cholinergic agents, mechanical factors, and prostaglandins. Once in the alveolar space intra-alveolar metabolism takes place and the secreted lamellar bodies are transformed into tubular myelin structures in the presence of calcium. The events at this stage, although not clearly understood, suggest that there is clearance of some of the material, degradation and incorporation by alveolar macrophages of a portion, and recycling and reprocessing of the remainder by type II pneumocytes, Clara cells and perhaps other parenchymal cells. Thus surfactant composition is both morphologically and functionally heterogeneous, and there are differences in form and activity which correlate with apoprotein content. It has three main functions: as a tenso-active material, as an anti-oedema barrier, and as an active and important agent in pulmonary defence. In addition, there are several secondary roles, in control of transepithelial transport of water and ions, in metabolism of xenobiotics, in defence against oxidative agents, in synthesis of components of the extracellular matrix, in reparation of cellular damage and in the defensive functions associated with alveolar macrophages, among others (Wright and Clement 1987; van Golde et al. 1988; Joyce-Brady and Brody 1990; Kobayashi et al. 1990; Voorhout et al. 1991; Kuroki et al. 1992; Wirtz and Schmidt 1992; Hawgood et al. 1993; Kondepudi and Johnson 1993; Murata et al. 1993; Neagos et al. 1993; Scott et al. 1993; Risco et al. 1994).

Glucocorticoids are known to accelerate lung maturation in the fetus by activating the synthesis and secretion of pulmonary surfactant, and administration of glucocorticoids (cortisol, dexamethasone) to mothers of premature infants at risk or to very premature babies has lowered significantly the incidence of respiratory distress syndrome in these groups. The effect appears to be a result of interaction between pulmonary interstitial fibroblasts, which are in direct contact with the type II pneumocytes and produce the *fibroblast pneumocyte factor*, which stimulates the type II cells. This activity, mediated by several enzymes, accelerates the maturation of the granular pneumocytes, using the glycogen stored within the cells and resulting in a marked increase of lamellar inclusion bodies and maturation of the air–blood barrier. Thyroid hormones also accelerate fetal lung maturation, with early disappearance of glycogen from type II pneumocytes. Their administration results in a decrease in the incidence of respiratory distress syndrome, but the mechanism is unknown. It is possible that there is an interaction between the two hormones acting in synergy at different chemical sites or through the interstitial fibroblasts, which have surface receptors for both endogenous and exogenous corticosteroids whereas thyroid hormones have nuclear binding sites. Sex hormones also appear to play a role in lung maturation. Oestrogen accelerates lung maturation apparently by direct action on the lung or in cooperation with interstitial lung fibroblasts, which are partly responsible for sex difference in surfactant synthesis by type II pneumocytes. It has been shown that fibroblasts from female fetuses produce more fibroblast pneumocyte factor than those from males. Insulin receptors are also present on type II pneumocytes and are known to play an important role in the presence of high levels of insulin. Fetuses of diabetic mothers are both hyperglycaemic and hyperinsulinaemic, and this results in a diminished production of surfactant in this category, thus leading to respiratory distress syndrome (Van Golde et al. 1988; Shimizu et al. 1991; Kari et al. 1994).

It is generally accepted that pulmonary surfactant is deficient in infants presenting with hyaline membrane disease; however, it is not certain what factor(s) may be responsible for its absence from the lungs. Absence may be the result of inadequate production and secretion or of delayed synthesis in the immature lung. These speculations about the cause of the condition have led to the introduction of various therapeutic approaches to the mother as a prenatal preventive measure or to the newborn.

It is now apparent that respiratory distress syndrome in premature babies has clinical and physiopathological features similar to those encountered in the adult respiratory distress syndrome. The mechanisms by which the lung respond to various injuries (primary or secondary) are similar in infants, children and adults, although the response may be variable depending on the many factors involved in the process (Royall and Levin 1988; Donnelly and Haslett 1992; Davis et al. 1993).

Various lesions are found in association with hyaline membrane disease. *Pulmonary infection* is common in infants dying with this condition. The pulmonary infiltration may be mild or may involve large areas of several lobes or the entire lung.

Squamous debris may be observed in the terminal air spaces, suggesting the aspiration of amniotic fluid. *Pulmonary haemorrhage*, although less common, can also be associated with hyaline membrane disease. The haemorrhage can be focal, but occasionally presents as massive lesions. Pulmonary infection and haemorrhage can coexist with hyaline membranes (Fedrick and Butler 1970a).

*Intraventricular haemorrhage* is commonly associated with hyaline membrane disease. It is observed mainly among premature infants, especially among those weighing less than 1500 g. When associated with hyaline membrane disease, intraventricular haemorrhage is often the cause of death among infants dying early in the course of the illness, usually within the first 24 h of life (Fedrick and Butler 1970b; Machin 1975; Anderson et al. 1976; Wigglesworth et al. 1976; Leviton et al. 1977). *Tentorial tears* occur with elevated frequency in infants with hyaline membrane disease, mostly among infants of advanced gestational age, at or near term. Many of these cases have presented obstetric difficulties at the time of delivery (Barson 1978).

*Complications Associated with Therapy. Bronchopulmonary dysplasia* remains the most significant complication in premature babies of low birth weight (below 1500 g) receiving oxygen at high concentrations and artificial ventilation at high pressures for long periods (3–4 weeks). The morphological changes are variable and depend on a number of elements, including gestational age, duration and mode of treatment, and possible associated infections. Macroscopically the general appearance depends on the many factors described above, but the cut surface reveals collapsed areas alternating with emphysematous zones. Both the clinical and pathological features have been divided into phases or stages, but with much overlapping.

Histologically, in the early stages of the disease there is necrosis of the epithelial cells lining the distal bronchi, bronchioles and terminal airways, associated with an interstitial oedema involving the vessel walls. There is widespread capillary damage with intraluminal and interstitial haemorrhages. At later stages the interstitial oedema has regressed, but it leaves marked thickening following fibroblastic and myofibroblastic proliferation (Fig. 7.39) associated with a predominantly mononuclear inflammatory reaction. Regenerative changes of the bronchial and bronchiolar epithelium take place with some degree of hyperplasia and squamous metaplasia. In severe cases there is obliterative bronchitis and bronchiolitis, often associated with marked squamous metaplasia of the epithelium. The muscular layers of the bronchi and bronchioles are thickened and there is fibrosis of the adventitia. There is fibrous thickening of the alveolar septae (often infiltrated by inflammatory cells), and the alveoli may contain macrophages and inflammatory cells. The lung parenchyma presents areas of hyperexpansion and/or emphysematous zones. Hyperplasia and hypertrophy of the pulmonary arteries and arterioles are not uncommon findings. The lymphatics may appear normal or somewhat distended and surrounded by inflammation. There is muscularization of the intra-acinar arterioles, indicative of pulmonary hypertension. In infants with bronchopulmonary dysplasia who have survived for long periods, fibrosis is usually very extensive and hyperexpansion is more widespread. There is marked reduction in the peripheral arterial density.

Pneumothorax, pneumomediastinum with pneumopericardium and sometimes gas embolism are complications generally related to positive pressure ventilation especially among very low birth weight babies. They may be responsible for the high morbidity and mortality rates in this age group; retrolental fibroplasia is related to oxygen toxicity.

Although the heart may be normal in size, there is often hypertrophy of either the right or the left ventricle or both, sometimes associated with transient systemic hypertension. There may also be areas of scarring, predominantly in the papillary muscles. The ductus arteriosus, especially in the very premature, may remain patent and present abnormalities of its wall (necrosis, abnormal elastic lamina) resulting in additional complications (left to right shunting) with unfavourable outcomes. For these reasons many centres insist on closing the ductus either by surgery or by medication. The neuroendocrine cells, and especially the neuroendocrine bodies of the lung, are usually increased in number (Rosan 1975; Bonikos et al. 1976; Anderson and Engel 1983; Stocker 1986; Westgren et al. 1986; Erickson et al. 1987; Northway 1990; Northway et al. 1990; Gorenflo et al. 1991; Van Lierde et al. 1991; Crapo and Wright 1995).

*Interstitial pulmonary emphysema* is often associated with barotrauma due to positive pressure ventilation in the very premature baby, resulting in air leaks and dissection of the lung parenchyma mainly along the bronchovascular bundles. The condition may be acute, occurring within the first week, or persistent over longer periods. In the acute phase, the air cysts may be located in one or more lobes or involve both lungs; they are usually peripheral in the form of numerous bullae of variable sizes scattered below the distended pleura. Histologically they are located in the region of the interlobular septa and peribronchial spaces, resulting in compression of the neighbouring structures (Fig. 7.40a). In persistent interstitial emphysema the bullae are numerous, of variable size, often widespread and larger than those seen in baro-

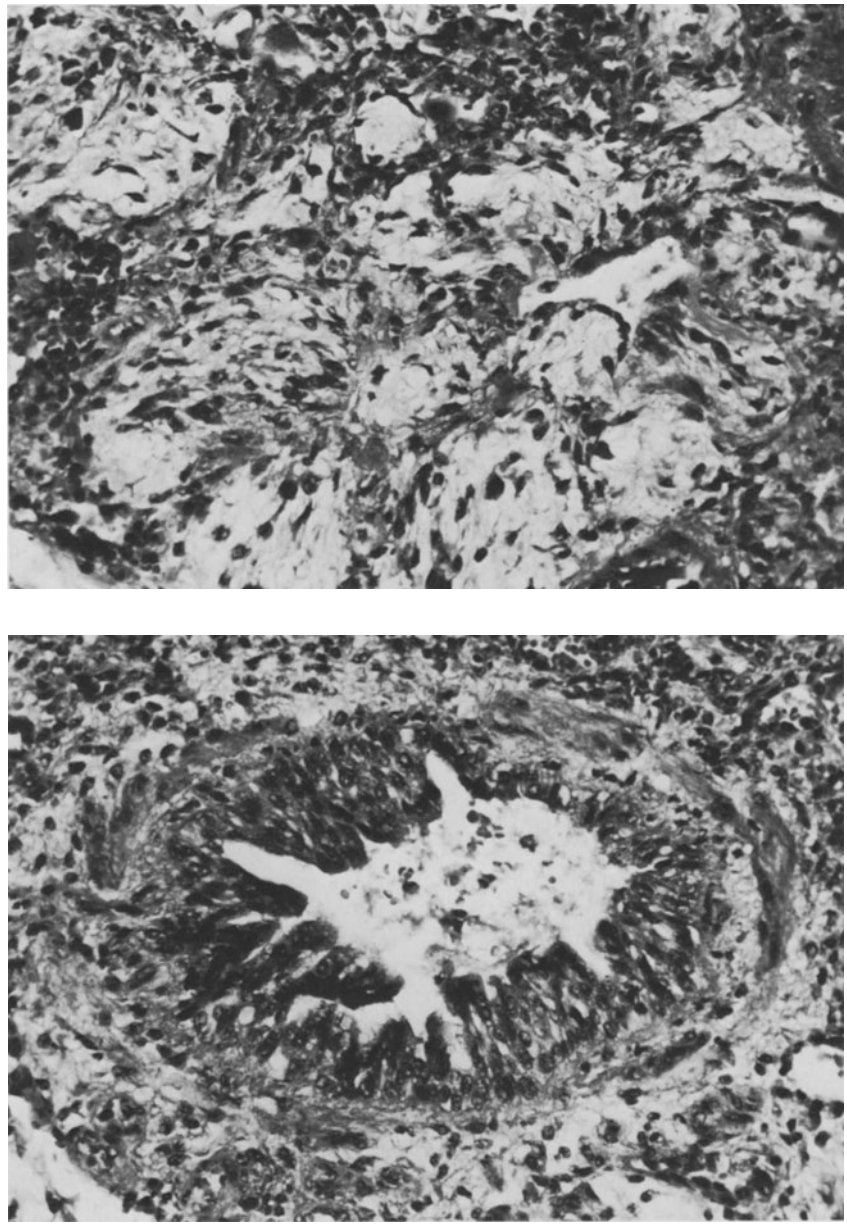
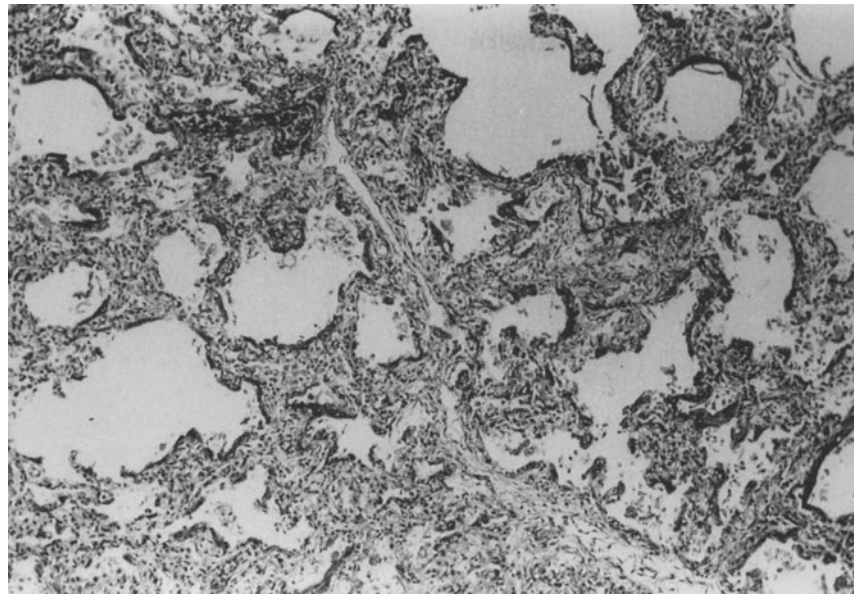


**Fig. 7.39.** Bronchopulmonary dysplasia in a premature infant as a complication of prolonged oxygen therapy for respiratory distress syndrome. **a** Alveolar saccules obliterated by proliferating fibroblastic tissue. **b** Metaplasia of the bronchial epithelium. (H&E, × 225)
*Continued on next page*

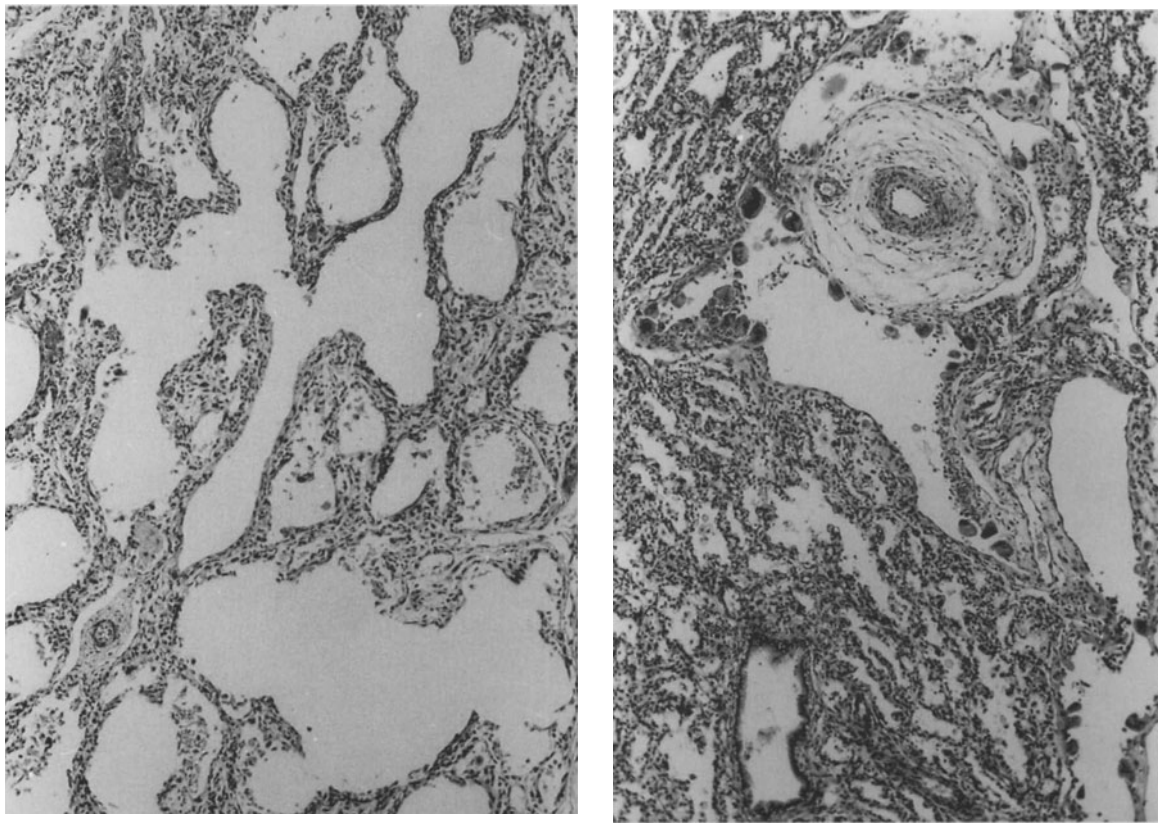
trauma, and involve most of the lung, often associated with bronchopulmonary dysplasia. On section, the cut surface may present a Swiss cheese appearance. Histologically, the bullae are bordered by a fibrous wall of variable thickness lined by foreign body giant cells, alone or in strings (Fig. 7.40b). The adjacent parenchyma is generally compressed (Stocker and Madewell 1977; Stocker 1986; Morisot et al. 1990).

Three elements appear to have major roles in the pathogenesis of the lesions: the developmental immaturity of the lung parenchyma, barotrauma due to high ventilation pressures, and oxygen toxicity. Recent studies suggest that high ventilation pressures on the epithelial structures of the distal airways (which are undergoing continuous differentiation and maturation) cause epithelial disruption at the time when the various components of surfactant are



c

**Fig. 7.39.** (*continued*) **c** Marked alveolar thickening associated with thick scarred areas and organizing hyaline membranes in the lung of a 628-g premature infant after $5\frac{1}{2}$ weeks' survival. (Masson's trichrome, × 20)



a b

**Fig. 7.40.** **a** Acute interstitial pulmonary emphysema showing radial cystic dilatations bordered in places by compressed airspaces. (H&E, × 20) **b** Persistent interstitial pulmonary emphysema. The irregular cystic walls are lined by giant cells, alone or in strings. (H&E, × 50)

incompletely organized. The high levels of oxygen delivered create toxic radicals whose action at the immature cell junctions causes disruption of cellular contacts at sites where the concentration of protective antioxidant enzymes and factors promoting lung differentiation and regeneration are low, leading to lung tissue damage. This encourages an inflammatory reaction with the accumulation of neutrophils and macrophages in the lumen of the airways. The proteolytic enzymes liberated by the neutrophils may cause further damage to the lung parenchyma, and the cytokines and growth factors secreted by the macrophages may result in an excess production of fibronectin and provoke pulmonary fibrosis.

Specific immunohistochemistry on fetal lung tissue has shown that the superoxide dismutases are closely related to lung maturation and that copper–zinc superoxide dismutase is low in intensity and area distribution in both hyaline membrane disease and bronchopulmonary dysplasia, whereas manganese superoxide dismutase is unaltered in hyaline membrane disease but increased in bronchopulmonary dysplasia. These results have produced a change of attitudes in the prevention and treatment of these conditions (Walti et al. 1989; Margraf et al. 1990; Northway 1990; Papadopoulos et al. 1990; Dobashi et al. 1993; Jacobson et al. 1993; Groneck et al. 1994). Several authors have now turned their attention to the nutritional states of premature babies prone to develop bronchopulmonary dysplasia; others have concentrated on antioxidant protection. Vitamins A, C and E together with some metallic ions have been introduced as preventive and therapeutic measures to enhance the premature lung's defence mechanisms and favour a more appropriate repair (Frank and Sosenko 1988; Kurzner et al. 1988; Fariss 1990; Northway 1990; Shenai and Chytil 1990).

*Late sequelae of bronchopulmonary dysplasia* are as follows. Alveolar septal fibrosis may be variable in quantity and distribution, and is usually more severe in infants of very low birth weight. There are important residual or active lesions of the tracheobronchial tree, often with squamous metaplasia of the mucosa associated with a chronic mononuclear inflammatory reaction. Ulceration of the mucosa is an occasional finding. Hyperplasia of the bronchial and bronchiolar muscle layers is constant, sometimes with scarring of the submucosal tissue. Bronchial gland hyperplasia is prominent. Alveolar septal fibrosis may be minimal, moderate or severe, and in some cases diffuse with scarred areas. The alveoli often contain macrophages, some of which contain iron pigment, as well as inflammatory cells. Some cases present with emphysematous or cystic lesions consistent with persistent pulmonary emphysema, and this has led some authors to postulate that these features in longstanding cases are the pathological correlates of the radiological images classically described in the Wilson–Mikity syndrome. Others have shown, however, that this syndrome is associated with a high incidence of intrauterine infection. The important point is that the alveolar population is reduced, large and simplified, and that there is a severe and persistent reduction in alveolar multiplication with little evidence of compensatory alveolar development, resulting in decreased lung volume and size. There is also an abnormal distribution of elastic fibres. The arteries and arterioles show thickening of their muscular layers and muscularization of the intra-acinar arterioles, whose lumen may be significantly reduced. Perivascular fibrosis is prominent, together with that of the interlobular septa, which often extend to the thickened pleura. Secondary infection, bacterial and/or viral, may provoke further lung injury and be detrimental to these patients (Stocker 1986; Erickson et al. 1987; Fujimura et al. 1989; Nakamura et al. 1990; Margraf et al. 1991; Gillan and Cutz 1993).

Although most survivors of bronchopulmonary dysplasia have apparently normal development, others suffer from various symptoms. These children may have weights below those of age-matched controls, and their head circumference is also somewhat smaller. Some patients are more susceptible to frequent and repeated lung infections; others present with exercise-induced bronchospasm with air trapping. Neurological sequelae are a major problem and may be non-progressive or progressive. In the former, there are deficiencies in coordination, a greater need for academic support, and hearing abnormalities (among others); in the latter, there is a progressive encephalopathy with seizures, movement disorders with progressive neurologic deterioration and even death (Perlman and Volpe 1989; Northway et al. 1990; Blayney et al. 1991; Vohr et al. 1991; Giffin et al. 1994; Crapo and Wright 1995).

Within recent years *extracorporeal membrane oxygenation* has become an established mode of therapy for neonatal respiratory failure (meconium aspiration, congenital diaphragmatic hernia, persistent pulmonary hypertension, shock, respiratory distress syndrome) in neonates unresponsive to conventional treatment. There are several complications which may result from the use of this treatment, of which the most common are central nervous system haemorrhages, infarcts and haemorrhages in various organs. In the lung, interstitial and intra-alveolar haemorrhages associated with hyaline membrane formation appeared within the first 2 days, and reactive epithelial hyperplasia of the distal airways, squamous metaplasia and smooth muscle hyperplasia occurred

between the second and third days, followed by interstitial fibrosis after a week. Various other lesions have been described after longer applications of this treatment (Chou et al. 1993; Beca and Butt 1994; Kanto 1994; Walsh-Sukys et al. 1994).

*Surfactant replacement therapy* is now widely used for the treatment of respiratory distress syndrome and also as a preventive measure for neonates of very low birth weight susceptible to develop the syndrome. Since its introduction there has been a significant decline in morbidity and mortality rate among premature newborns. There are numerous compositions of surfactants, many of which carry special brand names, and several collaborative group studies are in progress. Several reports have indicated a slight increase of pulmonary haemorrhage among infants receiving surfactant therapy. Haemorrhage appears to be more prevalent in the intra-alveolar spaces, but some authors have not observed any difference between intra-alveolar and septal spaces. Globular deposits of hyaline material were observed in the alveolar spaces by some authors but no hyaline membranes, whereas others, like ourselves, have noticed typical hyaline membranes in some infants as well as haemorrhages (Pinar et al. 1993; Pramanik et al. 1993; Raju and Langenberg 1993; Pappin et al. 1994; Berry et al. 1994; Gortner et al. 1994; Thornton et al. 1994). Prenatal glucocorticoid administered to mothers at risk, in combination with exogenous surfactant therapy to the newborn, has recently been introduced and gives favourable results. (Jobe et al. 1993; Leviton et al. 1993; Kari et al. 1994; Schwartz et al. 1994).

*Persistent pulmonary hypertension* (persistent fetal *circulation*) may be the cause of respiratory failure in the newborn. It is often described in association with meconium aspiration syndrome, perinatal asphyxia, intrapartum infection, congenital diaphragmatic hernia and elective repeat caesarean delivery. It is most often encountered in those born at term or in post-term infants who present with shunting across the foramen ovale and/or ductus arteriosus accompanied by severe hypoxaemia. Morphologically the right ventricle is usually hypertrophic, and the characteristic histological finding is muscularization of intra-acinar pulmonary arteries, which are normally non-muscularized or only partially muscularized (Fig. 7.41a). Treatment in a number of centres consists of administration of *nitric oxide*, which is known rapidly and selectively to relieve pulmonary vasoconstriction; Other centres have used extracorporeal membrane oxygenation. The lungs in infants receiving nitric oxide in this setting may show hyperplasia of the bronchial and bronchiolar mucosa with a depletion of goblet cells together with a marked hyperplasia of type II pneumocytes (Fig. 7.41b). These changes may be apparent as early as 2 days after establishment of treatment (Heritage and Cunningham 1985; Haworth 1987, 1993; Pison et al. 1993; Roberts and Shaul 1993; Zopal et al. 1994).

Pulmonary hypertension may also be observed in infants and children with cardiac malformations of various types, bronchopulmonary dysplasia, SIDS, sickle cell disease, intravenous drug addiction and congenital myotonic dystrophy among others (Williams et al. 1979; Dupuis et al. 1993; Haworth 1993; Rais-Bahrami et al. 1994).

## Common Infections

### *Bacterial*

The antibiotic era has dramatically modified the morphological appearances of inflammation of the pulmonary parenchyma. This is especially true in the industrialized nations, where both mortality and morbidity rates have been significantly reduced. In many developing nations, however, these modifications are less spectacular and classic pathological lesions can still be encountered among infants and children and the aged, principally because of inadequate medical services and poor handling of antibiotics. Inflammation of the lung in infants and children is by far the most common pathological lesion observed at autopsy, and may be the primary cause of death or a terminal episode accompanying other pathological conditions.

In lobar *pneumonia*, a lobe, an entire lung or both lungs may be involved at any one time. The lesions usually begin in the terminal air spaces or alveoli and spread to adjacent tissue. The involved lobes show lesions at the same stage of evolution. In the case of *bronchopneumonia*, the primary inflammatory reaction begins in the distal respiratory tract, extending into the surrounding parenchyma; lesions are generally at various stages of evolution. It is not necessary to describe the typical pathological features of pneumonia, with its characteristic four stages, but certain specific features should be considered.

*Streptococcus*. Streptococcal infections are an important cause of pulmonary infections among infants and children. *Streptococcus pneumoniae* is the principal cause of lobar pneumonia in this age group, especially after the first year of life, when over 90% of cases of pneumonia are related to this organism. Bacteria can be demonstrated in the lung in large numbers in the early stages of the disease. The various products and toxins produced by organisms are responsible for their virulence, independently or in combinations. Pneumococcal pneumonia may be

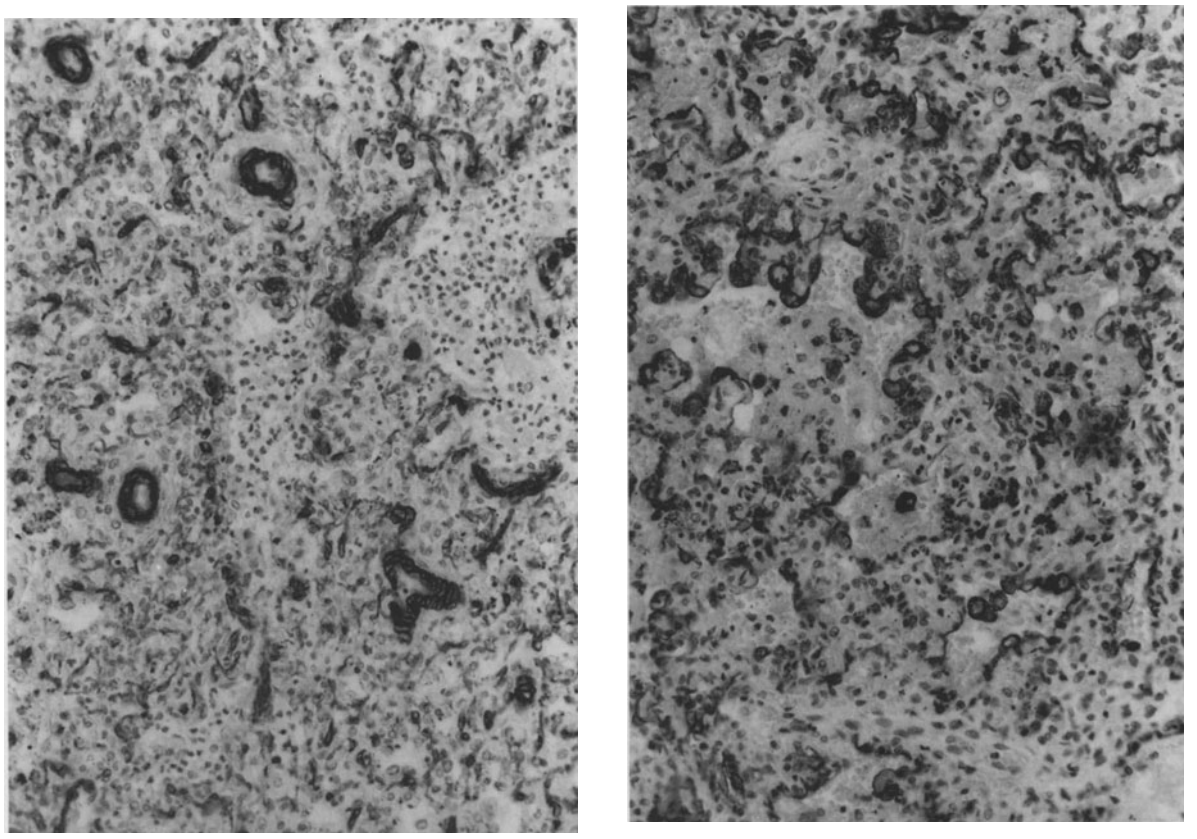


**Fig. 7.41.** **a** Persistent pulmonary hypertension: thickened muscularized intra-acinar arteries with stenosis of their lumini. (Smooth muscle $\alpha$-actin, × 160) **b** Hyperplasia of type II pneumocytes after 36 hours of NO treatment, keratin CAM-5.4, × 160.

found to be associated with viral or other infectious agents when infants are carefully investigated. Lung abscesses and empyema are significant complications and septicaemia may occur in rare instances, especially in the neonatal period. (Naylor and Wagner 1985; Tomashefski et al. 1989; Webber et al. 1990; Johnston 1991; Boulnois 1992).

Other types of streptococcal infection ($\beta$-haemolytic) can occasionally cause lobar pneumonia, but are more often the cause of bronchopneumonia. The involved lung is oedematous but the inflammatory response is moderate, with only scattered aggregates of polymorphonuclear leucocytes. Interstitial haemorrhages are common, and typical and atypical hyaline membranes may form. Gram-positive cocci are identifiable (Cayeux 1972; Franciosi et al. 1973; Ablow et al. 1976; Slack and Mayon-White 1978).

*Staphylococcus.* Staphylococcal infections usually produce bronchopneumonia. The great majority of cases occur within the first year of life, and may occur in small epidemics, especially among children in hospital. Staphylococcal infection is commonly associated with cystic fibrosis or other underlying conditions (Bryan and Reynolds 1984).

The affected lung is consolidated and shows focal haemorrhagic areas. The pleura may be covered by a fibrinous exudate, and empyema is not rare. The alveoli are usually filled with erythrocytes, oedema fluid and a few polymorphonuclear leucocytes. Sometimes macrophages are abundant, containing numerous microorganisms. Necrosis, often leading to abscess formation, is common. Interstitial emphysema and pneumatoceles are frequent complications of staphylococcal infections, and may cause pneumothorax (Oliver et al. 1959; Klein 1969; Boisset 1972; Gooch and Britt 1978; Asher et al. 1982).

*Haemophilus. Haemophilus influenzae* infection of the lung is increasing in frequency in the paediatric age group. It may be a cause of the respiratory distress syndrome in the neonate (Speer et al. 1978). The bacillus is a common inhabitant of the nasopharynx, and often causes acute laryngotracheobronchitis and bronchopneumonia. All lobes of the lungs can be involved, but the lower lobes are most often affected.

Well defined nodules around bronchi and bronchioles filled with pus are seen, with destruction of the bronchiolar epithelium and a mucopurulent exudate in the lumen. The bronchial and bronchiolar walls are infiltrated by mononuclear cells, chiefly lymphocytes, and some polymorphonuclear leucocytes. The inflammatory reaction extends into the surrounding alveoli, where oedema and interstitial haemorrhage may be found. Thrombosis of small vessels occurs in the acute phase of infection, and longstanding infections may produce obstruction of the bronchioles (Nicholls et al. 1975; Asmar et al. 1978b; Bale and Watkins 1978; Lilien et al. 1978). The recent introduction of a *H. influenzae* type B polysaccharide vaccine for children, which appears to give effective coverage except in those who present with some form of immune deficiency or other genetic factors, may have some effect on the frequency of this condition in the near future. Recent studies suggest that *H. influenzae* infection is principally a secondary infection to other bacterial and viral infections (Granoff et al. 1986; Korppi et al. 1992; Sawyer et al. 1994).

*Escherichia. Escherichia coli* is an important cause of gastrointestinal infections and septicaemia in the newborn period, and such infections are usually accompanied by neonatal (intrauterine) pneumonia. Histologically, the alveoli are filled with polymorphonuclears and macrophages, and are rich in fibrin. *E. coli* pneumonia is common after the 4th week of life. It can occasionally cause a pneumatocele (Klein 1969; Kuhn and Lee 1973).

*Klebsiella. Klebsiella pneumoniae* (Friedländer's bacillus) occasionally causes bronchopneumonia in infants and children. It is often associated with other bacterial or viral infections and is important in children with immunodeficiency states or in those receiving cytotoxic drugs for the treatment of malignancy. The lung in these cases shows many consolidated nodules of variable sizes disseminated in one or more lobes of both lungs. In the acute phase there is marked oedema extending into the interlobar spaces, alveolar destruction and a polymorphonuclear leucocyte infiltration. *Klebsiella* bacilli are numerous in gram-stained sections. These lesions often lead to abcess formation, and pneumatoceles may be encountered (Papageorgiou et al. 1973; Barter and Hudson 1974).

*Pseudomonas. Pseudomonas aeruginosa (Bacillus pyocyaneus)* affects premature infants and may be the cause of epidemics in nurseries. It is often found in children treated with broad-spectrum antibiotics, steroids or cytotoxic drugs. The lungs show firm irregular nodules, greenish-yellow in colour, scattered throughout the parenchyma, which is oedematous. The pleural cavities may contain a haemorrhagic pleural effusion. Histologically, the nodules often show a central necrotic zone and a polymorphonuclear leucocytic infiltrate surrounded by haemorrhagic areas. The distal arteries contain fibrinous thrombi, and organisms are frequently observed in the vessel walls.

*Moraxella catarrhalis (Branchamella).* Commonly known as *Neisseria catarrhalis*, this commensal microorganism of the upper respiratory tract may also be the cause of pulmonary infections, often in association with viral infection in childhood (Korppi et al. 1992).

*Listeria. Listeria monocytogenes* is a gram-positive motile bacillus, which has been associated with epidemics of abortion and encephalitis in animals. The exact distribution of the disease is not known, and its prevalence seems to be much higher in continental Europe than in the UK, the USA and Canada. Human infection is supposedly contracted by contact with infected animals, although proof of this means of transmission has not often been established (see also p. 736).

The disease can affect both infants and adults, and presents in various clinical forms. Epidemics have been described mostly in relation with contaminated food or food products, and in most instances, of the many known serotypes, type 4b is the most frequently incriminated. The condition is also described in debilitated patients, the immunocompromised and those with acquired immune deficiency syndrome (AIDS). In paediatrics, it is most common in the perinatal period, presenting either in a generalized form (*granulomatosis infantiseptica*) or as meningitis. Infection usually occurs during the second half of pregnancy and may be the cause of premature delivery, stillbirth or repeated abortions. Intrauterine infection can be acquired transplacentally, resulting in widespread lesions of various organs, or via the membranes, when the lung and gastrointestinal tract are mainly involved, probably as a result of aspiration and ingestion of infected amniotic fluid. Infection may also be acquired during delivery as the infant passes through the birth canal. Such infants usually present with meningitis in the first 10 days of life (Khong et al. 1986; Klatt et al. 1986a; Schlech 1986; McLauchlin 1990a, b; Svare et al. 1991).

