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Chapter 5

Infectious diseases

5.1 *Viral, mycoplasmal and rickettsial infections*

CHAPTER CONTENTS

VIRAL INFECTIONS

Many viruses infect the lower respiratory tract. They include the orthomyxoviruses (influenza virus), paramyxoviruses (parainfluenza viruses, measles virus and respiratory syncytial virus), adenoviruses, herpesviruses (cytomegalovirus, varicella-zoster virus and herpes simplex virus) and formerly variola virus (smallpox). Many of these viruses are of course also responsible for non-respiratory disease. The role of papillomavirus in neoplasia of the respiratory tract is discussed on page 535 and parvovirus is mentioned as a cause of hydrops fetalis on page 43. The role of herpes-like viruses in Kaposi's sarcoma and body cavity-based lymphomas is discussed on pages 635 and 734 respectively.

Viral infection of the lower respiratory tract occurs in three general situations: infections confined to the respiratory tract, systemic infections that involve the lung and opportunistic infection of the lungs in the immunocompromised (Box 5.1.1).

Respiratory viruses may strike any part or all the respiratory tract but on the whole each tends to affect particular parts and thereby elicit characteristic clinical effects (Fig. 5.1.1). This pattern varies however if there is some predisposing cause. Thus, the rhinoviruses, which usually cause nothing more serious than a cold, are the commonest viral trigger of acute exacerbations of chronic bronchitis, while in the immunodeficient herpes simplex virus and cytomegalovirus are serious pathogens in the lower respiratory tract.

The frequency of these various infections also differs in children and adults. In children, respiratory syncytial virus is the most important viral cause of lower respiratory tract disease, typically causing an obstructive bronchiolitis. Parainfluenza viruses are the most frequent cause of viral pneumonia in children, and the influenza virus in adults. These are followed by the measles and adenoviruses in children and varicella virus in adults, whilst the immunocompromised are also susceptible to cytomegalovirus and herpes simplex virus. A viral aetiology is responsible in 7–15% of adults admitted to hospital with community-acquired pneumonia (see Table 5.2.2, p. 178).

The virus responsible can be cultured from sputum or nasopharyngeal washings and evidence of infection by particular viruses may be provided by the demonstration of a rising titre of specific antibodies in the patient's serum. The advent of monoclonal antibodies has provided specific sensitive and reproducible probes that can be directly conjugated to a fluorescent tag so that the examination of exfoliated cells for viral antigen by immunofluorescent techniques is now the method of choice for the rapid identification of most respiratory

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Box 5.1.1 Classification of viruses that infect the lower respiratory tract

Normal host

Primary respiratory infection

Respiratory syncytial virus
Parainfluenza
Influenza
Adenovirus

Secondary to systemic infection

Measles
Varicella-zoster virus
Adenovirus

Immunocompromised host

Cytomegalovirus
Herpes simplex virus
Varicella-zoster virus
Adenovirus

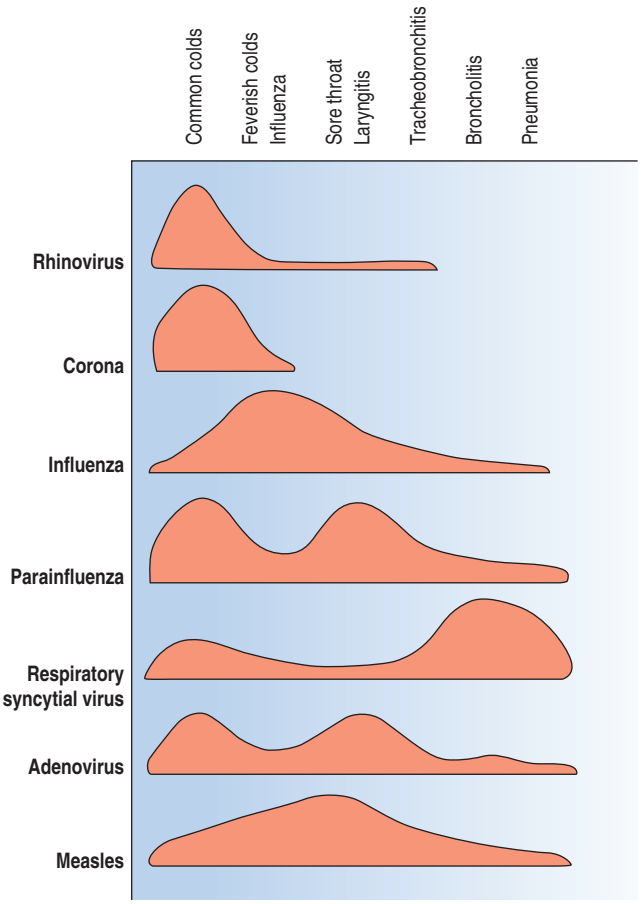

Figure 5.1.1 Clinical features of the common respiratory virus infections.

viruses. In tissue, the particular virus may be identified by immunocytochemistry, electron microscopy or gene probes.[1–7]

Most respiratory viral infections end in recovery. In fatal cases, the pathological changes in the lungs are often dominated by the effects of secondary bacterial infection, which is a very frequent complication. Few bacterial species have developed mechanisms for attachment to normal, intact human respiratory epithelium (notable exceptions being *Bordetella pertussis* and *Mycoplasma pneumoniae*) but viral injury to the epithelium permits bacterial attachment to take place and is associated with a greatly increased incidence of bacterial pneumonia.

From the occasional postmortem studies that have been undertaken in uncomplicated cases of viral pneumonia it is apparent that the inflammatory reaction in the lung is mainly lymphocytic and interstitial. Neutrophils are numerous only when there is a complicating bacterial infection. At the alveolar level viruses cause an atypical pneumonia characterised by a chronic inflammatory interstitial infiltrate rather than the acute inflammatory exudates that fill the air spaces in the bacterial pneumonias.

The pathology is modified to some extent by the type of virus responsible but infections caused by different viruses have many features in common.[8] In the lungs, as in other organs, some viruses have a cytopathic effect and kill the infected host cells, whilst others stimulate proliferative activity. Thus, influenza, adenovirus, varicella and herpes simplex pneumonia are all characterised by epithelial cell necrosis (Figs 5.1.2 and 5.1.3), whilst respiratory syncytial virus and measles virus stimulate mitotic division and cause characteristic proliferative changes in the bronchioles and alveoli respectively. The distribution of the changes is often characteristic of a particular virus, but not specific. Thus, within the alveoli, influenza tends to affect the epithelium diffusely. The effects of adenovirus, on the other hand, are generally maximal in the region of the terminal bronchioles, whilst varicella pneumonia is also focal but lacks any particular relationship to the acinar architecture. Viral inclusions are evident in certain viral pneumonias, notably measles, adenovirus, cytomegalovirus, varicella and herpes simplex pneumonia, but not in others.

Alveolar epithelial necrosis is a feature of severe viral pneumonia. It causes the formation of hyaline membranes (Fig. 5.1.3) and the pathology of such viral pneumonia is essentially that of diffuse alveolar damage (see Chapter 4). The regenerative changes seen in diffuse alveolar damage may be evident, possibly involving epithelial metaplasia.

Much of the damage caused by respiratory viruses is due to a direct cytopathic effect on the infected cells but there may also be indirect injury. The latter may be due to normal immune mechanisms such as cytotoxic T lymphocytes attacking infected host cells, depression of immunity by the virus (facilitating secondary infections) or the development of autoimmunity initiated by the virus.

The possible threat of bioterrorism is a feature of life today and, because of the ease with which they may be widely dispersed, respiratory pathogens figure large in the thinking of defence forces. The US Centers for Disease Control have classified six agents as category A threats. Several of these will be considered in this infectious disease section. The six category A agents are *Bacillus anthracis* (anthrax), *Variola major* (smallpox), *Yersinia pestis* (plague), *Francisella tularensis* (tularaemia), viral haemorrhagic agents and *Clostridium botulinum* toxin. Category B and C agents, which are seen as posing less of a threat, include the repiratory pathogens *Coxiella burnetti* (Q fever), Hantavirus and multidrug-resistant *Mycobacterium tuberculosis*.

Influenza

Microbiology and epidemiology

Influenza is epidemic almost annually in the winter months in many parts of the world and at long intervals the disease occurs in pandemic form, notably in 1889–92, 1918–19, 1957–58, 1968 and 2009. It is estimated that in the pandemic that followed the world war of 1914–18, some 20–30 million people died from the disease in little more

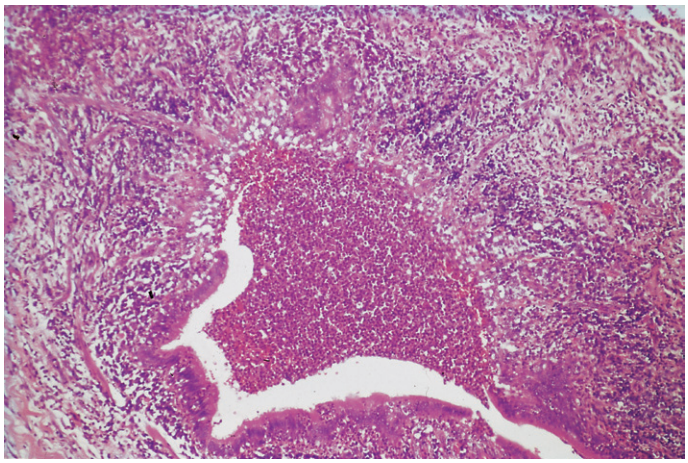

Figure 5.1.2 Necrotising viral bronchiolitis. The bronchiolar epithelium is partly destroyed and the lumen is largely filled with pus due to secondary bacterial infection.

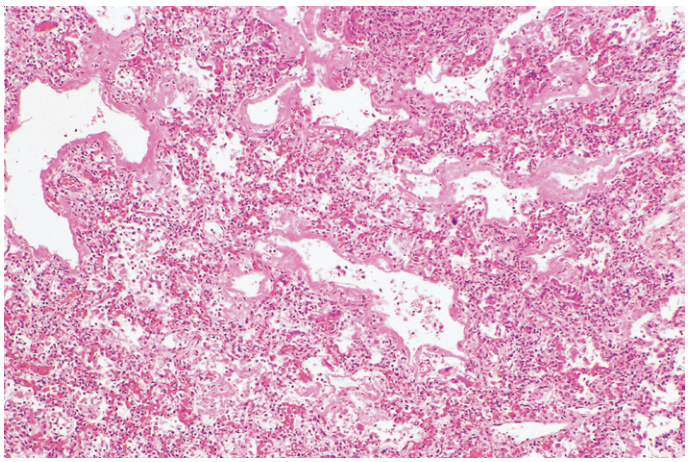

Figure 5.1.3 Viral pneumonia causing necrosis of the alveolar epithelium with the formation of hyaline membranes. The virus responsible in this patient was that of measles but many respiratory viruses have a similar effect, as do several other cytotoxic factors: see diffuse alveolar damage, in Chapter 4. *(Courtesy of Dr V Chrystal, Durban, South Africa.)*

than a year, more than were killed in the war itself. Until 1933 it was widely believed that the disease was caused by the bacterium *Haemophilus influenzae*. The discovery in 1933 that the disease could be transmitted to ferrets by intranasal inoculation of filtered washings from the noses of patients established its viral nature.[9]

There are several types of influenza virus. All are originally bird viruses, some crossing from birds to species such as humans, pigs, horses and seals. Once established in the new species they undergo constant changes in their antigenic makeup, a feature that necessitates the constant manufacture of new vaccines. The strains involved in most serious human infections belong to types A and B, with the former much the more virulent. Outbreaks of infection with influenza A occur most years, with epidemics every 5–15 years. Influenza B also causes epidemics, but less frequently. Influenza C does not appear to cause epidemics. Successive epidemics appear to be decreasing in severity, possibily due to natural selection involving evolutionary changes that favour transmissibility over pathogenicity.[10]

Antigenic lability involves changes in the principal surface antigens of the virus, haemagglutinin and neuraminidase. Minor changes ('antigenic drift') are seen progressively from season to season. Major changes ('antigenic shift') due to acquisition of a new haemagglutinin occur periodically and are responsible for the emergence of new subtypes to which populations have little immunity and which therefore cause epidemics or pandemics. Influenza epidemics generally occur in the winter months and often start in countries south of the equator or in the east, giving northern and western countries time to prepare and distribute appropriate vaccines to those most at risk, notably the infirm. Influenza A viruses are named after their haemagglutinins (H1, H2, etc.), their neuraminidases (N1, N2, N3, etc.), and the place where and year when the strain was first identified. Thus, the 1968 pandemic virus was H3N2 influenza A/Hong Kong/68.

The haemagglutinin molecule enables the virus to attach to host cells prior to infecting them and neuraminidase permits new virus particles to bud from the cell membrane. Although there are considerable differences between the influenza viruses that infect different species, the haemagglutinin molecule's lability occasionally permits its virus to switch from one host species to another, in which the disease is likely to spread in epidemic form. It appears that all the devastating influenza pandemics of the twentieth century, such as Spanish flu in 1918, Asian flu in 1957 and Hong Kong flu in 1968, were caused by viruses that made such a switch from birds to humans.[11]

Recent genomic studies of the H1N1 virus responsible for the 1918 pandemic suggest that it was an avian virus that adapted to humans, rather than developing by a reassortment of avian and human viruses, as in the 1957 and 1968 pandemics.[12]

The switch from animals to humans in the 'wet markets' of the Far East is also relevant to the severe acute respiratory syndrome (SARS), described on page 163.

In 2004, the H5N1 strain of the influenza A virus devastated flocks of poultry in Asia and was responsible for the deaths of some humans from what was termed 'Asian bird flu'.[13,14] This strain was not very infective to humans, possibly because the temperature of the human nose (32°C) is too cold for a virus whose natural host is the avian intestine (temperature 40°C).[15,16] However, when the virus succeeded in infecting humans it was particularly virulent for two reasons. First, it was resistant to the antiviral effects of human interferons and tumour necrosis factor-α, a property acquired by a simple mutation in the non-structural gene resulting in a change from aspartate to glutamate at position 92.[17] Second, it preferentially targeted the alveolar rather than the tracheobronchial epithelium.[18]

The year 2009 saw swine influenza A/H1N1 virus switch to humans and exhibit the ability to spread from case to case, rapidly assuming pandemic proportions. Pigs are unusual in that their respiratory epithelium has receptors for both avian and human influenza viruses so that they can be infected with these viruses simultaneously, providing the ideal environment for genetic reassortment. This appears to have taken place as the 2009 swine influenza virus shows a novel reassortment of genes derived from swine, avian and human influenza viruses, a feature that is probably responsible for this virus being able to infect both pigs and humans. Unlike seasonal influenza, the disease made its first appearance in the northern hemisphere, apparently originating in Mexico, and its first impact was during the summer months. There was much mild disease but again, in contrast to seasonal influenza, severe respiratory failure was seen in young, previously healthy persons, as is often the case in influenza pandemics. This feature is not well explained but it is possible that the healthy mount a more vigorous immune response that is in some way detrimental to the host. Older people were less susceptible but more likely to die when infected.[19] However, one year later it was apparent that the pandemic had not proved as severe as first thought.

Clinical features

The severity of influenza varies from one epidemic to another and from case to case. In its uncomplicated form it is relatively mild, with fever, coryza, headache and body aches as its main features, and recovery after a few days. When the viral infection is followed by invasion of the lungs by staphylococci, pneumococci, streptococci or *Haemophilus influenzae*, the condition assumes a much graver form and the fatality rate may rise alarmingly. Infection rates are highest among schoolchildren and decrease with age but death is commonest in infants, the elderly and those with underlying lung or heart disease, and is generally due to complications.