In listerial infection, the lung may be normal in appearance or it may be heavy and firm with numerous minute whitish nodules on both the pleural and the cut surfaces. Haemorrhagic areas may also be observed. Similar lesions may be seen on the skin,

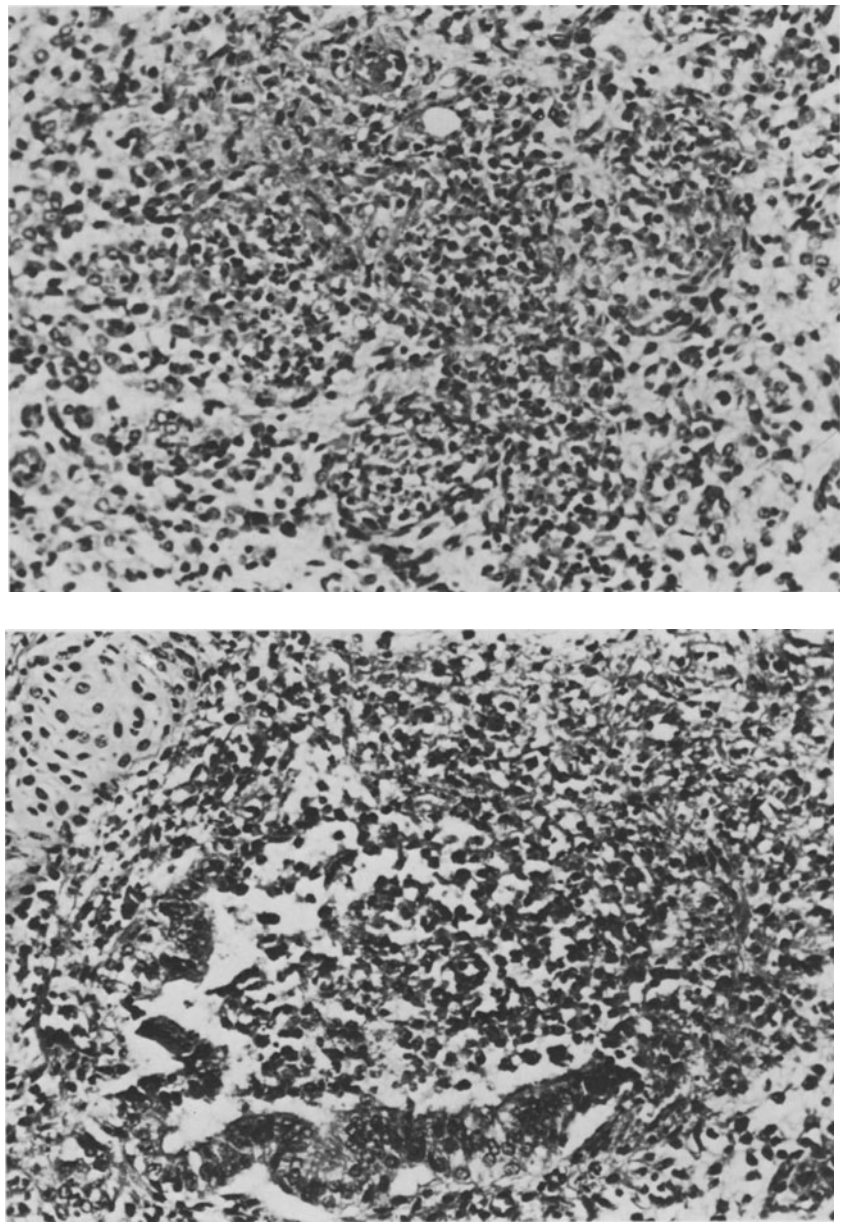


**Fig. 7.42** Listeriosis in a 3-day-old baby girl. (H&E, × 120)
**a** Confluent microabscesses in the pulmonary parenchyma.
**b** Necrosis of the bronchial wall and adjacent tissue.

where they present as a purpuric rash, and in other organs and the placenta.

Microscopically, the nodules are focal areas of necrosis or small granulomas, occasionally surrounded by congested vessels or haemorrhagic zones. The bronchi may be ulcerated or involved in the granulomatous process (Fig. 7.42). The necrotic tissue contains cellular debris and pyknotic nuclei and some mononuclear leucocytes. Gram staining reveals numerous gram-positive bacilli; some of the rods may appear gram-negative, and some take the shape of a comma. The vessel wall may be involved in the necrotic process, resulting in focal haemorrhages.

*Legionnaires' Disease*. Since the discovery of pneumonia called by the Legionnaires' disease bacterium, *Legionella pneumophila*, several other species have been identified (*L. micdadei*, *L. longbeachae*, *L. wadsworthii*, etc.) and there are some 28 known species, but in humans. *L. pneumophila* is by far the most prevalent cause of infection at all ages. It is known to occur in epidemics or sporadically, and, although it is not an uncommon cause of pneumonia, the exact mode of transmission is still not clearly defined. The disease is often associated with contamination of water distribution systems, cooling towers and air conditioners. Pulmonary damage is due

apparently to tissue-destructive protease liberated by the organism, leading to the various histological pictures observed in this condition. The aetiological agent is a gram-negative bacterium, which has special staining qualities in tissues and requires special media for its culture. The lungs show areas of consolidation and resemble lungs affected by confluent bronchopneumonia or lobar pneumonia, often with a fibrinous pleuritis. Pleural effusion is common. The alveoli contain an exudate that is rich in polynuclear leucocytes, macrophages and fibrin. Extensive lysis of the exudate, in areas, is a common feature, and abscess formation is not altogether uncommon. The oedematous and congested alveolar septa show areas of necrosis and an inflammatory reaction. Hyaline membranes may be associated with the lesions. Bronchial necrosis is common in affected areas. Legionnaires' disease bacterium can be demonstrated in the cells of the inflammatory exudate and cytoplasmic debris by the Dieterle silver stain (Fig. 7.43) or by immunohistochemical techniques. The majority of fatal cases have so far been diagnosed in adults, but children have also been affected. It is observed in patients after organ transplants, those receiving corticotherapy or cytotoxic drugs and in AIDS (Muldoon et al. 1981; Baskerville et al. 1986; Muder et al. 1986; Korvick and Yu 1987; Williams et al. 1987; Ezaki et al. 1990; Halablab et al. 1990).

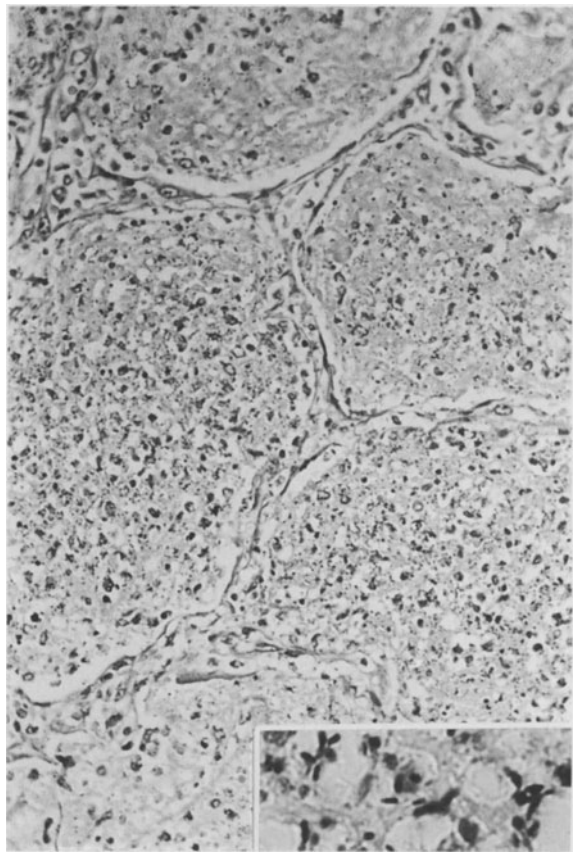


**Fig. 7.43.** *Legionella pneumophila* pneumonia. The alveoli are filled with inflammatory cells and necrotic tissue containing large quantities of bacteria stained by the Dieterle technique. (× 363; *inset* × 513)

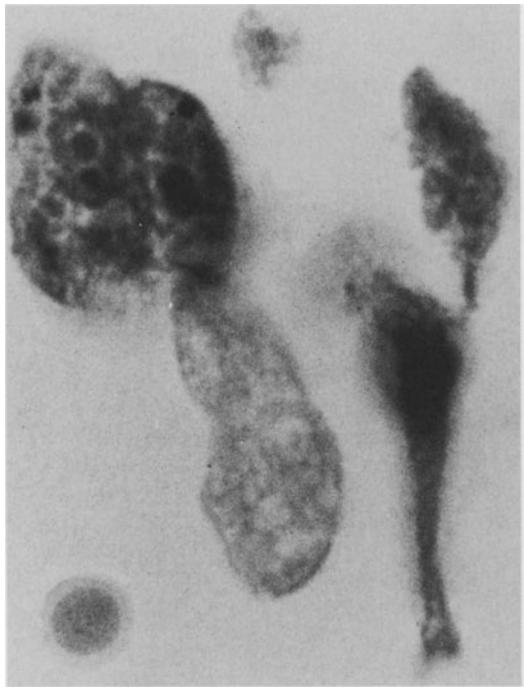
*Chlamydiaceae*. This family of obligate intracellular bacterial parasites depends on the host cell for ATP metabolites. It is made up of three distinct species of *Chlamydia*:

1. *C. trachomatis*, responsible primarily for urogenital and conjunctival diseases in humans, may also be the cause of upper and/or lower respiratory disease especially in infancy and those with immunodeficiency states
2. *C. psittaci* (*ornithosis*), aetiologic organism of infection in birds and transmissible to humans
3. *C. pneumoniae* (TWAR strains), known to cause upper and lower respiratory infections, including pneumonia in humans, especially in the young, the immunocompromised and the aged

The organisms present in two forms: an infectious metabolically inactive form, the *elementary body*, and a non-infectious metabolically active intracellular form, the *reticulate body*. They have a worldwide distribution, but appear to be more prevalent among peoples of lower socioeconomic status.

*C. trachomatis* is known to colonize the lower genitourinary tract in humans. In pregnancy the organisms may attain the uterine mucosa, resulting in chorioamnionitis and eventually intrauterine infection of the fetus, with possible premature delivery and low birth weight of the fetus. However, most infections appear to occur during the passage of the fetus in the birth canal at normal delivery. Symptoms may therefore occur between the first and third weeks after delivery and they are non-specific. In infancy *C. trachomatis* may be associated with other pulmonary infections (viral, mycoplasmal, bacterial), conjunctivitis, diarrhoea and sepsis. The pulmonary lesions are non-specific. Diagnosis is usually made by serological examination (IgG, IgM) or on tissue sections by Giemsa or iodine stains. Immunohistochemistry and ultrastructural studies are useful in confirming the diagnosis.

*C. psittaci* is not altogether uncommon among bird fanciers (psittacosis, parrot fever), who may present with a febrile illness, high fever, episodes of persistent cough and frequent headaches accompanied by bronchopneumonia. The pulmonary lesions are non-specific, and the diagnosis is usually made on serological examination or immunohistochemistry.



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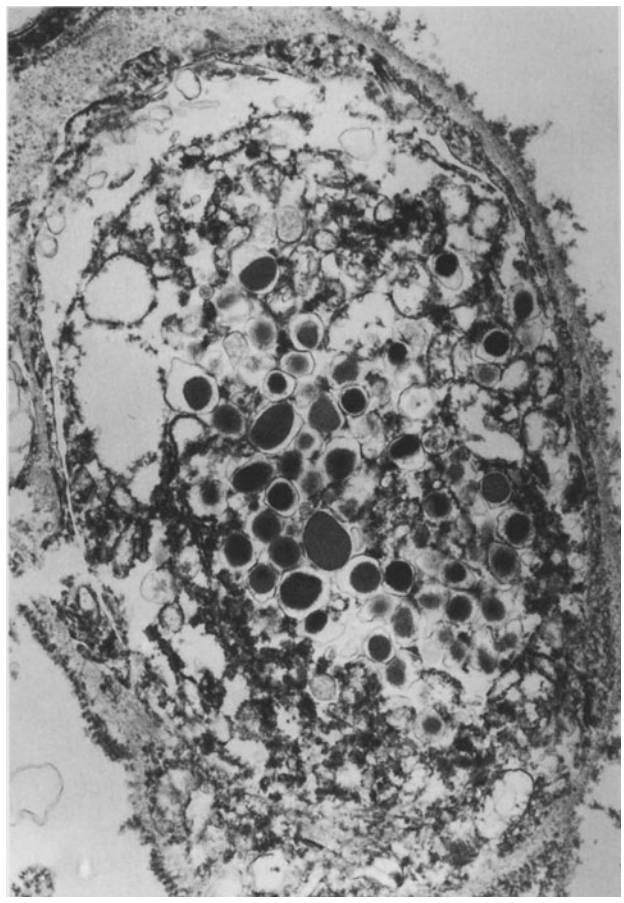


b

**Fig. 7.44.** **a** *C. pneumoniae* in intra-alveolar macrophages. (Giemsa × 330) **b** Ultrastructure showing oval forms surrounded by a wide halo suggestive of *C. pneumoniae*. (Electron micrograph, × 6560, reduced)

*C. pneumoniae* (TWAR) is associated with infections of the upper respiratory tract (sinusitis, pharyngitis) and the lungs, where it is responsible for bronchitis and pneumonia especially among young adults, the aged and the immunocompromised (AIDS, transplant patients). The infection is often associated with other pulmonary infections, primarily viral, in which case it may present as ARDS, multinodular bronchopneumonia or necrotizing pneumonia. Pneumothorax and mediastinal emphysema may be associated complications, and the condition may be the cause of chronic obstructive pulmonary disease. The disease can be both endemic and epidemic, and has a growing list of extrapulmonary manifestations. Its role in coronary artery disease is under investigation. Diagnosis is usually made by specialized serological tests and isolation from culture systems. Special stains, immunohistochemistry, molecular biology techniques and ultrastructural studies are additional methods applied on BAL fluids or lung biopsies (Fig. 7.44) as important aids in arriving at a correct diagnosis (Chi et al. 1987; Madan et al. 1988; Grayston et al. 1990; Klingebiel et al. 1989; Lundemose et al. 1989; Griffin et al. 1990; Kazanjians and Mark 1990; Shurbaji et al. 1990; Donders et al. 1991; Matsumato et al. 1991; Straumann Kunz et al. 1991; Marrie 1993; Blasi et al. 1994; Herrmann et al. 1994).

### *Viral*

Viral infections of the respiratory system are very common among infants and children. The viruses involved are varied, and new strains are isolated and identified each year. They usually affect the entire respiratory system and can cause severe damage to the lung parenchyma. The lesions produced by many viruses are histologically similar, and as a result one cannot rely solely on histological changes to establish a diagnosis with certainty. Furthermore, viral infections of the lung are not infrequently associated with one or more bacterial infections.

Where a viral infection is suspected, tissue should be taken for culture and for immunological and ultrastructural studies if adequate facilities exist. Serum

should also be preserved for appropriate examination. It is only by the isolation or identification of the virus that a definitive diagnosis can be established.

*Cytomegalovirus Infection.* Cytomegalovirus (DNA virus) is a member of the herpesvirus group, of which there are at least seven members (herpes simplex virus type I and II, varicella zoster virus, cytomegalovirus, Epstein–Barr virus and human herpesvirus 6 (HHP-6 and HHV-7)). It has a worldwide distribution and appears to be more prevalent among the lower socioeconomic group. Infection by the virus in childhood may be acquired in utero (congenital), perinatally or postnatally (see also p. 739):

1. *Congenital (intrauterine) infection* may occur in as many as 1%–2% of all newborns. Severe intrauterine infection, especially in the early part of the first half of pregnancy, may be the cause of death of the fetus in utero owing to disseminated disease. It has now become evident that maternal acquired immunity before pregnancy provides protection for the fetus. At birth these newborns are often asymptomatic of infection and the sequelae are limited and much less severe, although some may have viraemia and/or secrete the virus in their saliva for months or even years after birth. Infants whose mothers present with a primary infection during pregnancy are more likely to present symptoms at birth, with severe sensorineural hearing loss and severe handicap as a result of various neurological symptoms due to brain damage of varying degrees. These observations have further stimulated questions about vaccination campaigns against this virus. The disease has also been reported in siblings from consecutive pregnancies.
2. *Perinatal infection* is believed to be acquired during delivery, probably from the cervix, as the infant passes through the birth canal, and it is assumed that infants infected in this way are usually asymptomatic. Accumulating evidence now points to the fact that infection is not limited to the mucosa of the birth canal, but that uterine mucosa and endothelial cells may serve as reservoirs for the virus, and that environmental factors, virus reactivation during pregnancy and maternal antibody may all have important roles in the timing of primary infections. Furthermore, like many authors, we have been able to demonstrate by immunohistochemistry widespread placental involvement where at birth the infant was clinically normal. The reasons for the type of clinical presentation (symptomatic/asymptomatic) is still uncertain. Maeda et al. (1994), found that immediate early antigens (proteins) were seldom demonstrated in intrauterine cytomegalovirus infection; this may result from the dynamics of viral replication. These depend on the duration of the infection and the immaturity of the immune response.
3. *Postnatal infection* is considered to be common, and is generally asymptomatic. The mode of transmission is varied and infants in daytime maternal homes as well as adolescents with a high frequency of promiscuity are usually exposed to a high rate of infection. Among the most frequently incriminated is blood transfusion, in which case the patient may present with a syndrome referred to as *cytomegalovirus mononucleosis*. This has clinical and haematological features resembling those of infectious mononucleosis, but there is a negative Paul–Bunnell reaction. Infection by the virus is also prevalent among infants receiving chemotherapy for malignant disease in immunodeficiency states, in those with monoclonal macroglobulinaemia, and in those with renal allografts treated with immunosuppressive agents. Many of these patients present with interstitial pneumonitis.

Cytomegalovirus infection of the lung has also been observed with other pulmonary conditions, such as hyaline membrane disease, congenital syphilis, bacterial or viral pneumonias, and *Pneumocystis carinii* infection. It is one of the most common infections encountered after transplantation of organs, as well as among patients with AIDS, and is responsible for high morbidity and mortality rates among these patients, often in association with other viral (including HHV-6), mycotic and/or bacterial infections. Its transmission through blood transfusions is of great hazard, especially to recipients of organ transplants (Gorelkin et al. 1986; Griffiths and Grundy 1987; Paradis et al. 1988; Porter et al. 1990; Demmler 1991; Fowler et al. 1992; Yow and Demmler 1992; Huang et al. 1993; Bauman et al. 1994; Furukawa et al. 1994).

On gross examination the lungs may show little change unless affected by some other condition. Histologically the diagnosis may go unnoticed if one is not attentive. The presence of the characteristic viral inclusion with its clear halo (owl's eye) in some other organ (kidney, liver, pancreas, salivary gland, etc.) may draw the pathologist's attention to possible pulmonary involvement. Careful examination will reveal an occasional grossly hyperplastic alveolar cell with its intranuclear inclusion. In severe disseminated pulmonary disease the virus is observed in the nuclei or cytoplasm of the enlarged alveolar lining cells and is sometimes seen free in the alveoli (Fig. 7.45). In the early stages, the intranuclear inclusions are aci-

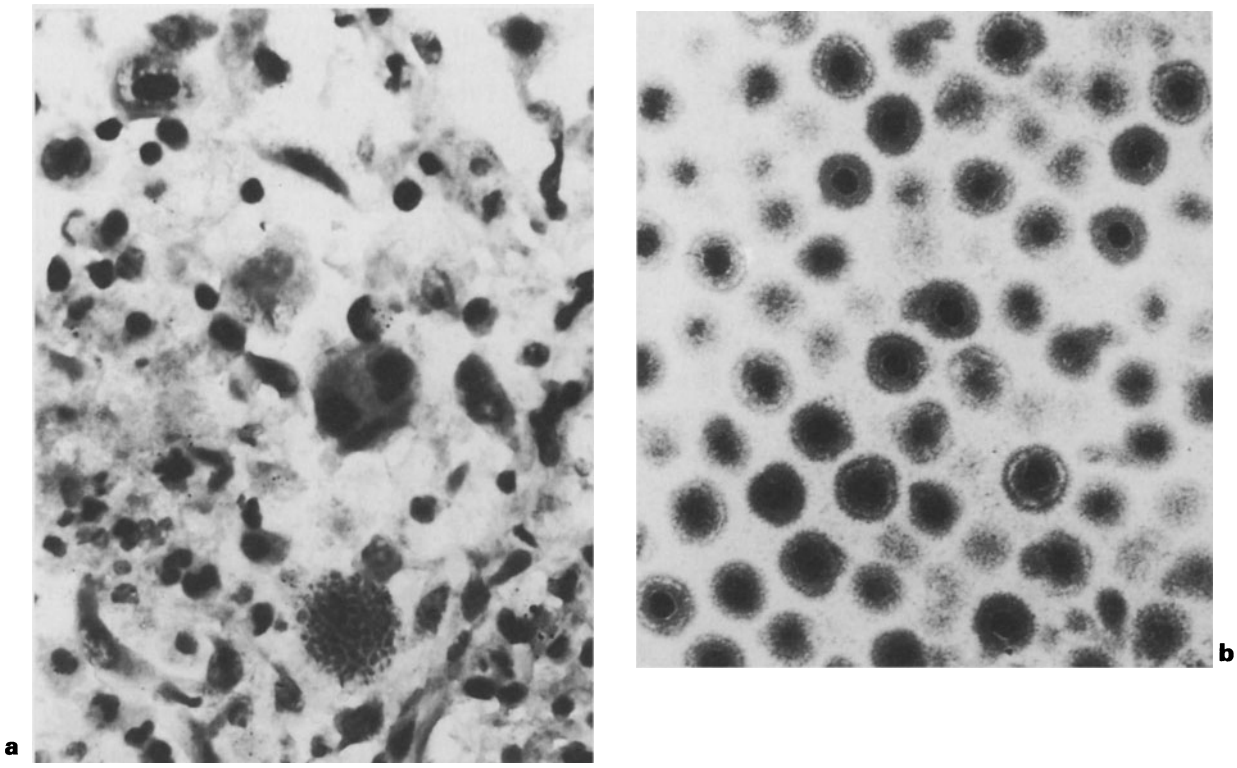


**Fig. 7.45.** **a** Cytomegalovirus inclusion disease in a 6-day-old premature girl. (In situ hybridization, × 430) **b** Electron micrograph showing the virus elements. (Courtesy of Dr J. Briner)

dophilic, but they become basophilic with time. The acidophilic intranuclear inclusion body stains purple with Masson's trichrome, and the intracytoplasmic inclusions stain intensely with PAS stain or Giemsa. Gomori's methenamine silver and Masson–Goldner stains are also helpful in identifying the virus. More specific staining with the immunoperoxidase antibody technique, in situ hybridization (alone or in combination), molecular biology and ultrastructural examination can help to identify the many strains of this structurally diverse collection of viruses. The cytoplasm of the infected cell is basophilic and granular. There is no inflammatory reaction unless secondary infection occurs. Bronchial and bronchiolar epithelial cells may be infected in addition to the epithelial cells of the peribronchial glands. Viral inclusions can often be demonstrated in endothelial cells of blood vessels.

*Human Herpesvirus 6 (HHV-6).* This recently identified herpesvirus is ubiquitous in the human population, with over 90% seroconversion by 3 years. There are two types (A and B), which are highly prevalent and last for a lifetime. The virus is known to be the causative agent of exanthem subitum (roseola) in infancy, often associated with a febrile illness and sometimes with seizures and encephalopathy. It may, on occasion, present with a mononucleosis-like syndrome or, more likely, a varied spectrum of ill-defined clinical manifestations which could, in some instances, lead to a fatal outcome. Fever, otitis and upper and lower respiratory tract symptoms are the most characteristic presentations, often associated with gastroenteritis, hepatitis and even viraemia. Pneumonitis is often documented in association with the virus, especially in the immunocomprised host and transplant patients, principally after bone marrow transplantation. Although HHV-6 is genetically similar to cytomegalovirus, with which it shares many characteristics, it is distinct biologically, immunologically and by molecular analysis from other herpesviruses. The virus can be demonstrated in peripherial mononuclear cells and saliva in older children and adults, and its genome and DNA in salivary and bronchial glands, which may explain latent infections. It has also been localized in macrophages in lymph nodes (Hodgkin's disease, Kikuchi lymphadenitis). Very recently lymphotropic herpesvirus (human herpes virus-7, HHV-7) has been identified, making the future very bright for surprises as to the

role of these viruses in the pathology of the respiratory system (Pruksananoda et al. 1992; Agut 1993; Akashi et al. 1993; Cone et al. 1993; Dewhurst et al. 1993; Drobyski et al. 1994; Asano et al. 1994; Ward and Gray 1994; Asano et al. 1995).

*Measles (Rubeola) Pneumonia* (see also p. 771). Measles is caused by an RNA virus of the myxovirus group. The disease is still common in countries with low socioeconomic status and those with little or no immunization programmes, and it occurs in epidemics. In these countries, pulmonary complications are common and the mortality rate is high, especially among children suffering from various types of malnutrition. Secondary bacterial infection is common and is responsible for the high mortality rate in many series. Fatal cases have been described in apparently healthy children and in adults or patients with immunological disorders, including those receiving cytotoxic or immunosuppressive treatments for malignancies. The majority of these patients do not present the exanthema characteristic of the disease and have not necessarily had previous contact with patients suffering from the disease.

Atypical pulmonary lesions are known to occur and persist in individuals receiving killed measles vaccine, and fatal cases of measles pneumonia have been recorded after the administration of live measles vaccine to infants with immunodeficiency disorders (Mihatsch et al. 1972). In recent years the condition has made its reappearance among young army recruits and adolescents in countries where vaccination programmes were not properly carried out.

The main feature of the pulmonary lesion is the multinucleated syncytial giant cell, which should be distinguished from the pathognomonic giant (Warthin–Finkeldey) cell observed in the lymphoid tissues during the prodromal stage of the disease or in the very early phase of the rash. Hecht's giant-cell pneumonia was formerly considered to be a separate entity; however, recent studies have shown that the virus responsible for this condition is identical with that observed in cases of measles pneumonia, and therefore it is now generally admitted that the two conditions are the same. Immunohistological staining with specific measles antibody can now be used to identify the viral inclusions not only in the lung but in the gastrointestinal epithelium and other organs (Gustafson et al. 1987; Drut and Drut 1988; Radoycich et al. 1992; Rupp et al. 1993; Frenkel et al. 1994).

Macroscopically the lungs are heavier than normal. They show homogeneous firm greyish-white consolidated areas, variable in size, sometimes occupying an entire lobe or lung. The lesions are generally bilateral.

Microscopically there is interstitial pneumonia with oedema of the interstitium and alveolar wall. The inflammatory infiltrate consists mainly of mononuclear cells. The numerous multinucleated syncytial giant cells have a crescent shape and are found lining the alveolar wall, the alveolar ducts and the distal bronchioles. These giant cells may contain 10–50 or even 100 nuclei. Intranuclear and intracytoplasmic eosinophilic bodies are conspicuous, and stain with the phloxine–tartrazine stain. The alveolar spaces are rich in oedema fluid mixed with fibrin, and hyaline membranes may be present (Fig. 7.46), giving the characteristic features of diffuse alveolar damage. The bronchial and bronchiolar epithelia show degenerative changes in places, and in other areas there is marked epithelial hyperplasia with loss of ciliated epithelium. Squamous metaplasia may be prominent. There is a peribronchial mononuclear infiltration with hyperplasia of the lymphoid tissue. It is not unusual to observe endothelial hyperplasia of the small vessels with some degree of stenosis. The lesions may, however, present a spectrum of histological features different from those observed normally: areas of organizing diffuse alveolar damage and/or zones of interstitial pneumonia with a moderate number of giant cells in which viral inclusions cannot be demonstrated. Serology and ultrastructural examinations are necessary to make the correct diagnosis.

*Influenza Pneumonia.* Influenza can occur sporadically, but often occurs in epidemics. During these outbreaks fatal cases may occur in children, in particular in the immunosuppressed. Several types of virus are known to be responsible for infection of the respiratory system, and new strains and subgroups are isolated each year. Mutational modifications take place in the polypeptide surface antigens, giving rise to antigenic variations requiring constant adaptation of new vaccines (CDC 1994). The virus provokes an interstitial pneumonitis, which can progress to haemorrhagic pneumonia and death. Pneumonia due to superimposed bacterial infection is the main cause of death (Hers and Mulder 1961; Aherne et al. 1970; Lindsay et al. 1970; Zinserling 1972; Joshi et al. 1973; Laraya-Cuasay et al. 1974; Sabin 1977; Foy et al. 1979).

Macroscopic examination of the lungs may reveal nothing in the early phase of the disease; in the full-blown disease they are heavy, reddish and markedly haemorrhagic, with abundant oedema. The bronchi and bronchioles are congested, and the epithelium of the main bronchi may be ulcerated. Their lumen may be filled with a thick yellow blood-stained exudate. Histologically, congestion of the capillaries is a prominent feature. The capillaries are extremely dilated; the septa are oedematous and thickened and

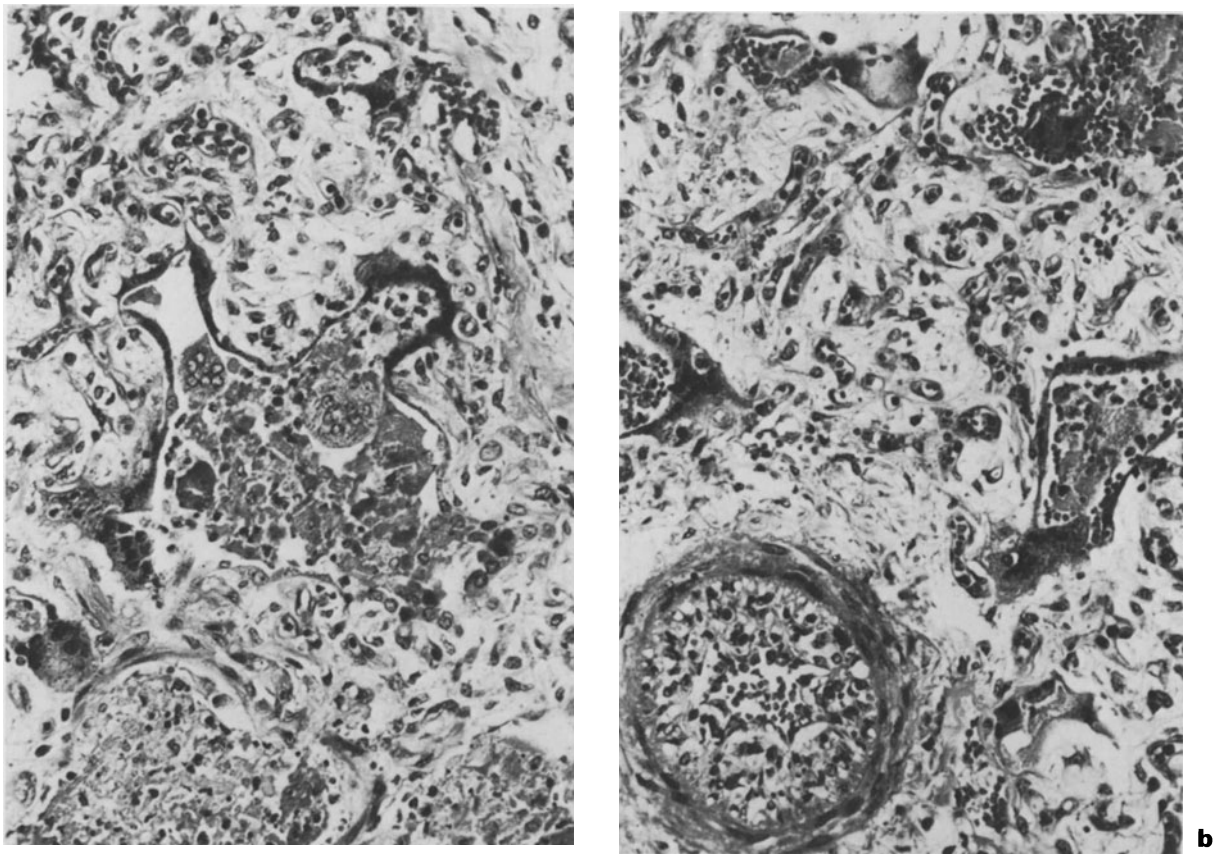
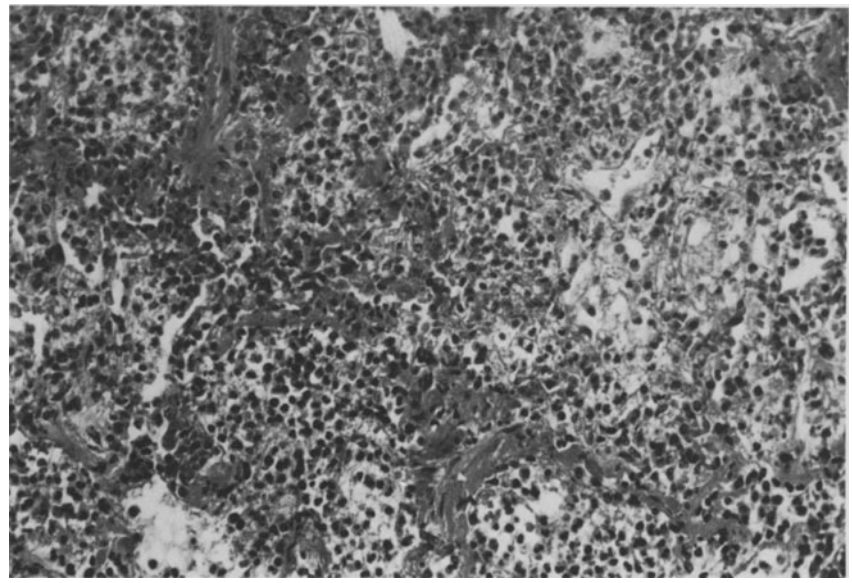


**Fig. 7.46.** **a** Giant-cell penumonia in a 12-year-old African girl. The syncytial cells contain intranuclear and intracytoplasmic inclusion bodies consistent with those of measles. **b** Arteritis and endothelial proliferation associated with giant-cell pneumonia. (H&E, × 225)

contain mononuclear inflammatory cells. There are areas of focal necrosis with interstitial haemorrhage. Hyperplasia of the alveolar lining cells is conspicuous, and there is some desquamation into the alveolar spaces, where fibrin, erythrocytes, macrophages and mononuclear cells may be seen. Hyaline membranes are also present. In some areas the alveolar epithelium regenerates. The bronchi and bronchioles show marked congestion, with areas of mucosal necrosis, oedema of their wall, and a diffuse mononuclear infiltrate. Squamous metaplasia of the bronchial epithelium is an indication of regeneration; simultaneously there is epithelial hyperplasia of the bronchioles and alveolar ducts. Healing of the lesions may lead to alveolar fibrosis. Delage et al. (1979) described a giant cell pneumonia due to parainfluenza type 3 virus in infants with immunodeficiency diseases, which histologically resembled measles pneumonia.

*Rhinoviruses.* These viruses are often the cause of an influenza-like infection of the upper respiratory tract in infants and children. Neonates and premature babies are particularly subject to infection. The disease often runs a benign course, but fatal cases can occur. The viruses may cause an interstitial pneumonia or bronchopneumonia affecting one or more lobes or an entire lung, and the involvement is often bilateral (Fig. 7.47). Rhinoviruses have been associated with the sudden infant death syndrome.

*Adenovirus.* Adenovirus infection of the respiratory system is relatively common among infants and children and in young adults. The disease is hardly ever fatal, although it may cause severe chronic lung damage, including chronic bronchitis, bronchiolitis and bronchiolitis obliterans, sometimes associated with pulmonary fibrosis. The upper respiratory tract is often the site of infection by the virus. The disease appears to be more common in countries of low socioeconomic status, and especially among children suffering from severe malnutrition or other debilitating conditions. It may be the cause of fatal pneumonia in the newborn and has been documented in



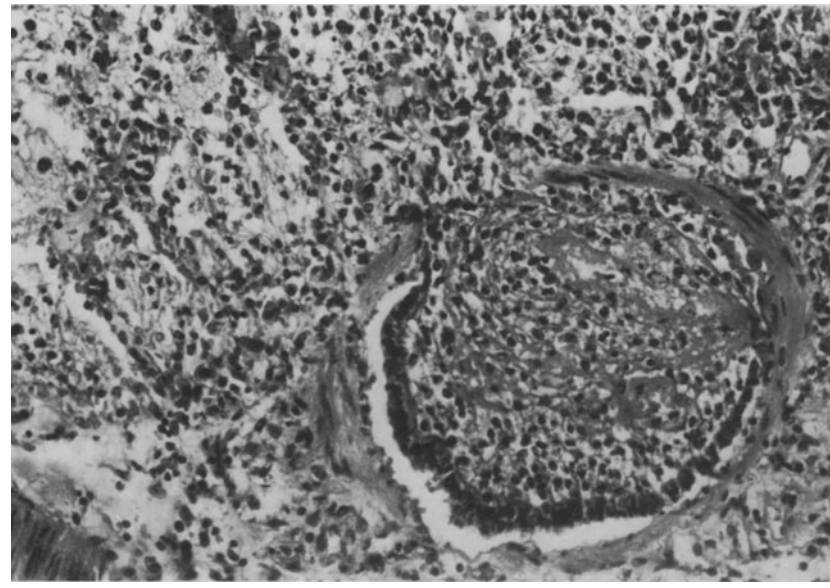




**Fig. 7.47.** Rhinovirus pneumonia in a 4-year-old African girl. (H&E, × 120) **a** Extensive necrosis of the alveolar wall with distension of the alveolar spaces filled mainly with mononuclear cells. **b** Necrosis of the bronchial wall with bronchiolitis obliterans.

sudden infant death syndrome (SIDS) as well as the immunocompromised host and transplant recipients. It has also been described in association with other viruses, including measles, and/or bacteria. Numerous strains of adenovirus have been isolated with some 41 serotypes identified, and although several types are known to cause respiratory disease in humans only a few have been recorded as being responsible for fatal diseases in children (Sun and Duara 1985; Landry et al. 1987; Green and Williams 1989; Hoggs et al. 1989; Shikes and Ryder 1989; Van Lierde et al. 1989; Mistchenko et al. 1992; An et al. 1993).