Primary influenzal pneumonia is generally rare but figured prominently in the 1918–19 pandemic. It carries a high case fatality rate and in the 1918–19 pandemic it was notable that mortality was highest in adults aged 25–34, possibly because older people had been exposed earlier to a similar strain of the virus.[20,21] Primary influenzal pneumonia may be fulminant, leading to the death of a previously healthy person within a few hours of the onset of symptoms.[22]

Recent years have seen the development of effective antiviral agents such as the drugs oseltamivir (Tamiflu) and zanamivir (Relenza) which inhibit viral neuraminidase (in contrast to anti-influenza vaccines, which target viral haemagglutinin).

Pathology of uncomplicated influenza

The cytopathic effect of influenza virus is seen microscopically in characteristic degenerative changes in the epithelial cells of the bronchial and bronchiolar mucosa. These changes involve all cells of the surface epithelium and often the cells lining the bronchial glands: swelling of the cells, vacuolation of their cytoplasm and degeneration of the nucleus proceed to cell loss and frank necrosis (Fig. 5.1.4). Viral inclusions are not evident but the virus can be identified in tissue sections by immunocytochemistry and in situ hybridisation.[23,24] The deeper tissues show oedema, hyperaemia and a moderate to marked accumulation of lymphocytes; neutrophils are present but account for only a small proportion of the cellular infiltrate.

Alveolar involvement is unusual but cases of fulminating influenzal viral pneumonia are occasionally encountered, particularly with the 1918 and more recent H5N1 and H1N1 strains.[14,24,25] Autopsy in such cases shows that the lungs are bulky and deeply congested.[14,22,24a] Blood-stained, frothy fluid oozes freely from the cut surface. Areas of haemorrhage are present and may be extensive. The mucosa of the bronchial tree is very hyperaemic. Microscopically, the alveoli contain a fibrin-rich oedema fluid, which is often frankly haemorrhagic. Macrophages may be numerous in the exudate and hyaline membranes are often found lining the alveoli. T lymphocytes are often prominent in the alveolar interstitium while focal necrosis of alveolar walls and thrombosis of capillaries are conspicuous features in the parts most severely affected.[26]

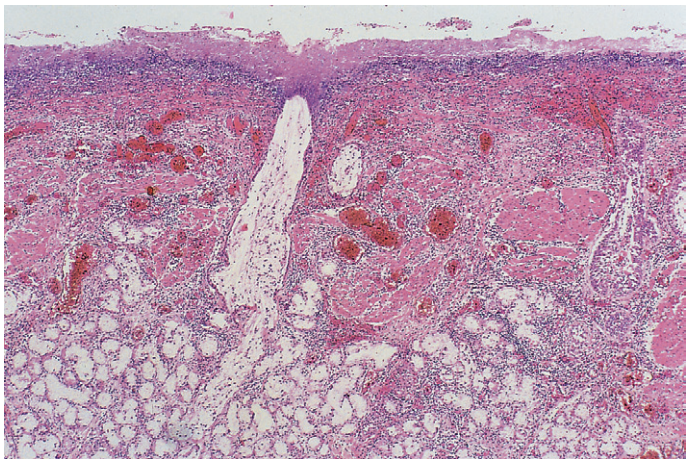

Figure 5.1.4 Influenza. This cytopathic virus has totally destroyed the bronchial epithelium, predisposing to bacterial superinfection.

Postmortem examination of two victims of the H5N1 virus showed similar evidence of diffuse alveolar damage but it was also found that viral replication in the respiratory tract had resulted in particularly high levels of cytokines such as interferons and tumour necrosis factor-α, which, with the resultant haemophagocytic syndrome, was considered to be the chief cause of death.[27] Generally, however, H5N1 viral pneumonia shows no special features and it may be difficult to distinguish the changes brought about by the H5N1 virus from those caused by viruses such as that responsible for SARS or by factors such as acid aspiration or oxygen toxicity. More specific tests such as viral isolation, in situ hybridisation and reverse transcription-polymerase chain reaction (RT-PCR) are required to confirm H5N1 infection.

Fulminant uncomplicated influenzal pneumonia is often associated with changes in other parts of the body that indicate the occurrence of influenzal viraemia[14]: among these are haemorrhagic encephalomyelitis, which is an acute infective condition distinct from postinfluenzal encephalomyelopathy, rhabdomyolysis and placentitis.[28,29]

In the healing phase of influenzal pneumonia there is conspicuous swelling of the alveolar lining cells, which proliferate and in places may virtually fill the lumen. The proliferation of alveolar lining cells may be so marked as to produce appearances somewhat resembling a neoplastic state. The changes reach their peak on about the third to fifth day of the disease and then regress, eventually subsiding completely. Also during the phase of recovery, regeneration of the bronchial epithelium may involve squamous metaplasia, but this soon gives place to normal ciliated pseudostratified respiratory tract epithelium.

Bacterial superinfection in influenza

Although pneumonia is the usual cause of death in epidemics of influenza, it is often a secondary bacterial pneumonia that is responsible. Neutrophilic exudates, organising pneumonia and bronchiolitis obliterans are then added to or replace the changes seen in uncomplicated cases.[22,24,30–33] The impact an influenza epidemic has on respiratory death rates in general is shown in Figure 5.1.5.

Before the discovery of the influenza virus in 1933, the changes that are now known to be due to the viral infection were often confused with those of complicating infections, mainly caused by bacteria. *Haemophilus influenzae* was first isolated in the 1889–90 pandemic and so named because its discoverer, Pfeiffer, recovered it from a large proportion of cases and mistook it for the cause of influenza. In the 1918–19 pandemic *H. influenzae* was again found, along with *Streptococcus pneumoniae* and *Staphylococcus aureus*.[32] With the advent of antibiotics, resistant strains of *Staphylococcus aureus* emerged and in the 1957–58 pandemic staphylococcal superinfection of the lungs was the major fatal complication of influenza. In the 1968 epidemic *Streptococcus pneumoniae* was the principal bacterial pathogen in the elderly and *Staphylococcus aureus* in the young.[30]

The relationship of the staphylococcus and the influenza virus has been much studied and there is evidence that each promotes the growth of the other.[34] Thus, certain staphylococci have a protein in their cell wall that binds to the Fc region of immunoglobulin G. In the presence of anti-influenzal serum this protein enhances staphylococcal binding to cells infected by the influenza virus[35] and in this way the staphylococcus takes advantage of the host's immune reaction to the influenza virus. In turn, the staphylococcus aids entry of the

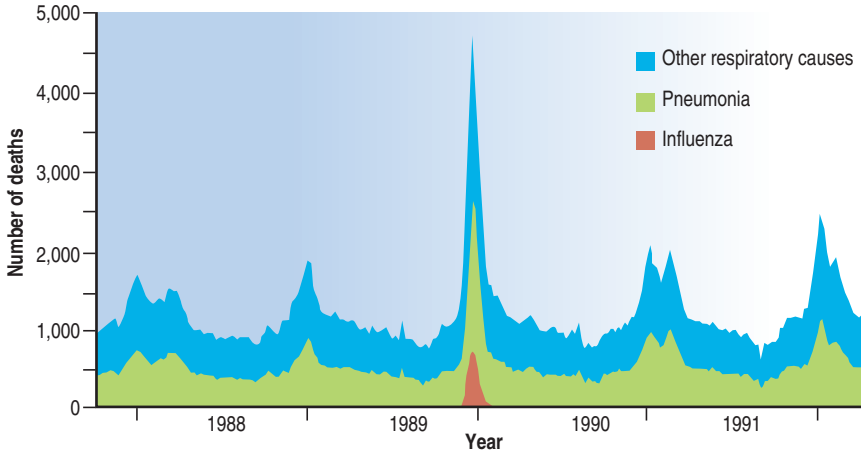

Figure 5.1.5 Weekly deaths from respiratory disease in England and Wales 1987–92, showing the impact of an influenza epidemic in 1989/90 on deaths from other respiratory diseases. *(Data supplied by the Lung and Asthma Information Centre.)*

virus into the host's cell. It does this by secreting a protease that activates a viral surface protein necessary for penetration of the host's cells[36]: normally such proteases are in short supply, so limiting the rate at which influenza virus can infect cells and reproduce. The relationship of influenza and *Streptococcus pneumoniae* infection has been studied in less detail but there is evidence of similar enhancement of bacterial adherence to tracheal epithelium following influenza infection.[37]

Parainfluenza

Parainfluenza is caused by the parainfluenza viruses, not by *Haemophilus parainfluenzae*. It is commoner in children and particularly affects the larynx, causing croup. There may be necrosis of the mucosa as in influenza (Fig. 5.1.6A), and quite frequently small polypoid growths of the bronchial and bronchiolar epithelium develop, similar to those associated with infection by respiratory syncytial virus (see below). In the lung there is hyperplasia of the alveolar epithelium and a serous exudate containing increased numbers of macrophages is seen. In immunosuppressed individuals, parainfluenza type III virus may result in a giant cell pneumonia that is indistinguishable from that of measles except that the inclusion bodies typical of measles pneumonia are not a feature (Fig. 5.1.6B).[38–41]

Respiratory syncytial virus

Epidemiology

Respiratory syncytial virus was first isolated in 1956 from an outbreak of coryza in a colony of chimpanzees and its infectivity for Man was shown when one of the investigators of this epizootic illness contracted the disease. It has since been shown that the virus frequently infects the lower respiratory passages of Man, particularly the young.[42] Specific neutralising antibodies indicative of an earlier infection are found in the serum of almost all children over the age of 5 years in Britain. Most children merely develop a cold but a few suffer from severe bronchiolitis, which in the developing world is an important cause of death in the very young.[42a,b] Those that recover are prone to develop recurrent wheeze later in childhood.[42c] The immunity infection conveys is incomplete and reinfections may occur throughout life.

Respiratory syncytial virus infection shows a marked seasonal pattern, producing annual epidemics each winter in temperate climates and in the hot rainy season in tropical countries. During an incubation period of 3–6 days the virus replicates in the upper

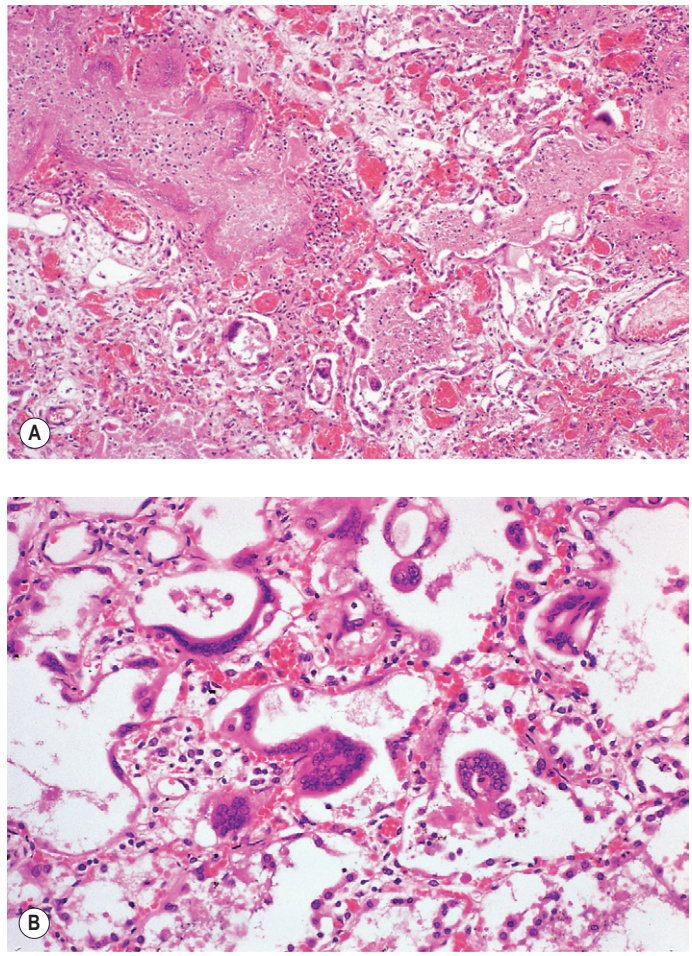

Figure 5.1.6 Parainfluenza in an immunosuppressed patient. (A) The epithelium of the bronchiole seen upper left has been destroyed and giant multinucleate epithelial cells are seen in adjacent alveoli. (B) Higher magnification of the giant cell pneumonia.

respiratory tract, causing fever, cough and coryza. Spread from the upper to the lower respiratory tract may occur, with consequent bronchiolitis and pneumonia.

Particularly important is the bronchiolitis that respiratory syncytial virus is prone to cause in infants. The conductive airways of small infants are quite narrow and easily blocked by relatively small amounts of inflammatory exudate: because of this, fatal asphyxia is liable to follow respiratory syncytial virus infection. This is particularly the case in those who have airflow obstruction as a consequence of prematurity and its treatment. Several epidemics of acute bronchiolitis due to this virus have been described among infants. These outbreaks are often remarkably focal in distribution, affecting only a comparatively small area or community. Infants with bronchopulmonary dysplasia and those who have congenital heart disease or are immunocompromised are particularly at risk and units specialising in these underlying conditions have to guard against nosocomial spread of infection.[43–45] However, most children with respiratory syncytial virus infection have no predisposing factors and even previously healthy children may suffer fatal infection.[42,46]

Pathogenesis

It is notable that infants under six months of age are particularly prone to respiratory syncytial virus infection. Although this is a period when the infant benefits from the presence of maternal antibodies, placental antibody transmission is selective, being better for immunoglobulin G than A. Breast-feeding protects against respiratory syncytial virus infection,[47] presumably by virtue of breast milk being rich in immunoglobulin A. It has been noted that infants immunized against the virus and subsequently infected naturally, suffer a more severe illness than those not so immunised,[48] suggesting that the damage is mediated immunologically.[49,50] This is supported by the finding that the typical bronchiolitis is characterised by scanty virus whereas in the rarer pneumonic form of the disease the virus is abundant. This is compatible with the bronchiolitis representing an adverse immune reaction and the pneumonia being the result of direct viral damage to the lungs.[51] The cytokine profile suggests that the reaction involved in the bronchiolitis involves a predominantly type 2 response characterised by high interleukin-10/interleukin-12 and interleukin-4/γ-interferon ratios.[52] Suspicion has fallen upon the formaldehyde inactivation of the vaccine creating reactive carbonyl groups on the antigen.[52a] Passive immunisation, conferred by monthly injection, is free of the hazards induced by active immunisation and is recommended for high-risk babies.[53]

Histopathology

The virus infects the bronchiolar epithelium and usually leads to its destruction.[54,55] Occasionally cytoplasmic inclusion bodies may be seen in degenerating bronchiolar epithelial cells or the virus may be demonstrated by immunocytochemistry.[1,55] Regeneration involves the proliferation of poorly differentiated cells which form a stratified non-ciliated epithelium. Occasionally micropolypoid epithelial protrusions are evident (Fig. 5.1.7).[8] The bronchioles are occluded by plugs of mucus, fibrin and epithelial cell debris, and cuffed by an infiltrate of lymphocytes, plasma cells and histiocytes. Except in the immediate vicinity of the bronchioles, alveoli are generally not involved in the inflammatory process. If, however, infection is on a major scale there may be pneumonia with the general features of a viral pneumonia, as described above.[46] In severe immunodeficiency, respiratory syncytial virus may cause giant cell pneumonia,[56] a condition that is more often caused by measles virus.

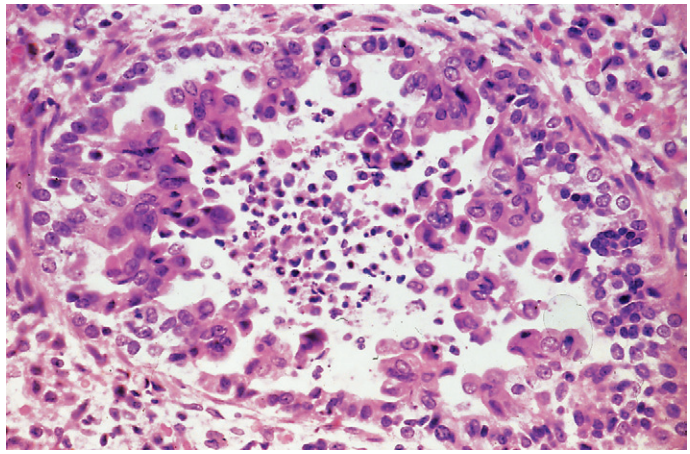

Figure 5.1.7 Respiratory syncytial virus infection in which the patency of the bronchioles is compromised by epithelial proliferation forming micropolypoid intrusions into the lumen. The bronchiolar lumen is further narrowed by a neutrophil exudate in response to secondary bacterial infection.