Macroscopically the lungs are heavy and firm, with bilateral grey consolidated zones mainly occupying the posterior lower lobes. The parenchyma is markedly oedematous, and the trachea and large bronchi are hyperaemic and ulcerated in places. Their lumen is often filled with thick mucoid material that is rich in fibrin. Histologically there is extensive denudation of the epithelium lining the bronchi and bronchioles, with occasional vesicles in the residual mucosa. In other areas, there is widespread eosinophilic necrosis of the mucosa, which may form a pseudomembranous layer in places. The inflammatory reaction in the wall may be mild or moderate,

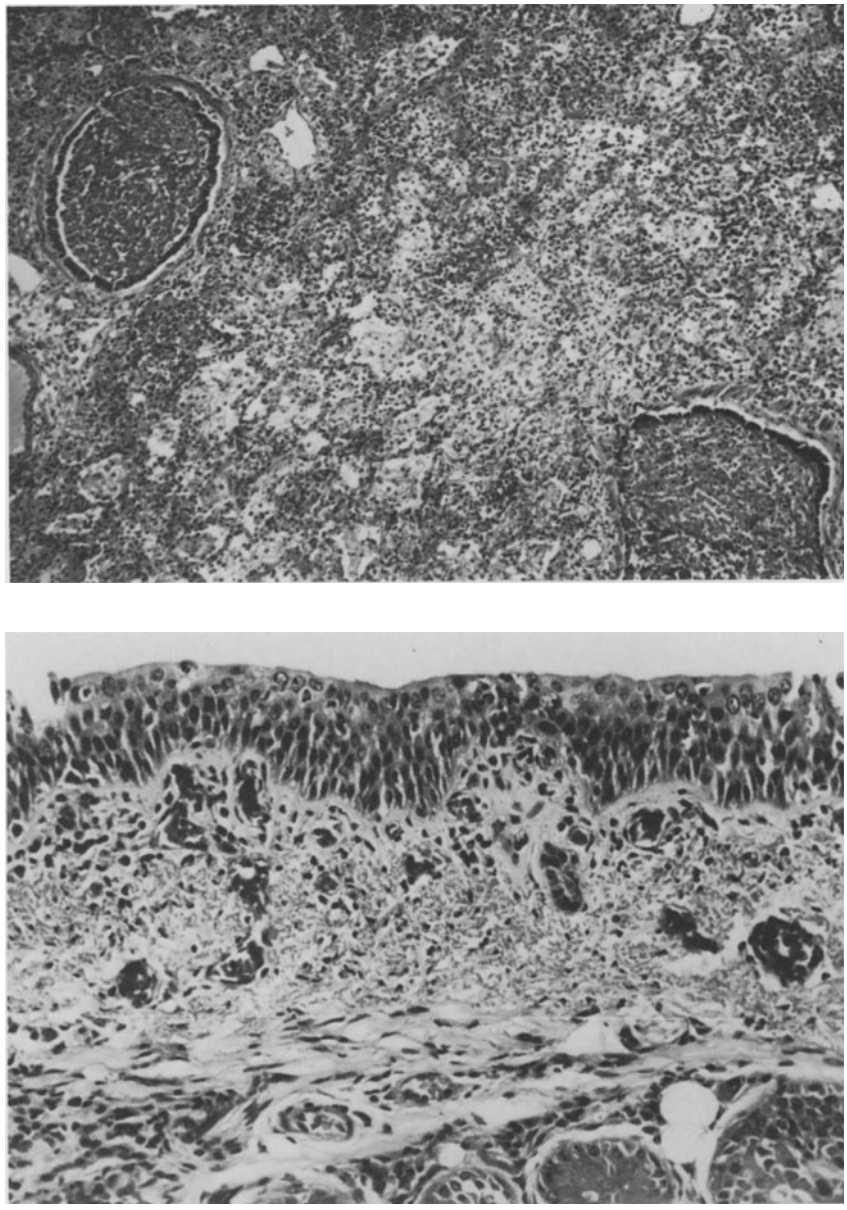


**Fig. 7.48.** Respiratory syncytial virus pneumonia in a 22-month-old boy with Reye's syndrome. **a** Bronchitis and bronchiolitis obliterans with pneumonitis. (H&E, × 35) **b** Squamous-cell metaplasia of the tracheal epithelium. (H&E, × 225) (Courtesy of Dr J.W. Keeling)

and consists of lymphocytes, plasma cells and some histiocytes. In some instances polymorphonuclear leucocytes may be conspicuous. The alveolar ducts and alveoli are filled with eosinophilic material containing oedema fluid mixed with fibrin and dense hyaline membranes. Parenchymal necrosis may be focal or widespread, with little or no inflammatory reaction. The alveoli and bronchioles contain desquamated necrotic granular pneumocytes, macrophages and damaged epithelial cells, whose nuclei may show nuclear inclusion bodies. These inclusion bodies are of two types: eosinophilic inclusions, well defined and surrounded by a clear halo rim (Feulgen-negative), and basophilic, amorphous inclusions (smudge nuclei) without a halo (Feulgen-positive). The bodies may be observed in the nuclei of the cellular debris, but principally in the nuclei of the desquamated bronchial and bronchiolar epithelial cells and in the regenerating hyperplastic epithelium. Immunohistochemical labelling, in situ hybridization and electron microscopic studies are valuable aids in diagnosis.

*Respiratory Syncytial Virus*. This virus is known to have a worldwide distribution and is one of the most important causes of acute respiratory disease among

infants and children, especially the premature and those less than 6 months of age. Although it is not often fatal it can cause a diffuse interstitial-type bronchopneumonia or pneumonia. Very often infection is asymptomatic; it has been described in association with SIDS, Reye's syndrome and bronchopulmonary dysplasia. It is the most common cause of severe pulmonary lesions among premature infants and the immunocompromised host. Most fatal cases have been documented in the neonatal period or in infancy. (Groothuis et al. 1988; Nielson and Yunis 1990; An et al. 1993; Jamjoon et al. 1993; Midulla et al. 1993; Moler et al. 1993; Murguia de Sierra et al. 1993; Sigurs et al. 1995).

Macroscopically the lungs show focal areas of consolidation indistinguishable from those seen in most other conditions. Histologically, there is hyperplasia of the epithelium lining the medium-sized bronchi and bronchioles, with desquamation, cellular debris and/or a dense granular eosinophilic material filling the lumen (Fig. 7.48). The wall is sometimes infiltrated by mononuclear cells, with some polymorphonuclear leucocytes. There is also marked shedding of the epithelial cells lining the alveoli, into a lumen sometimes filled with a dense oedematous fluid. Cytoplasmic inclusion bodies may be observed at the periphery of the bronchial, bronchiolar and alveolar pneumocytes, the peribronchial glandular epithelium and the syncytial giant cells protruding into the bronchial lumen or lining the alveoli or bronchiolar walls. There are no nuclear inclusion bodies as in adenovirus infections. Areas of necrosis may be prominent, and these are infiltrated by lymphocytes, plasma cells and macrophages, which play an essential role in the host defence. Very large multinucleated giant cells may border the bronchial and alveolar lesions, mimicking measles pneumonia. Specific immunohistologic staining, in situ hybridization and ultrastructural studies may be necessary to differentiate the two conditions.

*Varicella (Chickenpox) Pneumonia.* Varicella is a common childhood infection, which is seldom fatal. Specific serological examinations aided by immunohistochemistry and electron microscopic studies are very useful complements to arrive at the correct diagnosis. It is estimated that the mortality rate among infants and children is 1%, whereas it is probably between 10% and 50% among adults. Varicella pneumonia, which may manifest itself a few days after the rash, is considered to be the most serious complication among adults and pregnant women, and it can be accompanied by secondary bacterial infection. In both children and adults the disease may run a fatal course in patients who are receiving steroids or cytotoxic drug therapy for malignancies.

Virus can be transmitted to the fetus in utero and can result in congenital varicella (fatalities occur as a result of pneumonia). Newborns who develop the rash 5 days or more after birth have a higher mortality rate than those who develop the rash within the first 4 days. Varicella infection has become one of the most serious infectious problems among transplant recipients, and in such patients the infection may appear alone or in association with other viral and/or bacterial infections. It is also often reported in patients with AIDS (Charles et al. 1986; Preblud 1986; Alkalay et al. 1987; Saito et al. 1989; Martin et al. 1991; Enders et al. 1994; Puchhammer-Stöckl et al. 1994).

Macroscopically, the lungs are often oedematous, enlarged and rose-coloured, with firm dark-red areas. The bronchi contain abundant blood-stained mucus. Histologically the thickened oedematous alveolar septa show areas of necrosis in places, while in others the alveolar spaces are filled by a dense eosinophilic serous fluid mixed with fibrin and numerous desquamated hyperplastic alveolar epithelial cells with occasional multinucleated giant cells (Fig. 7.49). The bronchi, bronchioles and blood vessels in the involved areas are often necrotic. Intranuclear acidophilic inclusion bodies can be seen in the hypertrophied alveolar cells and in the tracheal and bronchial epithelium as well as endothelial cells of capillaries and other blood vessels. Specific immunohistochemistry and electron microscopy are very useful aids towards correct diagnosis. The inflammatory reaction is moderate and is composed chiefly of mononuclear cells. Healing of the necrotic areas may leave granulomatous lesions, but more often calcified nodules disseminated within the pulmonary parenchyma.

*Herpes Simplex Virus* (see also pp. 177, 678). There are two antigenically different types of herpes simplex virus known to affect humans (type 1 and type 2). Herpes type 2 virus appears to be venereally transmitted, and as a result is responsible for most congenital herpes virus infection. Fetuses and neonates infected by the virus in utero may present with a fatal disseminated form of the disease involving the brain, liver, adrenals, gastrointestinal tract, lungs and myocardium. It may be the cause of hydrops and is also responsible for cystic degeneration of the brain. Herpes simplex virus infection of the fetus or newborn may be acquired during passage through an infected birth canal, or in utero as a result of premature rupture of the membranes with ascending transplacental transmission. Subclinical latent intrauterine endometrial infection may also infect the conceptus. Transplacental transmission may not be uncommon, as most cases are asymptomatic at birth and the search for the virus may not be undertaken in

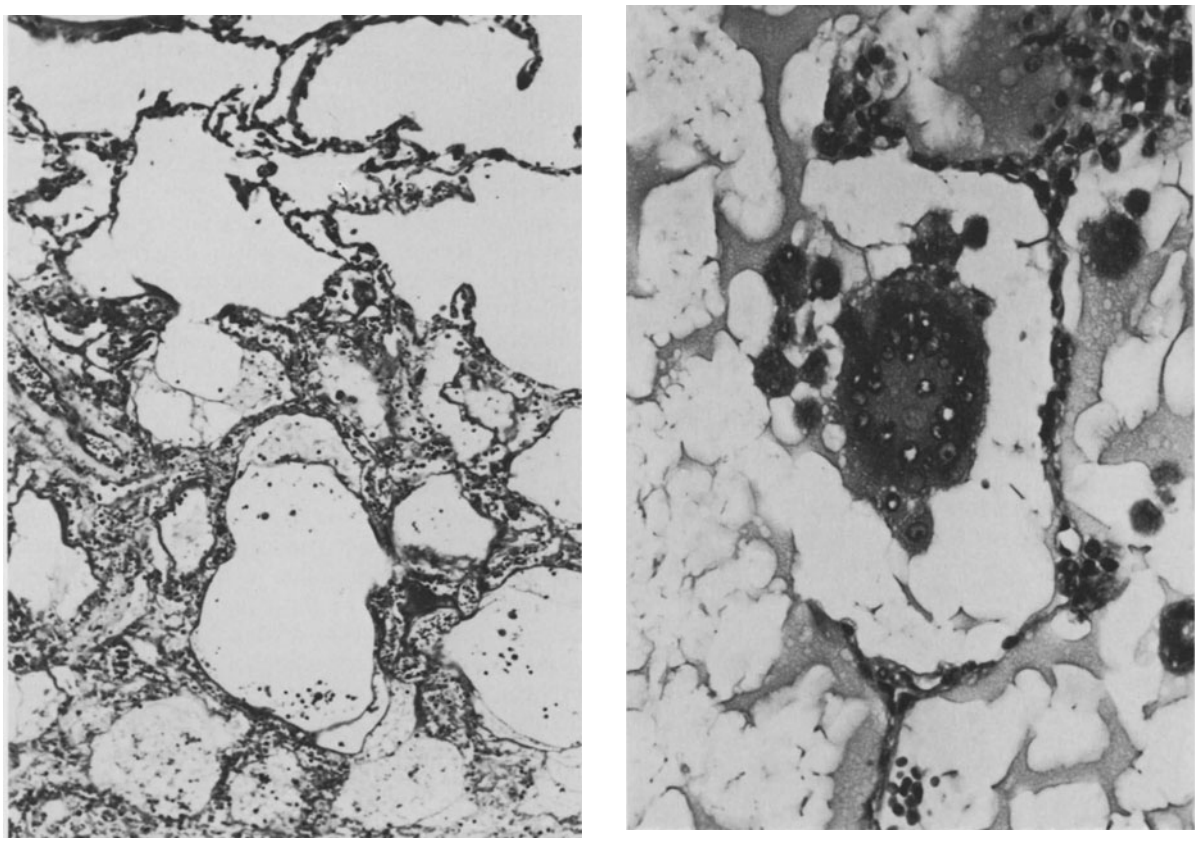


**Fig. 7.49.** Varicella pneumonia. **a** Extensive necrosis of the alveolar walls with mild mononuclear cell infiltration. (H&E, × 35) **b** Interstitial giant-cell pneumonitis with intranuclear inclusion bodies. (H&E, × 225)

macerated fetuses, their placentae, membranes or umbilical cords. The period during which infection is transmitted seems to play an important role in the outcome in the fetus or newborn. Small intranuclear calcifications in necrotic areas in a macerated fetus, without an inflammatory reaction, may be the only sign indicating the possibility of herpes viral infection (Benjamin 1989; Kimura et al. 1991; Malm et al. 1991; Martin et al. 1991; Gibbs and Mead 1992; Kulhanjian et al. 1992; Hyde and Giacoia 1993; Nicoll et al. 1994; Malm et al. 1995).

Macroscopically the lungs may appear normal; however, areas suggestive of bronchopneumonia are sometimes conspicuous, and in some cases the cut surface shows some miliary whitish nodules. Microscopically there are multiple round or oval foci of necrosis. Inflammatory cells may be absent or occasionally found at the periphery of the involved zone. The exudate is made up principally of mononuclear inflammatory cells. Bronchioles in the area may undergo necrosis, while in other areas of the lung the bronchial and bronchiolar epithelium is hyperplastic. Focal areas of squamous metaplasia can also be seen. Eosinophilic intranuclear bodies are sometimes seen in the hyperplastic epithelial cells or in the necrotic cells at the periphery of the lesions (Fig. 7.50). In patients who survive, calcification of the necrotic area may occur. Immunohistochemistry, in situ hybridization and molecular biological techniques are vital aids, not only in making the diagnosis, but also in extending our knowledge to improve our understanding of this infection.

*Echovirus* (see also p. 781). Echovirus infection may have many clinical presentations, including upper respiratory tract infection with or without pneumonia, and may be the cause of perinatal death.

Histologically, tracheobronchitis, bronchiolitis and an interstitial-type pneumonia are the main findings, in association with lung oedema and congestion. Echovirus II is one of the most frequent offenders and may be associated with SIDS (Jones et al. 1980; Berry and Nagington 1982; Wreghitt et al. 1984).

*Parvovirus*. Human parvovirus B19 is now known to be related to several clinical conditions in the adult as well as in children (aplastic anaemia, erythema infectiosum), and can be the cause of transplacental infection of the fetus leading to cardiac failure, hydrops

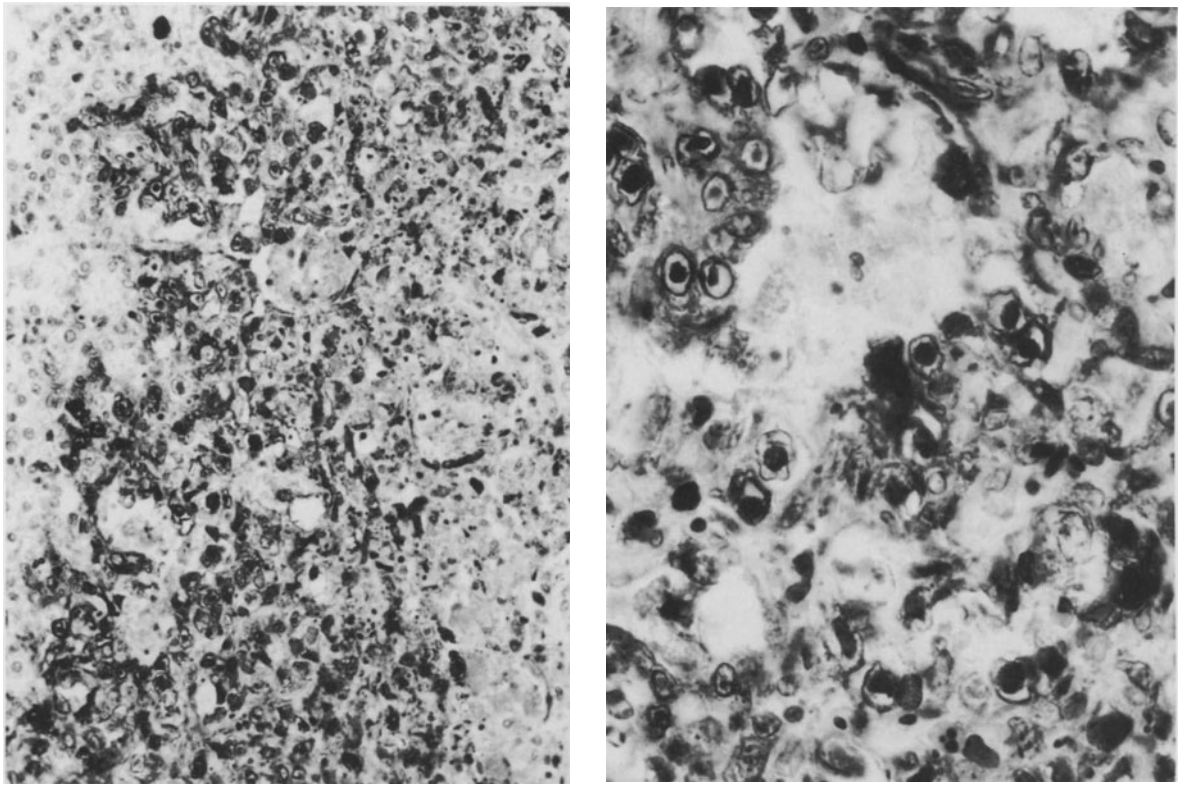


**Fig. 7.50.** Congenital herpetic infection in a 12-day-old infant. **a** There are extensive multifocal necrotic areas within the lung parenchyma. On the external borders of these zones, the cells are heavily infected. (Immunoperoxidase, × 115) **b** Note the nuclear inclusions. (× 290)

fetalis (non-immunological or other common known causes), intrauterine death and termination in abortion, and is associated with a raised maternal serum $\alpha$-fetoprotein level. It is common in patients with sickle cell anaemia. As the virus (DNA) has a strong affinity for the rapidly dividing erythroblasts, it can be found within the nuclei of these cells in the bone marrow, liver and spleen, as well as in the circulating erythroblasts in the microcirculation of every organ including the lung (Fig. 7.51a). The nuclei are markedly swollen, containing intranuclear viral inclusions, which may stain blue, lilac or red with haematoxylin with eosin, depending on their size, and bright red with phloxine–tartrazine even on macerated material. They may also be identified on electron microscopy (Fig. 7.51b) and by specific DNA probes, which have shown that there is a wide diversity of B19 viruses in the infected fetus. Haemosiderosis of the liver and spleen – evidence of haemolysis – is also observed (Hassam et al. 1990; Berry et al. 1992; Mark et al. 1993; Rogers et al. 1993; Umene and Nunoue 1993).

*Hantavirus*. This recently recognized group of viral zoonosis may cause severe pulmonary lesions which could lead to death in children (Khan et al. 1995).

## *Mycoplasmal*

Mycoplasmas are members of the class Mollicutes, family *Mycoplasmataceae*, sharing common properties with both bacteria and viruses. There are many strains.

*Mycoplasma pneumoniae* infection is endemic; it occurs in epidemics and has a worldwide distribution. It affects mainly the respiratory system, especially in children and young adults, but can cause many non-respiratory infections. Pulmonary infection can be mild or severe, causing bronchopneumonia or pneumonia (primary atypical pneumonia). Atelectasis, bullous emphysema, pulmonary abcesses and pleuritis with pleural effusion are associated complications. Meningoencephalitis is a common complication of mycoplasma infection. Myocarditis with pericarditis and pancreatitis have also been described, as well as severe anaemia, thrombocytopenia, disseminated intravascular coagulation and glomerulitis; the latter often in AIDS by *M. Fermentans*. Fatal cases have been documented, many of them in patients with immunodeficiency states or sickle cell anaemia. Transplacental infection has been reported. The diagnosis, in disease of the respiratory system, is usually

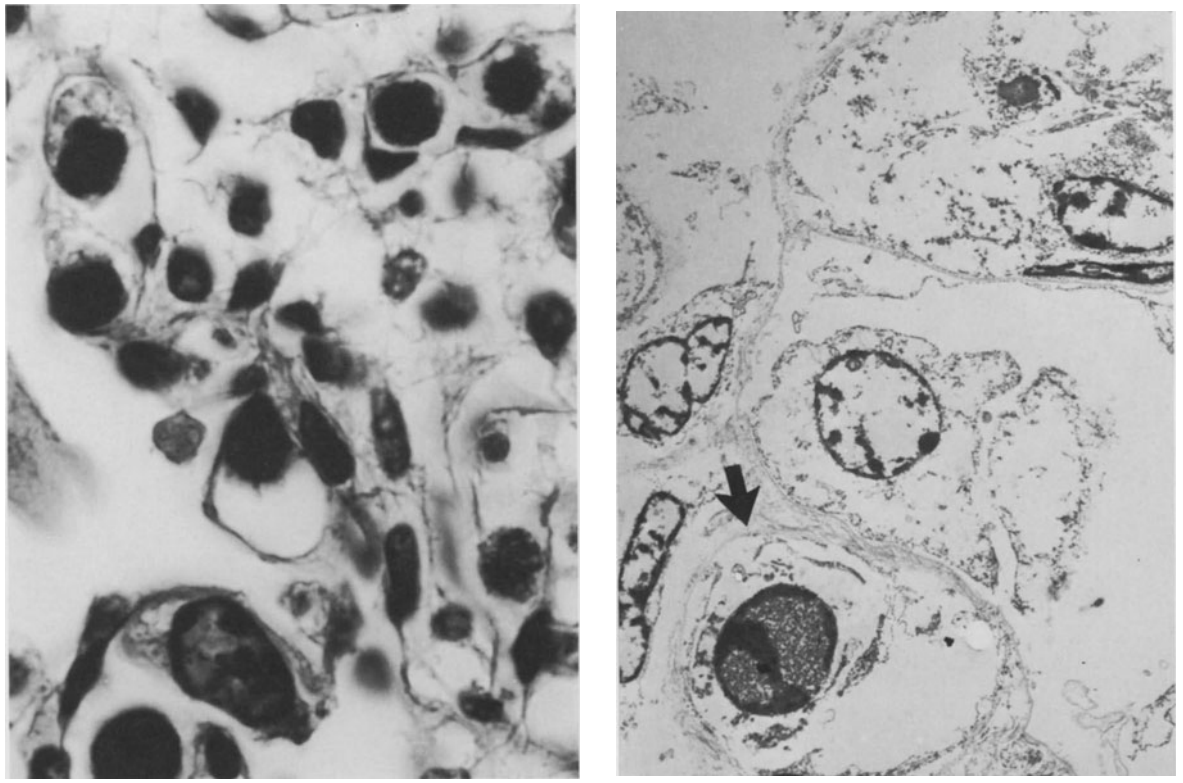


**Fig. 7.51.** **a** Parvovirus infection showing the infected circulating normoblasts in the lung tissue. (H&E, × 980) **b** Electron micrograph showing the virus particles within the nucleus of the normoblast. (Courtesy of Dr P. Burton)

made by isolation of the organisms from material taken from the upper respiratory tract or bronchial secretions and by specific immunological and serological tests. These examinations have indicated that the condition is far more prevalent than was once estimated, with a non-negligible morbidity and mortality rate. The organism can now be identified by appropriate immunohistochemistry and by ultrastructural studies (Lutsky et al. 1986; Brasfield et al. 1987; Bauer et al. 1991; Foy 1993).

Macroscopically, the lungs are markedly oedematous, reddish and heavy. Focal zones of intrapulmonary haemorrhage can be seen, sometimes associated with areas of bronchopneumonia. The bronchi and bronchioles are congested, and the distal branches can be partially obliterated by a thick oedematous fluid rich in mucus and mucopus.

Microscopically, the lesions are often indistinguishable from those of viral pneumonias, hence the term "atypical viral pneumonia". The alveolar septa are markedly thickened by a dense oedematous fluid and are infiltrated by lymphocytes, plasma cells and macrophages. The alveolar spaces contain numerous hyperplastic desquamated alveolar cells mixed with erythroctyes, macrophages and fibrin. Lysis of the desquamated alveolar cells is prominent in places, and hyaline membranes are observed in some areas. Single or grouped organisms may be recognized in the nuclei of the modified alveolar epithelial cells or those of the bronchial mucosa. Bronchiolitis is prominent and widespread. There is marked congestion of the vessels, some of which may contain fibrinous thrombi or show necrosis of their walls.

There is now growing interest in *Ureaplasma urealyticum* and pulmonary infection and sepsis in the newborn, principally those of low birth weight (below 1250 g). The organism is known to colonize the lower genital tract in most women and especially among those of low socioeconomic status. Transmission to the fetus may be: in utero secondary to an ascending infection via the transplacental route; during normal delivery and passage through a birth canal heavily infected; or postnatally by nosocomial transmission (horizontal). Infection of the fetus in utero is often associated with chorioamnionitis, and on occasion with a febrile illness of the mother. *U. urealyticum* infection of the newborn, especially in premature infants, is often associated with respiratory distress syndrome, sepsis and meningitis. It may

be responsible for diffuse pneumonitis and/or interstitial fibrosis, sometimes with pulmonary haemorrhage. Together with *Mycoplasma hominis*, it has been associated with development of persistent pulmonary hypertension and bronchopulmonary dysplasia in the newborn (Waites et al. 1989; Brus et al. 1991; Walsh et al 1991; Eschenbach 1993; Ollikainen et al. 1993; Sànchez 1993; Waites et al. 1993; Wang et al. 1993a).

## *Fungal*

Mycotic infection of the lung in childhood are uncommon, and the majority of such infections encountered are secondary or opportunist infections. However, a few cases of congenital infection have been described with some species of fungus. In most instances the particular mycotic infection is observed in association with children receiving antibiotic or steroid treatment or in those suffering from some form of chronic debilitating disease. In recent years there has been an increasing number of reports among children treated with immunosuppressive drugs or cytotoxic agents for malignancies. These infections are more common in tropical and subtropical zones, where certain species of fungus are prevalent. Special stains (Gram, PAS, Grocott's silver methenamine) may be necessary to identify the organisms in sections; culture and immunological studies are essential in determining the exact species involved.

*Moniliasis (Candida).* Several species of *Candida* can affect humans, but *C. albicans* is usually responsible for pulmonary lesions in the paediatric age group. Both congenital and neonatal pulmonary moniliasis have been described. In childhood the lesions may be localized in the tracheobronchial tree, where the fungus may produce ulceration of the mucosa, or in the pulmonary parenchyma, with the formation of microabcesses. In severe cases, there is diffuse pulmonary and sometimes vascular involvement. Associated bacterial infection is common, and in these cases an inflammatory infiltrate is often pronounced. In the neonatal period moniliasis may be associated with prolonged umbilical vein catheterization, which is also seen in older children who have had other intravenous catheters in place for long periods (Smith and Congdon 1985; Knox et al. 1987). The condition is a particular hazard to immunocompromised patients (those with AIDS, those subject to immunosuppression therapy and transplant recipients).

*Pulmonary Aspergillosis.* This condition is also uncommon in children, and it has been observed mainly as an opportunistic infection. It can be a complication of tuberculosis, pneumatocele and/or an infected bronchogenic cyst. Eosinophilia is a common feature of the condition.

As in adults, the disease may present in several forms: allergic bronchopneumonia, which is extremely rare; aspergilloma, a more common entity; and disseminated or septicaemic pulmonary aspergillosis. The morphological features are identical to those observed in adult cases. In recent years there has been a marked increase of the condition among children treated for malignancies, those with AIDS and transplant recipients, as well as those with cystic fibrosis and chronic granulophthisis (Neijens et al. 1989; Denning and Stevens 1990; Kurup and Kumar 1991; Loire et al. 1993; Cowie et al. 1994; Miller et al. 1994; Simmonds et al. 1994).

Pulmonary thrombi containing fungal hyphae, sometimes associated with infarction, are the most striking features (Fig. 7.52). There is sometimes necrosis of the vessel wall with secondary infection of the surrounding tissue in disseminated infection.

*Histoplasmosis.* Two forms of histoplasmosis are thought to exist: *H. capsulatum* (North American form) and *H. duboisii* (African form).

The North American form of *H. capsulatum* has a worldwide distribution and is known to be endemic in certain regions. The clinical and radiological features are non-specific and can resemble those of a viral lung infection or, in some instances, tuberculosis. The disease is common in children and can cause death in endemic areas. It may present as:

1. An acute influenza-like illness with a variable outcome (usually the infection is benign)
2. A chronic pulmonary infection with one or more pulmonary cavities, resembling tuberculosis, in which secondary calcification is frequently observed; it may even present as a non-caseating granulomatous lesion resembling sarcoidosis
3. Disseminated histoplasmosis, with widespread dissemination by the bloodstream, generally affecting younger children, and often rapidly fatal

The disease is also described in association with AIDS. The organism can now be identified by an immunoperoxidase histoplasma antibody stain (Body et al. 1988; Loyd et al. 1988; Wheat et al. 1989).

African histoplasmosis, *H. duboisii*, is more restricted to the tropical and subtropical belt of Africa. The organisms occasionally produces pulmonary lesions, which are mainly granulomatous; in rare instances cavities develop (Oddo et al. 1990).

*Pulmonary Pneumocystic Carinii (Interstitial Plasma Cell Pneumonia). Pneumocystic carinii* has recently

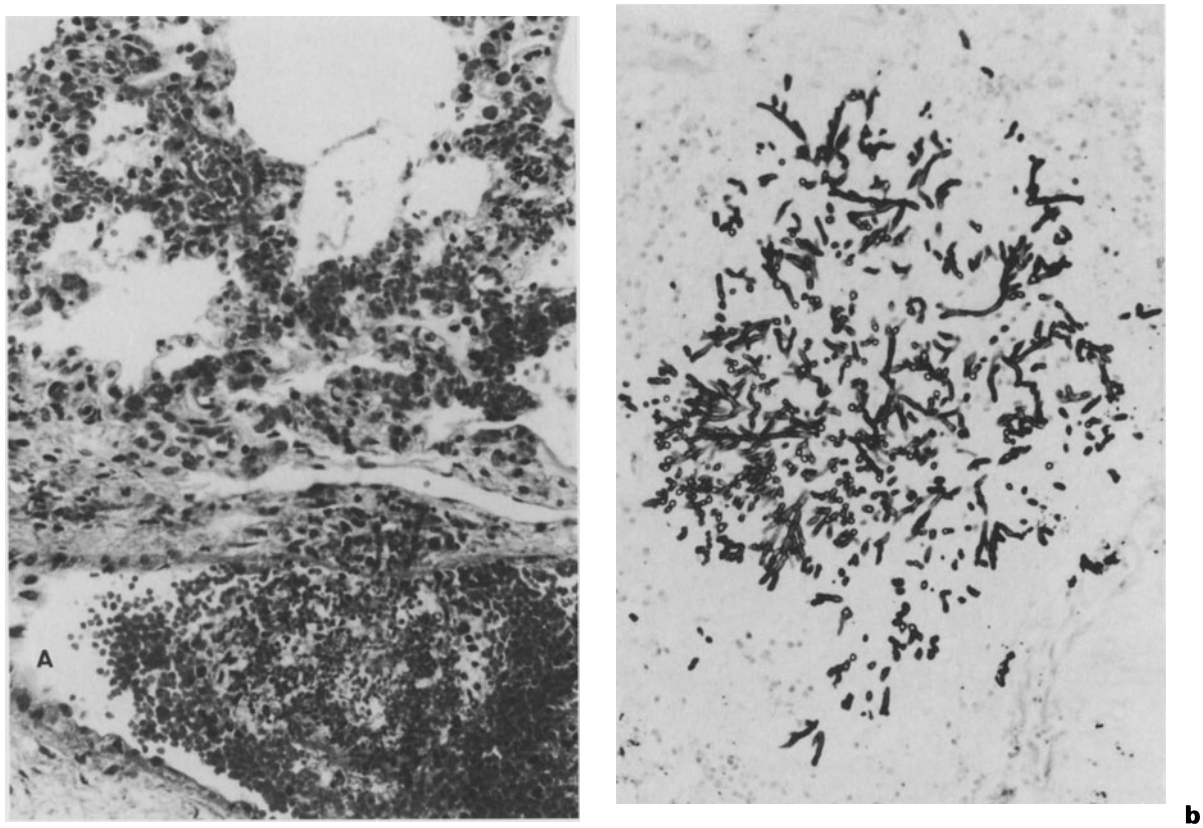



**Fig. 7.52.** Pulmonary aspergillosis in an 8-month-old boy. **a** Thrombosis with infiltration of vessel wall (*A*). (H&E, × 225) **b** Silver stain to show fungi. (Grocott, × 360)

been shown to be a diverse group of exotic fungi, which may include several species. It has a worldwide distribution and appears to be a saprophyte in the lungs of several domestic animals as well as humans. Its mode of transmission still remains unclear; however, it is generally accepted that the organisms may reach the lungs by inhalation. Whatever the route may be, in humans, exposure occurs early and most children by the age of 3 present serum antibodies to the organism. The disease is known to be endemic in some areas, and it is not uncommon among the inmates of institutions. Epidemics have been described, principally in Central Europe. The lung is the organ most often affected, but the organisms have been observed in the regional lymph nodes and, in severe disseminated cases, the bone marrow, liver, spleen, adrenals and kidneys. Multiple organ failure may ensue.

The condition has been described among premature babies and debilitated infants, especially those with congenital immunological abnormalities, recurrent infections or severe malnutrition. The disease has been severe and rapidly progressive, with a high mortality rate in most cases reported. *P. carinii* has been reported in siblings, and transplacental transmission has been documented. Effective therapy has now greatly modified the course of the disease.

At present, *P. carinii* is most commonly encountered as an opportunistic infection in immunodeficient subjects, especially those with AIDS and organ transplant recipients, and after prolonged antibiotic and chemotherapies. It has also been described in association with congenital heart disease, severe aplastic anaemia, systemic lupus erythematosus and acute disseminated Langerhans' cell histiocytosis, and in association with various bacterial infections, cytomegalovirus infection, and infection by *Candida albicans*.

The clinical and radiological features are nonspecific and may be accompanied by lung cavities, pneumatoceles, pneumothorax and/or pleural effusion. The organisms may be recovered from the latter. Serological and immunological studies are often necessary for establishing the diagnosis, and BAL fluids and lung biopsy can be additional assets (Millard and Heryet 1988; Limper et al. 1989; Davey and Masur

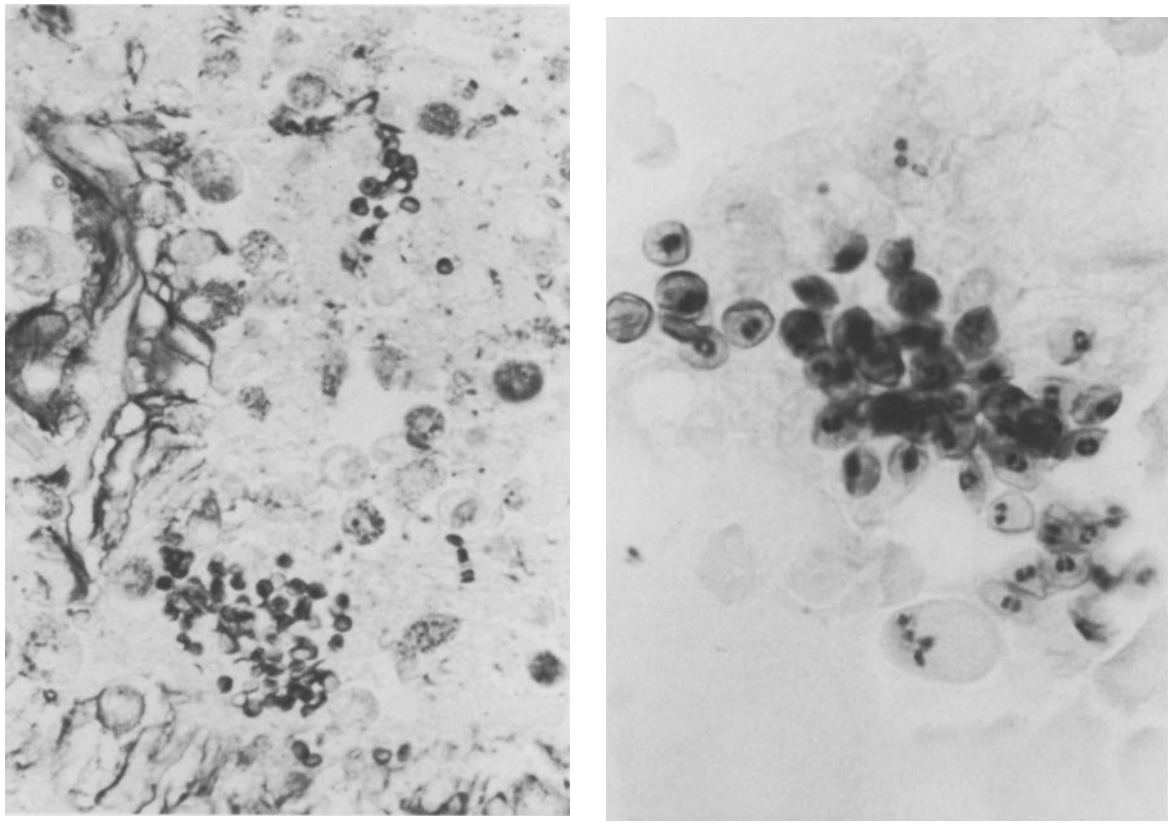


**Fig. 7.53.** *Pneumocystis carinii* pneumonia in a case of treated leukaemia. **a** The alveoli are filled with a granular material, foam cells and cellular debris. (H&E, × 650) **b** Abundant *P. carinii* of various forms in intra-alveolar exudate. (Grocott)

1990; Telzak et al. 1990; Chave et al. 1991; Leong et al. 1991; Walzer 1991a, b; Hidalgo et al. 1992; Murray and Schmidt 1992; Martin 1993; Smyth et al. 1994; Stringer 1993).

Macroscopically, the lungs are heavier than normal, firm, oedematous and may show focal reddish or brownish-grey areas of consolidation. In severe cases the lesions may be diffused, involving one or more lobes or the entire lung, but there are numerous variations between the two extremes. Emphysematous areas may be conspicuous, associated sometimes with pneumothorax and/or mediastinal emphysema. The hilar lymph nodes are often swollen.

Histologically, there is some degree of hyperplasia of the alveolar lining cells, with desquamation into the alveolar spaces mixed with macrophages in the early stages or in mild infection. The organisms can be observed within the macrophages or alveolar cells when stained with the appropriate stains (PAS, Grocott and specific monoclonal antibody). The interstitial inflammatory reaction is usually mild and composed chiefly of lymphocytes, plasma cells and macrophages. In the severe form, the alveoli are distended and filled with an exudate of foamy material mixed with desquamated cells and macrophages. The organisms are seen in large numbers within the cells, but are present mainly in the amorphous debris (Fig. 7.53). The alveolar wall is thickened, cellular, even fibrosed in places, and diffusely infiltrated by mononuclear cells and macrophages. Cysts and trophozoites may be identified, not only within the cells, but also in the scarred areas. Giant cells and non-caseating granulomas have been observed, and calcification has been recorded in these lesions and the hilar lymph nodes, where organisms can be seen. Survivors may show pulmonary fibrosis of varying degrees, sometimes with organisms.

*Other Mycoses.* Blastomycosis, mucormycosis, paracoccidioidomycosis, nocardiosis, etc, may be responsible for pulmonary lesions in infants and children, especially in humid tropical countries; however, they are unusual (Powell and Schuit 1979; Ramos et al. 1981).

## *Parasitic*

The lung is commonly affected by parasitic disease, and in many tropical countries parasites or their eggs can be observed in the lung parenchyma. The extent of pulmonary involvement is variable.

*Toxoplasmosis of the Lung. Toxoplasma gondii is* a protozoon, a member of the sporozoa group. The parasite has a worldwide distribution and infects many animal species. In humans it has a wide spectrum of manifestations, varying from subclinical or mild infection to severe generalized disease. Although the mode of transmission is not fully understood, the organisms may be acquired in utero or during childhood, and various surveys have shown that over 90% of some populations, notably those living in hot humid climates, have antibodies to the parasite.

Infection of the mother during pregnancy may result in intrauterine death, stillbirth or neonatal death in about 10% of cases. Should the parasite be acquired during the first 6 months of gestation transplacental transmission is infrequent, but the lesions are severe in the fetuses and infants who do acquire the disease. After the 6th month there is a much higher rate of transplacental transmission, and the infection is more often benign or asymptomatic in the offspring. A few reports have suggested that persistent maternal infection results in repeated abortion in successive pregnancies, but this has not been substantiated. Congenital toxoplasmosis may cause perinatal death, serious abnormalities of the central nervous system and the eyes (chorioretinitis) or latent disease. Because of the significant morbidity and mortality rates in the perinatal period, various routine immunological tests have been devised to detect the disease during pregnancy or in the neonatal period. Over 60% of infants born to mothers who have the disease during pregnancy show no evidence of infection. Infants may acquire the disease during passage through the birth canal or in childhood. In many countries emphasis is now placed on the routine screening of pregnant women and those of childbearing age. Toxoplasma infection is not uncommon among patients with malignant disease or other conditions requiring corticosteroid drugs and/or cytotoxic or immunosuppressive agents. In these patients the disease often runs a fatal course if not treated adequately. (Pinon et al. 1987; Berger et al. 1992; Thulliez et al. 1992).

Macroscopically, the lungs can appear normal or show reddish firm, sometimes confluent, nodules. Areas of consolidation have been observed in the diffused neonatal form of the disease. Microscopically, the alveolar spaces are filled with desquamated epithelial lining cells and macrophages. The alveolar wall is thickened, containing numerous macrophages with many plasma cells and lymphocytes, and few eosinophils and polymorphonuclear leucocytes. Toxoplasma pseudocysts may be seen free in the alveolar spaces, but occur principally in the cytoplasm of the desquamated alveolar cells and macrophages. Sometimes they can be seen in the cytoplasm of the swollen endothelial cell.

*Amoebic Lung Abscesses.* The protozoon *Entamoeba histolytica* (class Rhizopoda) is endemic in tropical and subtropical countries. It is also known to exist in certain temperate countries, and in recent times has been encountered more frequently than before, as a result of rapid air travel and the shifting of populations.

The parasite attacks principally the colon (see p. 793), but can spread to the liver by way of the portal system, and can eventually reach the lung and brain. The disease has been observed at all ages, but there are no figures for its true incidence. Intestinal infection in children is not altogether uncommon, but secondary spread to the liver with formation of liver abscesses is rare, and pulmonary involvement is even less common. The lung is infected from an amoebic liver abscess. The liver capsule overlying the abscess may adhere to the diaphragm, and eventually the abscess ruptures into the thoracic cavity, extending into the pulmonary parenchyma. A bronchopulmonary fistula has been observed in certain instances. There is little or no secondary inflammatory reaction (Abioye and Edington 1972; Jessee et al. 1975; Strauss and Bove 1975; Woodruff 1975; Shabot and Patterson 1978).

## *Other Parasites*

Several other parasites can be observed in the lungs during childhood. The lung may be involved in the life-cycle of some of these parasites, or it may be infected secondarily by the eggs, larvae or adult parasites.

*Hydatid cystic disease* (*Echinococcus granulosus*) is one of the most important of these. This parasite has a worldwide distribution, and there is a high morbidity in areas where the disease is endemic. *E. multilocularis*, another species, is limited to certain parts of Europe, including Switzerland. The larval form of *E. granulosus* is responsible for the classic hydatid cyst, whereas *E. multilocularis* is associated with the alveolar (multilocular) hydatid cyst (Poole and Marcial-Rojas 1971).

Four types of schistosomes are known to affect humans: *Schistosoma mansoni* and *S. haematobium*, *S. japonicum* and *S. intercalatum.*

Eggs of *S. mansoni* and *S. haematobium*, and to a lesser extent of *S. japonicum*, have been described in the lungs of patients harbouring the parasites in endemic zones. In some cases the eggs lodge in the alveolar wall of the interstitial tissue with little or no reaction; in others they may produce a granulomatous reaction with marked septal fibrosis. Embolism of the eggs in the pulmonary circulation is one cause of pulmonary hypertension. The adult worms can occasionally be observed in the lumen of the pulmonary vessels, with little or no reaction of the endothelial cells (Berthoud 1972; Cowper 1973; Pettersson et al. 1974).

The larvae of *Strongyloides stercoralis* have been reported in the lungs of infants and children in association with hyperinfection, especially among those suffering from severe malnutrition or receiving treatment with cytotoxic or immunosuppressive agents (Boyd et al. 1978; Burke 1978; Scowden et al. 1978).

Larvae of *Ascaris lumbricoides* can be observed in the lungs in children infested with this parasite. The larvae reach the lung by way of the blood vessels and can be seen in the capillaries or free in the alveolar wall, where there is sometimes an inflammatory reaction with numerous eosinophils. The larvae of *A. lumbricoides* must be distinguished histologically from those of *S. stercoralis* (Arean and Crandall 1971).

In endemic zones where *filariasis* is a major problem, microfilariae can be identified in the lung. The organisms are often free in the alveolar wall or in the capillaries. Occasionally there is a secondary inflammatory reaction around the microfilariae. Filiarasis of the lung is often associated with pulmonary eosinophilia (Webb et al. 1960; Meyers et al. 1977).

There are several types of *pentastomiasis*, and the causative parasites are known to inhabit the nasopharynx of birds and mammals in various parts of the world. Humans may become infected secondarily, and the second-stage larva may be found in several organs, including the lung (Fig. 7.54) (Self 1969).

Recently a case of *capillariasis* (*Capillaria acrophila*) was described in a child in Iran by Aftandelians et al. (1977). Pulmonary paragonimiasis may be encountered in children coming from the Far East (Mayer 1979).

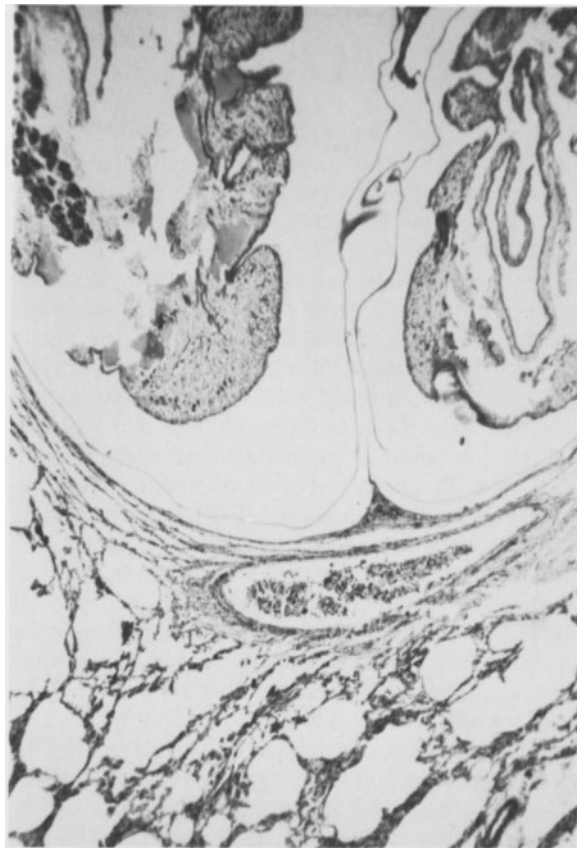


**Fig. 7.54.** Pulmonary pentastomiasis in a 6-year-old African girl with fatal disseminated infestation. (H&E, × 25)

## *Bronchoalveolar Lavage*

In children, bronchoalveolar lavage (BAL) is widely used in sarcoidosis, AIDS, asthma, extrinsic allergic alveolitis (hypersensitivity pneumonitis), transplant patients (renal, bone marrow, cardiac) and now increasingly in respiratory distress syndrome and bronchopulmonary dysplasia. It may be helpful in the diagnosis of Langerhans' cell histiocytosis (histiocytosis X), in which the cells stain for OKT6, CD1a and S-100 protein, but it is in no way specific. The technique has the advantage of permitting rapid diagnosis of various kinds of infection, with the possibility of promoting therapeutic intervention. In addition, study of the cellular population in the fluid obtained makes data available on immune status and the evolution of some specific conditions. These, together with the study of the other components making up the fluid, have become important tools in both normal and pathological conditions.

## *Acquired Immune Deficiency Syndrome*

In the paediatric age group with AIDS, the pulmonary lesions have been the best documented, and these appear to be somewhat different from those observed in adults. The thymus, lymph node, gas-

trointestinal tract, brain and spinal cord are also severely affected (see also p. 821).

The pulmonary lesions may take one of several forms. Opportunistic infections are not uncommon and may be the only pathological findings, with *Pneumocystis carinii* often heading the list, or in association with some viral infections, principally cytomegalovirus infection, or mycotic infections (*Candida, Aspergillus*), *Toxoplasma*, and/or bacterial infections (*Haemophilus influenzae, Mycobacterium avium intracellulare*). By far the most common lesion, however, is *pulmonary lymphoid hyperplasia* (PLH), which consists of nodular peribronchial lymphoid hyperplasia with or without germinal centres scattered about the lung fields. The alveolar septa are infiltrated by mild to moderate amounts of mononuclear cells. The next most common finding is the *lymphoid interstitial pneumonitis* (LIP) characterized by a diffuse mononuclear infiltrate of the alveolar wall and peribronchiolar spaces. The infiltrate is composed of lymphocytes, immunoblasts and plasma cells often containing Russell bodies. Some alveolar spaces may be filled with macrophages and desquamated alveolar cells, and the alveolar wall may be lined by metaplastic cuboidal cells and infiltrated by varying quantities of mononuclear cells, thus taking on the appearance of *desquamative interstitial pneumonitis* (DIP). The alveolar infiltration may be accompanied by scattered nodular aggregates of lymphoid tissue, sometimes centred on germinal centres. In general there may be great overlapping of these various histological appearances within the same lung or even within a given lobe. Lesions consistent with pulmonary hypertension may be present, especially among intravenous drug users; the lesions may be widespread. Malakoplakia has also been described with this syndrome.

Some areas may take on the appearance of secondary alveolar proteinosis (partial staining for surfactant apoprotein), especially when this is associated with *Pneumocystis carinii* or *Mycobacterium tuberculosis*.

It has been shown recently that a monoclonal antibody (anti-P18) labels cytoplasmic and membranal viral proteins in lymphoid tissue associated with AIDS or AIDS-related complex (ARC), and this could be a valuable aid in diagnosing the condition in infants with a negative serology. Several new tests have been added to those already existing (Anderson and Lee 1988; Beers et al. 1990; Mills and Masur 1990; Murray and Mills 1990; Schwartz et al. 1990; Travis et al. 1990; Garcia et al. 1991; Klapholz et al. 1991; Kovacs et al. 1991; Russler et al. 1991; Speich et al. 1991; Polos et al. 1992; Sepkowitz et al. 1992; Travis et al. 1992; Karlinsky and Mark 1993; Yousem 1993).

## *The Lung in Transplantations*

Lung transplantation and heart–lung transplantation have become relatively common procedures worldwide, as well as transplantations of other organs isolated or in combinations. Although the control of rejection is one of the principal element, determining management, secondary infections in these immunocompromised patients often cause significant morbidity and mortality. Major problems may arise in the interpretation of lung biopsies, and it is not always easy to differentiate rejection from opportunistic infections. Bacterial, fungal, viral and parasitic infections must be taken into consideration when evaluating a lung biopsy for rejection. Immunohistochemistry, in situ hybridization, molecular biology and ultrastructural techniques on biopsy material or BAL are often necessary to arrive at a diagnosis. In cases coming to autopsy, other pathological conditions must also be taken into consideration, principally *bronchiolitis obliterans*, its consequences and complications, as well as associated bronchial and vascular lesions (Tazelaar and Yousem 1988; Clelland et al. 1990; Fend et al. 1990; Weiss et al. 1990; Abernathy et al. 1991; Groussard 1993).

## *Pulmonary Lesions after Bone Marrow Transplantation*

Pulmonary complications are responsible for a considerable proportion of the morbidity and mortality among bone marrow transplant patients. These complications are more prevalent among those receiving allogenic marrow transplantation than those receiving syngenic autologous transplantation.

Many predisposing factors have been incriminated, including pretreatment radiotherapy. Total body irradiation in a single dose would appear to predispose to a higher frequency of pulmonary complications than fractionated irradiation. Chemotherapy due to drug toxicity on the lung parenchyma may also be a contributing factor.

The symptoms are generally non-specific, with fever, cough, dyspnoea and tachypnoea. Chest radiography may be unrevealing, but more often shows bilateral nodular infiltrates. BAL is of great value in arriving at a rapid diagnosis.

The pulmonary lesions are variable and consist of:

1. *Opportunistic Infection.* One or more pathogens may be involved, including bacteria (atypical mycobacteria, *Legionella*, etc.), fungi (*Candida, Aspergillus* spp., *P. carinii*), viruses (cytomegalovirus,

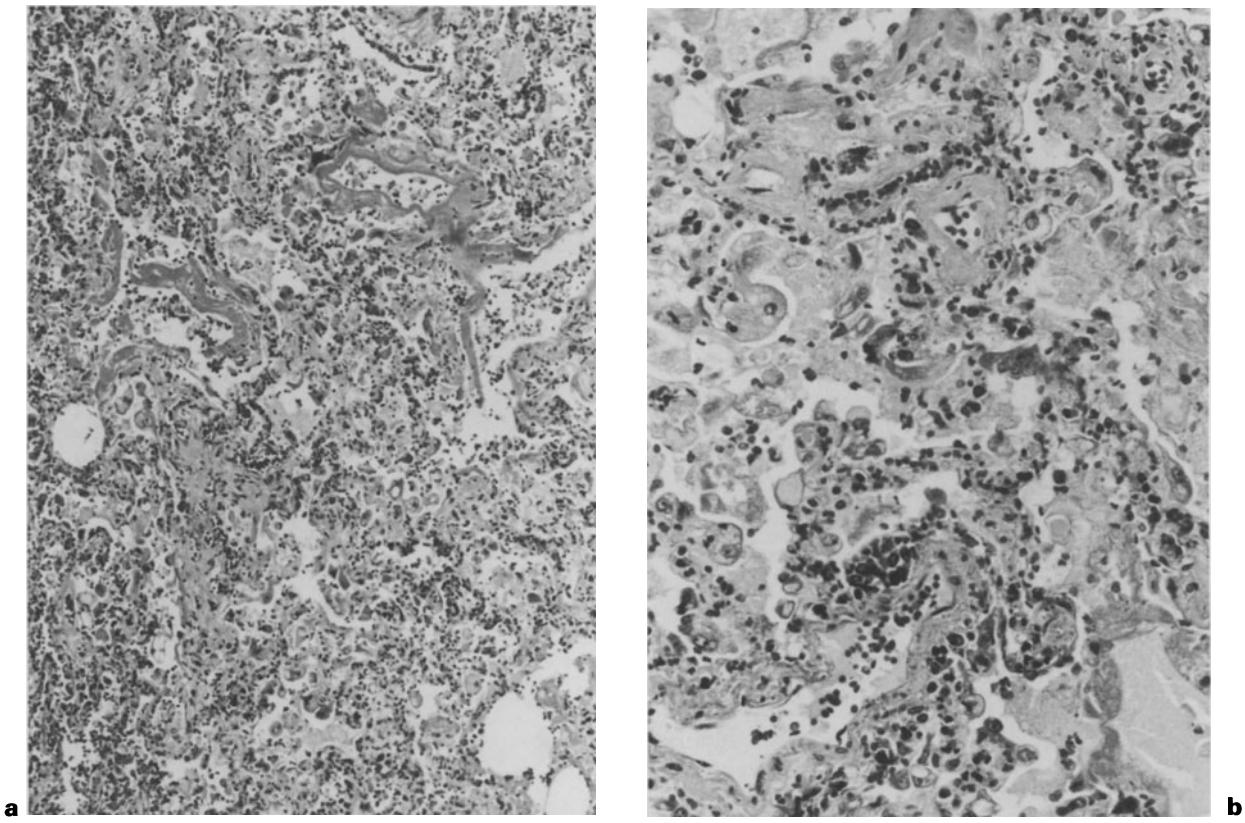


**Fig. 7.55.** Idiopathic interstitial pneumonia in a case of bone graft. **a** The alveoli are covered by hyalin membranes and their lumina are filled with desquamated alveolar cells and macrophages. Mononuclear cells are observed in the alveolar wall in small groups. (H&E, × 60). **b** The hyperplastic alveolar cells are evident, some taking on a giant cell appearance.

herpes simplex, Epstein–Barr, parvovirus 19, respiratory syncytial virus, HHV-6 and HHV-7).

2. *Interstitial Pneumonitis (Idiopathic).* No infectious agent can be identified by the various means at our disposal. The lung tissue presents thickening of the alveolar wall, infiltrated by mononuclear cells or aggregates of lymphocytes. There is marked hyperplasia of the alveolar lining cells, some having a giant cell appearance (Fig. 7.55). No viral inclusions can be identified even by *in situ hybridization* or by ultrastructural means. The alveoli often contain a granular oedematous fluid with numerous desquamated alveolar cells accompanied by several macrophages. Here and there one observes a moderate peribronchial and/or peribronchiolar mononuclear infiltrate. The condition may present in one of two forms: with severe clinical symptoms with diffuse radiological involvement and a rapid fatal course, or with discrete or mild clinical symptoms, evolving chronically, and not leading to death. In this case the lung usually presents diffuse fibrous thickening of the alveolar wall.
3. *Bronchiolitis Obliterans.* The terminal bronchi and bronchioles are obliterated by proliferating fibrous tissue with focal or complete necrosis of the wall or complete scarring. This lesion is usually associated with late acute or chronic graft-versus-host disease. (Roy et al. 1989; Holland et al. 1990; Jochelson et al. 1990; Benz–Lemoine et al. 1991; Burgart et al. 1991; Gucalp et al. 1991; Rosenfeld and Young 1991; Corrin 1992; Garaventa et al. 1992; Harrington et al. 1992; Ezri et al. 1994).

## *Bronchus-associated Lymphoid Tissue (BALT)*

*Bronchus-associated lymphoid tissue*, also referred to as idiopathic follicular bronchitis or follicular bronchiectasis, may be encountered in fetuses, premature babies and even abortuses, and in the majority of cases it is associated with intrauterine infection and chorioamnionitis. It is a relatively frequent finding in SIDS and may also be observed in infants, children and adults with immunodeficiency states, autoimmune conditions or hypersensitivity states.

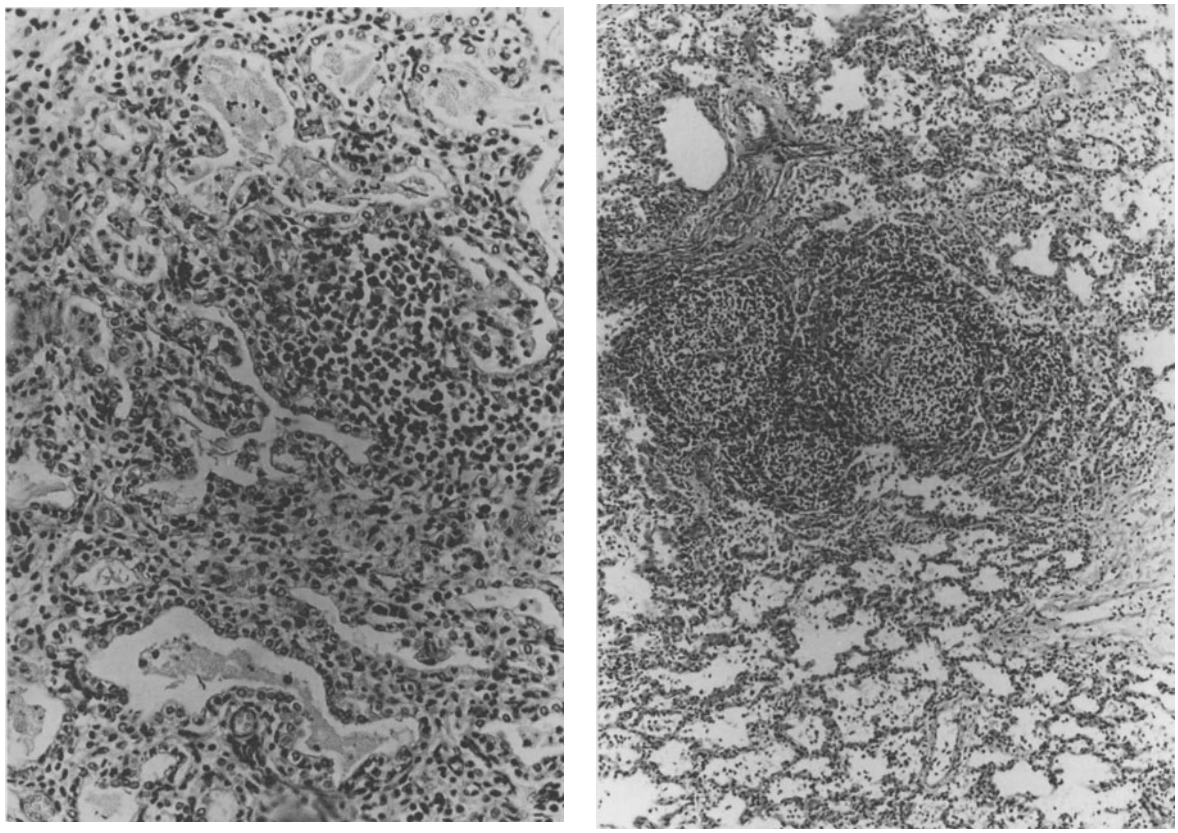


**Fig. 7.56.** **a** Intrauterine pneumonia in a fetus at 27 weeks' gestation with well develop lymphoid aggregates. (H&E, × 125) **b** SIDS with well developed peripheral lymphoid follicules in the lung, age 15 months. (H&E, × 50)

The condition is thought to be induced by infection in some cases and by antigenic stimulus in others, and therefore may represent a host defence mechanism of the lung. Histologically there is lymphoid tissue or lymphoid follicles in close proximity to the bronchial and/or bronchiolar epithelium, most often in the region of their bifurcation or along their channel (Fig. 7.56). A mild or moderate bronchitis and or bronchiolitis may be associated (Emery and Dinsdale 1974; Yousem et al. 1985; Pabst 1992; Gould and Isaacson 1993; Holt 1993; Kinane et al. 1993).

### *Diffuse Interstitial Pneumonia (Desquamative Interstitial Pneumonia)*

Diffuse interstitial pneumonia in infancy and childhood is a rare condition in this age group, and many of the histological patterns are similar, in many respects, to those observed in adults; in the latter, it has a worldwide distribution and carries many synonyms (Hamman–Rich syndrome, diffuse fibrosing alveolitis, fibrotic lung disease, interstitial pulmonary fibrosis, cryptogenic alveolar fibrosis, idiopathic pulmonary fibrosis). Diffuse interstitial pneumonia has been described in association with pathological changes in other organs in some cases, especially among patients suffering from Sjögren's syndrome, chronic active hepatitis, Hashimoto's thyroiditis, ulcerative colitis. It has also been described in families, and in most of these cases it seems to have an autosomal dominant mode of inheritance. Histological patterns are often indistinguishable from those produced by drug allergic reactions and certain viral pneumonias (Katzenstein 1985; Burkhardt 1989; Burkhardt and Cottier 1989; Dunnill 1990; Smith et al. 1990; Cherniack et al. 1991; Thompson et al. 1992). The condition may present in an acute form (desquamative interstitial pneumonia), which is distinct from the chronic interstitial pneumonias but may represent a spectrum of the same disease process. Lung biopsies and BAL have become valuable aids in confirming diagnosis (Robinson et al. 1988; Hällgren et al. 1989; Katzenstein et al. 1995).

The disease has been documented in both infancy and childhood, sometimes with repeated relapses; it

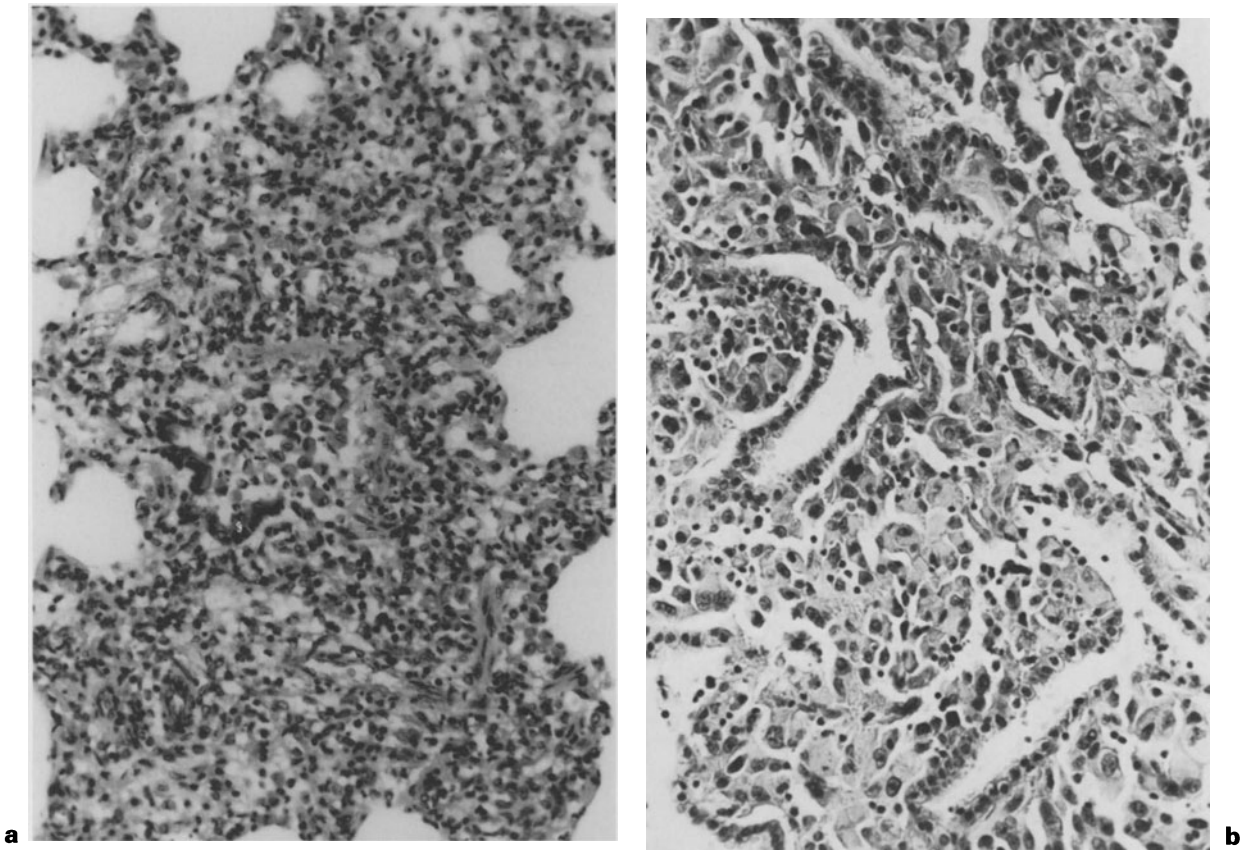


**Fig. 7.57.** **a** Acute desquamative interstitial pneumonia in a 5-week-old infant. Note the partial obstruction of the bronchiole containing macrophages and the few inflammatory cells extending into the thickened alveoli. (H&E, × 55) **b** Desquamative interstitial pneumonia in a 7-month-old boy, which progressed to diffuse pulmonary fibrosis by the 20th month. (H&E, × 225)

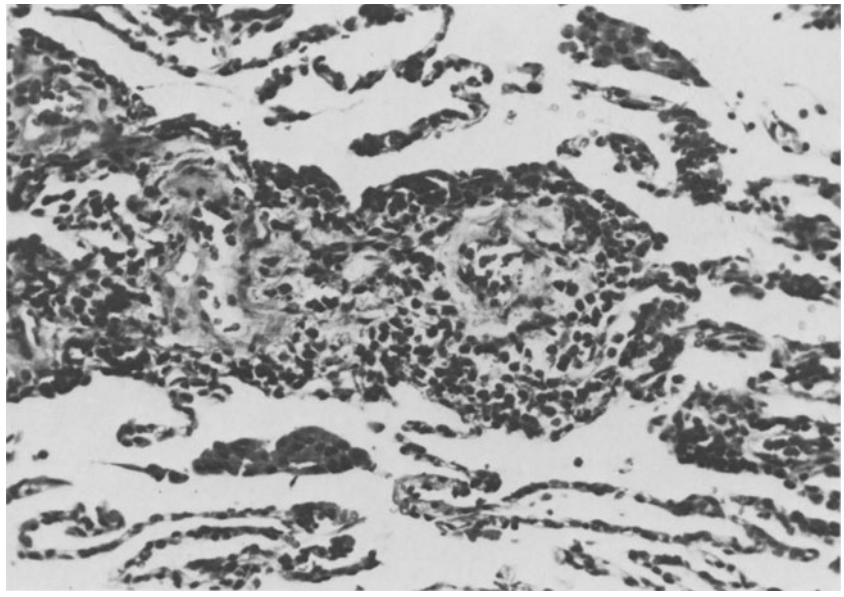
has also been described in association with segmental glomerulosclerosis (Hewitt et al. 1977; Steinkamp et al. 1990; Sheth et al. 1992; Usui et al. 1992). Recently, Schroeder et al. 1992 have described a cellular interstitial pneumonitis in infants which they consider a different entity from those described above.

Hewitt et al. (1977) reviewed the literature on cases of fibrosing alveolitis occurring in childhood. All pertinent features of the disease in the paediatric age group were evaluated, and a comparison of fibrosing alveolitis in children and adults was made.

Macroscopically the lungs are heavier than normal, firm, non-crepitant and airless. They are greyish in colour and in the late stages present a honeycomb appearance. Macroscopically, in the early phase, the air spaces are distended, filled with desquamated, PAS-positive, granular pneumocytes (type II cells) and some macrophages (CD68+) which may contain haemosiderin pigment. The alveoli are lined with hyperplastic alveolar cells, some of which show cuboidal metaplasia. The alveolar wall is thickened and infiltrated by a mononuclear exudate but there are no polymorphonuclear leucocytes (Fig. 7.57). There is no necrosis, and hyaline membranes are not found. Lymphoid aggregates may be conspicuous, and follicles with prominent germinal centres are frequently observed, especially in the crytogenic phase.

During the late stages, the alveolar wall shows varying degrees of thickness and fibrosis. The extent of these changes depends on the evolution and duration of the disease. Reticulin and collagen fibres are increased; elastic fibres are numerous and thickened. There is an active proliferation of smooth-muscle cells. Some alveoli may become obliterated by the process, while others become cyst-like, leading to the typical honeycomb appearance. The bronchiolar epithelium may show metaplasia, and the bronchial wall is usually thickened as a result of muscular hyperplasia. The bronchi and bronchioles are often surrounded by lymphoid follicles.

Platelet aggregates have been observed in capillaries in the early phase. In general, vessel walls are thickened due to muscular hyperplasia with moderate



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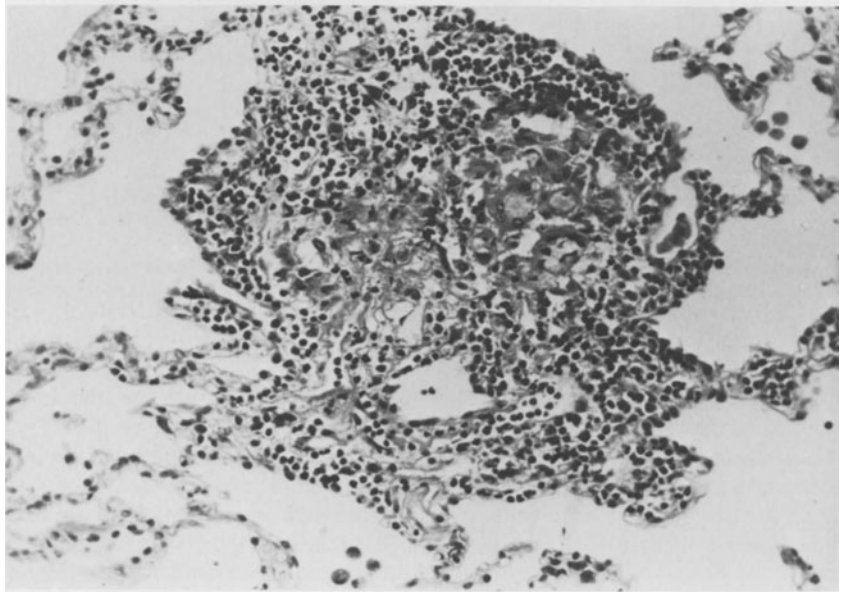


b

**Fig. 7.58.** **a** Hypersensitivity pneumonitis associated with animal furs, principally horsehair, in an 11-year-old girl. (H&E, × 180) **b** Hypersensitivity pneumonitis associated with pigeon proteins (pigeon fancier's lung) in a 13-year-old girl. (H&E, × 180)

to severe fibrosis. In the late stages, the large and medium-sized vessels are thickened and fibrosed.

### *Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonia)*

Extrinsic allergic alveolitis is an inflammatory reaction of the distal airways to various inhaled antigenic materials. A variety of agents, including proteins of animal and avian origin, fungi and thermophilic organisms, have been incriminated as responsible for the lesions, and new aetiological agents continue to be identified. Extrinsic allergic alveolitis is often an occupational hazard; however, social and environmental factors are also contributory elements. Although the majority of cases have been reported in adults, infants and children are also affected. The condition is not infrequently encountered among adolescent drug abusers who inhale various narcotics, often contaminated with other substances, or among "sniffers". It has also become more prevalent among those exposed to an excessive quantity of hairspray.

Extrinsic allergic alveolitis is mainly associated with type III immune reaction, and the pathogenesis is believed to involve both immune-complex disease

and cellular hypersensitivity (cell-mediated) reactions in the terminal air spaces in association with complement ($C_3$). Genetic and environmental factors seem to play an important role and may determine the host's response to the particular antigenic insult. HLA antigens and antibodies to the $P_1$-erythrocyte antigen also appear to be of some importance, at least in some cases, in determining the response of the host. Antigen, immunoglobulins (mainly IgG with smaller quantities of IgA and IgM) and complement ($C_3$) can be detected in the lungs of patients suffering from the disease. Their identification depends partly on the sensitivity of the tests, and in particular on the evolution of the disease process. They are more frequently found in the early stage of the disease, before extensive phagocytic infiltration or fibrosis has occurred. The condition is thought to be the result of a complex series of immunological events in which the alveolar macrophages, T-lymphocytes, neutrophils and their secretions have a role under well defined genetic factors.

Pathologically it is not possible to distinguish between immune-complex disease and cellular hypersensitivity lesions in the lung. Furthermore, in the late stages of the disorder, it is not possible to differentiate between extrinsic allergic alveolitis and fibrosing alveolitis.

Diagnosis is made on the basis of the clinical and immunological findings in susceptible individuals. The radiological findings are non-specific. The presence of specific antigens in the serum is of prime importance; the analysis of cells and proteins from BAL may be helpful and more so their T-cell components. Predominantly CD8+ T-lymphocytes in BAL is highly suggestive of an acute phase of hypersensitivity pneumonitis, whereas an increased number of CD4+ T-lymphocytes would favour a fibrotic process which on histology would be indistinguishable from idiopathic pulmonary fibrosis. Microbiological and specific immunohistological studies may be of help in arriving at an aetiological diagnosis, and this can be strengthened by specific skin tests (Lipscomb et al. 1986; Salvaggio and de Shazo 1986; Coleman and Colby 1988; Semenzato et al. 1988; Selman et al. 1990; Murayama et al. 1993).

Macroscopically, the lungs present features similar to those of fibrosing alveolitis. However, in most cases, lung tissue is obtained by biopsy for histological and immunological studies during the course of the disease. Microscopically, there is a wide variability in the lesions, depending on the state of the disease. In the early stages there is oedema of the alveolar wall, which is thickened and infiltrated by aggregates of lymphocytes, some plasma cells, and many histiocytes with a foamy cytoplasm. The alveolar spaces and bronchiolar lumen may contain few desquamated epithelial cells with some histiocytes (Fig. 7.58). At a later stage the inflammatory reaction is more prominent, histiocytes are more numerous, and there are well developed lymph follicles, sometimes with well defined germinal centres. Epithelioid-cell granulomas with foreign body-type giant cells are now conspicuous and may contain cholesterol clefts. Some giant cells may also be seen in the alveolar spaces among the few histiocytes and desquamated epithelial cells. Schauman bodies may occasionally be present. The small bronchi and bronchioles are also involved in the inflammatory disease process, with features characteristic of organizing pneumonia. Their walls are thickened and infiltrated by mononuclear cells and histiocytes, and bronchiolitis obliterans may occur as the disease progresses. Small vessels may also participate in the reaction, and arteritis with eventual thickening and fibrosis of the vessel wall is sometimes observed.