Metapneumovirus

Metapneumovirus was only discovered in 2001[57] but is now recognised to be ubiquitous; serological evidence of past infection is universal by the age of 5 years. Much of this goes unrecognised but metapneumovirus infection is nevertheless a leading cause of lower respiratory tract illness in young children. In one investigation the virus or its DNA was found in 20% of nasal-wash specimens previously declared virus-negative that had been collected from otherwise healthy infants and children suffering from a lower respiratory tract illness: the infection was associated with bronchiolitis in 59% of cases, pneumonia in 8%, croup in 18% and exacerbation of asthma in 14%, a spectrum of disease similar to that found with respiratory syncytial virus.[58] The pathological changes are not well described.

Measles

Clinical features and epidemiology

Measles (rubeola) is highly infectious and most children are infected soon after their maternal antibodies have waned, the peak incidence being between 1 and 5 years of age. After an incubation period of 1–2 weeks the patient develops coryza, cough and fever. The subsequent development of small red spots with a white centre (Koplik's spots) on the buccal mucosa followed by an erythematous maculopapular rash first involving the face and then the rest of the body facilitates the diagnosis. The infection resolves in about a week, following which the patient enjoys lifelong immunity.

In those parts of the world where measles has been prevalent for centuries the disease is almost invariably mild and, unless complicated by bacterial pneumonia, it has a very low mortality. In contrast, the mortality from measles may be appallingly high in lands to which the virus is newly introduced. When the disease was carried to Fiji from Australia in 1875, almost the whole population contracted it and a quarter of them succumbed. Similar outbreaks have occurred in more recent times, when the infection first reached Greenland for instance.

Measles has been regarded as one of the inevitable infections of childhood but with an effective safe vaccine now available this is no longer necessary (Fig. 5.1.8).[59] In the developed countries first and

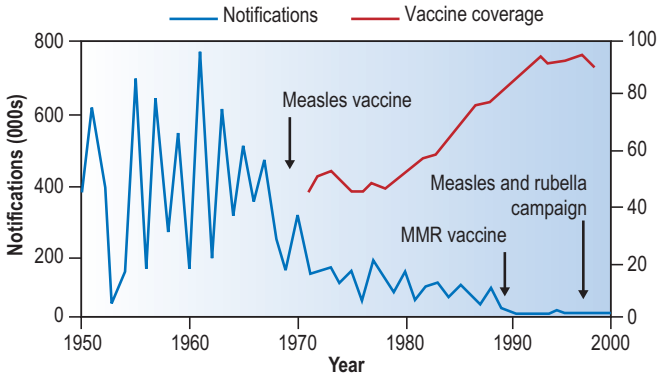

Figure 5.1.8 Annual measles notifications and vaccine coverage in England and Wales 1950–1999. *(Adapted by permission from BMJ Publishing Group Limited.[56])*

more recently in the developing world, immunisation against measles has been promoted vigorously, with spectacular success. Between 2000 and 2007 mortality from measles fell by 74% worldwide and by 89% in Africa, where it was formerly a major cause of death in childhood. The Americas were declared free of endemic measles transmission in 2002 and cases there now occur only as a result of its importation from other countries.[60,61] The disease has not yet been eradicated in the UK, partly because unfounded claims that the vaccine is responsible for autism led to declining vaccine uptake with consequent focal outbreaks of measles.[62] Other European countries still experiencing large outbreaks include the Ukraine, Switzerland and Austria.

Where measles is prevalent, the incidence is usually highest in the early spring, when droplet infections are particularly rife. The epidemics have a remarkably consistent biennial character (see Fig. 5.1.8) and the explanation of this has been the subject of several interesting hypotheses. The one most favoured envisages waning immunity over the succeeding 2 years in those children who had only a subclinical illness in the last epidemic. With the influx of two further entries into infant schools, a new population of susceptible children is formed that is liable to contract overt disease when the seasonal conditions are again favourable for the spread of the virus. In this way a fresh epidemic develops. Overt clinical disease, on the other hand, confers lifelong immunity.

If the lower respiratory tract is infected, the measles virus propagates in the epithelial cells of the main respiratory passages, leading to the destruction of many of the infected cells. In time there is recovery and multiplication of surviving cells, but at the height of the disease the natural defences of the lower respiratory tract are greatly compromised and secondary invading bacteria can successfully establish themselves in the lungs, causing bronchiolitis and pneumonia.

Pneumonia is a rare complication of measles in the western world but is common in malnourished African children, in whom it frequently proves fatal.[63] That pneumonic foci may develop in prosperous countries in the course of severe but non-fatal attacks of measles is shown by the demonstration in some such cases of patchy opacities on chest radiography; in almost all these cases the condition resolves rapidly. The cause is usually one of the common bacterial pathogens but it can be another virus taking advantage of the patient's debility and impaired cellular immunity. Measles virus infection is characterised by both the development of a strong antiviral immune response and abnormalities of immune regulation: there is often a poor skin response to common antigens and helper/suppressor T-cell ratios may be low in both the blood and bronchoalveolar lavage, suggesting that cellular immunity is impaired.[64] Thus, measles has predisposed to both adenovirus and herpesvirus pneumonia.[65,66] Secondary pulmonary infection is responsible for about half the mortality in measles.[67] Other causes of death include measles pneumonia and measles encephalitis.

Measles may also be very severe when it affects immunodeficient patients, whether they are suffering from primary immunological defects, acquired diseases such as leukaemia or conditions which require treatment with cytotoxic or immunosuppressant drugs.[68] Such patients may have unpredictable responses to measles virus. They may have a rash but fail to produce antibodies, or they may fail to develop a rash although infected with the virus. Fatal measles pneumonia in a previously healthy adult is very rare.[69]

Pathology of measles pneumonia[70,71]

Death from measles pneumonia occurs typically about 2 weeks after the appearance of the rash. At necropsy, the lungs are heavy and of rubbery consistency, and their cut surface is pale pink. Close examination may show that the small bronchi are cuffed by a greyish zone. Extensive vascular thrombosis has been a feature of some cases.

Microscopically, there are degenerative changes in the epithelium of the bronchi and bronchioles, often accompanied by hyperplasia, particularly in the small airways. As in influenzal pneumonia, squamous metaplasia may occur and mitotic figures may be numerous. Measles pneumonia may take the form of diffuse alveolar damage with hyaline membrane formation (see Fig. 5.1.3), or, more characteristically, multinucleate giant cells may line the alveolar ducts and alveoli (Fig. 5.1.9). Electron microscopy shows that the giant cells are formed from type II alveolar epithelial cells.[71,72] The giant cells contain prominent cytoplasmic and nuclear viral inclusion bodies that are clearly evident in eosin-stained sections. Being epithelial, the pulmonary giant cells are quite different from the Warthin–Finkeldey giant cells that are found in lymphoid tissue throughout the body in measles, particularly in the immediately pre-exanthematous stage.

As well as the epithelial changes, there is a heavy accumulation of macrophages, lymphocytes and plasma cells in the alveolar walls. This cellular infiltrate extends into the connective tissue surrounding the bronchioles and small bronchi, accounting for the pale cuff that is seen around them on naked-eye examination. Neutrophils are not numerous unless there is a secondary bacterial infection. The appearances are closely comparable to those found in the lungs of dogs that have died of distemper (Carre's disease), which is also caused by a paramyxovirus.

Differential diagnosis

Measles is the commonest cause of giant cell pneumonia but occasionally other viruses such as parainfluenza, respiratory syncytial and varicella-zoster viruses are responsible, especially in the immunocompromised (see Fig. 5.1.6).[38,56,73] The diagnosis is usually evident clinically or is made serologically but immunohistochemistry can be performed on tissue sections. Hard-metal disease is also characterised by the presence of alveolar epithelial polykaryons but these are more focal than those of measles, lack viral inclusion bodies and are not accompanied by such severe interstitial pneumonia (see Fig.7.1.25, p. 354).

Adenovirus

Like measles, adenovirus causes a febrile rash and infects the upper respiratory tract much more commonly than the lungs. However, adenovirus may infect the lower respiratory tract at all levels and it is a relatively common cause of pneumonia in malnourished children throughout the world.

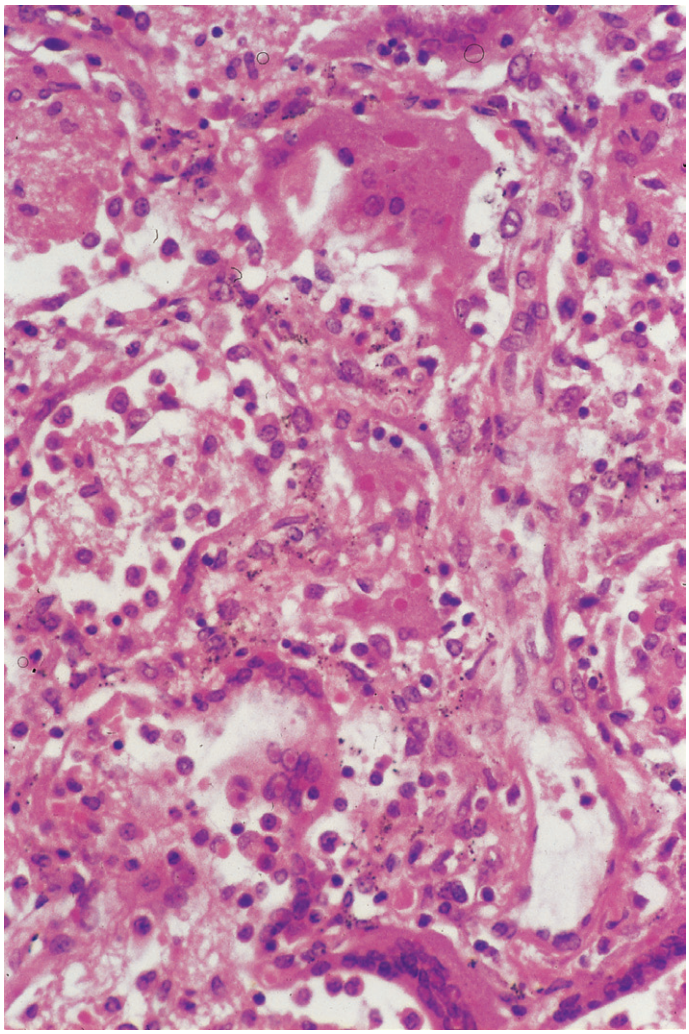

Figure 5.1.9 Measles giant cell pneumonia. There is a syncytial proliferation of type II pneumocytes containing eosinophilic cytoplasmic and nuclear viral inclusions. This response is typical of measles pneumonia but is occasionally encountered with other forms of viral pneumonia (see Fig. 5.1.6).

Adenovirus pneumonia occurs sporadically and in epidemics, particularly in children and young adults, and occasionally complicates measles.[65,66] Adenovirus pneumonia is usually combined with bronchiolitis and the lesions are most severe at the centres of the acini, being concentrated on the bronchioles. The virus causes necrosis of the bronchioles, many of which are totally destroyed or are recognisable only by their muscle coat: hyaline membranes replace the necrotic epithelium (Fig. 5.1.10A). Surviving epithelial cells show nuclear inclusions of varying staining reaction: some are diffusely basophilic or amphiphilic and fill the entire nucleus apart from a rim of chromatin (Cowdry type B) while others are eosinophilic and surrounded by a clear halo (Cowdry type A). The bronchioles are cuffed by a lymphoid infiltrate and may show proliferative epithelial activity, variously interpreted as being the result of viral stimulation or of regeneration.[54,74] The alveolar tissue shows a mononuclear interstitial pneumonia.

The intranuclear viral inclusions measure up to 5 µm and eventually disrupt the nucleus, leaving so-called smudge cells (Fig. 5.1.10B, C). Healing may be by complete resolution or the pneumonia may be complicated by bronchiolitis obliterans or bronchiectasis.[75]

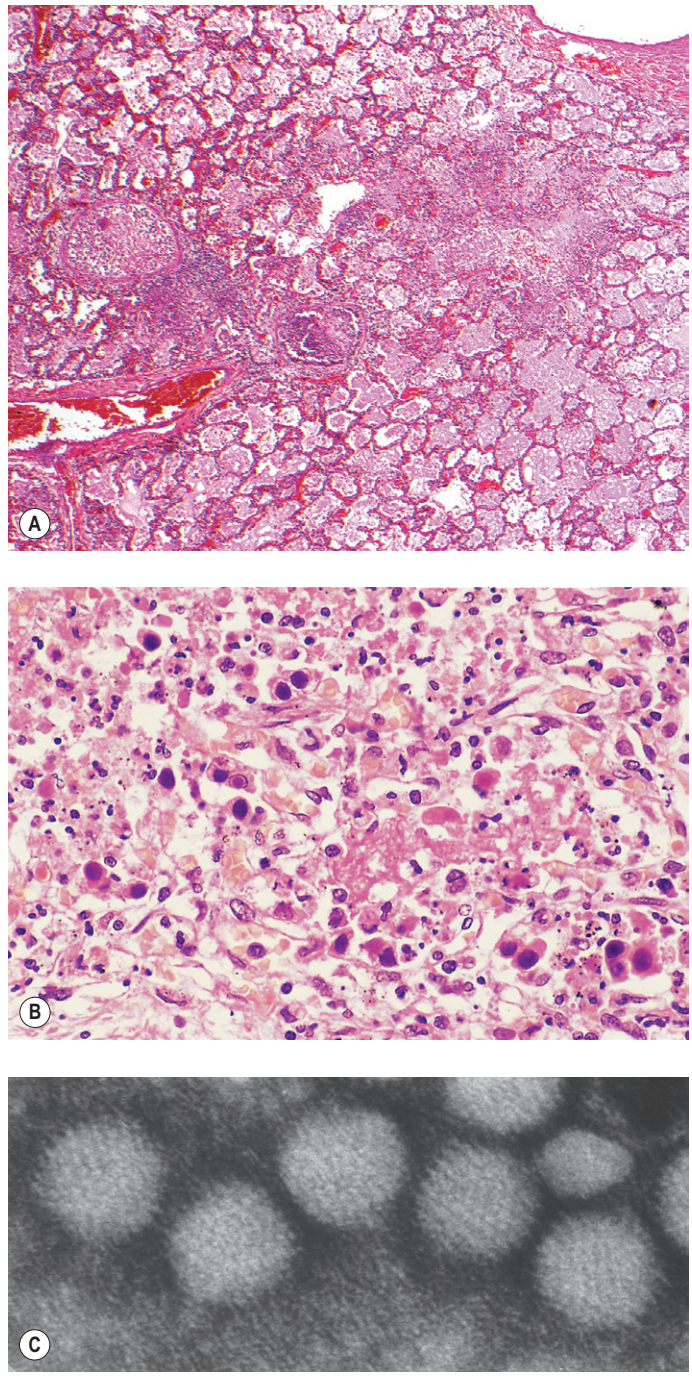

Figure 5.1.10 Adenovirus pneumonia. (A) Bronchioles bear the brunt of the damage and here show necrosis of their lining epithelium. (B) Viable alveolar lining cells contain basophilic nuclear inclusions while others are necrotic, having been reduced to eosinophilic 'smudge cells' by the viral inclusions disrupting the nucleus. (A and B from sections provided by the late Dr N Rossouw, Tygerberg, South Africa and Dr V Chrystal, Durban, South Africa.) (C) Electron microscopy shows that adenovirus particles measure 70–100 nm and have a naked icosahedral structure. *(Courtesy of Miss A Dewar, Brompton, UK.)*