In the late stages, there is moderate to severe thickening of the alveolar wall, which is rich in collagen and reticulin fibres. The inflammatory reaction is now patchy or almost absent, and granulomas are no longer present. Remodelling of the parenchyma and formation of cystic spaces gives rise to the honeycomb appearance, which is indistinguishable from that seen in fibrosing alveolitis.

## *Eosinophilic Pneumonias*

Eosinophilic pneumonias are a group of allergic inflammatory reactions in the lungs, characterized by a marked eosinophilic exudate in the lung parenchyma, which must be distinguished from the hypereosinophilic syndrome; they can occur with or without blood eosinophilia. The clinical manifestations may be variable and are often non-specific; however, two modes of presentation, acute and chronic, have been documented. The classic fluffy peripheral radiological features and/or peripheral computed tomographic images are often diagnostic of the condition, and BAL fluids often contain a high percentage of eosinophils. The disease generally responds to corticosteroids. Löffler's syndrome describes a particular clinical presentation.

The eosinophilic pneumonias occur in childhood. They are generally associated with certain drug reactions, fungi or parasitic diseases, but there are other instances where the aetiology remains unknown or uncertain. Various drugs, including penicillin, sulphonamides and *p*-aminosalicylic acid, have been described in association with this entity, and among the fungi *Aspergillus fumigatus* appears to be the most important offender. Numerous parasites known to cause blood eosinophilia (tropical eosinophilia) are

associated with the condition; among the most common are microfilariae and the larvae of *Ascaris lumbricoides, Strongyloides stercoralis, Ascaris duodenale, Toxocara canis* and *Toxocara cati.*

The pulmonary lesions may be caused by a local immunological type I or type III reaction. There is diffuse inflammation in the pulmonary parenchyma. Eosinophils usually predominate, and histiocytes are also present. Focal areas of necrosis can be observed, and granulomas are not uncommon. The most striking feature in many cases is fibrinoid necrosis of the peripheral arteries and arterioles in and about the lesions. In parasitic infections, sections of microfilariae or larvae can sometimes be identified within the granulomas (Alfaham et al. 1987; Jederlinic et al. 1988; Allen et al. 1989; Naughton et al. 1993; Winn et al. 1994).

### *Wegener's Granulomatosis*

A relatively uncommon condition of unknown aetiology, Wegener's granulomatosis has been described in children. The disease is generally characterized by a pathological triad of necrotizing granulomas of the upper and lower respiratory tracts, systemic vasculitis and glomerulonephritis. The disease can be limited to the lungs, which may have nodules of variable sizes presenting with central necrosis resembling infarcts but with little haemorrhage. There is necrotizing granulomatous bronchitis and bronchiolitis, and angiitis of both arteries and veins of medium and small size often containing fibrin and/or thrombi within their lumen. Capillaritis is a common associated finding. Deposits of IgG and $C_3$ can be demonstrated in both the alveolar and the vessel walls. In the disseminated or generalized form, the disease shows widespread necrotizing and granulomatous vasculitis of arteries and veins of the upper and lower respiratory tracts, as well as most other organs or systems, including the joints, and central and peripheral nervous systems. In the lung, the necrotic areas of variable size can be isolated or confluent, or involvement could be diffuse affecting an entire lobe. These lesions may present haemorrhagic areas, sometimes massive or confluent and of different ages. These areas usually contain aggregates of chronic inflammatory cells of variable quantities, sometimes mixed with few polymorphonuclear cells but numerous monocytes. Giant cells of foreign body type are often seen on the periphery of the lesions. Stains for fungi and acid-fast bacilli are always negative. The vascular lesions may vary from fibrinoid necrosis of the vessel wall with an inflammatory cell infiltrate, a granulomatous vasculitis, to a scarred obliterative vasculitis, or combinations of these, and may be associated with diffuse pulmonary haemorrhage. The association of Wegener's granulomatosis with the antineutrophil cytoplasmic antibodies directed to the neutrophil cytoplasmic enzyme, proteinase 3, makes it possible to differentiate this condition from some of the entities presenting with diffuse pulmonary haemorrhage. The limited form of this condition must be distinguished from *lymphatoid granulomatosis*, which has also been reported in childhood. Lymphatoid granulomatosis is characterized by an infiltrative process of the lung by small lymphocytes, plasma cells, histiocytes and atypical lymphoreticular cells associated with necrotizing angiocentric and angiodestructive lesions. Extrapulmonary involvement, especially of the skin and brain, is not uncommon. The sensitivity and specificity of the *antineutrophil cytoplasmic antibodies* in the diagnosis of this disease is now well established (Travis et al. 1987; Mark et al. 1988; Hoffman et al. 1992; Yoshimura et al. 1992; Dreisen 1993; Rottem et al. 1993).

### *Asthma*

Bronchial asthma, a complex syndrome, is characterized by paroxysms of dyspnoea, wheezing and cough due to airway hyper responsiveness resulting in variable airway obstruction, usually over short periods and reversible. Bronchial hyperresponsiveness may also be present with this condition. It appears to be on the increase.

Asthma is now divided into two categories: extrinsic or IgE mediated (atopic or allergic), and intrinsic (non-atopic). The condition can be induced or triggered by a large variety of stimuli, including allergens (indoor or outdoor pollutions, foods, aerosols), medicaments ($\beta$-agonists, methotrexate, aspirin), chemical irritants (various gases, e.g. ozone), physical stimuli (exercise, cold air), infections (viruses, fungi, bacteria), psychologic status and many others.

There is accumulated evidence that the inflammatory mechanisms in asthma depend largely on various inflammatory cell types, principally the eosinophil and its secretion products (major basic proteins, eosinophil cationic protein, eosinophil peroxidase, eosinophil-derived neurotoxin), which serve as important proinflammatory mediators. Other cell types (mast cells, neutrophils, macrophages, platelets, lymphocytes) also play essential roles in the pathophysiology of the condition. Significant mucociliary clearance impairment and circulation adhesion molecules are also important factors in the exacerbations of the disease. The presence of Creola bodies (non-ciliated fragments of bronchial epithelium), Curshmann's spiral (condensed mucus bands),

Charcot–Leyden crystals and eosinophils in the sputum and/or BAL fluids are of clinical importance in the clinical diagnosis. Bronchial biopsy has now become an important tool in the diagnosis of the condition (Jeffery et al. 1989; Djukanovic et al. 1990; Jeffery 1991; Laitinen and Laitinen 1991; Messina et al. 1991; Aikawa et al. 1992; Kuwano et al. 1993; Gaillard et al. 1994; Janson et al. 1994; McBride et al. 1994; Montefort et al. 1994; Suissa et al. 1994; Sigurs et al. 1995).

Macroscopically, the lungs are very large, distended, filling the thoracic cavity, but they are not heavy unless superadded infection has occurred. Microscopically, the lesions are non-specific and largely confined to the medium-sized and small bronchi. The distal airways are distended, partially or totally obliterated by a thick, tenacious mucus (mucoid impaction) plug containing macrophages, desquamated epithelial cells, eosinophils (granulated and non-granulated), lymphocytes and sometimes neutrophils. In cases of sudden death the bronchial lumen may be free. There is a marked increase in goblet cells of the distal bronchial and bronchiolar epithelium, with hypersecretion of mucus. Mast cells, eosinophils and lymphocytes can be seen in the epithelium. The basement membrane appears to be thickened, but is supported by a hyaline-like collagen (collagens III and V and fibronectin, but no laminin) deposit containing reticulin but no elastic fibres. Submucosal glands are markedly enlarged showing hypersecretion. The smooth muscle of the bronchial wall shows varying degrees of hypertrophy, and aggregates of chronic inflammatory cells accompanied by eosinophils and mast cells stream across the bundles (Fig. 7.59). The blood vessels are congested and their walls are sometimes oedematous; there is an increase of nerve fibres containing substance P, but an absence of fibres containing VIP. The bronchioles and alveoli in the immediate vicinity of the bronchial lesions may be thickened and infiltrated by lymphocytes, plasma cells and some eosinophils; they may be distended. The large bronchi also show goblet-cell hyperplasia, and there can be some degree of squamous metaplasia. The peribronchial glands are also hyperplastic.

### *Idiopathic Pulmonary Haemosiderosis (Ceelen's Disease)*

Idiopathic pulmonary haemosiderosis is an uncommon disorder of unknown aetiology. It has been reported mainly in infants and children and among young adults. The disease is characterized by repeated widespread intrapulmonary haemorrhages leading to respiratory distress, haemoptysis and severe iron-deficiency anaemia.

In children the majority of cases occur before the age of 10 years, and the incidence is about equal in both sexes; among adults there is a male predominance. The clinical symptoms are variable but the severity may increase, leading to marked disability and eventually to a fatal outcome. Some cases are asymptomatic. The radiological appearance is not diagnostic for the condition. The prognosis is unpredictable, and in the chronic stages pulmonary fibrosis may result. The condition has been described in association with myocarditis, and some cases have presented with diabetes. Chromosomal abnormalities and familial cases have been reported.

The diagnosis is usually made by elimination, as other conditions (mitral stenosis, pulmonary hypertension, veno-occlusive disease, etc.) can be accompanied by pulmonary haemosiderosis. The pathogenesis is unknown; however, some authors have proposed an immunological mechanism at the level of the basal membrane of the alveolar capillaries. This would suggest a mechanism similar to that occurring in Goodpasture's syndrome; however, immunoglobulins and complement have not been demonstrated on the basal membranes in idiopathic pulmonary haemosiderosis. Other authors have envisaged a connective tissue abnormality limited to the elastic tissue in the lung, and principally at the level of the small vessels. Cows' milk proteins acting as allergens on the capillary wall have been suggested as causative agents, but there is no conclusive evidence to support this theory; some reports have described the condition in association with coeliac disease. Within recent years the association with systemic lupus erythematosus in older children has been documented, and one report has shown acute alveolar capillaritis and focal alveolar necrosis in such cases. Ultrastructural studies in one case have shown mineral deposits (iron and calcium) on an altered basement membrane (Kjellman et al. 1984; Miller et al. 1986; Myers and Katzenstein 1986; Cutz 1987; Travis et al. 1987; Bonsib and Walker 1989; Travis et al. 1990; Harrity et al. 1991).

Macroscopically, the lungs are firm, somewhat nodular and reddish-brown in colour. The hilar lymph nodes are enlarged and brown. Microscopically, the changes depend on the stage of the disease. Initially the distended alveolar spaces are filled with numerous macrophages laden with haemosiderin. Macrophages are accompanied by erythrocytes, indicating recent haemorrhages, which are also observed in the bronchiolar wall. Intra-alveolar fibrin deposits can be demonstrated by means of special stains or immunofluorescence. The alveolar wall is oedematous and somewhat thickened, and contains iron-filled histiocytes. This thickening is accentuated by the hyperplasia of the alveolar epithe-

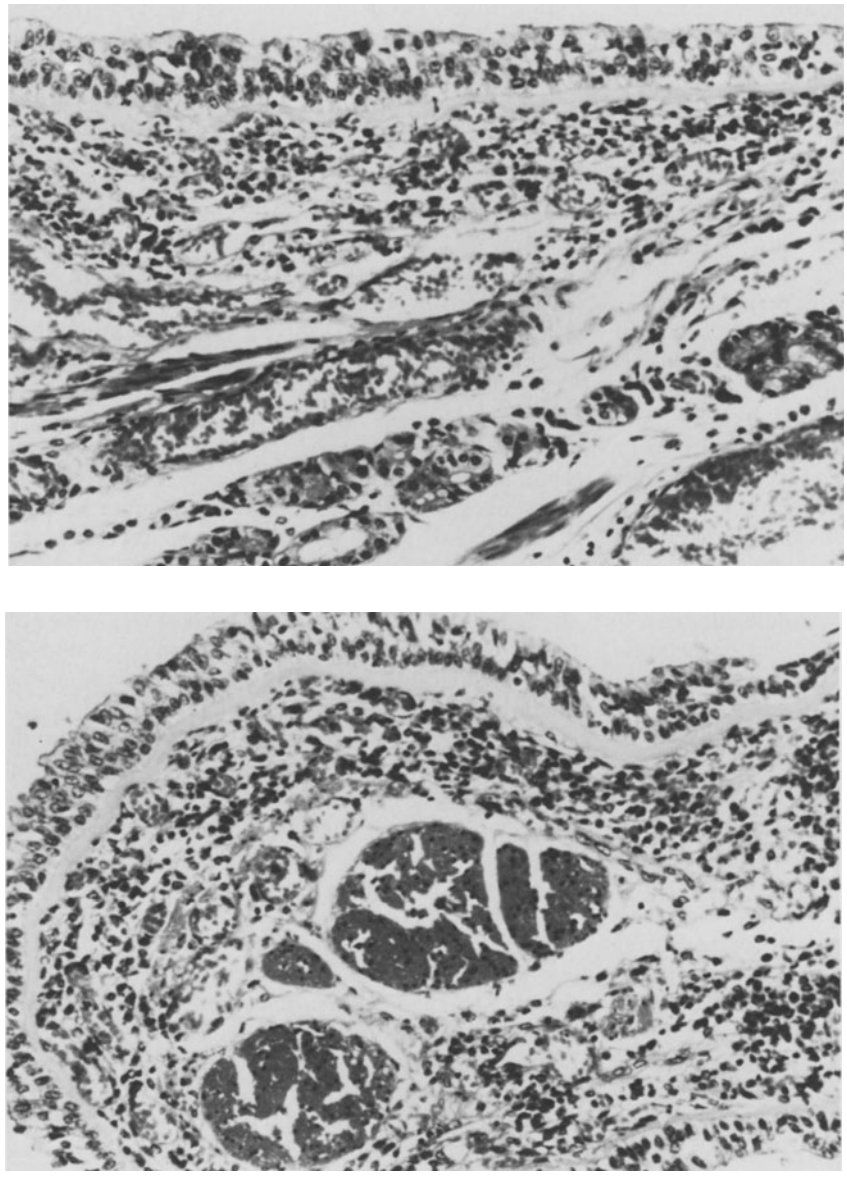


**Fig. 7.59.** A 17-year-old female patient, hospitalized for asthma on many occasions since the age of 3. (H&E, × 225) **a** Hyperplasia of goblet cells and marked thickening of the basement membrane. **b** Similar changes in the main stem bronchus. Note the marked muscular hypertrophy.

lial cells (mainly type II cells), which appear cuboidal. The capillary basement membrane shows some degree of thickening. There is no tissue necrosis or vasculitis. During the later stages, the thickening of the alveolar wall is more apparent, and fibrosis may be marked. There is an increase in collagen and reticulin fibres, accompanied by thick fragmented elastic fibres. Intra-alveolar and interalveolar haemorrhages may be widespread. Haemosiderin pigment deposits are abundant at this point, diffuse, and also observed in the interlobular spaces. Fibrotic nodules, some of which are siderotic, can be identified, and elastic tissue fragments are also impregnated by the pigment. Foreign-body giant cells containing elastic fragments are seen in the alveolar spaces and elsewhere in the parenchyma. There are few inflammatory cells, and they are observed in the alveolar wall or the peribronchial and perivascular spaces, often associated with histiocytes containing haemosiderin pigment. Mastcells and eosinophils are sometimes prevalent.

## *Goodpasture's Syndrome*

Goodpasture's syndrome is a rare condition characterized by pulmonary haemorrhages and acute glomerulonephritis. The disease has a predilection for

young adults, and males are predominantly affected. The condition has also been recorded in infants and children.

The clinical symptoms closely resemble those of idiopathic pulmonary haemosiderosis but, in addition, the patients present with proteinuria and haematuria, indicating renal involvement. They may present with pulmonary disease only, especially when the condition is in its acute phase. In such patients antiglomerular basement membrane antibody is helpful in diagnosis. An influenza-like infection often precedes the symptoms, but the aetiological factors are many and varied. The course of the disease is variable and depends on the stage, but it often has a rapidly fatal outcome. The disease has been described in children with sickle cell disease (Albelda et al. 1985; Travis et al. 1987; Bonsib and Walker 1989; Travis et al. 1990; Harrity et al. 1991; Rosenblum and Colvin 1993).

Macroscopically, the lungs are heavy and there are subpleural haemorrhages in the acute stages, but later reddish-brown firm areas are found. The cut surface shows numerous old and recent haemorrhages scattered throughout the lung. Microscopically, the alveolar spaces are distended, filled with erythrocytes and macrophages laden with haemosiderin pigment. Fibrin strands can be identified by special stains or immunofluorescence. The alveolar wall is oedematous, generally thickened, and may be infiltrated in some cases by few inflammatory cells, mainly lymphocytes with few plasma cells and histiocytes. Polymorphonuclear leucocytes are rare. The alveolar epithelial cells are hyperplastic, cuboidal or even multilayered. Scattered foci of alveolar wall necrosis are occasionally observed and vasculitis has been reported. The histology is variable and by no means specific. Arteritis, when present, may be suggestive of periarteritis nodosa or some form of hypersensitivity reaction, and thus make diagnosis difficult. Immunofluorescent staining for immunoglobulins reveals the presence of extensive fluorescence for IgG and $\beta_1$c on the alveolar basement membrane and capillary basement membrane as a linear almost continuous pattern. Similar patterns are also observed on the glomerular basement membrane and portions of Bowmans capsule (see p. 473).

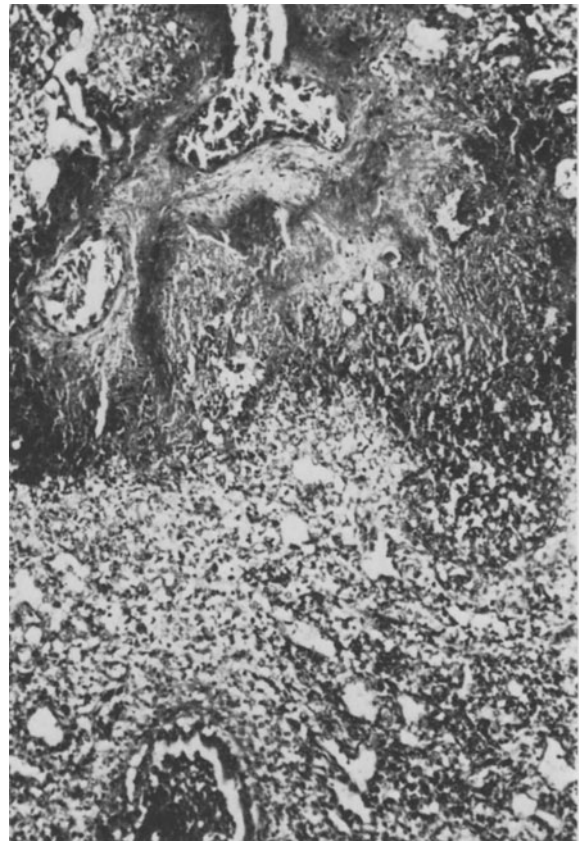


**Fig. 7.60.** Aspiration pneumonia due to aspiration of gastric juice, causing necrosis of the pulmonary parenchyma (*left*). (H&E, × 60)

## *Aspiration Pneumonia*

Although considered a rare condition, aspiration pneumonia may be more prevalent than is readily admitted. The condition may often go unrecognized and be incorrectly diagnosed as some other disease. The pulmonary lesions depend largely on the material inhaled, the quantity and the time elapsing between the episode(s) and medical examination.

*Gastric secretions or contents* may be inhaled into the lungs and may be the cause of severe respiratory insufficiency, occasionally resulting in death of the patient. Inhalation of gastric contents in infants and children is more likely to occur among those who suffer with dysphagia, diaphragmatic hernias, gastro-oesophageal reflux, or pyloric or oesophageal stenosis; in mentally retarded, wasted and debilitated children; in certain comatose states and during or after general anaesthesia; and in any condition associated with repeated vomiting.

When pure gastric secretion, with its high hydrochloric acid content, is inhaled into the lung, oedema results immediately with stasis, followed by widespread haemorrhage. Destruction of the tracheobronchial mucosa ensues, and within hours a diffuse inflammatory reaction occurs in the pulmonary parenchyma. The lesions contain few or no bacteria and are caused by the action of the hydrochloric acid on the lung tissue (Fig. 7.60).

In mild cases there is usually consolidation, which finally resolves, leaving mild pulmonary fibrosis; in severe cases there may be abscess formation. The lungs may eventually become fibrosed, with significant changes in pulmonary function.

In instances in which the gastric secretions are mixed with foreign material (partially digested food), the pulmonary lesions depend largely on the quantity of foreign material aspirated and on whether the process is acute or chronic. In the acute stage the lesions are non-specific, and the only indication of the pathogenesis is the presence of food particles (vegetables, meat, etc.) identifiable in histological sections. In chronic aspiration, there is often a foreign body giant cell reaction, some cells containing particles of foreign material.

Numerous microorganisms (including saprophytic anaerobes) are commonly associated with aspiration of foreign material. Abscesses are quite common in the lungs of these patients. The right lung is most often involved, and principally the lower segment of the right upper lobe and superior segment of the right lower lobe. The presence of saprophytic organisms can cause putrefaction of the lung tissue, giving it a characteristic foul odour (Awe et al. 1966; Cameron et al. 1967; Sladen et al. 1971; Bartlett et al. 1974a; Kaplan et al. 1978; Nelson 1984).

*Exogenous Lipid (Lipoid) Pneumonia.* This occurs when oily substances of different chemical natures are inhaled or aspirated into the lower respiratory system. The oily substance may be of vegetable, animal or mineral origin, and the tissue reaction produced will vary according to the lipids involved. Vegetable oils generally produce little or no pulmonary reaction; animal oils, which are rapidly hydrolysed to give fatty acids, produce necrosis of the tissue with a severe inflammatory reaction. Mineral oils, which are not hydrolysed but emulsified, produce little or no necrosis but do lead to extensive fibrosis.

Lipoid pneumonia is more common among infants and old people but may be observed at all ages. In childhood the disease is usually associated with the intake of cod liver oil, oily nasal sprays or drops, and mineral oils used as laxatives. It is also the result of repeated inhalation by infants of milk or milk products, resulting in severe respiratory distress, and can lead to severe bronchopneumonia. The condition is more common in debilitated or mentally retarded infants, especially those affecting swallowing, palatal or cough mechanisms, and also in cases of anorexia nervosa. It has also been reported in fire eaters and in patients employing excessive quantities of lip gloss. The condition has been documented in many patients in countries where there is practice of ethnic customs or habits particular to their societies. Deposits of fat droplets have also been described in pulmonary arteries, capillaries, macrophages, lymphatics and regional lymph nodes, especially in infants or children who have received intravenous fat emulsions (Levene et al. 1980; Shulman et al. 1987; Brown et al. 1994; Spickard and Hirschmann 1994).

The pulmonary lesions are described as diffused (infantile) and localized (adult type). The lesions are generally located in the lower segment of the upper and middle right lobes and/or the apical segments of the lower right and/or left lobes. However, both lungs may be involved to varying degrees.

The clinical manifestations are often misleading, and the radiological patterns are non-diagnostic. Lipophages or free lipids may be recovered from the sputum, and macrophages laden with lipid droplets may be seen in material from bronchial washings. Macroscopically, the area involved is fairly well delimited, heavy and firm. It is often grey or yellowish in colour, with a thickened pleural or significant pleural adhesion, and enlarged hilar lymph nodes may also be yellow. Microscopically, the lesions are variable, depending on the oily substance involved. The alveoli may be distended and filled with macrophages with a clear cytoplasm (foam cells) and occasionally free fat globules. The macrophages may be slightly positive with PAS or negative, light blue with Sudan black B, and orange with oil red O stains. The alveolar wall can be thickened, somewhat congested, and oedematous. The inflammatory reaction is also variable. When there is secondary bacterial infection, both the alveolar spaces and alveolar wall contain polymorphonuclear leucocytes and lymphocytes, with few plasma cells. When the pneumonitis is due to animal or mineral oils, the inflammatory reaction is more intense and there is active remodelling of the alveolar walls, which show varying degrees of thickening. In the chronic stages there is diffuse fibrosis with emphysematous blebs and/or bronchiectasis, the latter due largely to elastic tissue degeneration of the walls of the bronchi and bronchioles. The lesions usually progress to the mural stage of fibrosing alveolitis. Foreign-body giant cells can be observed in the chronic stages.

*Endogenous Lipid (Lipoid) Pneumonia.* This is the result of the accumulation of lipid substances, principally cholesterol and its esters, in the alveolar spaces, as a result of their liberation from damaged alveolar cells and bronchiolar epithelium. The condition is usually observed in cases of bronchial obstruction, most often by a malignant or chronic inflammatory process with lung tissue damage. It has also been described with secondary pulmonary hypertension, certain drugs (amiodarone), fat emboli, lipid storage

disorders and immune deficiency states. Macroscopically, the lesion is golden yellow, and histologically cholesterol crystals are numerous within macrophages and giant cells, and there are few among the cellular debris, hence the name *golden* or *cholesterol* pneumonia.

The lesion can be distinguished from exogenous lipoid pneumonia by special histochemical techniques. The macrophages in the alveolar spaces, rich in fine fat droplets, are strongly PAS-positive after amylase digestion; they stain intensely with oil red O, black with Sudan black, and are birefringent under polarized light.

Because of its various clinical presentations, macroscopic appearance and histological and ultrastructural features, endogenous lipoid pneumonia is now considered by some authors as one of the phases making up the spectrum of *alveolar proteinosis*. They may have a common pathophysiological basis – alteration of pulmonary surfactant metabolism in which repeated gastro-oesophageal reflux plays an important role (Verbeken et al. 1989; Fisher et al. 1992; Spickard and Hirschmann 1994).

*Pulmonary Alveolar Proteinosis (Idiopathic Alveolar Phospholipoproteinosis).* The rare condition of pulmonary alveolar proteinosis (PAP) is characterized by the accumulation in the alveolar spaces and bronchioles of large amounts of an amorphous material rich in lipids and proteins, leading to severe respiratory insufficiency. There is a male predominance.

The symptoms of PAP are non-specific and variable. They may regress spontaneously or proceed to progressive pulmonary insufficiency, and sometimes death if not adequately treated. The radiological pattern is not diagnostic for the condition, and pulmonary function tests are suggestive of a restrictive type of disease.

Although the aetiology of PAP is unknown, it has been considered as a form of lung response to a variety of agents, but two types are now recognized: a primary form of unknown aetiology, and a secondary form reported in association with tuberculosis and neoplasms often with bronchial obstruction in the lung as well as a number of mycotic, viral or parasitic agents. *Nocardiosis* is by far the most prevalent among these infections. *Aspergillosis*, *cryptococcosis*, *mucormycosis*, *candidosis*, *cytomegalic inclusion pneumonitis* and *pneumocytis* have also been reported, but less frequently. In childhood the condition is very often associated with some form of immune abnormality or haematological disorder, and has also been reported in siblings, suggesting a genetic disorder of autosomal recessive inheritance, for example lysinuric protein intolerance. It has also been documented in patients with AIDS.

Primary PAP is now considered a familial congenital condition most often in full-term infants who present with the respiratory distress syndrome at birth or shortly thereafter. These infants are resistant to all forms of intensive-care treatment, and death ensues within days or weeks later. The condition may be observed in siblings and both sexes may be affected. It has been shown recently that in the majority of cases there is an abnormal expression of SP-B gene product with little or no staining for SP-B, while SP-A, SP-C and SP-D show increased staining. In one case, however, the pattern was different suggesting that although the disease is related to a dysfunction of surfactant apoproteins, it may be heterogeneous and more than one gene, and/or other mechanisms, may be involved (deMello et al. 1994; de la Fuente 1994).

Extensive research on the amorphous material in the alveolar spaces has shown that it is quite heterogeneous and complex, composed of insoluble lipids, proteins and carbohydrates with large quantities of cellular debris, macrophages and granular pneumocytes (type II). The lipid concentration is several times that observed in normal lungs or in other pathological conditions and is composed principally of phospholipids. The proteins are largely surfactant apoproteins (A, B, C, D) associated with immunoproteins from the serum. The other constituents are disintegrating granular pneumocytes and macrophages with various types of inclusion body, including lamellar bodies tubular myelin and several other structures such as membraneous vesicles, electron-dense bodies and amorphous material (Gilmore et al. 1988; Rubinstein et al. 1988; Verbeken et al. 1989; Fisher et al. 1992; Parto et al. 1993).

The excessive production of surfactant, or its accumulation as a result of impaired removal or combination of both abnormalities, may be implicated in the pathogenesis of the condition or an alveolar macrophage catabolic defect. A defect in the processes during the formation of tubular myelin must also be considered (Ruben and Talamo 1986; Zijlstra et al. 1987; Gilmore et al. 1988).

Macroscopically, the lungs are enlarged and firm with consolidated areas. The cut surface is moist, revealing yellowish-grey zones alternating with dark red areas. Microscopically the alveolar spaces and bronchioles are distended with an abundant quantity of amorphous eosinophilic granular material in which cellular debris is associated with varying numbers of granular pneumocytes at different stages of disintegration and numerous macrophages (Fig. 7.61). The alveolar wall is not altered and shows no inflammatory reaction. It is mainly lined by cuboidal or flattened type II pneumocytes.

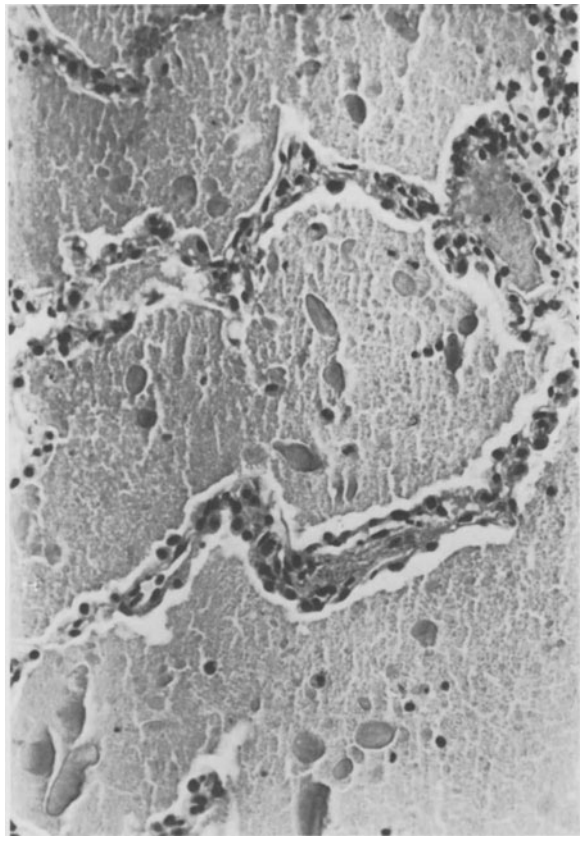


**Fig. 7.61.** Alveolar lipoproteinosis with distended alveoli full of an eosinophilic proteineous material. Absence of inflammatory reaction. (Courtesy of Dr Bozic) (H&E, × 225)

The intra-alveolar granular material, like that observed in endogenous lipid pneumonia, is strongly PAS-positive even after amylase digestion, and is metachromatic when stained with toluidine blue, and stains black with Sudan black B. Under polarized light, there are numerous doubly refractile crystals, mainly cholesterol. The macrophages also contain large quantities of this lipoprotein material in their cytoplasm, as shown by special stains and ultrastructural studies. Surfactant apoprotein labelling both in lung tissue sections and BAL fluid is of considerable importance in differentiating primary (uniform, diffuse labelling) from secondary (focal, patchy labelling) in this condition. In chronic stages of the disease pulmonary fibrosis ensues.

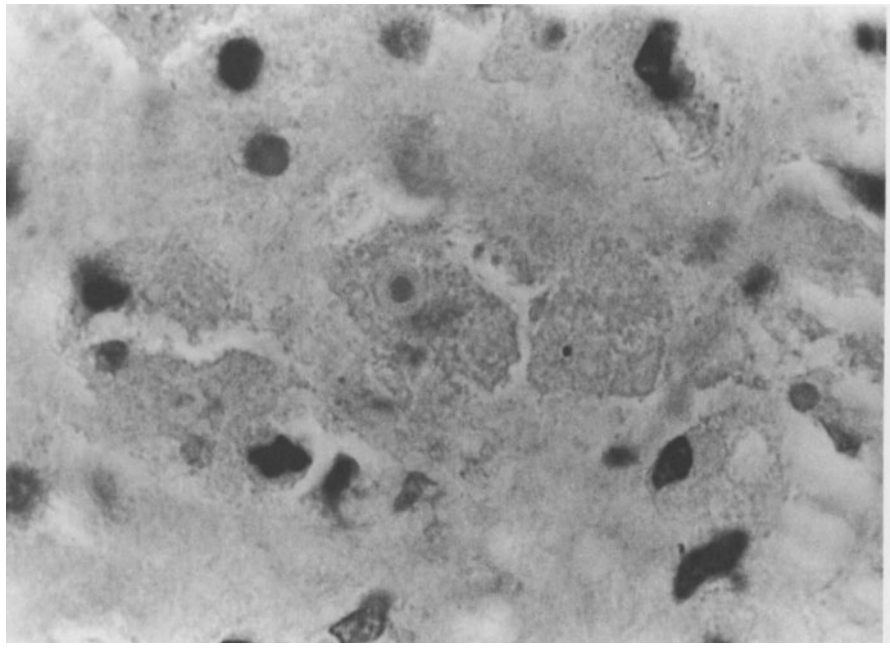
*Malakoplakia*, a rare granulomatous inflammatory disease of unknown aetiology, may occasionally involve the lung (Byard et al. 1990) and must be distinguished from these lesions. It is characterized by the presence of large foamy histiocytes containing the characteristic intracytoplasmic Michaelis–Gutmann inclusions which are strongly PAS-positive, diastase resistant and also positive with Von Kossa and Prussian blue stain (Fig. 7.62).

*Kerosene Pneumonia.* Kerosene is a by-product of petroleum and is the cause of a significant form of pneumonitis in childhood. Kerosene is widely used for fuel and lighting in many developing countries or areas not supplied with gas or electricity. Infants and children may inadvertently swallow the substance, which causes severe irritation of the stomach followed by severe vomiting and regurgitation. Under these circumstances the substance can be inhaled and reach the distal airways, producing a diffuse necrotizing pneumonitis. Death may follow due to pulmonary, gastrointestinal or central nervous system effects.

In the respiratory system, there is an immediate, marked, diffuse oedema with congestion of the lungs. This is followed by widespread necrosis of the pulmonary parenchyma, with a severe inflammatory response. The exudate is rich in fibrin and polymorphonuclear leucocytes, and fibrin may line the alveolar ducts and bronchioles. The lesions are generally bilateral, but are more frequently located in the right lung than in the left. There is extensive necrosis of the bronchial and bronchiolar epithelium, accompanied by infiltration of the walls by mononuclear cells and polymorphs. Necrosis of the peripheral vessels with haemorrhages is common, and in the healing stages the vessel walls are usually markedly thickened and sclerosed. Patients who survive show extensive pulmonary fibrosis (Press et al. 1962; Nouri and Al-Rahim 1970).

*Powder Aspiration.* Occasionally, the aspiration of powder can cause respiratory distress in infants under 2 years of age; a relatively high mortality rate is associated with this condition. The accidental aspiration of talcum powder (rich in zinc oxide) causes bronchial obstruction, and after a relatively long latent period produces massive bronchitis with bronchiolitis. Oedema and congestion of the lungs may precede the inflammatory reaction. When there is complete obstruction of the bronchial lumen atelectasis ensues, and if death does not occur compensatory emphysema follows (Pfenninger and D'Apuzzo 1977; Motomatsu et al. 1979).

Pulmonary talc granulomatosis is not an uncommon finding in chronic adolescent drug addicts who administer narcotics mixed with talc or mixtures containing talc by intravenous injection. Pulmonary thromboembolism may be another complication which can lead to severe pulmonary hypertension. Electron-probe radiography may be of help in identifying the elements involved, as may X-ray



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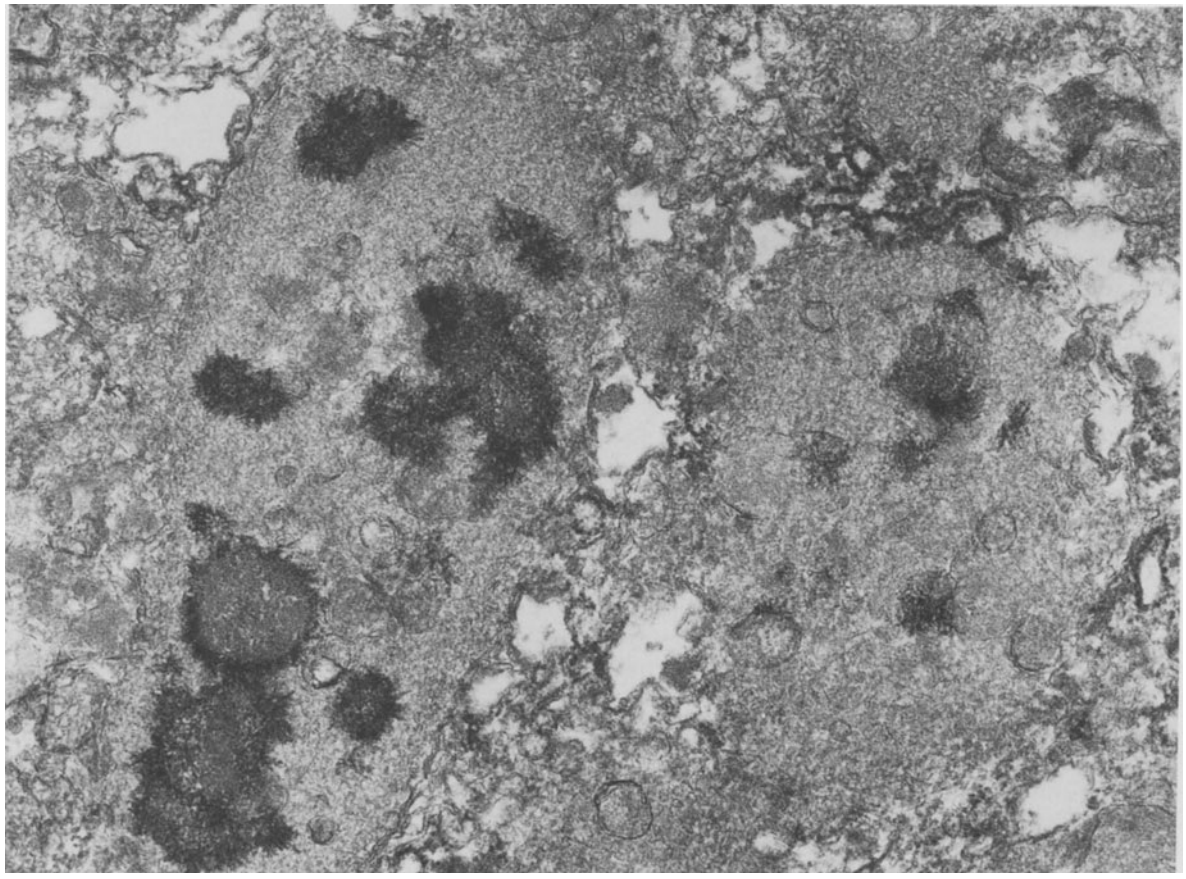


b

**Fig. 7.62.** **a** Malakoplakia showing alveolar macrophages containing classical cytoplasmic Michaelis–Gutmann inclusions. (PAS, × 340) **b** Ultrastructure of Michaelis–Gutmann inclusions of variable form and size. (Electron micrograph, × 39 000)

diffractometry and scanning electron microscopy (Berner et al. 1981; Ghadially et al. 1984).