Severe acute respiratory syndrome

SARS first appeared in southern China in 2002, from where it quickly traversed the globe, facilitated by air travel and coming to international attention particularly after an outbreak in Hong Kong in 2003.[76–81] Cases were subsequently identified in many countries and about 10% of those affected died.[82–85] The cause was a previously unknown coronavirus that had switched from civet cats encountered in Asian food markets and adapted to human transmission.[86,87] Transmission is air-borne but requires close person-to-person contact. There is no evidence of transmission following casual contact. The virus has subsequently been identified in Chinese horseshoe bats and it is likely that these animals represent the natural reservoir of the virus, with the civets merely acting as carriers.[88,89]

Clinical features

The incubation period ranges from 1 to 10 days, following which there is a prodromal fever, cough and dyspnoea. Less common symptoms include headache, diarrhoea, dizziness, myalgia, chills, nausea, vomiting and rigor.[90] There is no apparent sex predilection and the age distribution is wide. Common laboratory features include lymphopenia involving both CD4 and CD8 lymphocytes, thrombocytopenia, prolonged thromboplastin time, elevated alanine transminase, lactate dehydrogenase and creatinine kinase. Positive viral recovery rates from urine, nasopharyngeal aspirate and stool specimen have been reported to be 42%, 68% and 97% respectively on day 14 of illness, whereas serological confirmation may take 28 days to reach a detection rate above 90%. However, quantitative measurement of blood SARS coronavirus RNA using real-time RT-PCR techniques has a detection rate of 80% as early as day 1 of hospital admission.[91]

Radiographic abnormalities include focal, multifocal or diffuse opacities. Computed tomography is more sensitive, sometimes showing extensive consolidation in patients with normal chest radiographs. However, the radiological features are not specific and need to be correlated with the clinical and histological findings.[92]

Pathogenesis

Although pulmonary involvement is the dominant clinical manifestation, extrapulmonary features are common and the virus can often be recovered from faeces and urine, indicating that it is widely distributed in the body. The identification of a specific receptor for the virus is relevant to its tissue distribution. The receptor, a metallopeptidase known as angiotensin-converting enzyme 2, is expressed particularly strongly by pulmonary alveolar and small intestinal epithelia and vascular endothelia.[93–95]

Pathology

The histology varies according to the duration of illness but the predominant pattern is diffuse alveolar damage.[96–100] Cases of less than 10 days' duration show air space oedema and hyaline membranes whereas those of longer duration exhibit type II pneumocyte hyperplasia, squamous metaplasia, multinucleated giant cells and acute bronchopneumonia succeeded by intra-alveolar organisation.[26,96] The alveolar pneumocytes may also show striking cytomegaly with granular amphophilic cytoplasm (Fig. 5.1.11), that sometimes contains eosinophilic inclusions akin to the Mallory bodies of alcoholic hepatitis.[96,97] Less common features include haemophagocytosis and thrombosis.[97,99] The virus can be identified by RT-PCR in fresh or formalin-fixed, paraffin-embedded lung tissue. Electron microscopy may reveal the viral particles in the cytoplasm of epithelial cells.[97–99]

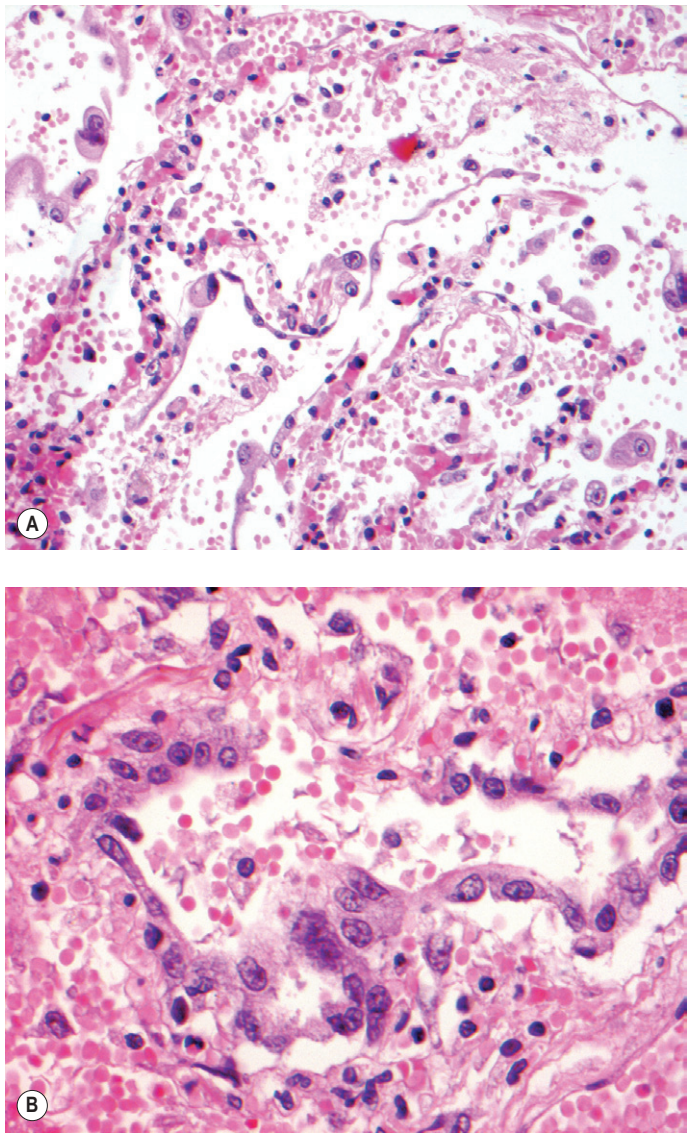

Figure 5.1.11 Severe acute respiratory syndrome. (A) The features of early diffuse alveolar damage are seen, consisting of extravasation of red blood cells, desquamation, an acute and chronic interstitial inflammatory infiltrate and a few hyaline membranes. (B) Regenerating epithelial cells show nuclear atypia.

Treatment and prognosis

Treatment with corticosteroids, broad-spectrum antibiotics and antiviral agents has been beneficial.[98,102] Interferon-α may also have a role.[103] However, infection control is as important as pharmacological therapy in this disease.

In the acute phase, SARS is associated with considerable morbidity and mortality, with a global case fatality rate ranging from 7 to 27% (average about 11%). Adverse prognostic factors include advanced age, coexistent disease, high lactose dehydrogenase levels and high initial neutrophil counts. CT data on the extent of the disease are also useful in assessing prognosis.[104] Clinical follow-up of patients who recover has demonstrated residual abnormalities of varying degree, including abnormal lung function and patchy fibrosis.[105,106] Many survivors also experienced transient pituitary dysfunction.[107]

Herpes simplex[108,109]

Virology and predisposing causes

Herpes simplex virus typically causes mucocutaneous vesiculation, serotype 1 (HSV1) generally affecting the oronasal area and serotype 2 (HSV2) the genital mucosae. As with all herpesviruses, infection is lifelong; the virus remains dormant until immunity weakens, which may be triggered by a variety of factors. In these circumstances either serotype may involve the lower respiratory tract. Respiratory infection by HSV1 is more commonly encountered in adults, the infection spreading from the oropharynx, whereas neonatal respiratory infection is usually due to HSV2 as a component of generalised haematogenous disease.[110,111] Infection of the lower respiratory tract takes the form of tracheobronchitis or pneumonia. Herpes simplex tracheobronchitis is predisposed to by damage to the respiratory epithelium, especially factors that lead to squamous metaplasia, such as endotracheal intubation and burns.[112–116] Risk factors for herpes simplex pneumonia include transplantation,[117] cytotoxic chemotherapy and human immunodeficiency virus (HIV) infection[118]: herpes simplex pneumonia is rare in the immunocompetent.[119]

Pathology

In herpes simplex tracheobronchitis there is extensive mucosal ulceration and pseudomembrane formation. Viral inclusions are most prominent at the periphery of the ulcers and may be identified in exfoliated cells (Fig. 5.1.12). If they are not well developed an immunostain may establish the diagnosis. Long-standing airway infection leads to luminal narrowing and obstructive features. In the lungs the changes are very similar to those of adenovirus pneumonia, including the presence of Cowdry type B ground-glass intranuclear viral inclusions, although these are more eosinophilic than those of adenovirus. Both adenovirus and herpes simplex pneumonia bear a superficial resemblance to bacterial bronchopneumonia but the similarity is in the distribution of the lesions rather than their character: the bronchioles and centriacinar alveoli are mainly affected but the lesions are characterised by necrosis and the accumulation of nuclear debris rather than exudation of neutrophils. Occasionally herpes simplex infection takes the form of a focal necrotising pneumonia more typical of varicella infection (see below). Alternatively there may be arterial involvement in herpes simplex pneumonia with a necrotising vasculitis affecting small and medium-sized pulmonary arteries.[120] Sometimes the pneumonia is diffuse: it is suggested that focal disease represents extension of oral mucocutaneous herpesvirus infection down the tracheobronchial tree into the lung whereas diffuse pneumonia is the result of haematogenous spread.[108]

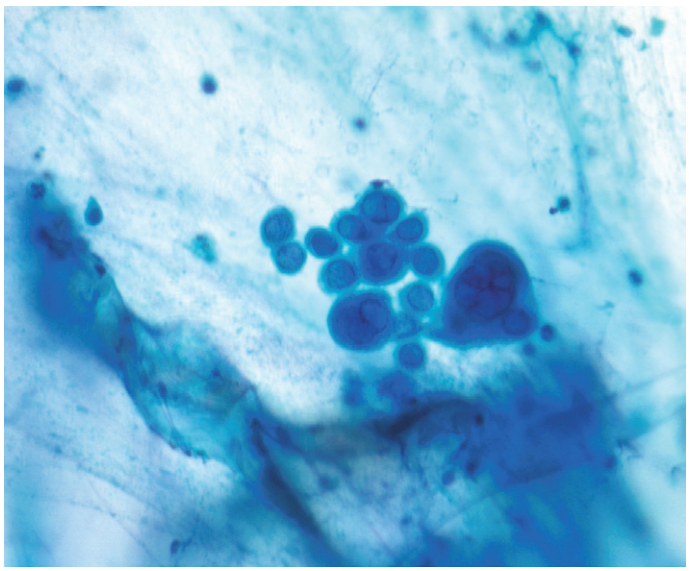

Figure 5.1.12 Herpes simplex virus. Bronchial brushings from an ulcer in the lower trachea show multinucleate epithelial cells with glassy nuclear features. From a patient with oral herpes who had started steroid therapy for asthma.

Cytomegalovirus

Virology and epidemiology

Cytomegalovirus is the largest of the herpesviruses and is widespread in most communities, persisting for life, like all herpesviruses. It is transmitted in saliva and blood and by sexual contact and organ transplantation. Seropositivity, taken to indicate carriage of the virus, steadily increases with age. The prevalence of seropositivity in adults is generally over 50% and approaches 100% in homosexual men. However, carriage of the virus does not necessarily equate with disease. The immunocompetent host is unlikely to experience any recognisable clinical effects of cytomegalovirus infection.

Symptomatic cytomegalovirus infection is seen in newborn children infected before birth by virus carried by their mother, and in adults who have undergone organ transplantation or have been infected with HIV. In the newborn the disease presents as an acute fatal infection with jaundice and leukoerythroblastic anaemia.

Cytomegalovirus is a serious pathogen in transplantation recipients,[121] possibly because the virus replicates best in cells that are activated, as in a transplanted organ. The risk is greatest with bone marrow transplantation, intermediate with heart, lung and liver transplantation and lowest with renal transplantation. However, donor and recipient matching for cytomegalovirus status has reduced the incidence of transmission from the donor. Before the introduction of this policy, fatal cytomegalovirus pneumonia or systemic infection was common. Today reactivation of latent infection is a more common problem but it is important to distinguish the mere presence of viral inclusions from pneumonitis. When a lymphoid infiltrate accompanies the viral inclusions it is also important to distinguish an infective pneumonitis from lung allograft rejection: generally, the infiltrate of cytomegalovirus pneumonia lacks the perivascular lymphocyte distribution seen in rejection. As well as causing a pneumonitis that has to be distinguished from rejection, cytomegalovirus may be involved in chronic lung rejection.[122] It has been speculated that cytomegalovirus could promote allograft rejection by stimulating the production of proinflammatory cytokines or increasing the expression of major histocompatibility complex molecules.

The position of cytomegalovirus in regard to pulmonary disease in acquired immunodeficiency syndrome (AIDS) can also be difficult to determine. Cytomegalovirus inclusions are frequently encountered in AIDS but it is often difficult to determine whether pathological changes are due to the virus or to accompanying bacterial or *Pneumocystis* infection. Only occasionally is cytomegalovirus the only pathogen identified in severe pneumonia in AIDS patients.[123] Some investigators claim that cytomegalovirus contributes to the high mortality from pneumonia in AIDS patients[124] while others view it merely as a bystander rather than the primary pathogen in these patients.[125] Sometimes, replication of the virus is unaccompanied by any significant degree of pulmonary inflammation or damage,[126] indicating a poor host response, which, as in other viral infections, largely involves T lymphocytes, cells that are particularly defective in AIDS. The differing roles of cytomegalovirus in AIDS and transplant recipients have led to the view that the pathological changes are not a direct

effect of the virus but an immunopathological condition attributable to the T-cell response to the virus.[127]

Pathological features

The pneumonia may be unilateral or bilateral, and generally involves the lower lobes; advanced lesions may appear as reddish purple nodular areas. Two patterns of pulmonary involvement have been described in bone marrow transplant recipients: a fulminant systemic infection characterised by a miliary pattern of disease and a more insidious disease with a more diffuse distribution in the lungs.[121]

Histologically, there is a chronic interstitial pneumonitis and some of the alveolar epithelial cells are enlarged and contain characteristic inclusions. These measure up to as much as 10 µm in diameter and are surrounded by a clear zone inside the nuclear membrane (Fig. 5.1.13). These Cowdry type A intranuclear inclusions have been likened to an owl's eyes. The inclusions represent clumped chromatin and the clear zone the virus. Cytoplasmic inclusions up to 2 µm in diameter are often also present. Severe cases may show a necrotising pneumonia or tracheobronchitis without the inclusions being well developed, in which case immunocytochemistry or in situ hybridisation may be used to advantage as these techniques show that many more cells are infected than those containing the characteristic inclusions (see Fig. 5.1.13D).[6,7,128] Diffuse alveolar damage is a further pattern of disease that is occasionally seen in cytomegalovirus pneumonia.

HIV and AIDS

Virology and means of spread

The HIVs belong to the lentivirus subfamily of the retroviruses and are thought to have originated from chimpanzees, which harbour the closely related simian immunodeficiency virus. They are the cause of AIDS and are transmitted primarily through sexual contact, by anal or vaginal intercourse with an HIV-positive person. Other routes of transmission are by exposure to infected blood, generally through the use of contaminated needles and syringes by drug addicts. Infected blood products and donor tissues are other potential sources of infection. An infected woman can pass the virus to her child in utero, at delivery or through breast-feeding. Occupational acquisition of HIV is unusual but has occurred, chiefly through needlestick injuries. In histopathology departments, particular care is required in handling unfixed tissues, as in preparing frozen sections and conducting autopsies. Fixed tissues do not present a risk of infection. Most national bodies have produced guidelines for safe laboratory practice in the AIDS era.[129] HIV infection is not always recognisable and a practical approach is therefore to treat every cadaver and all unfixed tissue as if it were infectious.

Pathogenesis of AIDS

Following entry into the body and the development of neutralising antibodies, HIV is found in highest concentration within the germinal centres of lymphoid tissue where it can be demonstrated by immunohistochemistry attached to a follicular dendritic cell.[129a] The virus attacks both the follicular dendritic cells and the CD4+ helper T lymphocytes and blood levels of these latter cells below 200/µL are associated with the development of a variety of AIDS-defining conditions. The interferon-γ-secreting Th1 cells that are central to immune defence against a variety of other infections are particularly vulnerable to attack. Once HIV infection has occurred, antibody develops, generally within a month, and after a period that is usually measured in years CD4 counts drop and manifestations of AIDS develop. Concentrations of virus in the blood and body fluids are particularly high around the time of seroconversion and when AIDS develops.

Epidemiology

AIDS was first recognised in 1981 in Haiti, since when it has spread widely and few countries are now spared its ravages. A quarter of a century after its first recognition AIDS had killed about 25 million people and about 65 million had been infected with HIV. Many of those harbouring HIV do not know they are infected. The number of people infected with HIV is rising, because of population growth and because drug treatment is prolonging life. The epidemic is worst in sub-Saharan Africa and next the Caribbean but it is growing fastest in eastern Europe and central Asia. Worldwide, women make up about half of those infected with HIV, with the largest number in sub-Saharan Africa. Since the introduction of highly active antiretroviral therapy (HAART) mortality rates have declined and life expectancy improved amongst those so treated, but these benefits have so far been largely confined to the industrialised countries.

Pathology

Few organs escape the ravages of fully developed AIDS but the lungs are those most frequently involved in many series.[130,131] AIDS has many pulmonary manifestations, all of which are described in detail under their relevant headings. Most are secondary to the immunodeficiency but it is possible that certain lymphocytic infiltrates reflect HIV infection of the lung. These are generally non-specific T-cell infiltrates, which are largely CD8+ and milder than those that characterise lymphoid interstitial pneumonia[132–136]; HIV has been identified in the lung tissue by in situ hybridisation in a minority of cases.[135] The heavier lymphoid infiltrates of lymphoid interstitial pneumonia seen in HIV-infected children largely comprise CD8+ HIV-specific lymphocytes. Such children have fewer opportunistic infections and survive longer than other HIV-positive children, suggesting that in this setting lymphoid interstitial pneumonia reflects an effective immune response.[137] Experiments in mice suggest that viral persistence and interferon-γ production are involved.[138,139]

The commonest pulmonary manifestations of AIDS are listed in Table 5.1.1.[140–150] Rarer pulmonary manifestations include infection by herpes simplex[118,151] and varicella-zoster[152] viruses, *Blastomyces dermatitidis*,[153] *Candida* species,[152] cryptosporidia,[154] microsporidia[155] and *Strongyloides stercoralis*.[152] There is also an increased incidence of respiratory infection by common pyogenic organisms,[143,156,157] especially *Streptococcus pneumoniae* and *Haemophilus influenzae*,[152] sometimes resulting in obliterative bronchiolitis[158] or unusual diseases such as bacterial tracheitis[159] where the trachea is narrowed by pus or necrotic material containing colonies of mixed bacteria. Tuberculosis has also made an unwelcome resurgence since the advent of AIDS.[160–162] Opportunistic mycobacterial infection,[163] malakoplakia,[164,165] bacillary angiomatosis,[166] secondary alveolar lipoproteinosis,[167] follicular bronchitis and bronchiolitis[149] are also encountered in AIDS patients. However, there are marked geographical differences in the incidences of these manifestations of AIDS: tuberculosis is particularly common in poor countries whereas *Pneumocystis*, non-tuberculous mycobacteriosis and lymphoma are commoner in richer communities. Since the 1990s there has been a trend towards multiple infections, more mycobacterial disease and less *Pneumocystis* infection and Kaposi's sarcoma.[130,142,168]

In most cases the secondary pulmonary infections can be diagnosed from material obtained through the fibreoptic bronchoscope (brushings, washings, lavage or biopsy)[169] or from sputum[170] but occasionally a particular pulmonary manifestation of AIDS is not revealed until open biopsy is undertaken or examination is made postmortem.

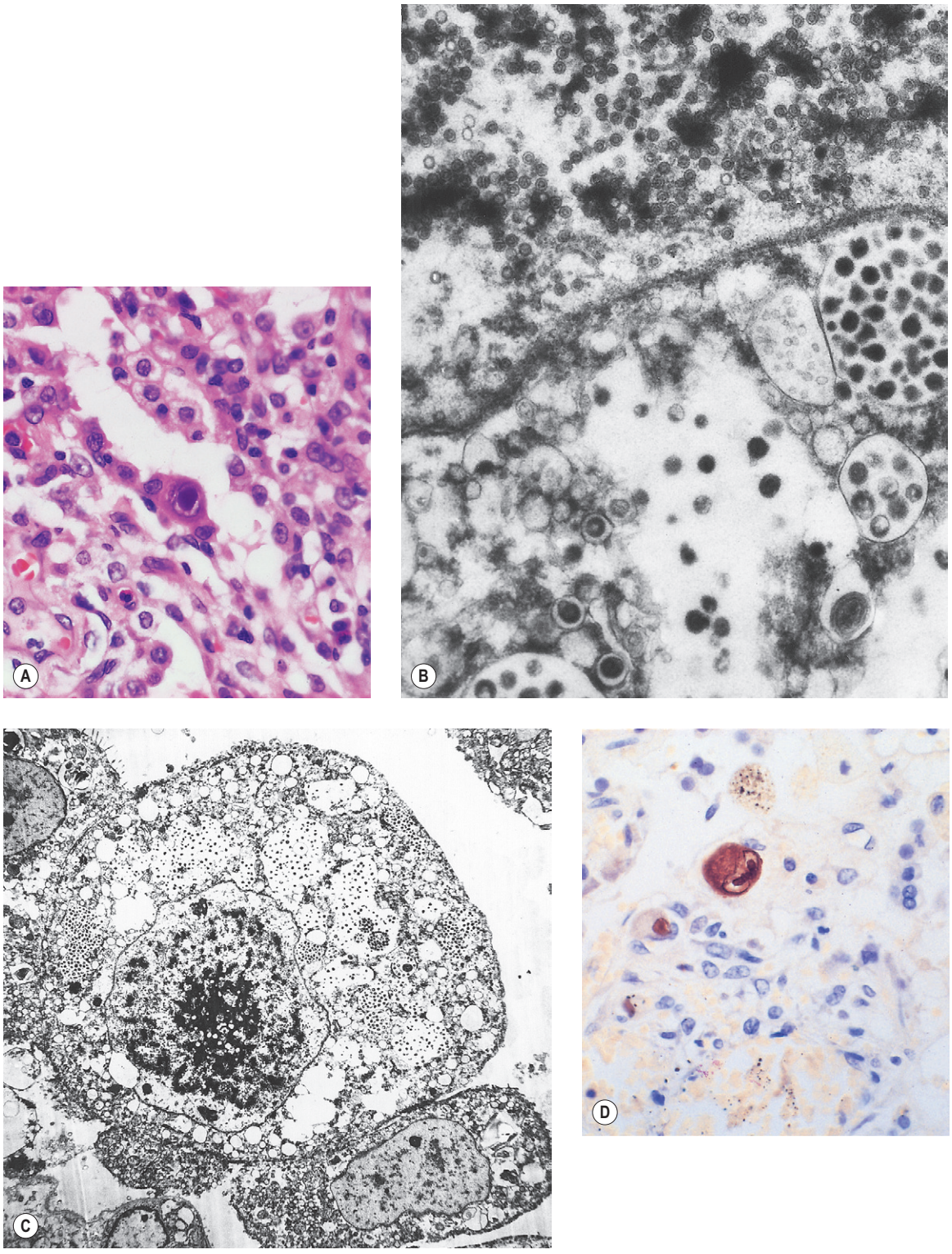

Figure 5.1.13 Cytomegalovirus pneumonia. (A) There is a prominent nuclear inclusion in the centre of the field. (B) Electron micrograph of an alveolar epithelial cell infected by cytomegalovirus. Numerous viral particles are evident in both nucleus (above) and cytoplasm (below). As the viral particles leave the nucleus and enter the cytoplasm they acquire a coating derived from the nuclear envelope and consequently enlarge. (C) Low-power electron micrograph of the cell seen in (B), showing that it is greatly enlarged compared with its neighbours. Coated viral particles are evident in the cytoplasm but uncoated particles in the nucleus are too small to be recognised at this magnification. However, characteristic central clumping of the chromatin is evident. (B and C courtesy of Miss A Dewar, Brompton, UK.) (D) Immunocytochemistry shows abundant virus in the cytoplasm as well as the nucleus (immunoperoxidase stain).

Table 5.1.1 The varieties of pulmonary disease described in 131 patients with AIDS.[137,138] The opportunistic invaders are often present in combination and the inflammatory reaction to them is often atypical: for example, the reaction to mycobacterial infection (frequently *Mycobacterium avium-intracellulare*) is often non-granulomatous, whilst *Pneumocystis jirovecii* may provoke a granulomatous response or diffuse alveolar damage, rather than the usual foamy alveolar exudate

	Patients (%)
Opportunistic infection	
Pneumocystis jirovecii pneumonia[a]	63
Cytomegalovirus pneumonia	19
Mycobacterial pneumonia	13
Bacterial pneumonia[a]	8
Invasive candidiasis	2
Toxoplasmosis	2
Cryptococcosis	1
Invasive aspergillosis	1
Histoplasmosis	1
Non-infectious diseases	
Diffuse alveolar damage	15
Kaposi's sarcoma	9
Non-specific interstitial pneumonitis[a]	5
Pulmonary haemorrhage	3
Pulmonary lymphoid hyperplasia[b]	0
Lymphoid interstitial pneumonia	2
Lymphoma[a]	2

[a]Since the introduction of highly active antiretroviral therapy (HAART), *P. jirovecii* pneumonia has become less common while bacterial pneumonia and lymphoma have increased.[139–141]

[b]Pulmonary lymphoid hyperplasia is seen particularly in children suffering from acquired immunodeficiency syndrome (AIDS)[142–145] but is also recorded in occasional adults.[146] Together with lymphoid interstitial pneumonia, pulmonary lymphoma and the sicca syndrome,[147] it forms a spectrum of pulmonary lymphoproliferative disease in AIDS and other conditions.

Rapidly progressive plexogenic pulmonary hypertension is also reported in persons infected by HIV but generally not evincing AIDS.[171–176] The lungs are often otherwise normal. The virus has not been identified in the pulmonary vessels but tubuloreticular structures suggestive of cytokine accumulation have been identified there by electron microscopy in HIV-positive individuals.[177] Less frequently, veno-occlusive disease or thrombotic arteriopathy is the basis of HIV-associated pulmonary hypertension. Emboli of foreign particulate material may also be found in the lungs of patients who have acquired their HIV infection through the intravenous injection of drugs formulated for oral use, while a variety of vasculitides affecting various organs including the lungs is described.[178]

As well as the neoplastic manifestations of AIDS listed in Table 5.1.1 (Kaposi's sarcoma and lymphoma), the incidence of carcinoma of the lung is increased in AIDS and the affected patients are younger than those in the general population.[179–181] All these tumours may present as endobronchial lesions, as may tuberculosis and aspergillosis in AIDS patients.[182] The lymphomas include diffuse large B-cell lymphomas that take the form of mass lesions within the lungs and primary effusion lymphomas affecting the pleura.

Drug toxicity

HAART drug toxicity contributes up to 2% of deaths among HIV-infected patients so treated. The toxicity is mainly hepatic but sarcoid-like nodules have been reported in the lungs,[183] probably reflecting immune restoration.[184] Recovery of immune status may give rise to an active and often dramatic inflammatory response to previously indolent infections, which has been termed the immune reconstitution syndrome (IRIS).[185] It is also suggested that it is HAART rather than HIV that is responsible for the pulmonary hypertension referred to above.[186]

Chickenpox (varicella) and herpes zoster

The manifestations of chickenpox and herpes zoster are generally confined to the skin but visceral involvement occurs on rare occasions.[187,188] Since chickenpox is so common in childhood, most adults are immune. However when chickenpox affects adults, especially pregnant women, it carries a risk of fulminating varicella pneumonia, which can be rapidly fatal. The fetus is also at risk: in the first two trimesters of pregnancy chickenpox may result in embryopathy and in the last trimester it may cause neonatal pneumonia. The immunocompromised, including those receiving systemic corticosteroids, are particularly prone to suffer severe infections, including pneumonia.[189] The severe forms of chickenpox sometimes encountered in otherwise healthy adults may involve the lungs but recognition of this is often retrospective; the healed lesions may produce characteristic radiographic changes, namely innumerable small foci of calcification.[190,191] Such patients are generally cigarette smokers.[192]

Pathological features

The pneumonias of varicella and herpes zoster pneumonia are identical.[193] They represent a focal necrotising condition that lacks any apparent relation to the acinar architecture (Fig. 5.1.14A). It starts as a fibrinous exudate, involving several adjacent alveoli, and goes on to destroy the intervening alveolar walls. Eosinophilic intranuclear viral inclusions may be evident in bronchiolar or alveolar epithelial cells. Giant cell pneumonia is a rare manifestation of varicella-zoster infection.[73]

Healing results in circumscribed fibrous nodules that measure up to 5 mm in diameter and are prone to calcify (Fig. 5.1.14B, C).[190,191] Numerous calcified opacities scattered throughout the lung fields present a radiographic appearance that, outside the USA and other countries where histoplasmosis is endemic, is virtually diagnostic of previous chickenpox pneumonia.

Smallpox (variola)

In 1980 the world was declared free of smallpox and it is to be hoped that this section is only of historical interest. Severe smallpox was often accompanied by acute ulcerative tracheobronchitis and pneumonia. The latter was ordinarily due to secondary bacterial infection, but interstitial lesions of viral type were also found.