*Starch in the Lungs.* Dain et al. (1970) have described the presence of starch granules in the lungs of newborns treated with positive pressure ventilation for respiratory distress syndrome, chiefly hyaline membrane disease. They suggested that the source of the starch was the sterile gloves used in handling the endotracheal catheter. The substance was not usually recognizable with routine haematoxylin and eosin stains, but exhibited the characteristic maltese crosses when observed under polarized light. The starch granules may be free in the alveolar spaces or intermingled with the bronchial and alveolar exudate in the early stages. After a few days they are found in macrophages or in foreign-body giant cells within the alveoli.

## *Paraquat Lung*

Paraquat (1,1-dimethyl-4,4-dipyridilum dichloride) is a herbicide. When ingested, it causes a rapid onset of diffuse pulmonary fibrosis, with severe respiratory failure and death within weeks of intake. The substance may be swallowed accidentally by children, and it can be taken up through the skin.

Paraquat causes ulceration of the mouth and upper gastrointestinal tract, with vomiting and diarrhoea. These symptoms are accompanied by acute renal failure, jaundice and increasingly severe dyspnoea with cyanosis, leading to marked pulmonary insufficiency within days. Cerebral symptoms may also be present. Paraquat is poorly absorbed by the intestine, and is excreted in the urine. The substance is metabolized in the liver and reaches the lungs from the circulation. It causes hepatic necrosis and damage to the adrenals, myocardium and renal tubules. It accumulates in the lungs and muscles.

The pulmonary lesions and the prognosis in general seem to depend on the serum concentration of the active substance ingested. In general, pulmonary fibrosis occurs over a variable period, preceded by pulmonary oedema and haemorrhage. Surfactant is lacking, following destruction of the type II cells or granular pneumocytes, which seems to follow that of the type I cells (Bus and Gibson 1984; Skillrud and Martin 1984; Fukuda et al. 1985; Hirai et al. 1985; Martin and Howard 1986; Matters and Scandalios 1986; Bismuth et al. 1987; Vale et al. 1987) mainly due to the toxic effect of superoxide species.

Macroscopically, the appearance depends on the time lapse after the intake of the substance, because little if any of the substance reaches the lungs by way of the bronchial tree. Within the first 4 days the lungs are heavy congested and oedematous. Later they show areas of consolidation, or appear solid with a somewhat rubbery consistency, and within weeks they take on a honeycomb appearance.

Microscopically, in the first few days, there is congestion with marked oedema of the alveolar wall. Interalveolar and intra-alveolar haemorrhages are conspicuous. The alveolar spaces are filled with a fibrinous exudate containing desquamated alveolar lining cells (some of which are undergoing degeneration) and numerous macrophages and erythrocytes. Polymorphonuclear leucocytes and aggregates of lymphocytes and plasma cells may be seen. Hyaline membranes are prominent, lining both the alveolar spaces and the distal airways. There is destruction of the epithelial lining of the distal bronchi and bronchioles. Some of these lesions may be due to oxygen therapy. In later stages of the disease there is a very active, but variable, organization of the intra-alveolar exudate. The alveolar spaces are invaded by an active fibroblastic proliferation resembling the pattern of growth seen in a tissue culture. These cells have been referred to as "profibroblasts" and are probably myofibroblasts. Finally the alveolar space is obliterated by a fibrous process with collagen, reticulin fibres and a few elastic fibres. There is also a rich capillary network, and a few foci of chronic inflammatory cells are present. Simultaneously a similar process takes place in the alveolar wall, and eventually it is impossible to distinguish the alveolar wall from the alveolar space. As the lesion progresses there is continuous remodelling of the alveolar structure leading to diffuse pulmonary fibrosis, with an increase in collagen and reticulin fibres; and, although the lesions have a heterogenous distribution, they may resemble honeycomb (Takahashi et al. 1994).

The bronchial and bronchiolar walls are also affected by the fibrotic process, and can be obliterated. Bronchiectasis may occur, and other bronchi and bronchioles may show epithelial proliferation and hyperplasia. Small pulmonary arteries show thickening and fibrosis of their walls. Arterioles show distinct muscular hyperplasia.

## *Lung Abscesses*

There are many possible causes of lung abscesses in childhood, including bronchial obstruction by an inhaled foreign body, by an inspissated mucus plug, or by infected material associated with some surgical procedure in the mouth or oropharynx. The majority of abscesses are located in the lower segments of the

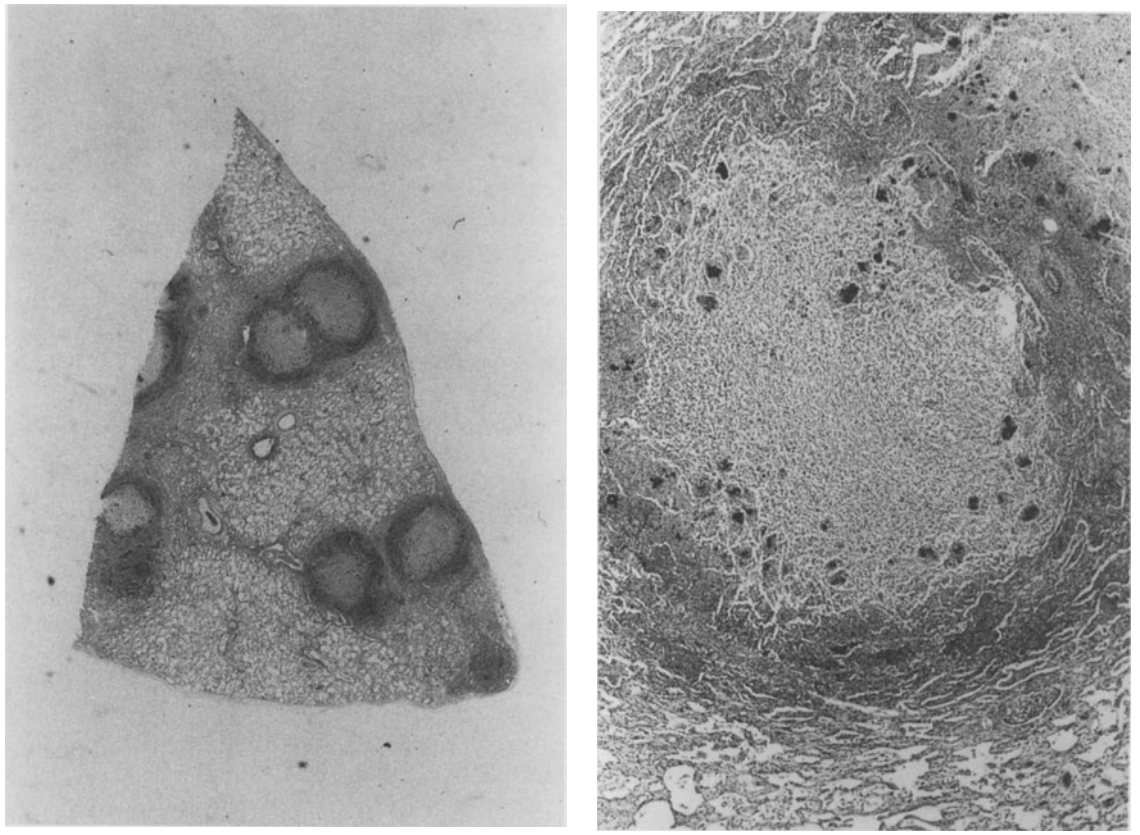


**Fig. 7.63.** **a** Multiple microabscesses, confluent in places, and formation of a pseudocapsule of compressed parenchyma. (H&E, ×4) **b** Abscess showing a necrotic central zone filled with neutrophils. Bacterial colonies are located in the necrotic areas, peripheral zones and lung parenchyma. (H&E, × 50)

upper lobes or the upper segments of the lower lobes, and they are more often found on the right side. Whatever the source, the material is generally accompanied by a mixture of both anaerobic and aerobic microorganisms. Necrosis of the bronchial wall takes place at the site of obstruction, with active bacterial proliferation and a marked inflammatory exudate. The related distal airways collapse and become necrotic, and a purulent inflammatory reaction develops. The centre of the lesion undergoes liquefaction, and partial drainage may take place by way of the eroded bronchus (Fig. 7.63).

In chronic cases the wall of the abscess is surrounded by a dense fibrous layer bordered by granulation tissue. The cavity may be lined with a squamous epithelial lining in continuity with the epithelial lining of the bronchus.

Lung abscesses may also be associated with bacterial pneumonia or bronchopneumonia. *Staphylococcus aureus*, which is known to cause extensive tissue destruction, is by far the most common offender. Other microorganisms commonly responsible for such lesions are *Klebsiella pneumoniae*, *Pneumococcus* and *Pseudomonas*.

Septic emboli may affect the lung in septicaemia, and in childhood an important cause is thrombophlebitis around an indwelling catheter. *Staphylococcus aureus* is most often associated with these abscesses (Pryce 1948; Mark and Turner 1968; Bartlett et al. 1974b; Brook and Finegold 1979; Asher et al. 1982).

## *Granulomatous Lesions*

Numerous agents are known to produce granulomatous lesions in the lung (Ulbright and Katzenstein 1980). In certain instances special staining techniques make it possible to identify the agent responsible for the lesions within the granulomas, and infectious causes including *Mycobacterium tuberculosis*, coccidioidomycosis, aspergillosis, blastomycosis and histoplasmosis are discussed elsewhere.

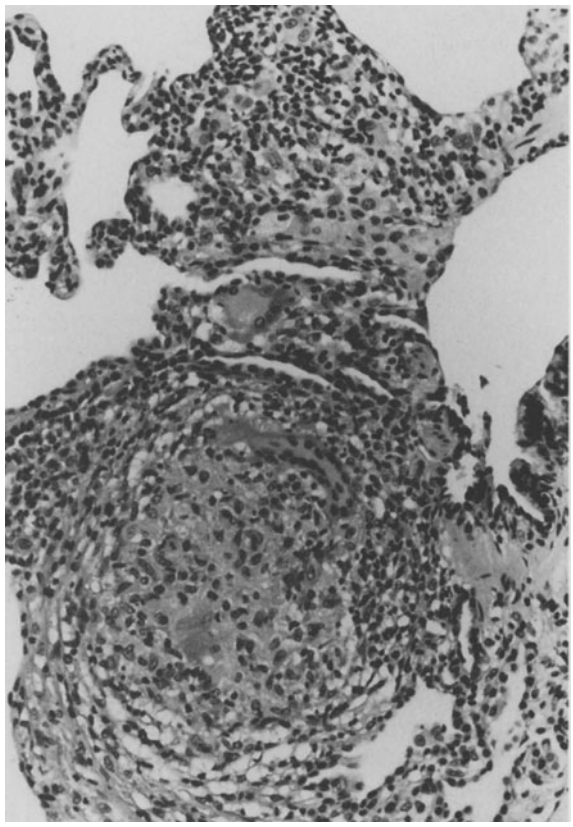


**Fig. 7.64.** Non-caseating granulomatous lesions in a male patient. The adjoining lung tissue is involved in the process. (H&E, × 125) (Courtesy of Dr J. Briner).

## *Sarcoidosis (Boeck's Sarcoid, Besnier–Boeck–Schaumann Disease)*

Sarcoidosis has a worldwide distribution, the incidence varying from one area to another, and even within the same region. The clinical and radiological features of the condition have been extensively documented. The disease usually presents as a slowly progressive chronic inflammatory reaction affecting the skin (erythema nodosum), lungs, lymph nodes and uveal tract. Spontaneous healing may occur after a long period. Less frequently, the disease also affects many other organs or systems (heart, kidney, skeletal muscles, central nervous system, bone and joints – arthralgia). The symptoms are often variable and may go unnoticed; in many instances the disease is an accidental finding on routine chest radiographs or at autopsy.

A female predominance has been indicated by some authors, but others claim that there is an equal male-to-female ratio. The disease has been reported in families, and there are strong indications that it is more common among negroes. Sarcoidosis is not common in childhood; it is prevalent among children in their teens and rare in infants below 5 years of age.

Descriptions of the disease in childhood show no features distinguishing it from the condition seen in adults. Severe obstructive vascular lesions in the lung may lead to pulmonary hypertension. Elevated serum angiotensin-converting enzyme activity is a common finding in active disease, and immunohistological staining for this enzyme will reveal positive staining of epithelioid and giant cells within the granulomata. BAL fluid as well as lung and skin biopsies show an increased ratio of helper/suppressor (cytotoxic) T cells, suggesting an increased activity of cell-mediated immunity; alveolar macrophages show a reduced capacity to produce arachidonic acid metabolites. Ultrastructural studies have revealed tadpole-shaped structures in granulomatous lung disease, consistent with sarcoidosis (Smith et al. 1983; Dewar et al. 1984; Allen et al. 1986; Pattishall et al. 1986; Van Maarsseven et al. 1986; Viale et al. 1986; Bachwich et al. 1987).

## *Chronic Granulomatous Disease*

Chronic granulomatous disease is characterized by severe, chronic and recurrent infections, usually involving the skin, lung, liver, bone and lymph nodes, but any organ can be involved. The first clinical symptoms generally appear during the first year of life, and the disease may run a fatal course before the age of 10 if inadequately treated.

The condition occurs in a number of forms, with variable modes of inheritance, but a recessive mode of transmission is most commonly found (see p. 635).

In the lung, pneumonia or bronchopneumonia with abscess formation may be present. There may also be numerous non-caseating granulomas with foreign-body giant cells, together with many histiocytes containing lipid pigments (Fig. 7.64). On the periphery of the lesions are lymphocytes, and occasionally central necrosis can be identified containing few polymorphonuclear leucocytes. Fungal infection is not an uncommon complication (Landing and Shirkey 1957; Holmes et al. 1966; Thompson and Soothill 1970; Schlegel 1975; Dilworth and Mandell 1977; Moskaluk et al. 1994).

## *BCG Granulomas*

Generalized BCG infection is a rare complication of BCG vaccination in childhood. It has been reported to have a fatal outcome in some instances, mainly among infants with some form of immune abnormal-

ity. Inadequate preparation of the vaccine may be responsible for the condition. The lung, the intestine and bones, as well as other organs, are the site of numerous granulomas, which may show caseation. Groups of acid-fast bacilli can be observed in the epithelioid cells and/or in the necrotic areas (Passwell et al. 1976; Genin et al. 1977; Torriani et al. 1979; Hanimann et al. 1987).

### *Rheumatic Pneumonitis*

There is still no unanimity as to whether the pulmonary lesions observed during the course of acute rheumatic fever are specific for the condition, although they are generally referred to as rheumatic pneumonitis.

The radiological images of diffuse pulmonary consolidation are in no way specific, and the morphological features may resemble those seen in a number of other conditions. Associations with the clinical aspects of the disease are the only guiding factors. The lesions are generally observed in cases presenting with severe valvular involvement or fulminant pancarditis (Massumi and Legier 1966; Grunow and Esterly 1972).

Macroscopically, the lungs are oedematous, large and heavy. They are often reddish in colour and rubbery in consistency. Microscopically, the lesions are widespread. The alveolar spaces are filled with a thick fibrinous exudate, which is haemorrhagic in some areas. There are fibrin strands and a few desquamated alveolar cells with some macrophages containing pigment granules. Scattered groups of inflammatory cells, chiefly mononuclear cells, are often present. Some of the alveolar spaces and alveolar ducts are lined with thick bands of hyaline membranes. The alveolar walls are thickened, oedematous and congested. Intraseptal and intra-alveolar haemorrhages are constant findings. Alveolar wall necrosis has been observed in a number of cases, and in many of these fibrinoid necrosis of the wall of the distal branches of the pulmonary artery is present (Fig. 7.65). In advanced stages there are signs of organization of the intra-alveolar exudate, characterized by the penetration of fibroblasts. The epithelium of the distal bronchi and bronchioles may show evidence of necrosis, and their walls may be infiltrated by a few mononuclear cells or surrounded by peribronchial lymphoid tissue. During regeneration there is metaplasia of the bronchial epithelium.

These lesions are in no way specific, and there is still some doubt as to whether they are primary lesions. Aschoff nodules are not identified with this pneumonitis.

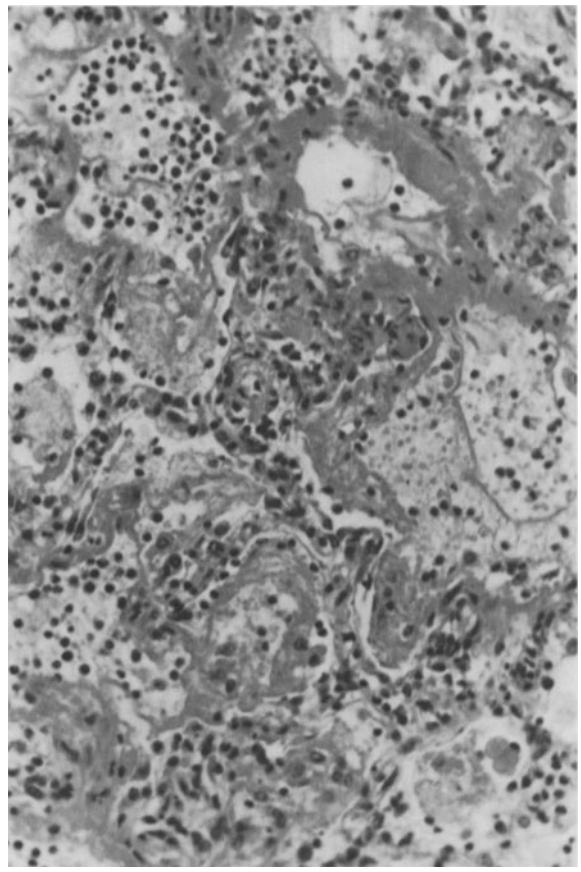


**Fig. 7.65.** Rheumatic pneumonitis in a 12-year-old boy with extensive pancarditis and severe valvular lesions. (H&E, × 120)

### *Pulmonary Alveolar Microlithiasis*

Pulmonary alveolar microlithiasis is a relatively rare pulmonary condition of unknown aetiology. The disease has a worldwide distribution and has been described in all races. All ages are affected, and it has been documented at birth. It was formerly thought that adults were principally affected, but the disease seems to be more prevalent among children in Japan. it has an equal distribution between the sexes or perhaps a slight male predominance. There is a familial tendency, suggesting that some genetically determined disturbance of metabolism may be present, although there are no abnormalities of the metabolism of calcium and phosphorus in these patients. The disease is often asymptomatic, and may be discovered at routine chest radiography or when dyspnoea of unknown origin is investigated. Surveys in families may reveal new cases. There is generally a significant discrepancy between the severe radiographic changes and the absent or mild clinical symptoms. Pulmonary function tests give variable

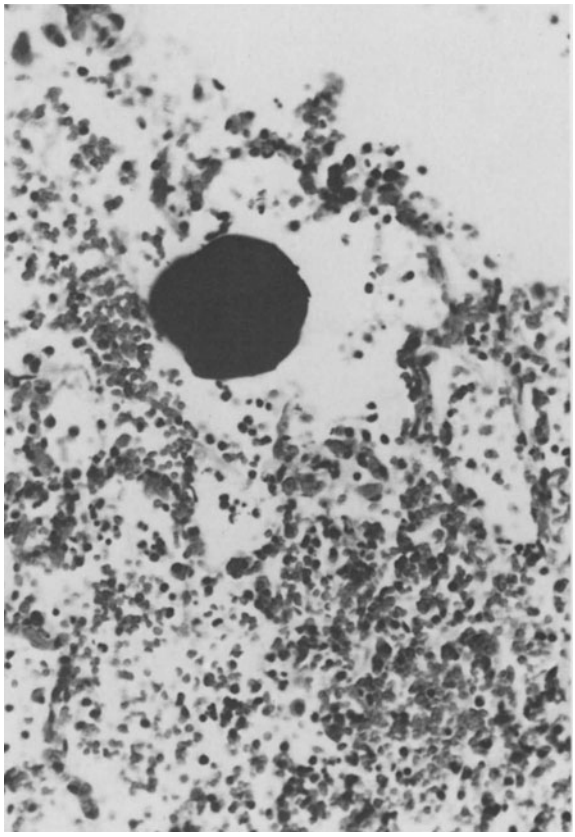


**Fig. 7.66.** Pulmonary microlithiasis in a girl of 2 years 5 months. (Courtesy of Dr C. Bozic) (H&E, × 180)

results, depending largely on the stage of the disease, its distribution and the extent of the lesions. Evolution is also quite varied, extending over a period of a few months or years or even several decades as the pulmonary function deteriorates. There is no satisfactory treatment (Sears et al. 1971; Onadeka et al. 1977).

Macroscopically, the lungs are much heavier than normal, very hard in consistency, and reddish in colour. The lesions may predominate in the lower lobes, but all lobes can be affected. Microscopically the lesions vary with the stage of evolution. In the early stages the alveolar spaces are filled with psammoma-like bodies, which are darker in their centres. These bodies are strongly PAS-positive, and stain intensely for calcium with the von Kossa stain. They are known as calcospherites, and are different from the *corpora amylacea* associated with chronic congestive heart failure or pulmonary fibrosis. The alveolar wall shows little or no histological modification at this stage (Fig. 7.66). Later the calcospherites not only appear as laminated bodies with radial striations, but also show extensive calcification, with ossification occurring at the periphery. The alveolar walls are thickened, fibrosed, disrupted in places, and infiltrated by mononuclear cells (chiefly monocytes and lymphocytes). Giant cells may be observed in some instances, and calcospherites may be incorporated within the thickened alveolar wall or situated in the proximity of small vessels.

The condition can now be diagnosed by BAL and/or transbronchial biopsy. Ultrastructural studies have shown that the psammoma-like bodies are composed partially of hydroxyapatite crystals; chemical analyses have shown that calcospherites are composed mainly of calcium phosphates with small quantities of iron and fat. Surfactant apoprotein has been demonstrated immunohistochemically as a component of these structures (Cale et al. 1983; Mascie-Taylor et al. 1985; Akino et al. 1990; Ucan et al. 1993).

Pulmonary calcification can also be observed in children undergoing long-term haemodialysis and/or peritoneal dialysis. The diagnosis is not readily made on chest radiographs, but can be confirmed by radionuclide pulmonary scintigrams (Drachman et al. 1986).

## *Pulmonary Alveolar Septal Calcinosis*

Pulmonary alveolar septal calcinosis, an uncommon metastatic pulmonary calcification, may be observed in the paediatric age group and often goes undiagnosed clinically. The condition is observed as a complication in many clinical settings such as primary or secondary hyperparathyroidism, chronic renal insufficiency, vitamin D intoxication, milk alkali syndrome, and primary or secondary conditions of the haematopoietic and lymphatic systems (Northcutt et al. 1985; Sinniah et al. 1986). Histologically, there is focal or diffuse calcification of the alveolar septa as well as the vessels and bronchial walls (Fig. 7.67). Emphysema may be prominent in areas, and metastatic calcifications are often seen in other organs such as the heart, kidney, liver and gastrointestinal tract.

## *Pulmonary Arterial Calcification*

Calcification of the pulmonary arterial trunk and/or its branches has been documented in cases of idiopathic arterial calcification in newborns and infants. The lesions may be multifocal and are more prominent in the main and secondary branches (Fig. 7.68). Thromboses, sometimes calcified, are frequent findings, often associated with pulmonary infarcts (Carles et al. 1992b; Beguin 1994). Recently, in utero pulmonary arterial calcification in monochorionic twins has been described (Popek et al. 1993).

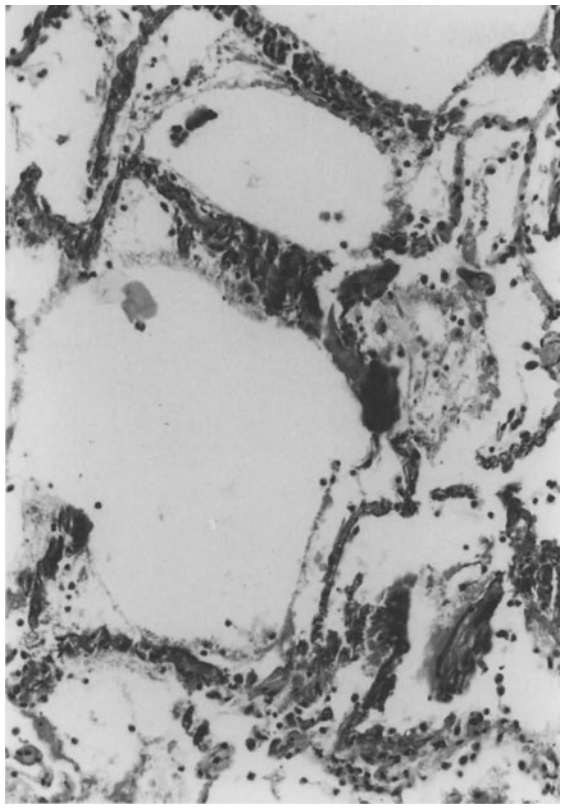


**Fig. 7.67.** Alveolar septal calcinosis involving also pulmonary arteries in a case of severe chronic renal failure. (H&E, ×50) (courtesy of Dr J. Briner)

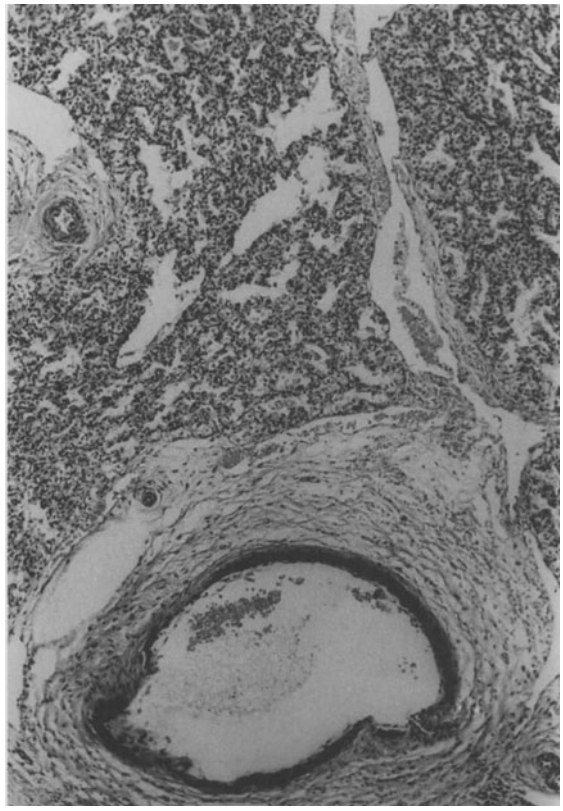


**Fig. 7.68.** Pulmonary arterial calcification at 32 weeks' gestation in a male fetus with diffuse arterial calcification and calcified thrombus resulting in extensive infarction in several organs, including the lungs. (H&E, × 20)

# Bronchial Lesions

## Intrauterine (Congenital) Bronchiolitis Obliterans

Bronchiolitis obliterans is not uncommon. It has been described in numerous conditions and is associated mainly with various inflammatory reactions of the respiratory tract. Bacterial and viral infections are chiefly responsible for the lesions, and all age groups can be affected.

Intrauterine bronchiolitis obliterans is rare, and only a few reports are recorded. The aetiology is not known; however, it is generally accepted that intrauterine infection may be responsible for the lesions (Sir 1962; Nezelof et al. 1970; Sueishi et al. 1974; Rosen and Gaton 1975).

Macroscopically, the lesions are observed in premature infants or in the immediate neonatal period. The lungs are diffusely consolidated and heavy, and appear dark red with some haemorrhagic areas. Microscopically, there are areas of intrauterine pneumonia. Some of the alveoli are filled with squames accompanied by polymorphonuclear leucocytes. Occasional giant cells with vacuolated cytoplasm may be present. The distal bronchi and bronchioles are obliterated by polypoid masses consisting of granulation tissue projecting into the lumen from an area of damaged wall. Some of the lesions show various degrees of organization, with fibroblasts, collagen fibres and hyalinization being present. Vascular penetration from the base of insertion of the polyp may be apparent (Fig. 7.69).

The bronchial epithelium shows signs of regeneration, sometimes with squamous metaplasia; in other areas there is evidence of hypersecretion. The bronchial wall and surrounding tissues are infiltrated with polymorphonuclear leucocytes and some lymphocytes. The lesions of bronchiolitis obliterans in children are similar to those observed in adults (Hardy et al. 1988; Marinopoulos et al. 1991).

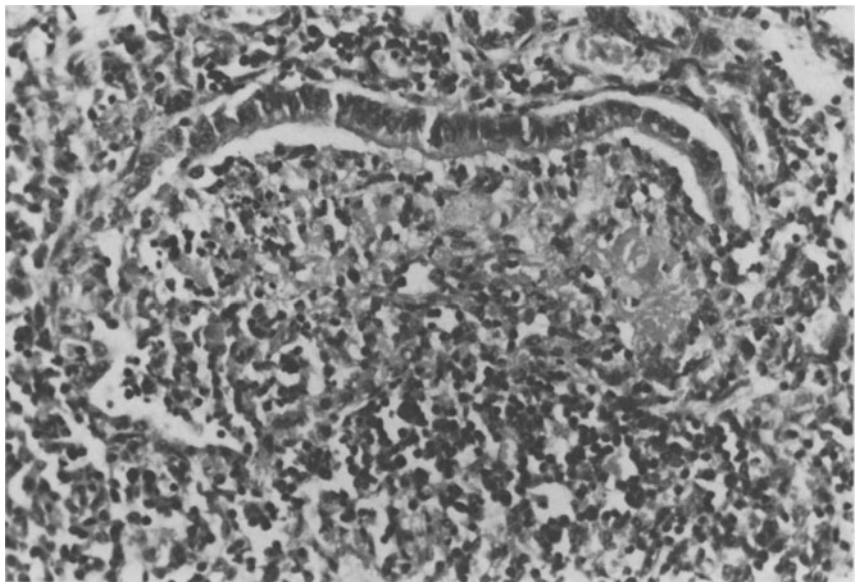


**Fig. 7.69.** Intrauterine bronchiolitis obliterans in a newborn infant who lived for 12 h. (H&E, × 180)

## Bronchitis and Bronchiolitis

Inflammation of the lower respiratory tract is extremely common in infants and children, and all levels of the bronchial tree are liable to injury by the agent or agents responsible. Bacterial infections have been considered to be responsible for most of the lesions; however, it is now well established that viral infections are the major cause of bronchitis and bronchiolitis in childhood and the principal cause in infancy. Secondary bacterial infections may be associated with viral infection.

The development of better tissue culture techniques and specific serological tests have resulted in the isolation and identification of the various viruses responsible for the lesions. Direct and indirect immunofluorescence antibody techniques and in situ hybridization have proved useful in the diagnosis of viral infections.

*Respiratory syncytial virus* infection is the commonest in infants during the first 2 years of life. Other viruses known to cause these illnesses include *adenovirus*, *parainfluenza viruses*, *influenza A and B viruses* and *measles virus*. Other organisms, e.g. *Bordetella pertussis* and *Mycoplasma pneumoniae*, can produce severe infections. Physical, chemical or gaseous injury to the distal airway may be responsible for similar lesions.

The clinical symptoms are in no way specific for any one virus. There is generally an upper respiratory tract infection with a catarrhal reaction, raised temperature, cough, dyspnoea and wheezing. Diffuse interstitial pneumonia is sometimes present, and hyperventilation may be observed. The radiological patterns are non-specific.

Although the mortality rate is relatively low for many of these infections, morbidity can be high and repeated infections may be responsible for significant abnormalities of lung function. The physiopathological features of the condition have been well documented and it has been shown that the respiratory difficulties are related principally to the obstruction of the distal bronchi and bronchioles. The severity of the lesions in infancy depends largely on the anatomical structure of the lung at that age. Other factors, including immunological ones, may also be important (Aherne et al. 1970; Becroft 1971; Gardner et al. 1973; Simpson et al. 1974; Kaul et al. 1978; Wohl and Chernick 1978).

Microscopically, the bronchial and bronchiolar mucosa show patchy or widespread ulceration with necrosis of the epithelium. Signs of regeneration are characterized by the proliferation of epithelial cells, which become cuboidal. The walls of the distal airways are congested, oedematous and infiltrated by mononuclear cells. The lumen may be partially or completely obliterated by an exudate composed of cellular debris, fibrin, some mucus and a large number of inflammatory, principally mononuclear, cells. Patchy atelectatic foci may be present when obstruction is complete. There is also peribronchial and peribronchiolar inflammatory infiltration extending from the walls of the affected airways into the surrounding pulmonary parenchyma, resulting in localized zones of pneumonia (Fig. 7.70).

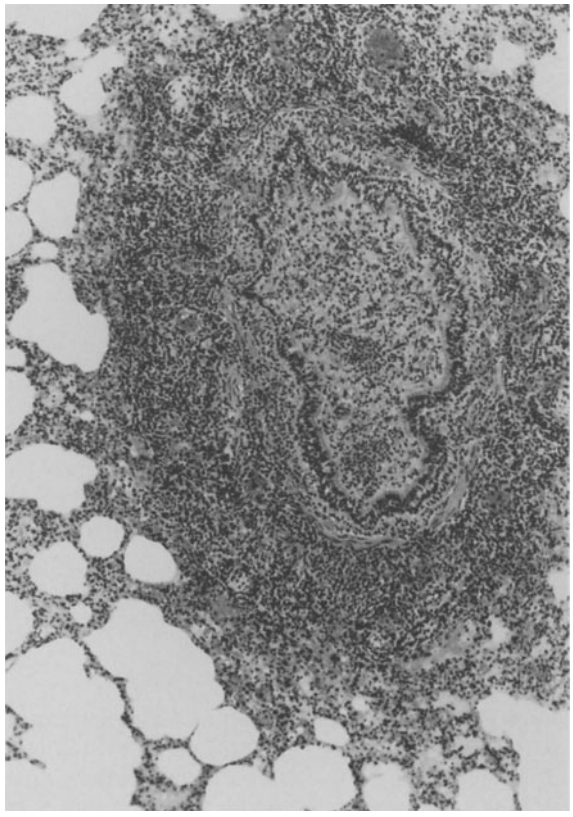


**Fig. 7.70.** Acute bronchitis with diffuse inflammatory infiltration of the entire bronchial wall and the surrounding lung parenchyma. The bronchial lumen is filled with numerous neutrophils in the mucus plug. (H&E, × 20)

These lesions are common to the majority of viruses involved; however some viruses (adenovirus, influenza A virus) may produce severe residual lung damage with extensive destruction of the distal bronchi and bronchioles and obliteration of the lumen. In chronic disease there is organization of the intraluminal material, resulting in bronchiolitis obliterans. In this case there is vascular granulation tissue initially, which progresses to fibrous scarring with partial or complete obliteration of the affected distal bronchi and bronchioles.

## Bronchiectasis

Bronchiectasis is not uncommon in infants and children, and it is often associated with chronic and frequently repeated lung infections. There is much controversy and debate on the aetiology and pathogenesis. Some authors maintain that there are two forms of the disease: *congenital*, related to malformations in the bronchial wall as a result of absent or deficient cartilage plates, and *acquired*, associated with acute respiratory infection resulting in severe pulmonary damage with sequelae. Most authors consider the lesions to be acquired in most cases, with only a very small percentage attributable to congenitally determined defects. In support of this hypothesis, it is true to say that bronchiectasis has never been observed at birth or in the neonatal period. In almost all cases, including most of those described as congenital, the condition has developed after a period of acute bronchitis or pneumonia during infancy (generally within the first 2 years of life). Obstruction (extrinsic or intrinsic) of a bronchus or of bronchi may also be associated with the development of bronchiectasis.

The disease begins in infancy, often during the first or second year of life, after an attack of what is generally referred to as bronchitis or pneumonia. In well documented cases, the association of the development of bronchiectasis with syncytial virus, adenovirus, influenza virus, measles, pertussis or *Mycoplasma pneumoniae* infections has been established. Sequelae of tuberculosis infection with parenchymal destruction and fibrosis could be responsible for the disease, as well as aspergillus and other fungal infections.

Bronchiectasis may affect only a small percentage of infants or children after viral epidemics, and is not apparent immediately after infection. Host as well as immunological factors probably play an important role in the development of the lesions. The stage of lung development may be an additional factor.

The disease may be progressive, with a high incidence of chronic and frequent recurrent infections of the respiratory tract. Cough is often associated with wheezing. Haemoptysis is a variable finding. In the chronic stages of the disease, dyspnoea occurs on exercise, and finger clubbing may be seen. Radiography, and principally bronchography, is important in establishing the diagnosis, and repeated examinations may be necessary to follow its evolution.