A condition described as 'smallpox handler's lung' was also observed. This affected nursing and medical staff attending patients with smallpox. It was characterised by high fever and prostration: radiological examination showed widespread mottling of the lungs

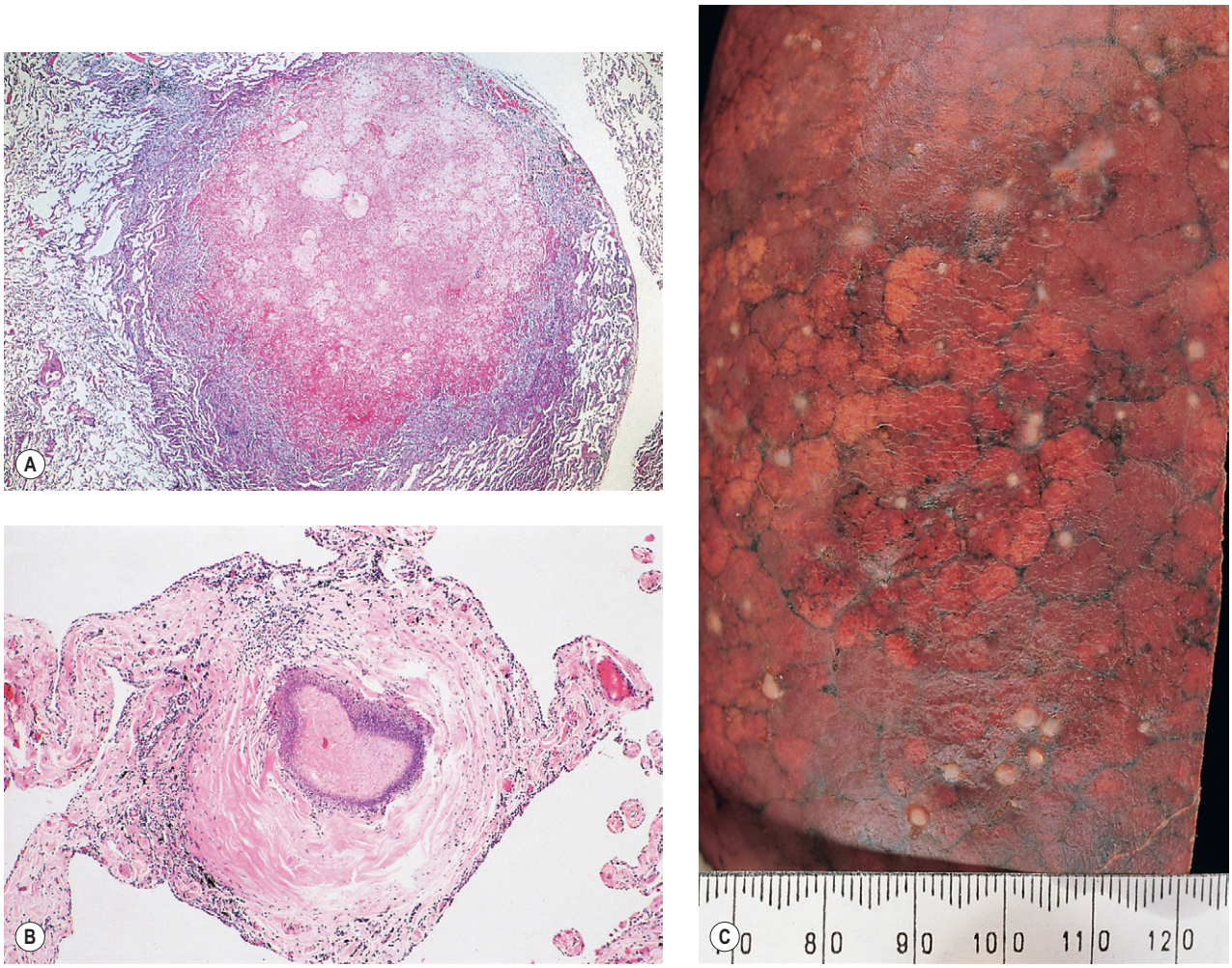

Figure 5.1.14 Chickenpox pneumonia. (A) Lung showing a focus of necrosis similar to that more commonly encountered in the skin. (B) Healed chickenpox pneumonia showing central dystrophic calcification. (C) Healed chickenpox pneumonia evident macroscopically as numerous hard, pale micronodules scattered through the lungs. *(Courtesy of Dr GA Russell, Tunbridge Wells, UK.)*

with shadows up to several millimetres across. Typically, there were no catarrhal symptoms and recovery appeared to be the rule. These patients were well immunised by previous vaccination against smallpox and did not develop a rash. The pulmonary changes may have represented an allergic reaction to smallpox virus inhaled in the dust of scales desquamated by their patients, but it was never possible to study the pathological changes.

Hantavirus pulmonary syndrome

Hantaviruses are best known as the cause of haemorrhagic renal fever but they also cause a (non-haemorrhagic) pulmonary syndrome. This was first recognised in 1993 when an unusual respiratory illness was noted in rural communities in the south-west of the USA and soon identified as a previously unrecognised hantavirus infection.[194–196] As with the previously recognised hantaviruses, that responsible for the pulmonary syndrome is maintained in the wild in a single species of rodent, in this case the deer mouse, *Peromyscus maniculatus*, which is widely distributed across North America. Like other mice they are inclined to impinge on humans in their hunt for food and there had been a marked increase in the number of deer mice in the south-west USA in 1993. Transmission of the virus is believed to be by inhalation of dried mouse excreta. Further cases have subsequently been identified in other parts of the USA and retrospective studies of archival material have shown that cases existed before 1993, the earliest in 1978.[197] The name Muerto Canyon virus was initially proposed for the hantavirus responsible for the pulmonary syndrome but this has given way to Sin Nombre virus. It is now know to be a member of the *Bunyaviridae* family of RNA viruses.

Cases of hantavirus pulmonary syndrome have subsequently been identified in several South American countries, with one outbreak in southern Argentina being unusual in that there appeared to be person-to-person transmission,[198] a feature that has so far not been observed in any other form of hantavirus infection.

Clinical features

The hantavirus pulmonary syndrome commences with a prodromal illness characterised by fever and myalgia, and perhaps nausea, vomiting, abdominal pain, headache and dizziness.[194,195] After a few days, a cardiopulmonary phase is heralded by progressive cough and shortness of breath. Common physical findings at this stage are tachypnoea, tachycardia, hypotension and fever. Radiographic findings include the rapid development of pulmonary oedema. Most of the

original 17 patients with laboratory-confirmed disease required intubation and mechanical ventilation and this led to large volumes of clear proteinaceous fluid being obtained by endotracheal suction. In 13 cases (76%) intractable hypotension terminated in cardiac dysrhythmia and death within 2–16 (median 7) days of the onset of symptoms.

Pathological features

Autopsy shows heavy oedematous lungs and large, serous pleural effusions. Microscopy confirms the oedema and shows interstitial lymphocytic infiltrates.[195,196,199] Hyaline membranes have been described in some studies.[200,201] Neutrophils are scarce and viral inclusions are not found. Despite the profound circulatory failure the heart is normal. Lymphocytosis is evident in the liver, spleen and lymph nodes. Immunocytochemistry shows viral antigen in pulmonary endothelial cells and virus-like particles are evident in these cells on electron microscopy. The target of infection appears to be the capillary endothelium in all organs with particularly heavy involvement of those in the lung, resulting in increased pulmonary vascular permeability.

The diagnosis is now made by serological tests that detect specific IgM antibodies or a fourfold rise in IgG antibodies. Immunocytochemistry and PCR are used to detect the virus in tissue. The danger to mortuary and laboratory staff is unknown but in view of the high mortality rate, full precautionary measures are advocated.[202] Treatment is supportive. Prevention is based on methods that minimise contact with the rodent vectors.

Mycoplasmal pneumonia

Epidemiology and microbiology

During the 1930s, cases of a mild form of pneumonia were reported that clinically were unlike those attributable to bacterial infection. None of the bacteria known to cause pneumonia could be recovered from the sputum, and as long as the condition was uncomplicated by secondary bacterial infection the leukocyte count in the blood showed little tendency to rise. Cases often occurred in small community epidemics in schools, colleges and camps, although even under these conditions, which are usually conducive to the spread of respiratory infections, the disease was not highly contagious. It became known as primary atypical pneumonia.

The aetiology of primary atypical pneumonia attracted much interest and the first advance came in 1944 with the isolation of an organism that became widely known as the 'Eaton agent' after its discoverer. That this agent is specifically concerned with the clinical disease is indicated by the rise in specific antibodies that occurs during the course of the illness. The infection, mainly in subclinical form, has become widely prevalent, as is shown by the frequency with which specific antibodies can be detected in the serum of healthy people in the general population. The clinical disease accounts for 18% of all community-acquired pneumonia requiring admission to hospital, a frequency second only to that of pneumococcal pneumonia.[203]

Because the disease could be transmitted to both experimental animals and human volunteers by filtrates of sputum from cases of primary atypical pneumonia, the Eaton agent was at first regarded as a virus. Later studies indicated instead that it belongs to the group of 'pleuropneumonia-like' organisms (PPLO) – the mycoplasmas which can pass through a coarse bacterial filter. The organism is now known as *Mycoplasma pneumoniae*: it is one of the considerable number of mycoplasmas that have been recognised in humans, animals, plants and soil. Because of their ubiquity in rats and mice, any experiments involving the lungs of these animals are soon bedevilled by the development of bronchiectasis, pneumonia, lung abscess and empyema, unless specific pathogen-free strains are used.

For a time, *M. pneumoniae* was regarded as the L form of *Streptococcus MG*, a non-haemolytic streptococcus that is agglutinated by the serum of some 10% of patients with *Mycoplasma* pneumonia and that was isolated originally from a case of the latter at necropsy: comparative studies of the nucleic acids of the two organisms have shown that they are in fact unrelated. The explanation of the presence of agglutinins against *Streptococcus MG* is probably a matter of shared antigens. In about half the cases the patient's serum agglutinates group O red blood cells at a temperature between 0 and 5°C (cold haemagglutination test), but the diagnosis is best established by demonstrating antibodies to *M. pneumoniae* in the patient's serum or more recently by PCR assay.[204,205]

Clinical features

The organism generally follows a 4-yearly epidemic cycle and predominantly affects younger patients. There is a wide spectrum of respiratory disease, including sore throat, otitis media, sinusitis, laryngitis, bronchitis, bronchiolitis and pneumonia. The chief clinical features are cough, fever, headache and malaise, sometimes associated with rashes, arthritis and haemolytic anaemia. Pneumonia develops in about 10% of cases and is characterised by a more gradual onset than acute bacterial pneumonia. Chest radiography shows irregular, ill-defined opacities, usually in the hilar region and sometimes bilateral. It is characteristic of the disease that the radiological changes are much more extensive than the comparatively mild clinical manifestations indicate. The case fatality rate is low, of the order of 1 in 1000 patients, and the pulmonary opacities that are conspicuous during the 10 days or so that the illness lasts gradually resolve during the ensuing days of convalescence.

Pathogenesis

The pathogenesis of *M. pneumoniae* infection has been studied in animal models and organ cultures of human respiratory epithelium. The organisms adhere to the respiratory epithelial cells and inhibit ciliary activity. Infected cells show cytoplasmic vacuolation and nuclear swelling, with progression to complete loss of cilia.[206,207] The loss of cilia predisposes the more distal lung to secondary bacterial superinfection but the *Mycoplasma* may also affect the distal parenchyma directly.

Immunodeficient animals show reduced severity of mycoplasmal pneumonia and it is likely that immune mechanisms are involved in the pathogenicity of the disease. Autoantibodies are produced in response to *Mycoplasma* infection, probably as a result of mycoplasmal antigens being shared by host cells; such antibodies could account for many of the bronchopulmonary and extrapulmonary manifestations of the disease.

Histopathology

There have been few opportunities for histological study of the lesions in primary atypical pneumonia but when undertaken it generally discloses widespread bronchiolitis and chronic interstitial pneumonia similar to that caused by many respiratory viruses.[208,209] The bronchiolitis sometimes progresses to epithelial ulceration. Lymphocytic infiltration of the walls of alveolar ducts and alveoli characterises the interstitial pneumonia whilst oedema fluid, red blood cells and macrophages are found in many groups of alveoli, and an occasional alveolus may contain hyaline membranes. Neutrophils are generally less numerous, both in the bronchioles and the alveoli, than in the

bacterial forms of pneumonia, but bacterial superinfection is a common complication.[208] The more heavily involved parts may become fibrotic and pleural adhesions may develop. There is nothing pathognomonic about any of these changes. Rarely, *M. pneumoniae* is responsible for fatal respiratory disease, in which case the histological appearances are those of diffuse alveolar damage.[210]

RICKETTSIAL INFECTION

Rickettsia are rod-like or coccobacillary organisms that are similar to but smaller than bacteria. However, rickettsial pneumonia is dealt with in this chapter rather than with the bacterial pneumonias because its clinical and pathological features more closely resemble those of mycoplasmal pneumonia. Of the tribe rickettsiae, three genera contain organisms pathogenic to humans: *Rickettsia*, *Bartonella* (formerly *Rochalimaea*) and *Coxiella*. *Rickettsia* species are responsible for typhus and certain spotted fevers, and whilst pneumonia may occur in several of these,[211–213] the most frequent rickettsial pneumonia is that which occurs in Q fever, the causative organism of which is *Coxiella burnetti*. Respiratory disease is rarely caused by *Bartonella*, but bacillary angiomatosis is one example.

Coxiella burnetti pneumonia (Q fever)[214,215]

Q fever ('query fever') was so named because of its 'questionable' nature prior to the isolation of the causative organism, now recognised to be a *Rickettsia* known as *Coxiella burnetti*. The disease was first recognised in a meat-packing plant in Queensland, Australia, in 1937 and is now known to have a virtually global distribution. It is essentially an infection of cattle, sheep and goats that is transmitted to humans, probably more frequently than is apparent from the incidence of the disease, for many people who have never had Q fever possess circulating antibodies against *C. burnetti*. Among cattle, the disease is sometimes transmitted by ticks, but possibly more frequently by the inhalation of contaminated dust from the floor of milking sheds. The organisms are excreted in milk, urine and faeces, and particularly during calfing when amniotic fluid and placentae are a rich source of infection. In humans, the disease may be acquired by the inhalation of infected dust through close contact with cattle, as in dairy farms, abattoirs and hide factories, or through drinking milk that has been inadequately pasteurised. *C. burnetti* is resistant to drying and may survive exposure to a temperature of 60°C, an important characteristic in regard to the pasteurisation of milk.

Clinical features

Q fever is a disease of sudden onset marked by general malaise, severe frontal or retro-orbital headache, high fever and muscle pain. Men are more often symptomatic than women, despite equal seroprevalence, and there is evidence that sex hormones such as 17β-oestradiol play a protective role.[216] Pneumonia develops in only a very small proportion of those infected. In these patients, chest radiographs at the height of the disease disclose numerous relatively small, but widely distributed, opacities. The symptoms generally subside after about a week and most patients recover completely within a few months without treatment. Chronic Q fever, characterised by infection that persists for more than 6 months, is uncommon but more serious. This form of the disease may also represent a recrudescence of acute Q fever years after apparent recovery. It generally takes the form of endocarditis, usually developing in patients with pre-existent valvular heart disease, transplant recipients or those with cancer. Q fever responds to treatment with doxycycline, quinolones or macrolides.

The organism can generally be recovered during the height of the disease by inoculation of the patient's blood or sputum into guinea pigs but few laboratories offer this test because of the danger of laboratory infection. The detection of specific antibodies is the laboratory test of choice.

Pathology

The case fatality rate in acute Q fever is very low, and few necropsies on cases uncomplicated by bacterial superinfection have been recorded. In these, the lungs show nodular or confluent areas of grey consolidation. The development of an inflammatory pseudotumour is recorded but is a very rare complication.[217]

Microscopically, the changes in the lungs resemble those seen in viral or mycoplasmal pneumonias. There is a diffuse interstitial infiltrate of lymphocytes and plasma cells and an alveolar exudate of fibrinous oedema fluid containing mainly macrophages and only a few neutrophils. Lymphocytic cuffing is seen about the bronchioles and small pulmonary arteries. The bronchioles contain an exudate similar to that in the alveoli and often lose their epithelial lining. Organisation of the exudates may lead to obliterative bronchiolitis and organizing pneumonia.[218]

The causative organisms may be demonstrable: they usually measure about 0.25 × 0.45 µm but bacillary forms measuring up to 1.5 µm in length also occur. The organisms form microcolonies in infected cells,

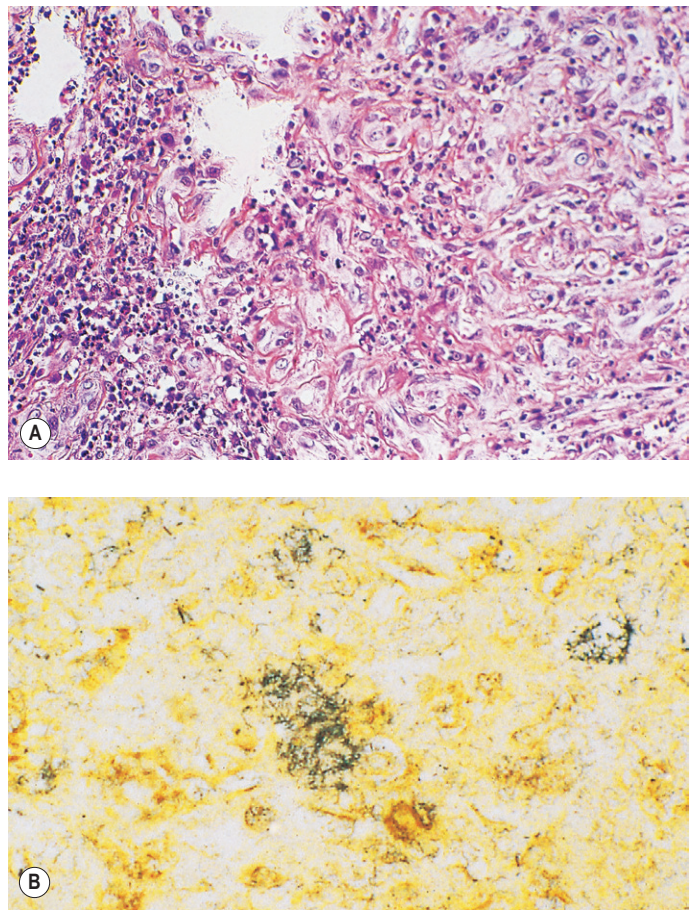

Figure 5.1.15 Bacillary angiomatosis. (A) There are many capillaries lined by plump endothelial cells, neutrophils and prominent cell debris. (B) Warthin–Starry staining reveals clumps of rickettsial coccibacilli. *(Courtesy of Dr I Abdalsamad, Creteil, France.)*

such as alveolar epithelium, and this facilitates their recognition in Giemsa-stained preparations. *C. burnetti* may also be identified in infected tissues by immunohistochemical staining and DNA detection. If the organisms are not demonstrable the changes are non-specific and, therefore, in suspected cases, coming to necropsy, blood should be taken for serology. It should be noted that there is a real risk of pathologists and postmortem room staff contracting the disease if precautions to avoid splashing and drying of body fluids are not taken. This infectivity has raised its profile as a potential agent in bioterrorism.[219]