Bronchiectasis has been observed in association with certain syndromes, notably the unilateral hyperlucent lung (Swyer–James syndrome or McLeod's syndrome), a clinical and radiological entity that was once thought to be congenital but is now recognized as being a sequela of various insults to the lung, including viral infections, tuberculosis, *Mycoplasma pneumoniae*, foreign-body aspiration, ingestion of hydrocarbons, and radiotherapy. It is also an integral part of Kartagener's syndrome, a condition with familial tendency, in which bronchiectasis is associated with situs inversus, chronic paranasal sinusitis and ciliary dysfunction. The Williams–Campbell and Stevens–Johnson syndromes may also be associated with bronchiectasis, and to a lesser extent the

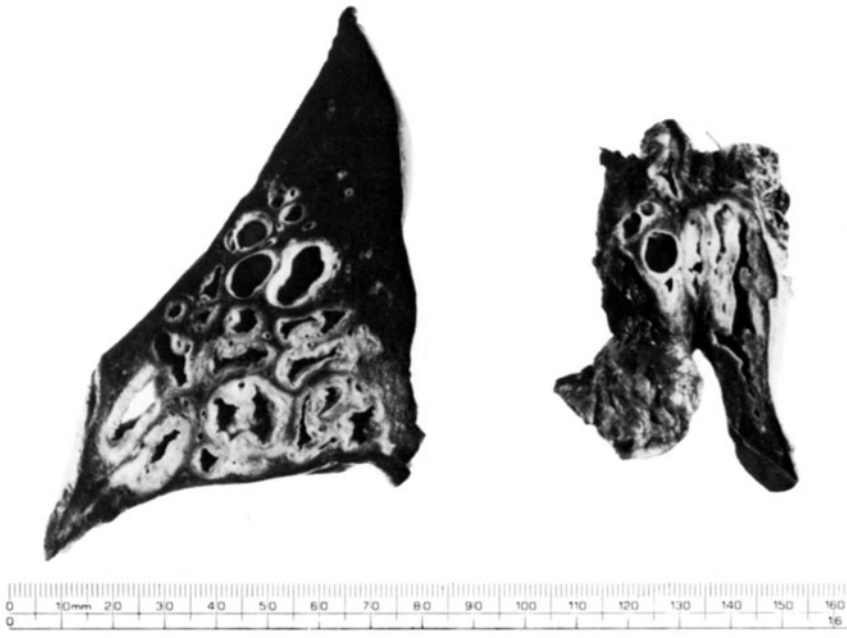


**Fig. 7.71.** Significant bronchiectasis in an 18-month-old infant. (Courtesy of Dr C. Bozic)

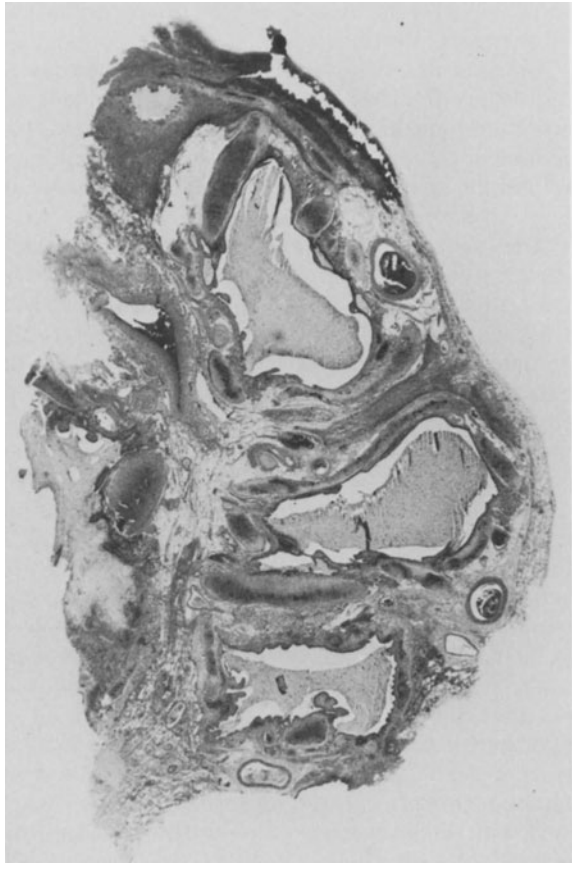


**Fig. 7.72.** Bronchiectasis with fibrosis and chronic inflammation of the wall containing lymphoid follicles. (H&E, × 25)

Ehlers–Danlos and Marfan syndromes. Bronchiectasis has also been described with certain immunodeficiency states, as well as pulmonary injury after ingestion or inhalation of certain toxic substances or drugs. It has recently been described in an infant after intoxication by inhalation of acrolein (Barker and Bardana 1988; Mahut et al. 1993; Nikolaizik and Warner 1994).

Bronchiectasis is associated with small-airway disease, with obstruction of the involved airways and bronchiolitis obliterans. Atelectasis of the parenchyma distal to the obstruction is often encountered. There is hypersecretion of mucus distal to the occlusion, with subsequent infection leading to abscess formation and foci of pneumonia. Destruction and weakening of the bronchial walls occur proximal to the lesions, with profound remodelling of the surrounding tissue as a result of chronic inflammation. Subsequently there is dilatation of these bronchi, due in part to the negative intrathoracic pressure and the traction exerted by the surrounding fibrous tissue. The basic physiopathological problem in bronchiectasis is one of perfusion/ventilation associated with airtrapping.

Macroscopically, dilated bronchi may be cylindrical in form or show saccular dilation, or both. The changes are often severe and widespread. They may be unilateral or bilateral, and may affect one or more lobes or segments. The left lower lobes, the lingula, the right middle lobe and the posterior basal segments are most frequently involved (Fig. 7.71). Microscopically there is marked dilation of the

bronchi, and mucus with an inflammatory exudate may occupy the lumen. The bronchial epithelium is variable from one area to another, being generally hyperplastic and lined with tall columnar cells whose cytoplasm contains large amounts of mucus. In other areas squamous metaplasia may be conspicuous. The wall is infiltrated by a dense mononuclear infiltrate, which is more prominent in the submucosa. In some instances the inflammatory reaction is overwhelming and consists of lymphocytes extending into the surrounding parenchyma. Well developed lymphoid follicles with prominent germinal centres can be seen in this infiltration (Fig. 7.72). The submucosal glands are usually atrophic but some glands may be dilated, containing large quantities of mucus englobing inflammatory cells. The bronchial muscular layer is hypertrophied in some places and atrophied in others. Fibrous bands may encircle, dissect or completely replace the muscle bundles. The peribronchial elastic fibres are fragmented and disorganized. In some instances, especially in areas where the dilatation is saccular, the bronchial wall is completely destroyed and the regenerated epithelium, which may show squamous metaplasia, covers a layer of granulation tissue with no other supporting structures.

The bronchial arteries show extensive hypertrophy of their walls; the pulmonary arteries in the neighbourhood may have been destroyed in the inflammatory process or may show severe endarteritis. As a result there is shunting of blood by bronchopulmonary anastomoses, leading to pulmonary hypertension.

In cases of congenital bronchiectasis there is hypoplasia of the involved lung. The inflammatory reaction is scanty and the cartilage plates are poorly developed. The most striking feature is marked hypertrophy of the bronchial muscle, which appears disorganized. Lymphangiectasis may be an associated abnormality.

## Cystic Fibrosis of the Pancreas (Mucoviscidosis)

Cystic fibrosis (CF) may be manifest at birth as intestinal obstruction resulting from meconium ileus, but pulmonary involvement is by far the most serious complication of the disease, and is responsible for the high morbidity and mortality rate. Pulmonary manifestations may be recognized during early infancy but may go unnoticed until adolescence or adult life.

The patients usually present with repeated chronic pulmonary infections, which become progressively more severe. Areas of bronchopneumonia may never resolve as other areas are affected. These pulmonary infections are often accompanied by severe pansinusitis, with or without nasal polyp formation. *Staphylococcus aureus* has been considered to be responsible for most infections, but recently it has been appreciated that other organisms are more important as the patients grow older, and that viruses may participate in promoting and/or maintaining secondary bacterial infections. *Pseudomonas aeruginosa* is the organism most often incriminated in these cases, and *Haemophilus influenzae* is also known to play an important role. Although the non-mucoid strains of *P. aeruginosa* seem to colonize the airways in the first instance, the mucoid strains predominate later during the course of the infection. They are associated with the active inflammatory and obliterature process in the lung, leading to bronchiolitis obliterans and alveolitis. The antigen produced from antigen–antibody complexes, which can be localized in many tissues in these patients, including the lung, and it is considered that some of the pulmonary damage may result from these complexes. *P. aeruginosa* also produces a number of enzymes (esterase, protease), which are capable of acting locally on the pulmonary parenchyma as well as the host defence mechanisms. *P. cepacia* also creates important problems among these patients, and mycoplasmal and other infections may be aggravating or complicating factors in most of these infections. Gastro-oesophageal dysfunction in the form of gastro-oesophageal reflux is now known to contribute significantly in the severity of the pulmonary lesions as well as hypersensitivity to *Aspergillus fumigatus*, which may be responsible for an allergic bronchopulmonary reaction in these patients.

The frequent, repeated and chronic pulmonary infections are the result of obstruction of the bronchial tree, in particular the distal airways, by a thick, viscoid mucus or mucopurulent secretion maintained largely by *P. aeruginosa*. Subsequently bronchopneumonia, bronchiectasis and bronchiolectasis, loss of lung elasticity and diffuse emphysema (more important in the upper lobe), with modifications in pulmonary function tests, develop. Immune complexes seem to play a minor role in the pathogenesis of the lesions. Pulmonary hypertension follows, leading to right ventricular hypertrophy associated with biventricular scarring. In most cases hypertrophy of the carotid body is found. Pneumothorax may be a troublesome complication. The ultrastructure of cilia in both nasal and bronchial epithelium in patients with cystic fibrosis may show various non-specific anomalies, including compound cilia, excessive cytoplasmic matrix, abnormal number and arrangement of microtubular doublets and rippled ciliary contours, abnormalities which have also been described in chronic inflammation of the respiratory tract (Sturgess and Turner 1984; Baltimore et al. 1989; Elborn and Shale 1990; Hoiby and Koch 1990;

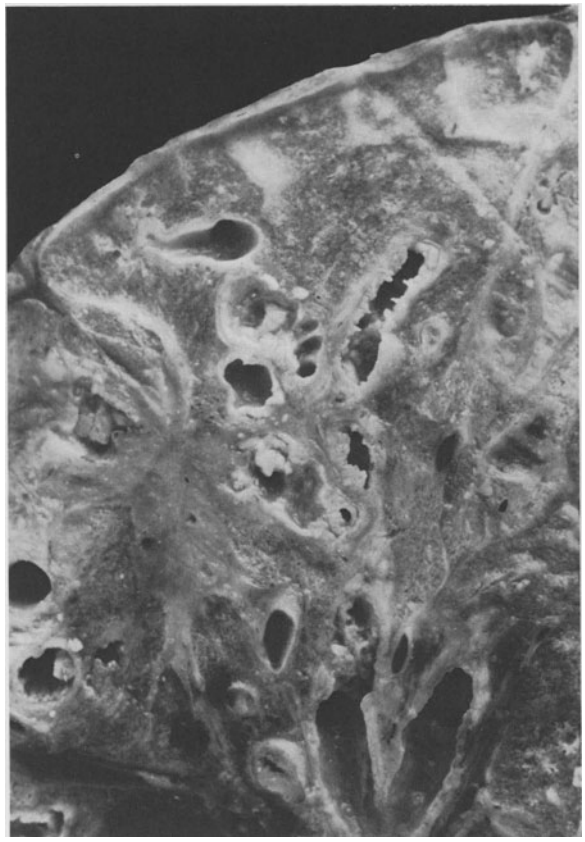


**Fig. 7.73.** Bronchiectasis and pulmonary consolidation in a 14-year-old boy with cystic fibrosis.

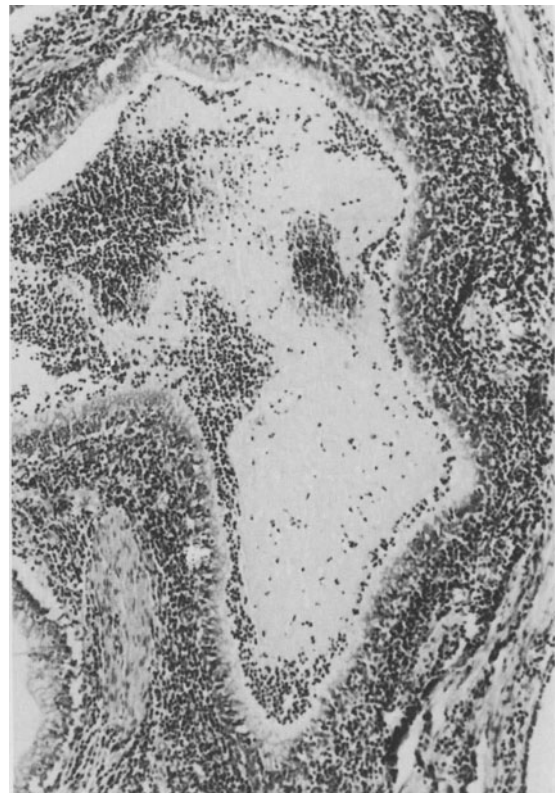


**Fig. 7.74.** Bronchiectasis in cystic fibrosis. Increased number of goblet cells and mucopus obliterating the lumen. The inflammatory exudate contains numerous polymorphonuclear leucocytes. (H&E, × 35)

Gustafsson et al. 1991; Betancourt and Beckerman 1992; Fuller et al. 1992; Tizzano and Buchwald 1992; Tomashefski et al. 1992; Tizzano 1993; Mrouch and Spock 1994).

Macroscopically, the entire lung is involved. It is large, reddish and emphysematous, especially at the anterior margin, while the posteriorly sited lobes may show areas of atelectasis. There are areas of consolidation, and the bronchi and bronchioles are dilated, containing abundant viscous mucus (Fig. 7.73). Abscesses are sometimes present. Microscopically, the most striking feature is diffuse bronchial and bronchiolar dilatation, with the lumen completely obliterated by adherent mucus plugs. The inspissated mucus secretions contain numerous inflammatory cells, chiefly polymorphonuclear leucocytes, but including eosinophils, lymphocytes and some plasma cells. Bacteria can be identified by gram staining.

The lesions involve the distal bronchi and bronchioles initially. These become obliterated, causing atelectasis of some of the pulmonary parenchyma distal to the obstruction. The larger bronchi are then affected, and as a result of repeated episodes of chronic inflammation there is partial destruction of the bronchial wall with cylindrical dilatation of the involved segments. These changes may involve one or more lobes, or the entire lung (Fig. 7.74).

The bronchial mucosa is covered by hypertrophic and hyperplastic mucus-secreting cells whose cytoplasm is filled with a strongly PAS- and Alcian blue-positive mucus. Squamous metaplasia of the mucosa may be observed in places. The bronchial wall is generally fibrous and thinned, but isolated areas show signs of muscular hypertrophy. Chronic inflammatory cells are abundant.

Areas of bronchopneumonia are found, and resolution of these zones leaves alveolar wall scarring. Abscesses are sometimes observed in the vicinity of affected airways or within the parenchyma. Most of the lung outside these areas is markedly emphysematous. Pulmonary arteries show the changes associated with moderate pulmonary hypertension.

# Lung Involvement in Metabolic Diseases (see also p. 837–866)

The lung is known to be involved in Gaucher's disease, an inherited deficiency of the enzyme glucocerebrosidase whose gene is located on chromsome I. The many mutations observed in this disease are responsible for the various clinical presentations and manifestations that exist in this condition. The lungs may be involved in all forms. In the more severe cases there may be large areas of consolidation, and an entire lobe or lung may be involved; in others the lesions are limited. Histologically, there is a diffuse infiltration of the alveolar spaces by Gaucher cells and numerous histiocytes (Fig. 7.75). Alveolar walls may also be infiltrated by histiocytes and some Gaucher cells. Some of the distal bronchi and bronchioles may also contain these cells (Beutler 1992).

In other forms of sphingolipidosis (Niemann–Pick), pulmonary involvement is more common, however, and it has also been seen in Fabry's disease (Bartimmo et al. 1972; Martin et al. 1972). The pulmonary parenchyma shows consolidated areas in which the alveoli are filled with foam cells. Lung involvement has also been recorded in cases of gangliosidosis (Volk et al. 1975) and mucopolysaccharidosis (de Montis et al. 1972). Recently, pulmonary vascular obstruction has been described in association with cholesteryl ester storage disease in a 15-year-old girl (Michels et al. 1979).

# Tumours

Although primary lung tumours are uncommon in infancy and childhood, both benign and malignant tumours have been described in this age group. Metastatic tumours are more prevalent.

## Benign

### *Vascular*

*Haemangiomas* of the lung are extremely rare. Most of the lesions described as haemangiomas or angiomas of the lungs in infants and children are congenital developmental defects of the pulmonary vasculature, which are referred to under several synonyms: pulmonary arteriovenous fistulae or aneurysms, congenital arteriovenous varix and pulmonary haemangiomatosis.

A significant proportion of patients with these lesions present with coexisting vascular anomalies in other organs (mucous membranes, skin, brain), forming part of a more generalized syndrome of hereditary telangiectasia of the Rendu–Osler–Weber type. Familial occurrence has been recorded.

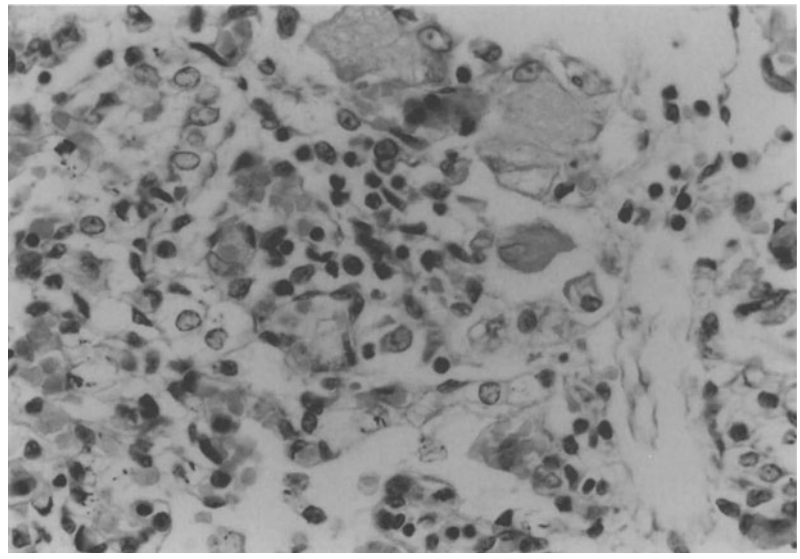
Vascular anomalies are generally located in the periphery of the lung or in the subpleural zones, and may involve extrapulmonary structures (mediastinum, pericardium, thymus and spleen). They are more common in the lower lobes, may present as localized structures, single or multiple, and are often bilateral with the appearance of either a low-grade neoplasm or a hamartomatous lesion. They may be the cause of primary pulmonary hypertension. An elevated incidence of cerebral abscesses has been reported among patients with these lesions (White et al. 1989; Galliani et al. 1992).

Microscopically, the lesions may resemble capillary or cavernous angiomas, the latter becoming distended as a result of large arteriovenous anastomoses (Fig. 7.76). These abnormal vessels are lined with flattened endothelial cells, and the structure of their walls varies, being arterial and venous in different areas.

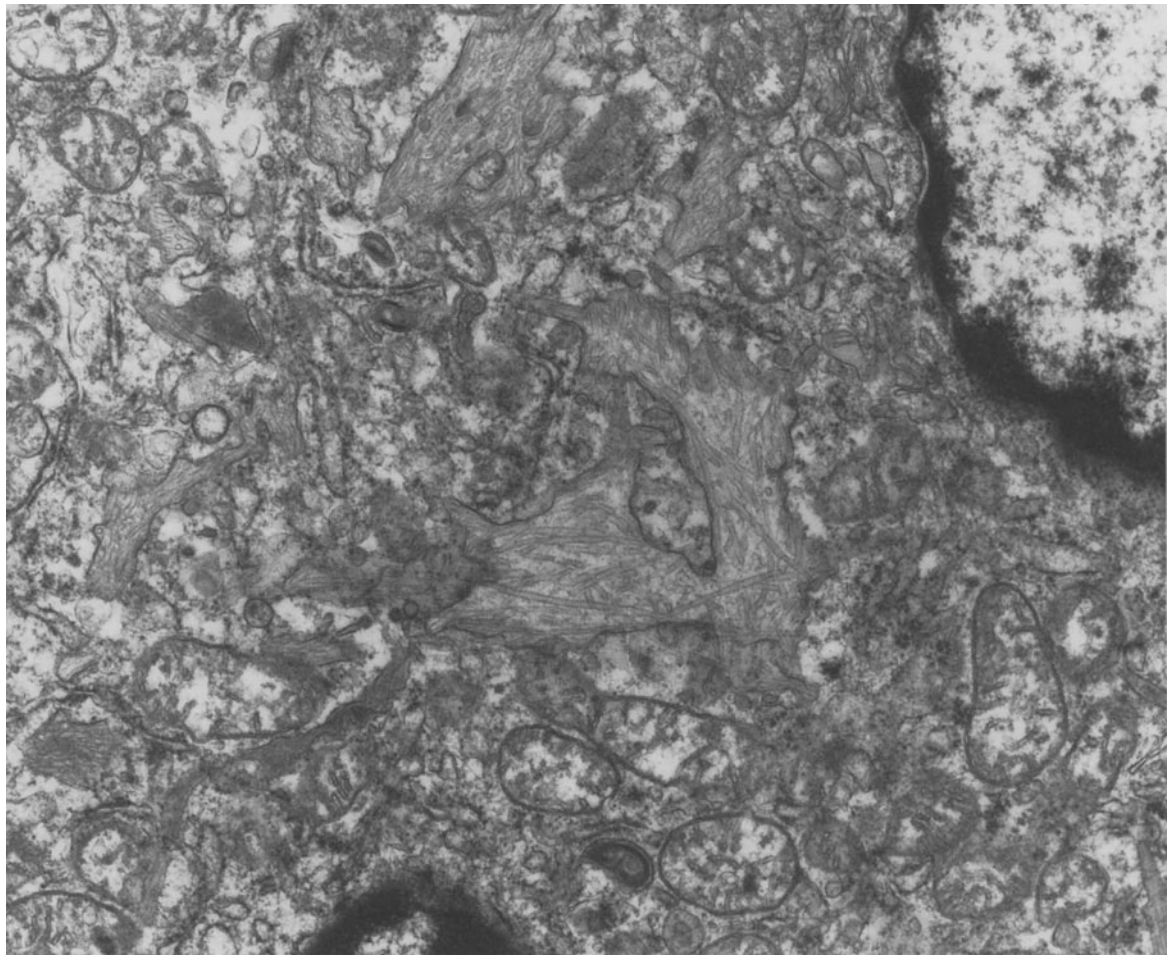
*Congenital alveolar capillary dysplasia*, also referred to as *congenital alveolar dysplasia*, is a developmental anomaly of the alveolar capillaries of the lung affecting full-term infants, and is among the causes of the syndrome of persistent fetal circulation (persistent pulmonary hypertension) in the newborn. The lungs, especially the lobes, are usually abnormal, accompanied by congenital pulmonary vascular abnormalities – mainly abnormal or malpositioned pulmonary veins and their branches. The lesion is characterized by a marked reduction in the number of alveolar capillaries and an increase in the thickness of the septa. The few capillaries are rarely in contact with the normal alveolar epithelium. The intra-acinar arterioles are thickened, muscularized and accompanied by large, abnormal, dilated veins. (Khorsand et al. 1985; Carter et al. 1989; Langston 1991). *Pulmonary acinar dysplasia*, another maldevelopmental process, in which there is an abortive development or arrest in the differentiation of the alveolar acini, has been reported (Rutledge and Jensen 1986).

*Sclerosing haemangioma* of the lung (Liebow and Hubbell 1956) is a circumscribed pulmonary lesion described in the literature under several synonyms (histiocytoma, fibroxanthoma, alveolar angioblastoma, mast-cell granuloma), depending on the histological patterns exhibited.

These lesions have been reported in children. They are often described in the lower lobes, but can be located in any lobe and occur mainly in the periphery of the lung. Most patients are asymptomatic and the



a



b

**Fig. 7.75.** **a** Gaucher cells and other macrophages in the alveolar lumen associated with few mononuclear cells. (H&E, × 300) **b** The lung in Gaucher's disease, showing the characteristic elements. (Electron micrograph, × 31 000)

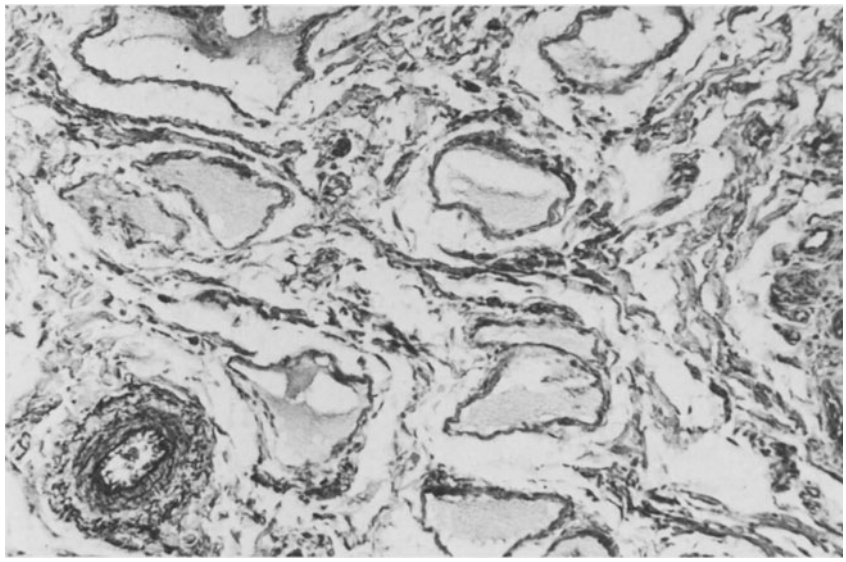


**Fig. 7.76.** Pulmonary arteriovenous shunt (pulmonary varix) in a newborn with cardiac malformation. (V6–Élastin, × 120)

tumours are discovered on routine chest radiography. Haemoptyses have been recorded as the most common clinical symptom.

The pathogenesis of the lesions is unknown and their aetiology remains obscure. Some authors still regard them as pseudoinflammatory reactions; others consider them to be vascular lesions in various stages of sclerosis with secondary epithelial proliferation, or as a proliferation of undifferentiated pulmonary epithelial and mesenchymal tissues with secondary changes, and yet others regard them as of mesothelial origin. These various morphological variations point to the great heterogeneity of the lesions: the different components may be variable in quantity in any given lesion. Recent ultrastructural studies have shown lamellar bodies within the lining cells similar to those observed in type II pneumocytes, and microvilli on the luminal surfaces of others. Immunohistochemical studies have confirmed that many of the lining cells are analogous to those of bronchiolar epithelial cells and type II pneumocytes and that they also contain surfactant apoproteins. Clara cells have also been identified among the type II pneumocytes. These recent findings have led some authors to consider these lesions as hamartomas, distinct from pulmonary histiocytomas. Although Haas et al. (1972) concluded from their observations that the lesions were primarily angiomatous in nature, Hill and Eggleston (1972) considered the primary lesions to be of epithelial origin with the other changes a secondary phenomenon. Recent immunohistochemical and ultrastructural findings would support the latter view; thus, some authors consider these lesions as hamartomas, distinct from pulmonary histiocytomas, and others have suggested "benign sclerosing pneumocytoma" or "type II pneumocytoma" as being more appropriate terms (Noguchi et al. 1986; Nagata et al. 1987; Yousem et al. 1988; Alvarez-Fernandez et al. 1989; Satoh et al. 1989).

Macroscopically, sclerosing haemangiomas are solitary, circumscribed, round or oval masses, firm or rubbery in consistency, yellow in colour, with tan or haemorrhagic areas. Multiple lesions, sometimes presenting as a principal mass with satellite nodules have been described, as well as bilateral tumours. Calcification and even ossification have been observed in some cases.

Microscopically, there may be papillary structures lined with alveolus-like mesenchymal cells, cuboidal and/or columnar in appearance, mainly at the periphery of the lesions. The supporting stroma is fibroblastic with some histiocytes, and contains many irregular dilated capillaries with an angiomatous appearance. In other areas the stroma is composed of numerous spindle cells separated by large bands of collagen. Hyalinization may occur in other regions, where the vessels may be seen as slit-like openings. Mitotic figures are few, and there is no cellular atypia. Evidence of both recent and old haemorrhage is seen. Plasma cells, lymphocytes and mast cells have been observed scattered throughout lesions of this type.

*Plasma-cell granuloma*, although a relatively uncommon tumour, is perhaps the most common benign tumour of the lung in childhood. The lesion, in which plasma cells predominate, must be distin-

guished from its malignant counterpart, the pulmonary plasmacytoma. Plasma-cell granuloma has been considered to be a postinflammatory pseudotumour, and some authors use the term "plasma-cell pseudotumour" when referring to the lesion. It has also been mistakenly called a fibroxanthoma, because of the presence of numerous fat-laden histiocytes, and has further been confused with sclerosing haemangioma and other fibrohistiocytic lesions.

The majority of plasma-cell granulomas have been reported in children, with apparently no predominance between the sexes. The youngest patient thus far was 13 months old, and there appears to be an increase in frequency with age. Although the aetiology is unknown, the condition is thought to be infectious in nature and it has been described in association with Q-fever pneumonia and *Mycoplasma pneumoniae* and *Coxiella burnetti* infections. Immunoperoxidase staining has shown the polyclonal nature of the plasma cells, indicating an inflammatory reactive process rather than one of a neoplastic nature. Clinically the condition is asymptomatic unless it produces obstruction of bronchi, causing dyspnoea. It is often discovered during routine chest radiography, and presents as a solitary circumscribed parenchymal mass or coin lesion. The prognosis is generally good, and surgery is the treatment of choice (Lebecque et al. 1987; Warter et al. 1987; Dardick et al. 1989; Anthony 1993; Haver and Mark 1994).

Macroscopically, the lesions are firm or rubbery in consistency, round or oval, and yellowish-white or grey in colour. They may appear brownish owing to haemorrhages, and occasionally show central necrotic zones. They may also contain fine granular calcification. The lesions are usually peripheral and intraparenchymatous, but may sometimes involve bronchi, causing obstruction.

Microscopically, the tumour is made up of mature plasma cells with some lymphocytes and mononuclear cells. Russell bodies may be conspicuous, but the plasma cells, immunohistochemically, are polyclonal. Polymorphonuclear leucocytes are occasionally observed. Histiocytes may be prominent, grouped together and located among fibroblasts arranged in whorls and supported by dense collagen bundles. Many of the histiocytes are laden with fat globules, giving the lesion a xanthomatous pattern. Mast cells are scattered throughout the tumour and some eosinophils may be present. Lymphoid follicles with germinal centres are sometimes visible. Iron pigment-laden macrophages may be prominent as a result of haemorrhages. The lesions may bulge into the adjacent alveolar spaces and may sometimes attain the bronchial and vascular walls, mainly venous, with intraluminal protrusions.

*Lymphangioleiomyomatosis* (lymphangiomyomatosis) is a rare clinicopathological entity with a worldwide distribution. The disease has been described almost exclusively in females of childbearing age, and rarely in males. Cases have been described before the age of 20 and the clinical symptoms often begin during childhood. The lesions are not confined to the lung, but may involve extrapulmonary structures, mainly the lymph nodes and lymphatics, but the uterus, ovaries and liver have also been documented. The condition has been reported in association with renal angiomyolipomas as well as with multiple soft tissue tumours and endocrine tumours, and this has led some authors to suggest the possibility that it may form part of the tuberous sclerosis complex; however, there are no proofs that the conditions are interrelated. Oestrogen and progesterone receptors have been documented on smooth muscle cells, which form part of the lesion, but their expression is variable from one case to another and depends somewhat on the techniques employed. In spite of these variations, hormonal therapy, among others, still remains the treatment of choice (Vincent et al. 1987; Colley et al. 1989; Berger et al. 1990; Cagnano et al. 1991; Ohori et al. 1991).

The clinical symptoms may go unrecognized for some time. The patients present with breathlessness, recurrent pneumothorax, and sometimes haemoptyses. Chylothorax is not an uncommon finding in this condition, and may be associated with chylous ascites. Pulmonary haemorrhages have also been recorded. The disease follows a relentlessly progressive course, with death from respiratory failure. The period over which this occurs is variable. Most patients affected die within 10 years of discovery; however, some have survived for more than 20 years.

Extensive hypertrophy and proliferation of smooth muscle in the wall of lymphatic vessels are the principal histological characteristics of the abnormality, but some authors have suggested that the proliferating cells in the lung may be derived from immature pluripotent myoid stromal cells or myofibroblasts. However, the cellular heterogeneity of the lesions would suggest one of two possibilities as proposed by some authors: either there are different degrees of differentiation from the same phenotypic cell line or there is coexistence of different cell types. Immunohistochemistry and molecular biology could be very instructive (Sherrier et al. 1989; Fukuda et al. 1990; Bonetti et al. 1991; Cagnano et al. 1991; Ohori et al. 1991; Bonetti et al. 1993; Matthews et al. 1993).

Macroscopically, the most characteristic picture is one of honeycombing of the entire lung, with enlarged hilar lymph nodes. Morphometric studies have shown abnormalities similar to those of centriacinar emphysema (Sobonya et al. 1985). The

pleura is thickened and the lymphatics are prominent and well defined. Microscopically the alveolar septa and other involved areas are diffusely thickened by proliferation and hyperplasia of smooth-muscle-like cells, some of which may form nodules about myoid stromal cells. The tumour cells stain variably with desmin, actin and vimentin, or in combinations. Some cells having epithelioid-like features have been shown to express melanoma-related antigens, which appear ultrastructurally as electron-dense membrane-bound granules. A tumour may therefore present various histological and immunohistochemical variations in different regions. The lesions may surround the lymphatics in the interlobular spaces (Fig. 7.77), the bronchial wall or the pulmonary vessels. When the veins are involved, venous obstruction may result. Intra-alveolar haemorrhages may follow, and numerous haemosiderin-laden macrophages may be observed in the alveolar spaces.

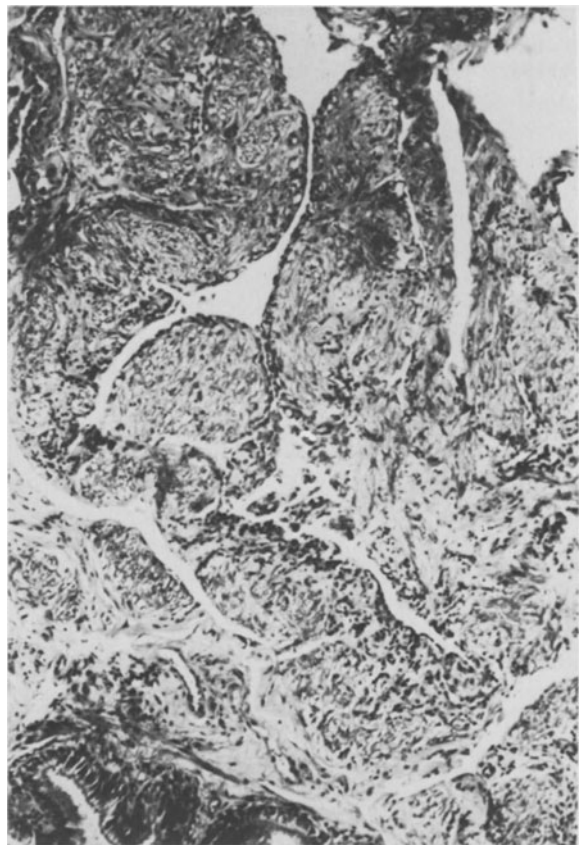


**Fig. 7.77.** Lymphangioleiomyomatosis from a female patient presenting with symptoms from the age of 11 years, with chylus effusion. (H&E, × 225)

## *Muscular*

Smooth- or striated-muscle tumours of the lung are exceedingly rare. *Leiomyoma*, the smooth muscle variant, may originate from the tracheobronchial tree or the lung parenchyma. In the tracheobronchial tree it may grow within the wall or protrude within the lumen forming a polypoid mass resulting in bronchial obstruction with distal bronchiectasis and secondary infection associated with haemoptysis, dyspnoea, fever and clubbing of the fingers. There is a female predominance. The tumours appear to originate from the smooth muscles of the bronchi or bronchioles or ultimately from the wall of the pulmonary vessels, and may be associated with cyst formation. Histologically, the lesions are characteristic of smooth-muscle tumours elsewhere; however, immunohistochemistry may be necessary to exclude carcinoids (Vera-Romàn et al. 1983; Uyama et al. 1988; Gotti et al. 1993; Kim et al. 1993).

Another group of smooth-muscle tumours is seen in young women of childbearing age and young men. There is much controversy over the many synonyms by which these lesions are known: "low-grade" leiomyosarcoma with malignant potential, the so-called benign metastasizing leiomyoma, fibroleiomyomatosis hamartoma, and more recently a specific entity composed of extrauterine smooth-muscle neoplasms with multifocal origin. Oestrogen and progesterone receptors have been demonstrated in the cells of some of these tumours, and they are known to be responsive to hormonal influences, such as pregnancy, oophorectomy and hormonal manipulations. The lesions are sometimes single but often multiple, diffuse and bilateral. The nodules may be variable in size and therefore may go unrecognized, or be discovered on routine chest radiographs. Histologically, they resemble leiomyomas or fibroleiomyomas, but a classic leiomyosarcoma (cellular atypia, mitotic counts, epithelioid nests, necrosis, haemorrhage) must be excluded. Immunohistochemistry is mandatory to arrive at a correct diagnosis and especially to exclude other tumours. Ultrastructural studies may be helpful (Cho et al. 1989; Gal et al. 1989).

*Congenital multiple fibromatosis* (*infantile myofibromatosis*) has also been described in association with multiple congenital mesenchymal tumours or fibromatosis. The lesions are present at birth or within the first weeks after birth. New lesions may occur in the perinatal period or a few months later, but spontaneous resolutions have been documented as well as death in some cases. There is a strong male predominance, and the condition has been described as having both an autosomal and a recessive mode of inheritance with some sporadic cases. The nodules are multiple, firm, yellowish or greyish-white, of variable size and distributed throughout the lung.

Similar lesions are also seen in various organs, including the skin, muscle, bone and viscera. The tumours are located adjacent to bronchioles and blood vessels, and may show central necrosis and even calcification. They may be responsible for severe respiratory distress in the neonatal period (Chung and Enzinger 1981; Jennings et al. 1984; Goldberg et al. 1988).

*Congenital peribronchial myofibroblastic tumour* is a term coined recently by McGinnis et al. (1993) as representative of a distinct clinicopathological entity in the neonatal period. Their gross appearance together with their immunohistological and ultrastructural features of the cells making up the lesions point to their myofibroblastic origin. These authors have grouped all the tumours commonly referred to as *bronchopulmonary fibrosarcoma, congenital fibroleiomyosarcoma, hamartoma of lung* or *massive congenital mesenchymal malformation* under this umbrella, separating them from true leiomyosarcomas seen in older children.

*Granular cell myoblastoma* is a very rare benign tumour of the respiratory tract, may be single or multicentric, and is sometimes associated with lesions involving the tongue, skin and other soft tissues. The tumour has been reported in childhood; the histology and histogenesis is similar to that described for other sites (Redjaee et al. 1990; Guillou et al. 1991; Deavers et al. 1995).

Pulmonary tumours of *nervous* origin are very rare, even though those arising in the mediastinum are common in childhood. Isolated cases of intrapulmonary tumours of nervous origin have been recorded in infancy and childhood. They include neurofibromas (often associated with generalized neurofibromatosis), neurilemmoma and benign schwannoma. Immunohistochemistry is valuable in arriving at a correct diagnosis (Gay and Bonmati 1954; Neilson 1958; Bartley and Arean 1965; Massaro et al. 1965).

## *Others*

*Fibromas* of the lung are very rare. When present, they may be located peripherally in the pulmonary parenchyma or the bronchial wall. The tumour has been reported in children. It is composed mainly of fibrocytes supported by collagen fibres, with some myxomatous areas (Roenspies et al. 1978).

*Chondromas* are benign well differentiated hyaline cartilage outgrowths arising from the cartilaginous plates of bronchi, and are often lined with bronchial epithelium. They have been observed in childhood and present as polypoid or lobulated masses, projecting into the bronchial lumen and causing stenosis or bronchial obstruction.

Chondromas must be distinguished from chondromatous hamartomas, benign lesions made up largely of cartilage. They are considered to be hamartomas, although they continue to grow after body growth ceases. Their histogenesis is still unsettled. The lesions are relatively common and are most frequently described in adults, with a peak incidence between the fourth and sixth decades; nevertheless, they do sometimes present in childhood.

Chondromatous hamartoma has been described by several synonyms (chondromas, fibroadenoma, lipochondroadenoma, adenochondroma), depending on the predominant tissue in the lesion. They are most commonly located in the lung parenchyma towards the periphery (intrapulmonary), and less frequently in the bronchial wall (endobronchial). The lesions are usually single and either lung may be affected. There is a male preponderance. Multiple tumours have also been described, but they are less common, often bilateral, and are observed almost exclusively in females. It is necessary to exclude Carney's triad (pulmonary chondroma, gastric leiomyosarcoma and extra-adrenal paraganglioma) in young females with pulmonary chondroma (Raafat et al. 1986).

The clinical features are non-specific and depend largely on the size and localization of the tumour. Although radiography may be of little help, computed tomography may better delineate the lesion (King et al. 1982; Austin et al. 1994).

Macroscopically, the tumour is variable in size and is generally made up of a round or oval mass with a smooth surface, often lobulated. It is whitish in colour, somewhat translucent, firm in consistency, well circumscribed, and separated from the surrounding parenchyma by a pseudocapsule. Microscopically, the greater portion is composed of lobules of well differentiated hyaline cartilage interrupted by cleft-like spaces lined by cuboidal or columnar epithelium resembling that of the respiratory tract. The remainder of the tumour is made up of an admixture of various amounts of fibrous tissue, fat tissue, muscle bundles (striated and smooth), and occasionally metaplastic bone and aggregates of lymphocytes. Calcification may occur occasionally.

Recent ultrastructural studies by Stone and Churg (1977) have shown that the epithelial component of the chondromatous hamartoma is made up of cells resembling those lining the distal bronchioles and alveoli of adult lung.

*Intrapulmonary teratomas* are rare. Day and Taylor (1975) found only 19 recorded cases of intrapulmonary teratoma in the literature, and added one of their own. In their review they reported one malig-

nant terotama in an infant: the ages in the other cases ranged from 16 to 66 years. The left upper lobe was most commonly involved, and of the 16 cases for whom adequate histological descriptions are provided nine tumours were benign and seven malignant.

Teratomas in the lung are usually large masses of greyish-white fleshy tissue, sometimes surrounding cystic cavities of variable diameter. Tissue derivatives of the three embryonic germ layers may be identified histologically. In a case described by Day and Taylor (1975) the tumour seems to have developed in ectopic thymic tissue within the lung. Besides the two additional cases described by Holt et al. (1978) and Präuer et al. (1983), there have been some cases described in the Chinese and Japanese literature and more recently by Kayser et al. (1993) in an adult.

## Malignant

### *Primary*

*Haemangiopericytoma* of the lung is exceedingly rare and most of the cases published have been described in adults with occasional cases in children. The sex distribution is about equal. The tumours may attain considerable size before symptoms appear, sometimes associated with paraneoplastic symptoms. The histological diagnosis can be difficult, but immunohistochemistry and ultrastructural studies are of considerable help. The course of the disease is unpredictable and its prognosis variable, but total excision remains the treatment of choice, with radiotherapy and chemotherapy when there are metastases (Yousem and Hochholzer 1987; Rusch et al. 1989).

*Primary fibrosarcoma* of the lung is uncommon in childhood and may involve the bronchial tree (endobronchial or transbronchial) or intraparenchymal. The endobronchial lesions may cause obstruction resulting in pulmonary atelectasis with distal secondary infection or endogenous lipoid pneumonia as complications. The intraparenchymal masses are often well circumscribed lobulated masses (Pettinato et al. 1989; Cohen and Kaschula 1992). Macroscopically, the lesions are firm, greyish-white to yellowish, with occasional haemorrhagic areas. Histologically the lesions are cellular, composed principally by fusiform or oval spindle cells with little cytoplasm. Immunohistochemistry is mandatory for arriving at a correct diagnosis. There is a strong cytoplasmic positivity for Vimentin, indicating their fibroblastic nature, but are negative with the other intermediate filaments.

*Malignant fibrous histiocytoma*, a common soft tissue sarcoma, may originate in the lung; some 40 cases have been described in this organ, two of which were in teenagers. Either lung may be affected, and the tumour may present as a single mass or occupy an entire lobe. Histologically the storiform–pleomorphic type predominates, but the lesion may be made up of the various components with dominant features of one or more of the four components (Yousem and Hochholzer 1987; McDonnell et al. 1988). The tumour is aggressive, often infiltrating the chest wall and mediastinum, with frequent vascular invasions. It must be differentiated from spindle cell sarcoma or carcinosarcoma, and immunohistochemistry can be helpful. The prognosis is generally poor.

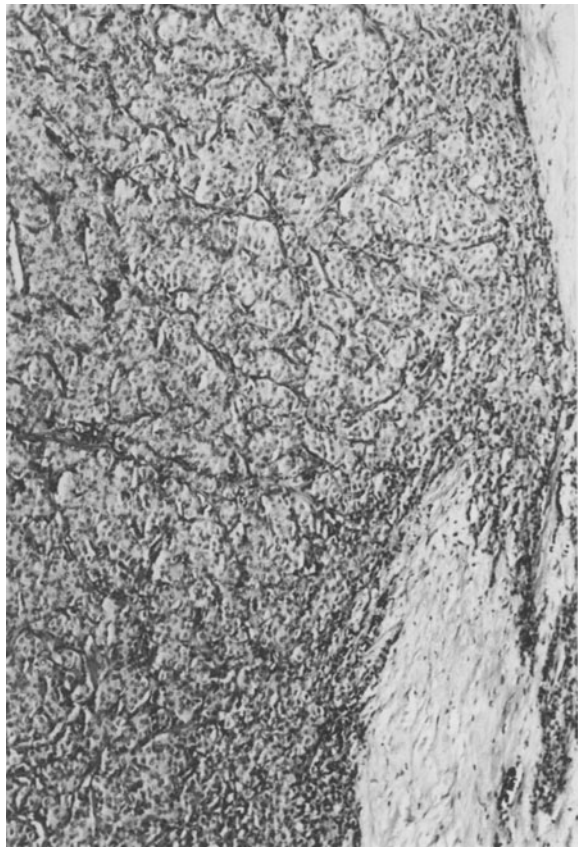
*Primary leiomyosarcoma* of the lung is also very rare in childhood. The lesion may originate in the bronchial or vascular wall as well as the pulmonary parenchyma, principally in the peribronchial mesenchyma. Certain authors prefer to refer to these tumours in the perinatal period as *congenital peribronchial myofibroblastic tumour*, indicating their myofibroblastic nature. The tumour may be the cause of bronchial obstruction in the newborn and could be associated with polyhydramnios and non-immune hydrops fetalis (Jimenez et al. 1986; Gal et al. 1989; Pettinato et al. 1989; Khong and Keeling 1990; McGinnis et al. 1993; Klaveren et al. 1994).

Histologically, it is important to differentiate this tumour from fibrosarcoma and certain tumours of neurogenic origin. Special stains, especially immunohistochemical staining for vimentin, desmin and antibodies to muscle-specific actin are necessary for arriving at a correct diagnosis. Ultrastructural studies, tissue cultures and flow cytometry are all useful aids in confirming the diagnosis. Leiomyosarcoma tends to metastasize by way of the blood stream; involvement of the lymphatic system appears to be infrequent.

*Primary rhabdomyosarcoma* in childhood is rare. The tumour may be endobronchial, parenchymatous or both. It is often described in association with cystic lesions of the lung – principally bronchogenic cysts, congenital cystic ademadoid malformation and mesenchymal cystic hamartoma – but is probably more often encountered with solid lesions like pulmonary mesenchymomas, pleuropulmonary blastoma (in childhood) and pulmonary blastoma (adult type) (Hartman and Schochat 1983; Allan et al. 1987; Pettinato et al. 1989; Domizio et al. 1990). Immunohistochemistry (myoglobin, desmin, actin and vimentin) and ultrastructural studies are most helpful in arriving at a correct diagnosis, especially in infancy and early childhood.

*Rhabdomyomatosis dysplasia*, the presence of non-tumoral striated muscle fibres in the lungs, has been described in association with congenital cystic adenomatoid malformations, hypoplastic lungs with anomalous vascular anomalies and major cardiopul-

a



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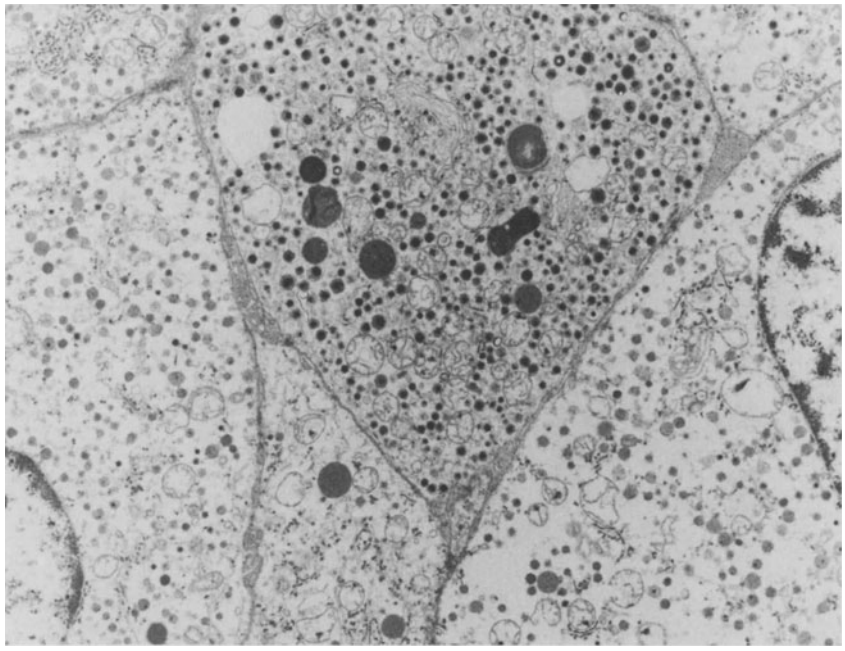

c

**Fig. 7.78.** **a** Carcinoid tumour in a 9-year-old girl; it is obliterating the bronchi, resulting in bronchiectasis and severe peripheral infection with abscess formation. **b** Tumour showing the classic picture of nests of tumour cells separated by thin fibrous bands. (H&E, × 120) **c** Electron micrograph showing the tumour cells laden with dense granules of variable sizes and densities. (× 48 404)

monary malformations. Either lung may be affected and the lesions may be bilateral. The striated muscle fibres or bundles may be patchy, and may affect one lobe or an entire lung. It has also been documented with abnormalities involving the diaphragm and with intralobular and extralobular sequestration (Chellam 1988; Drut et al. 1988; Chen et al. 1991; Meacham et al. 1991).

*A primary pulmonary embryonal liposarcoma* has been described in a 9-year-old girl who presented with the adrenogenital syndrome (Wu et al. 1974), and this tumour has also been reported in the pediatric age group by Lagrange et al. (1988) and Ruiz-Palomo et al. (1990).

*Chondrosarcoma* of the lung is rare and the cases reviewed by Daniels et al. (1967) included one in a 17-year-old girl.

The term *bronchial adenoma* is now generally used to include five distinct neoplasms arising in the bronchus. Each of these lesions forms a well defined entity. A total of 58 cases has been reported in childhood (Wellons et al. 1976).

The five tumour types are:

1. Mucous gland adenoma
2. Bronchial carcinoid
3. Cylindroma or adenoid cystic carcinoma
4. Mucoepidermoid tumour
5. Papillary adenoma

A possible sixth type, alveolar adenoma or bronchioloalveolar cell adenoma, has been recently described (Yousem and Hochholzer 1986; Miller 1990; Hancock et al. 1993).

*Mucous gland adenoma* is the only truly benign lesion of the group, and is also the rarest. Courtin et al. (1987) collected 34 cases from the literature and added one of their own. These tumours, rare in childhood, take their origin in the submucosal glands of the large bronchus, and involve both the glands and their ducts. They may cause obstruction of the bronchial lumen or stenosis by compression.

*Carcinoid tumours* are most common among this group, representing 80%–85% of all bronchial adenomas. They take their origin from the Kulchitsky cells (APUD) in the bronchial mucosa and have been reported at all ages. Lawson et al. (1976) subdivided this tumour into three histological subgroups, while others (Valli et al. 1994) suggest four based on the cellular morphology. Carcinoids are known to be of low-grade malignancy, and may metastasize to neighbouring lymph nodes or other sites after a long period (Fig. 7.78). The carcinoid syndrome has been reported in some cases (Ricci et al. 1973), and acromegaly has been associated with this tumour. Most go unnoticed as they infiltrate the bronchial wall and adjacent tissue or proliferate into the lumen until large enough to cause obstruction with atelectasis, infection and bronchiectasis (Wang et al. 1993b). Some undergo calcification or ossification. Haemoptysis is the most frequent clinical symptom and is associated with intraluminal growth.

*Cylindroma* is rare, accounting for about 12%–15% of all bronchial adenomas. They are derived from the mucus-secreting cells of the mucosa of the larynx and tracheobronchial tree, but mainly the large bronchi, and histologically they resemble tumours of the major salivary glands, having that characteristic histological pattern. The tumour, although of low-grade malignancy, may slowly infiltrate the surrounding tissues with metastases to the lymph nodes and other organs. It is considered that cylindrinoma, especially the solid pattern, is the most aggressive of the three malignant types, followed by the carcinoid (Schmitt et al. 1989; Ishida et al. 1990).

*Mucoepidermoid carcinoma*, with its origin in the larger airways, is the least common of these tumours (less than 5%) and has been documented in children (Yousem and Hochholzer 1987; Heitmiller et al. 1989; Corrao and Mark 1990).

*Papillary adenoma* may present as a single or as multiple well defined nodules in one or both lungs. Histologically, the lesions have a papillary appearance with fibrovascular buddings lined by cuboidal and columnar epithelial cells. These have been shown, by immunohistochemistry and electron microscopic studies, to be composed of both Clara cells and type II pneumocytes (Dempo et al. 1987; Fukuda et al. 1992; Hegg et al. 1992; Kurotaki et al. 1993).

*Primary carcinoma* of the lung is rare in childhood. Niitu et al. (1974) reviewed the literature, which included 39 cases, including their own in a boy of 15 years 7 months. The youngest patient in the Japanese series was 2 years 3 months old; the youngest reported case is in an infant of 5 months.

The condition is usually discovered during chest radiography for ill-defined clinical symptoms, and is often misinterpreted for long periods before the correct diagnosis is made with growth of the tumour. There is an equal distribution between the sexes. Undifferentiated carcinoma is the commonest histological type in western countries, whereas in Japan adenocarcinoma has been prevalent; however, it must be mentioned that in many western reports the tumour was unclassified. Squamous-cell carcinoma was rare. Metastases to one or both lungs or to distant organs have been reported. It is important to emphasize that some of the cases described as adenocarcinomas might prove to be carcinoids if reviewed critically. Long periods of survival have been

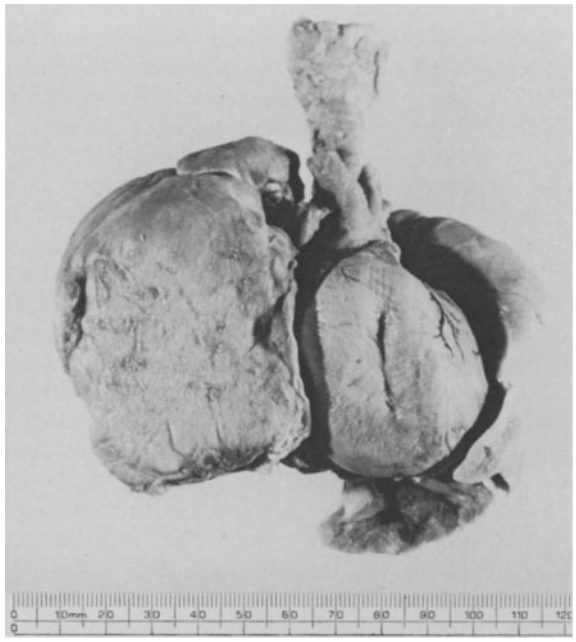

**Fig. 7.79.** Pulmonary blastoma occupying the inferior and middle lobes of the right lung in a 6-month-old boy. (Courtesy of Dr C. Bozic)

reported after surgery for localized tumours. Spencer et al. (1980), in a review of 21 cases of non-invasive bronchial epithelial tumours, found one case in a boy of 7. These tumours are usually undifferentiated neoplasms, and in the case of the boy described the peripheral tumour appeared to be composed of a complex papillary process covered by cuboidal non-ciliated columnar epithelial cells bearing a striking resemblance to Clara cells, with local invasion.

*Malignant small-cell tumour of the thoracic wall* (Askin's tumour), a highly aggressive tumour with origin in the chest wall and/or lung parenchyma, is rare. The tumour has a female predominance and appears to take its origin from the nerve sheath without involvement of the ribs. The tumour is usually bulky and lobulated; histologically, it may resemble one of many of the small round-cell tumours (Ewing's sarcoma, lymphoma, metastatic neuroblastoma, embryonal rhabdomyosarcoma). Recent studies have shown that this tumour, like Ewing's sarcoma, shares microscopic neuroectodermal tumour and they may form a single group of the same tumours (Tsokos 1992; Dehner 1993; Ramani et al. 1993; Perlman et al. 1994).

*Pulmonary blastoma* is a rare primary lung tumour and has been described in infants and children. Barnard (1952) coined the term "embryoma" because of its histological resemblance to fetal lung, but Spencer (1961) suggested the term "blastoma", assuming that the tumour arose from mesodermal blastoma similar to that of nephroblastoma. There is still much debate as to whether it is derived from the endoderm or a pluripotent pulmonary blastoma.

The tumours are usually bulky, nodular, intrapulmonary masses, which occasionally involve the bronchus. They are often solitary, sometimes multiple, located either at the periphery, centrally or both. They are generally variable in colour, well defined but unencapsulated, and may present haemorrhagic areas or cystic-like zones.

Histologically, they present two distinct components, which may be variable in composition. In the biphasic form, glandular or tubular structures lined by columnar cells with a brush border but no cilia are evident. The cells are rich in glycogen. The glands and stroma may take on an endometrioid appearance in areas. The stromal component may be made up of either a spindle cell-like sarcomatous tissue or a primitive embryonic mesenchyme embedded in an abundant myxoid matrix. Mesenchymal structures (cartilage, bone, striated muscle cells, fat) undergoing differentiation or neoplastic changes may be apparent.

In some cases the tumour may be composed mainly of epithelial elements forming glands or connecting tubules supported by a thin mature connective tissue structure, giving it the aspect of a well differentiated fetal adenocarcinoma; this was formally considered to be a separate entity, but is now accepted as a variant of pulmonary blastoma. These lesions may be single but are generally multiple and often bilateral. Neuroendocrine cells and morulas have been identified in both types and have shown immunoreactivity for regulatory peptides.

The clinical course is generally impredictable and, although the prognosis is poor, the outcome depends somewhat on the grading of the tumour (Heckman et al. 1988; Chejfec et al. 1990; Yousem et al. 1990; Koss et al. 1991).

Pulmonary blastoma of the adult type is rarely encountered in the paediatric age group, but they are seen in older children. Manivel et al. (1988) drew attention to the fact that the tumours referred to as blastomas in childhood were different from those normally observed in adults, especially among those below the age of 12 years. These tumours originate principally in the pleura and mediastinum or both, but rarely in the lung parenchyma, hence the name "pleuropulmonary blastoma". These tumours are solid, bulky, well circumscribed, lobulated and surrounded by a fibrous capsule, often the visceral pleura occupying an entire lobe or lung. They are firm or rubbery in consistency, greyish-white, and sometimes present large areas of necrosis and zones of old and recent haemorrhages (Fig. 7.79). They are usually in the

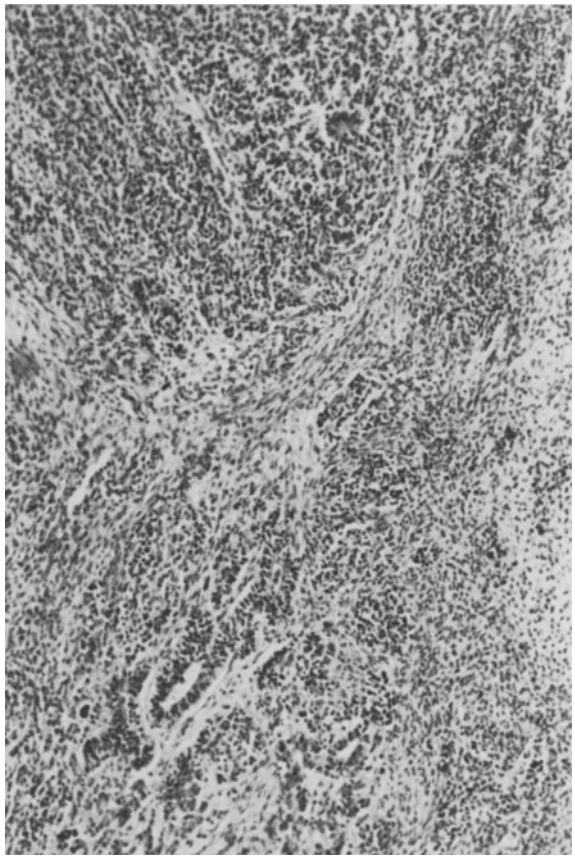

**Fig. 7.80.** Pleuropulmonary blastoma with entrapped epithelial nests in a diffuse proliferative, undifferentiated, mixed blastomal and abundant loose mesenchymal stroma. (H&E, × 60)

vicinity of or within cystic structures, with invasion of neighbouring tissues or adjacent structures.

Histologically, the tumour is characterized by a diffuse proliferation of undifferentiated blastemal cells with a storiform or alveolar pattern and areas of mesenchymal neoplastic differentiation (rhabdomyosarcomatous, chondrosarcomatous, leiomyosarcomatous, mesenchymomatous, liposarcomatous or combinations). The glandular and/or epithelial structures within the tumour are non-neoplastic but entrapped bronchial and bronchiolar elements of the lung (Fig. 7.80). The tumours are frequently described in association with cystic lung disease, principally with congenital cystic adenomatoid malformation type I, bronchogenic cysts or simple or multicystic lesions (Bove 1989; Domizio et al. 1990; Cohen et al. 1991; Delahunt et al. 1993; Hachitanda et al. 1993; Seballos and Klein 1994).

*Solitary pulmonary plasmacytoma* is extremely rare. Baroni et al. (1977) reported a case in a 14-year-old boy, associated with an abnormal secretion of IgM. This was corrected after surgical resection of the tumour. Microscopically the tumour is made up of plasma cells at various stages of maturation. Lymphocytes may be present, occasionally forming well defined lymphoid follicles.

Veliath et al. (1977) described a *primary lymphosarcoma* of the lung in a 5-year-old girl in whom a diagnosis was made on tissue obtained by percutaneous needle biopsy of a right pulmonary mass. The child was well 1 year later, following radiotherapy and chemotherapy.

The $8\frac{1}{2}$-year-old girl described by Liebow et al. (1972) with *lymphomatoid granulomatosis* of the lung was found, 2 years later, to have an eosinophilic granuloma of the skull. Furthermore, DeRemee et al. (1978) consider lymphomatoid granulomatosis to be identical pathologically with polymorphic reticulosis. It appears that one should be extremely cautious before making this diagnosis, which should be suggested only in the absence of other histological entities.

*Intrapulmonary thymoma*, although a very rare tumour, has been reported in children. It is often an incidental finding on chest radiography, presenting as a solitary mass. Immunohistochemical studies are important in differentiating this tumour from lymphomas and germ cell tumours (Kung et al. 1985).

*Lipomas* of the lung are rare. Lagrange et al. (1988) have described a lipoblastic liposarcoma in a 20-year-old woman, while Guinee et al. (1995) have documented various forms of lipomatous lesions of the lung in adults.

## *Metastases*

The metastases of many childhood tumours are blood-borne, and they generally produce massive secondaries in the lung. These may be limited in number, or occasionally there is a diffuse dissemination of small lesions scattered throughout the parenchyma. Metastases to the lung are common in *Wilms' tumour, hepatoblastoma, osteosarcoma, Ewing's sarcoma* and *sarcomas of soft tissues. Neuroblastoma* spreads to the lung less readily, but is a common tumour, so pulmonary deposits are frequently found (Vassilopoulou-Sellin et al. 1993; Cohen 1994; Fassina et al. 1994; Heij et al. 1994; Massimino et al. 1995).

In childhood *leukaemia* the vessels of the lung contain leukaemic cells, and these cells may be seen infiltrating the alveolar wall. Perivascular aggregates can be observed in severe cases. *Non-Hodgkin's lymphomas* may also be localized in the lung, either as a primary lesion or, more often, as a secondary infiltration. *Hodgkin's disease* in childhood may involve the

lung and infiltrate the parenchyma, forming nodules, or produce peribronchial or bronchial infiltrations with bronchial stenosis. The differential diagnoses of these various entities and their subgroups can be made with precision only by the use of detail and careful immunohistochemical labelling of the various cell types (Weiss et al. 1985; Weis et al. 1986).

### *Histiocytosis X and Similar Conditions*

*Langerhans' cell histiocytosis (histiocytosis X)*, formally referred to as histiocytosis X, frequently involves the lung. In acute disseminated Langerhans' cell histiocytosis, the pulmonary lesions are diffuse and bilateral; they often appear in successive crops and can be associated with pneumothorax. There may be numerous areas of necrosis with abscess formation. Microscopically there are numerous Langerhans' cells with large giant cells, containing a yellowish granular pigment in their cytoplasm. The inflammatory infiltrate may be minimal away from areas of necrosis, but scattered polymorphonuclear eosinophils sometimes accompany the lesion.

Multifocal Langerhans' cell histiocytosis invariably involves the lung. The lesions are bilateral and diffuse, with formation of granulation tissue containing numerous Langerhans' cells, sometimes associated with active fibrosis and a chronic inflammatory infiltrate. Accompanying macrophages often have a xanthomatous appearance. Lung involvement is always accompanied by lesions of other organs or systems.

Unifocal Langerhans' cell histiocytosis (eosinophilic granuloma) is generally described in bones. It has long been recognized that it can occur as an isolated lesion in the lung. The majority of cases have been reported in adults, with a male preponderance. Radiography of the chest reveals disseminated nodules in both lung fields, which are more prominent in the hilar region. High-resolution computed tomography and isotope ventilation/perfusion scanning are extremely helpful in diagnosing the condition at an earlier stage. Sometimes cavities of variable sizes are apparent, and emphysema is not infrequent. During the late stages of the disease fibrosis with honeycombing may be conspicuous. Pneumothorax and pleural effusion have been recorded in a number of cases.

Macroscopically the lungs show numerous small cavities throughout the parenchyma. There is also nodular fibrosis with a classic honeycomb appearance in some cases. Microscopically, in the early stages of the condition there is focal or nodular infiltration mainly around bronchioles and small vessels in the periphery, with some involvement of the pleura. More often there is a spectrum of lesions with variable amount of Langerhans' and mononuclear cells. Neutrophils are sometimes present. The Langerhans' cells are numerous in the cellular phase and may be few or totally absent in the late fibrotic stage, thus making diagnosis difficult. Some Langerhans' cells may have a foamy granular cytoplasm with pigment granules. The nuclei are large and folded; nucleoli are prominent. There is a moderate infiltration of lymphocytes and plasmocytes, accompanied by varying quantities of eosinophils scattered throughout the granulation tissue. Fibroplastic proliferation is also evident. Distal bronchi and bronchioles and the vessels in adjacent areas are involved in the granulomatous process and may be partially or completely obliterated. Similar lesions are sometimes observed in the pleura.

Recent studies have suggested that there may be a neutrophilic chemotactic defect in these patients due to some intrinsic impairment associated probably with an increased frequency of HLA antigens Bw61 and Cw7. Langerhans' cells are antigen-presenting (accessory) cells of the dendritic cell/Langerhans' cell lineage, which partially degrade protein antigens and express the peptides on their surface in association with HLA molecules. It is now well established that in all cases the diagnosis is based on the identification of Langerhans' cells in the lesions. These large cells are lobulated with grooved nuclei and with well defined granules (Fig. 7.81a). They stain with S-100 protein and OKT6 and strongly express the CD1a surface antigen, and ultrastructurally they contain the characteristic X-bodies or Birbeck granules (Fig. 7.81b). Giant cells may be conspicuous and the inflammatory reaction variable, containing neutrophils, eosinophils in variable quantities and some mononuclear cells. Although BAL fluid examination has been proposed by some authors, its usefulness is limited because several other pathological conditions may be accompanied by the presence of Langerhans' cells in the fluid. Lung biopsy (transbronchial or preferably open) produce more specific results (Rancy and D'Angio 1989; Foucar and Foucar 1990; McLelland et al. 1990; Ha et al. 1992; Soler et al. 1992; Goerdt et al. 1993; Travis et al. 1993; Emile et al. 1995).

Recently, William et al. (1994) have detected clonal histiocytes in all forms of Langerhans' cell histiocytosis, indicating that this condition is probably a clonal neoplastic disorder with highly variable biological behaviour.

### *Pleural Tumours*

*Mesothelioma of the pleura* is very rare in childhood. In a retrospective study, Grundy and Miller (1972)

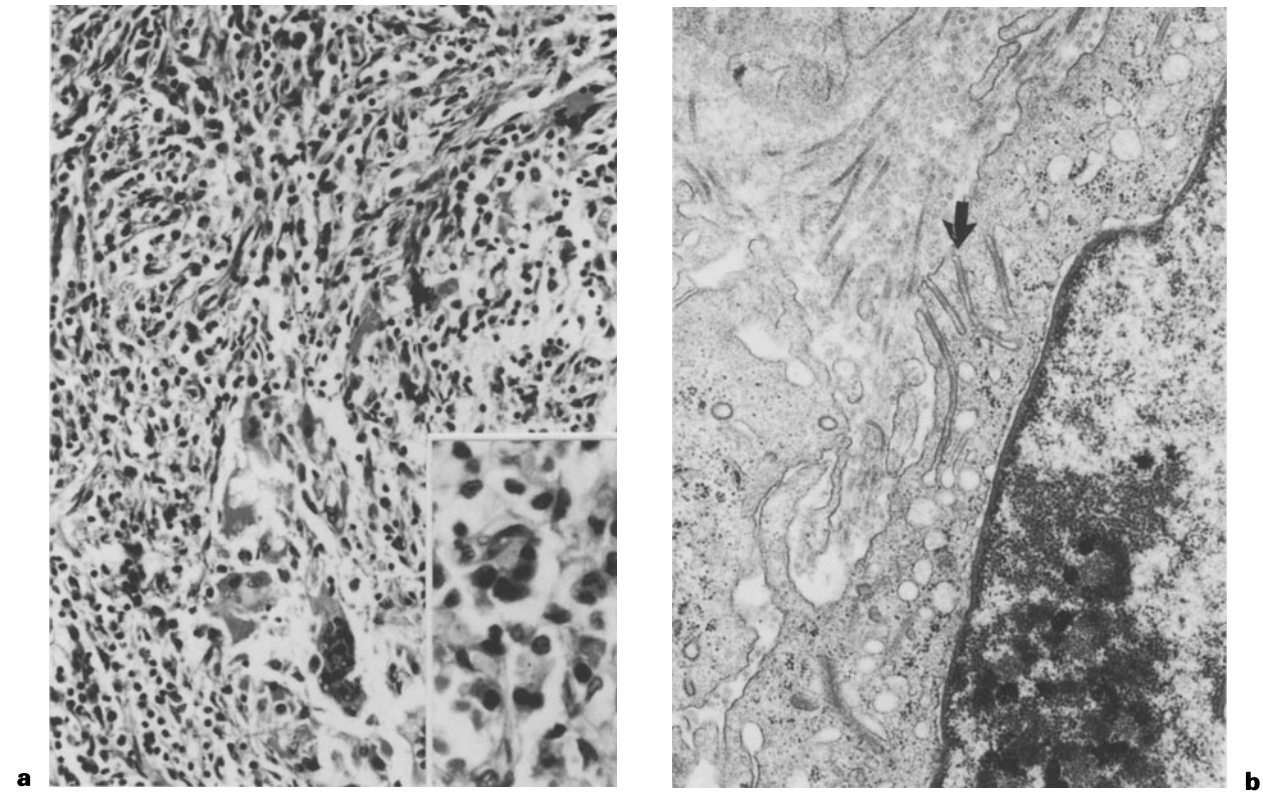

**Fig. 7.81.** **a** Histiocytosis X in a $7\frac{1}{2}$ year-old boy. **a** Note the granulomatous-like infiltration with numerous histiocytes and some giant cells. *Inset*, giant cell and typical histiocyte. (H&E, × 225) **b** Histiocyte with the classic Bw granule or X-bodies, confirming the diagnosis. (× 31 960)

were able to collect 13 well documented cases of malignant mesothelioma in the USA. Eight of the patients were 16 years of age or less and the remaining five were 17 years old. The youngest patient was 4. There are now over 30 cases recorded in the literature, with a significant male predominance. Histologically the majority of tumours showed a fibrous pattern, which is often described in the literature in the paediatric age group, but mixed types have also been documented (Dische et al. 1988; Lin-Chu et al. 1989). One must exclude an eventual secondary infiltration of the pleural cavities by a peritoneal mesothelioma in these patients (Nishioka et al. 1988; Geary et al. 1991).

The tumour often progresses without clinical symptoms until late in the course of the disease, when the patient presents with thoracic pain, sometimes dyspnoea, and pleural effusion. Death usually takes place within 12 months of the initial symptoms. Although malignant mesothelioma in adults is often related to environmental factors, principally exposure to asbestos (Whitewall et al. 1977), no such relationship was found in the cases studied by Grundy and Miller (1972). Li (1977), in a review of second malignant tumours after treatment of malignancy in childhood, recorded mesothelioma arising 16 years after radiotherapy and, similar to the case described by Anderson et al. (1985), 13 years after both chemotherapy and radiotherapy for Wilms' tumour. Mesotheliomas have been reported in a family, in siblings and in a pair of twins, suggesting that in some instances there may be hereditary predisposition (Martensson et al. 1984).

The microscopic pattern is often mixed, as can be elegantly demonstrated by histochemical and immunohistochemical techniques. This finding is confirmed by ultrastructural studies showing that these tumours are derived from both epithelial and fibroblastic components of the mesothelial layer and thus exclude a pulmonary adenocarcinoma (Brown et al. 1993; Moch et al. 1993a, b).

*Malignant mesenchymoma* of the pleura has been described by Darling et al. (1967; cited in Holdsworth Mayer et al. 1974) in a 3-month-old girl. This tumour showed the histological patterns encountered in similar tumours at other sites.

*Fibroma* or *benign localized mesothelioma* of the pleura, although rare, has been recorded in childhood.

The tumours can occur singly but are sometimes multiple and bilateral, and are known to evolve over very long periods, and may recur after excision. Fibromas of the pleura are variable in size and usually nodular, firm and yellowish-white. They take their origin from the subendothelial areolar tissues, and have been observed both on the visceral and parietal layers as well as within the pulmonary parenchyma (Scattini and Orsi 1973; Yousem and Flynn 1988). Spontaneous regression has been recorded in some cases. Microscopically they are composed of proliferating fibroblasts supported by thick collagen bundles and reticulin fibres, sometimes set in a myxoid ground substance. Mitotic figures may be prominent but metastases do not occur and the prognosis is favourable, supporting the benign nature of these lesions.

*Mesenchymal hamartoma of the chest wall* takes its origin from one or more ribs and may be the cause of chest wall deformity in the neonatal period. Cohen et al. (1992) in a review of the literature found 33 cases described in infancy and added three of their own. The lesion may be diagnosed during intrauterine life by echography and can be the cause of pulmonary hypoplasia and also respiratory distress in the newborn. It is generally lobulated, circumscribed, single or multiple, with a benign behaviour (D'Ercole et al. 1994; Dounies et al. 1994). Histologically, the lesion is composed of chondroid tissue with foci of hyaline cartilage, areas undergoing ossification associated with an important vascular component.

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