Bacillary angiomatosis

Bacillary angiomatosis is a reactive vascular proliferation that was originally described in the skin and regional lymph nodes of patients infected by HIV.[220,221] Mucosal surfaces may also be involved, sometimes in the absence of cutaneous disease. In the respiratory tract this results in polypoid endobronchial lesions.[166,222] Chest wall involvement with intrathoracic spread is also recorded.[223] The disease has subsequently been described in other forms of immunodeficiency and even in immunocompetent patients, implying that unrecognised cases preceded the AIDS epidemic. The organisms involved have been identified as the rickettsial coccobacilli *Bartonella* (formerly *Rochalimaea*) *henselae* and *B. quintana*,[224,225] These microbes also cause trench foot and bacillary peliosis hepatis and are responsible for some cases of cat scratch disease (which is also caused by the related bacillus *Afipia felis*).[226]

Histologically, the lesions are likely to be mistaken for granulation tissue or Kaposi's sarcoma. Capillaries lined by plump endothelial cells are separated by neutrophils and cell debris, often surrounding clumps of bacilli (Fig. 5.1.15). The bacilli are easily overlooked in haematoxylin and eosin-stained sections and do not stain well with conventional stains for bacteria. However, aggregates of them are evident in sections stained by the Warthin–Starry or Dieterle silver techniques, predominantly in the extracellular tissue surrounding blood vessels. It should be remembered that these techniques stain many different types of microorganisms and a positive result is only meaningful if conventional methods for bacteria fail to stain the bacilli.

The lesions lack the spindle cells of Kaposi's sarcoma and the endothelial cells are more readily recognisable as such, carrying a wide variety of endothelial markers (CD34, factor VIII-related antigen and *Ulex europaeus* lectin positivity) rather than the more restricted CD34 positivity of Kaposi's sarcoma. Similarly, Weibel–Palade bodies are readily identified on electron microscopy, which is not the case with Kaposi's sarcoma.[227] Bacillary angiomatosis responds well to treatment with erythromycin and its distinction from Kaposi's sarcoma is therefore important.

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Chapter 5

5.2 *Acute bacterial pneumonia*

CHAPTER CONTENTS

Acute bacterial infection of the lungs is still one of the commonest causes of death, especially in the young and the aged, but very often it is merely a terminal event secondary to some other debilitating process. Primary pneumonia is one that develops in a previously healthy individual. Whilst it is still possible to classify pneumonia on the classic basis of its lobar, bronchial (lobular) or interstitial distribution, an aetiological classification facilitates the choice of an appropriate antibiotic, and will be followed here as far as possible. Consideration of the clinical situation provides important clues to the likely bacterium responsible (Table 5.2.1), and so aids the initial treatment. Most bacterial pneumonia is endogenous, caused by microorganisms that make up the flora of the pharynx. Cultures taken at autopsy have identified similar bacterial species in lung and pharynx.[1–3]

Of outstanding importance is the Gram-positive diplococcus *Streptococcus pneumoniae*, which is generally known as the pneumococcus. This bacterium is responsible for almost all cases of lobar pneumonia and for most cases of bronchopneumonia. Other varieties of bacteria that may produce pneumonia, almost always in its bronchopneumonic form, include *Staphylococcus aureus*, *Streptococcus pyogenes*, *Haemophilus influenzae* (Pfeiffer's bacillus), *Klebsiella pneumoniae* (Friedlander's bacillus), and *Legionella pneumophila*.

Streptococcus pneumoniae is much the commonest cause of adult cases of community-acquired pneumonia requiring admission to hospital (Table 5.2.2).[4–10] However, the situation is very different in patients who develop pneumonia after admission to hospital (nosocomial pneumonia), in whom Gram-negative enteric bacilli such as *Pseudomonas aeruginosa* and members of the Enterobacteriaceae family (*Escherichia coli*, *Proteus* and *Klebsiella* species) are most commonly responsible.[11–15] This is largely due to the administration of wide-spectrum antibiotics. Soon after such antibacterial drugs are administered, the oral flora changes and the upper respiratory tract commonly becomes colonised by bowel organisms.[16,17] Acid suppressants also increase the risk of nosocomial pneumonia.[18] They act by countering an important natural defence mechanism against bacterial growth in the stomach and upper small intestine. The problem has been particularly seen in intensive care units where acid suppressants may be administered to minimise the risk of gastric stress ulceration.[12] Sometimes the lungs are infected by way of the blood stream and on rare occasions an exogenous source such as a contaminated ventilator or nebuliser has been identified.[19,20] The mechanisms involved in nosocomial pneumonia are summarised in Figure 5.2.1.

Bacteriological diagnosis is usually made from the direct examination or culture of expectorated sputum. Sputum is prone to be contaminated by upper respiratory tract commensals and bronchoscopic or transcutaneous tracheal aspirates free of this problem have much

Table 5.2.1 Acute pneumonia: inference of the bacterium responsible from the clinical situation

Clinical situation	Likely bacterium
Previously healthy individual	*Streptococcus pneumoniae*
Complication of viral infection	*Staphylococcus aureus* *Streptococcus pneumoniae*
Chronic bronchitis	*Streptococcus pneumoniae* *Haemophilus influenzae*
Cystic fibrosis	*Staphylococcus aureus* *Haemophilus influenzae* *Pseudomonas aeruginosa* *Burkholderia cepacia*
Immunosuppression	*Streptococcus pneumoniae* *Staphylococcus aureus* *Pseudomonas aeruginosa* *Klebsiella pneumoniae* Anaerobes
Hospital inpatient	*Pseudomonas aeruginosa* Enterobacteriaceae spp. *Staphylococcus aureus* (often methicillin-resistant)
Bronchial tumour	*Streptococcus pneumoniae* *Staphylococcus aureus* Anaerobes
Aspiration	Anaerobes
Alcoholism	*Streptococcus milleri* *Haemophilus influenzae* Anaerobes *Klebsiella pneumoniae*

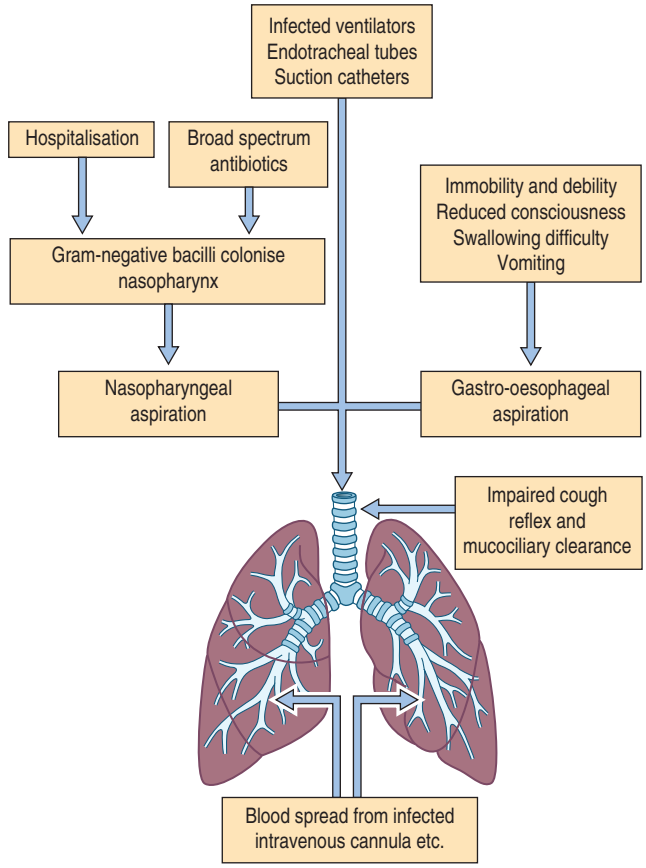


Figure 5.2.1 Mechanisms involved in the development of nosocomial pneumonia. Other risk factors include older age, underlying diseases such as cancer and diabetes mellitus, obesity and cigarette smoking.

Table 5.2.2 Microbial diagnoses (%) in adults admitted to hospital with community-acquired pneumonia

	UK[4]	New Zealand[5]	Spain[6]	Netherlands[7]	North America[a,8]	Chile[9]	Australia[10]
Streptococcus pneumoniae	34	27	39	20–60	11	24	5
Mycoplasma pneumoniae	18	6	16	1–6	4	2	9
Viruses	7	8	–	2–15	14	12	15
Haemophilus influenzae	6	8	11	3–10	0.4	3	5
Chlamydia	3	3	–	4–6	9	2	2
Legionella pneumophila	2	2	11	2–8	2	2	3
Staphylococcus aureus	1	–	–	3–5	–	1	1
Microbiologically negative	33	45	27	–	57	54	45

[a]Based on 15 separate reports.

to commend them. At autopsy, bacterial contamination is unavoidable and microbiological sampling of a consolidated area of lung should be through a surface sterilised by searing with a hot iron rod. A more elegant method entails the in situ culture of bacteria in the whole frozen organ using large Petri dishes.[21] By this method bacteria can be matched topographically to foci of consolidation, and contaminants recognised as being on the pleural surface of the lung.

BRONCHOPNEUMONIA

Although it has been resolved to follow an aetiological classification as far as possible, many bacteria cause a common morphological pattern of disease and this will be described before proceeding to specific aetiological agents. This pattern of pneumonia results from the successive infection of conductive airways and is therefore called bronchopneumonia.

Predisposing causes

Bronchopneumonia occurs most frequently in infants, debilitated young children and elderly people, and in such patients often proves fatal. The disease is particularly likely to complicate a condition that predisposes to infection by weakening either the local or general defence mechanisms. Local predisposing conditions include other acute infections of the respiratory tract, such as influenza, measles, pertussis and *Mycoplasma* infection, and chronic infective conditions such as chronic bronchitis and cystic fibrosis. Bronchopneumonia may also follow inhalation of irritant gases, aspiration of food or vomit, and obstruction of a bronchus by a foreign body or tumour.

Bronchopneumonia is also common after surgical operations. The pathogenesis of postoperative bronchopneumonia is complex. Tracheal intubation bypasses the nose, which normally warms and moistens the inspired air, whilst ether or other irritant vapours may further impair the ciliary defence mechanism of the bronchial tree. The unconscious patient may inhale infected material from the mouth or nose, and the temporary depression of the cough reflex may allow microorganisms to establish themselves in the lungs. Once the effect of the anaesthetic has worn off, the pain associated with movement, particularly of the abdominal wall, may restrict the normal aeration of the lower parts of the lungs. The haemorrhage and shock that may accompany any major surgical operation also result in some general depression of resistance to infection.

Other factors predisposing to bronchopneumonia include generalised metabolic disorders such as diabetes mellitus. Finally, bronchopneumonia is a very common terminal event in patients debilitated by cancer.

Clinical features

The onset of bronchopneumonia is insidious but once established it may have serious effects on respiratory function. The filling of many air spaces with exudate excludes air from much of the lungs and may lead to serious peripheral hypoxia. Healing is slow and the patient's temperature, which is seldom as high as in lobar pneumonia, subsides only gradually: resolution is said to be 'by lysis' rather than 'by crisis'.

Pathological features

Bronchopneumonia is characterised by widespread patchy areas of inflammation that begin as a widely dispersed bronchitis and bronchiolitis: focal areas of pneumonia then develop in the centres of the acini. The consolidated areas are generally larger and more

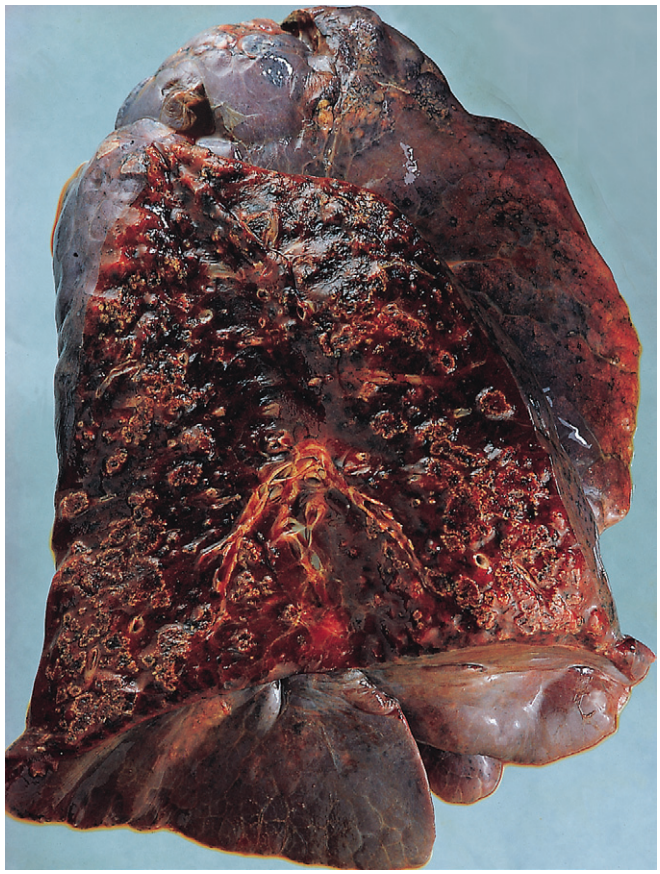


Figure 5.2.2 Bronchopneumonia. There are focal areas of pale consolidation surrounding small airways.

numerous in the lower lobes, where they may be several millimetres across. In the freshly cut lung they are commonly seen as pale, solid, centriacinar foci, often somewhat raised above the surface of the surrounding lung substance (Fig. 5.2.2). These consolidated areas can be felt as well as seen. Small beads of yellow mucopus can often be expressed from the bronchioles on the cut surface of the lung. In severe cases, the patches of consolidation may become confluent but even when this happens the affected area seldom presents the uniformity of texture and colour that is characteristic of lobar pneumonia, in which all parts of the lobe are involved almost simultaneously.

Once the organisms are established in the small bronchioles, they spread partly by the aspiration of pus and partly by penetrating the inflamed bronchiolar walls. When the bacteria reach the alveoli they excite an acute inflammation, with copious exudation of fluid and migration of neutrophils into the alveoli (Fig. 5.2.3). The air spaces nearest to the bronchioles show the most advanced degree of inflammation; those at a greater distance may be filled merely with fluid exudate.

The point at which neutrophils interact with the pulmonary vasculature is unusual. In contrast to other tissues where neutrophil migration takes place in postcapillary venules, in the lungs neutrophils leave the circulation through the thin walls of the alveolar capillaries, a difference that may serve to localise the inflammation to the alveoli.[22]

When recovery from bronchopneumonia takes place the exudate liquefies and is expectorated or absorbed and respiratory function is restored. However, healing by fibrosis rather than resolution is commoner in bronchopneumonia than in lobar pneumonia.

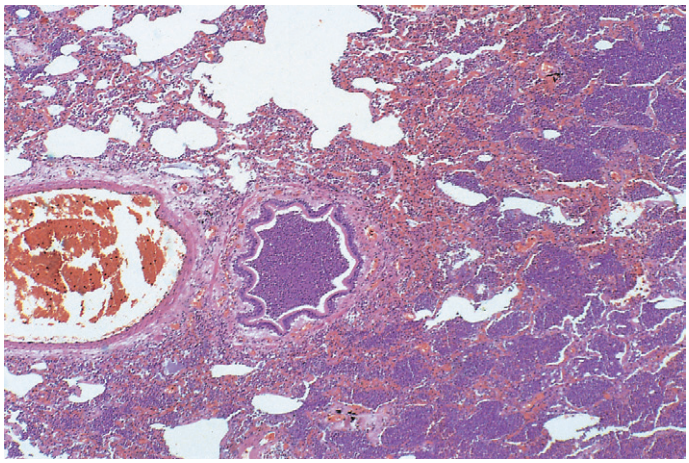


Figure 5.2.3 Bronchopneumonia. Pus fills a bronchiole (centre) and some of the adjacent alveoli.

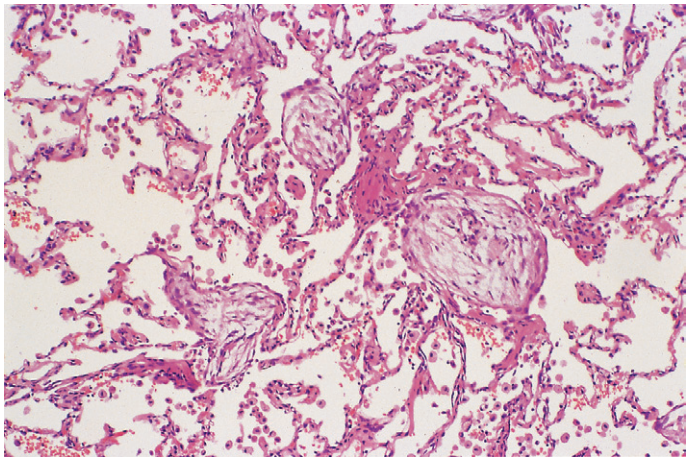


Figure 5.2.4 Organising pneumonia. Micropolypoid buds of pale, myxoid, granulation tissue (Masson bodies) are seen in three alveoli.

Bronchopneumonia healing by fibrosis is the commonest cause of organising pneumonia. It takes the form of granulation tissue polyps, which are often known as 'Masson bodies', protruding into the alveoli and bronchioles (Fig. 5.2.4).

PNEUMOCOCCAL PNEUMONIA

In 1880 Sternberg and Pasteur independently recovered pneumococci from saliva of ill patients[23,24] and it was soon recognised that this bacterium was an important cause of lobar pneumonia. At least 90 types of pneumococcus are distinguished serologically on the basis of antigenic differences between their capsular polysaccharides.[25] Any serological type may be found from time to time in sputum from normal people and most, if not all, are capable of causing serious disease in humans. However, some types are more pathogenic than others. Type 3 is particularly pathogenic and is commonly isolated from patients with acute respiratory illness[26] and pneumococcal bacteraemia.[27] The distribution of the various serotypes differs from country to country and between different age groups but overall type 14 is the commonest, particularly in young children, followed by types 4, 1, 6 and 3.[25]

Host resistance is very dependent upon the development of opsonic anticapsular antibodies because the polysaccharide capsule of the pneumococcus impairs phagocytosis. The identification of the serological type of the pneumococcus responsible for each case of pneumonia was of great importance when effective treatment depended on the prompt administration of the appropriate type-specific antiserum but the introduction of sulphonamides and then antibiotics made serum therapy obsolete. Unfortunately, penicillin-resistant strains have now emerged. Serological typing is based on the Quellung reaction, an easily recognisable swelling of the bacterial capsule when the specific antiserum is applied.

Pathogenesis

The widespread distribution of all types of pneumococcus in the throats of healthy people is relevant to the pathogenesis of pneumococcal pneumonia, the development of which must be regarded as attributable to circumstances that sharply lower resistance to a potentially pathogenic strain of pneumococcus that has been carried in the nose or throat, perhaps over a long period. Pneumococcal pneumonia is, essentially, an endogenous infection, due to failure of the natural defences of the respiratory tract to prevent the spread of a potentially pathogenic strain of pneumococcus from the nasopharynx to the lungs, where it causes acute inflammation. Pneumococci may also cause bacteraemia and meningitis.

Although most cases of pneumococcal pneumonia occur sporadically, minor epidemics sometimes occur as a result of the spread of newly introduced pathogenic strains into a community, such as a school or military camp, where personal contacts are especially close.[28] Under these circumstances, a rise in the carrier rate for the responsible type generally precedes the outbreak.

In temperate climates, pneumococcal infections of the lungs, especially in infants and the elderly, are much commoner in winter than in summer. Low external temperature probably has the greatest bearing on the seasonal occurrence of pneumonia, partly by impairing the natural defences of the respiratory tract through cold air chilling its mucosa and partly indirectly, by aggravating the overcrowding that occurs in inclement weather. Both these mechanisms also promote viral infections of the respiratory tract that predispose to subsequent pneumococcal infection. The carrier rate for pneumococci in the general population also tends to rise considerably during the winter and thus to increase dispersal of the more pathogenic strains by droplet spread.

An absent or non-functioning spleen (perhaps removed because of trauma or destroyed by sickle cell disease) also predisposes to pneumococcal infection. Other contributory conditions include alcoholic binge-drinking, chronic chest disease, respiratory-depressant drugs, debilitating metabolic diseases such as diabetes mellitus, cirrhosis, the nephrotic syndrome, carcinomatosis, immunodeficiency or immunosuppression due to treatment or disease, including human immunodeficiency virus infection, and any condition, such as coma, that depresses the cough reflex and so impairs clearance of the respiratory tract.[27,29] Chronically high-risk individuals and elderly people in residential nursing homes benefit from a polyvalent vaccine containing purified capsular polysaccharide that is now available.[30]

Pneumococcal infection of the lungs may result in either lobar pneumonia or bronchopneumonia. These two forms of pneumonia differ greatly in their clinical and pathological features but the contributory conditions outlined above underlie both.[31] Whether the pneumonia has a lobar or bronchial distribution appears to depend more on the virulence of the particular serotype than on host defence. However, host factors involving hypersensitivity have been implicated in the development of lobar pneumonia, largely because of the

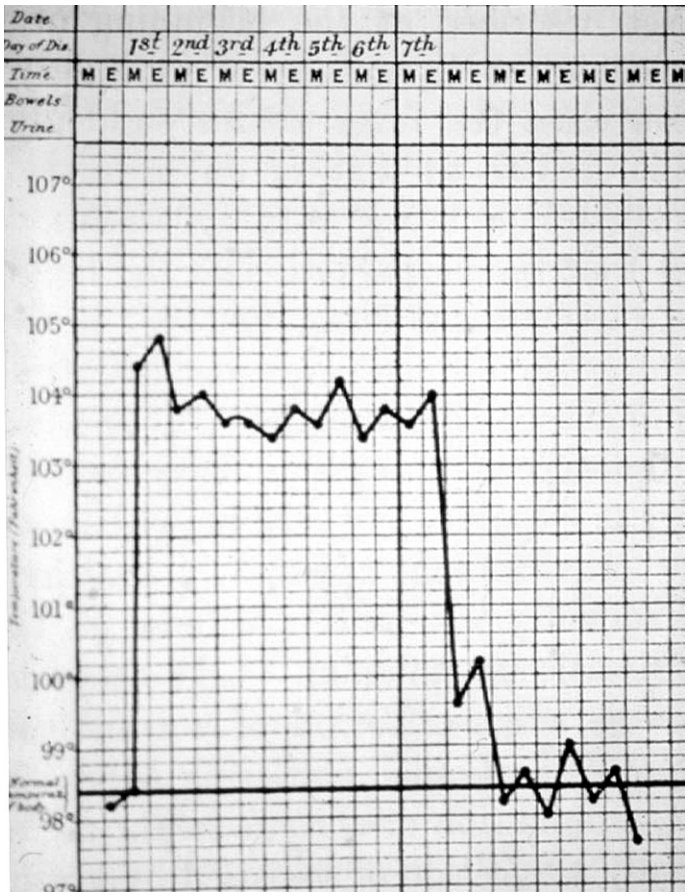


Figure 5.2.5 Temperature chart (Fahrenheit) of a patient spontaneously recovering from pneumococcal lobar pneumonia.

rapidity with which the disease spreads to involve a whole lobe. Bronchopneumonia is dealt with above and only lobar pneumonia will be considered here.

Clinical features

The onset of lobar pneumonia is typically abrupt. The patient feels ill, complains of a sharp pain in the side of the chest that is made worse by deep breathing, coughs up 'rusty' sputum, and quickly develops a fever of about 40°C. The respiration is shallow and its rate becomes fast, sometimes reaching 50 breaths/min or more: the ratio of pulse to respiration may fall from its usual 4:1 to 2:1. Cyanosis usually appears as the disease advances. A leukocytosis of 15–20 × 10^9/l, mainly neutrophils, is frequently found. In many cases, pneumococci can be cultured from the blood during the height of the fever. The patient is delirious and before effective treatment became available the death rate was high. Before the days of chemotherapy, resolution generally began on about the eighth or ninth day of the illness, if the patient survived that long. Quite frequently, the fever fell suddenly, sweating was profuse, respiration became deeper and less rapid, the delirium abated and the temperature quickly returned to normal (Fig. 5.2.5). The healing was said to be 'by crisis', as opposed to the gradual abatement of symptoms seen in bronchopneumonia, which was described as healing 'by lysis'. This rapid recovery followed the appearance of specific antibodies against the pneumococcus responsible.

Structural changes in the lungs

As the name lobar pneumonia implies, it is usual for the typical changes to be uniform throughout the affected lobe. Sometimes two or even three lobes may be involved simultaneously or after brief intervals, in which case 2 or 3 days may separate the onset of involvement of the different lobes. The lower lobes are most commonly affected; there is no significant difference in the frequency of involvement of the two lungs. Before the introduction of effective treatment, the morphological alterations in the lungs generally followed a classic sequence which, following Laennec's original description, comprised four stages:

1. congestion
2. red hepatisation
3. grey hepatisation
4. resolution.

It should be realised that these terms apply to typical appearances, and that each stage shades into the next. Antibiotic treatment has curtailed and modified the natural course of lobar pneumonia, and reduced both its incidence and its mortality so that the classic morbid anatomical appearances are now rare.

Congestion

The stage of congestion generally lasts less than 24 hours. It is exceptional for patients to die so early in the disease, but when such cases are seen at necropsy, the affected lobe is more or less uniformly involved and appears disproportionately large in comparison with the other lobes, which collapse in the usual way when the pleural sacs are opened. The pneumonic lobe is heavy and congested with blood. A blood-stained, frothy fluid oozes freely from the cut surface.

Histological examination shows that alveolar capillaries are much dilated, and the air spaces are filled with pale eosinophilic fluid in which there are a few red cells and neutrophils. The uniformity of the appearances throughout the lobe is taken to indicate widespread, rapid dissemination of the bacteria through the pores of Kohn by a flood of oedema fluid. In Gram-stained sections, the paired, lanceolate pneumococci can often be seen, mainly free, in the alveolar fluid. At this stage, little fibrin has formed, and the affected lobe has not yet acquired the firm consistency typical of hepatisation.

Red hepatisation

The feature that led Laennec to popularise Morgagni's term 'hepatisation' is the consistency of the affected lobe, which resembles that of the liver. The cut surface of the lung is dry and there is a serofibrinous pleurisy. Small rough tags of fibrin cover much of the visceral pleura of the affected lobe. Congestion persists and the lung remains red.

The changes in the gross features of the affected lobe are readily explained by the histological changes that have taken place during the preceding few hours. The copious fluid exudate, which at the time of its formation contained abundant fibrinogen, has clotted in the alveolar spaces and interlacing strands of fibrin now occupy each air space and can often be seen connecting with those in neighbouring alveoli through the pores of Kohn. At the same time, more and more neutrophils have migrated from the congested capillaries into the fibrin meshwork. Usually, at this stage, the pneumococci are numerous, and many of them have been ingested by neutrophils.

Grey hepatisation

After 2–3 days, the affected lobe gradually loses its red colour and assumes the grey appearance that it retains for the next few days (Fig. 5.2.6). This change in colour, which starts at the hilum and spreads towards the periphery, is brought about by a lessening of the capillary

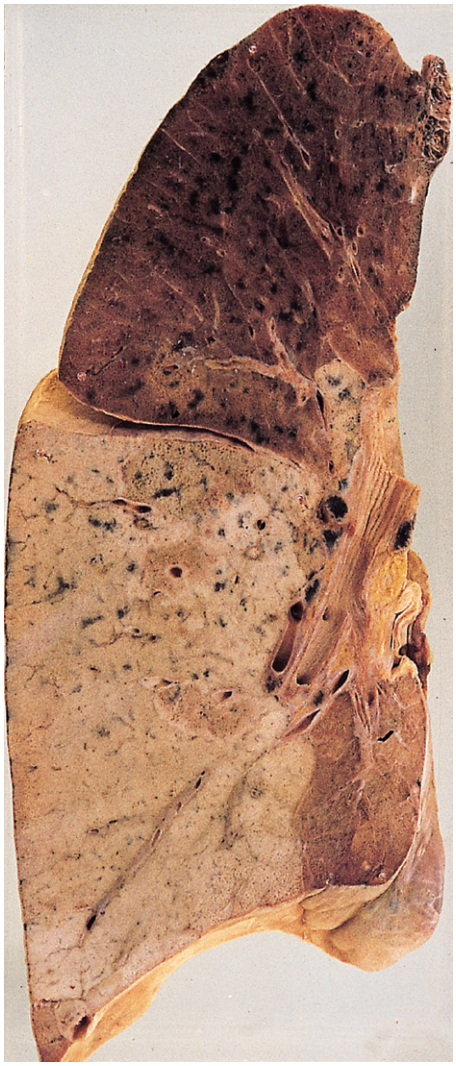


Figure 5.2.6 Lobar pneumonia in the stage of grey hepatisation. The lower lobe is uniformly consolidated.

congestion and by the migration of very large numbers of leukocytes, at first mainly neutrophils but later macrophages, into the fibrin in the alveoli. An almost complete shutdown of the vasculature of the affected lobe can be demonstrated in radiographs of the lungs after their injection at necropsy with radiopaque material. The temporary virtual cessation of blood flow through the unventilated lobe lessens the liability to systemic hypoxia that might otherwise develop, a good example of ventilation/perfusion matching (see p. 22).

The cut surface of the lung is now moist as the fibrin has contracted, expelling serum. Toward the end of the stage of grey hepatisation, pneumococci are less numerous and appear in degenerate forms, varying much in size, and often no longer Gram-positive.

Resolution

Resolution proceeds in a patchy yet progressive manner by liquefaction of the previously solid, fibrinous constituent of the exudate in the air spaces. Soon the affected lobe becomes more crepitant as the air spaces reopen. Liquefaction of the fibrin is thought to be due to a fibrinolytic enzyme liberated from senescent neutrophils. However, excessive neutrophil breakdown would probably damage the lung and an alternative form of cell death is also utilised, namely apoptosis: apoptotic neutrophils are ingested by macrophages and excessive lysosomal enzyme release is thereby avoided.[32]

The now fluid contents of the alveoli are removed, partly by expectoration but mainly through the lymphatics, resulting in the hilar lymph nodes being soft, moist and swollen. By the end of the stage of resolution, completion of which is shown by chest radiographs to require several weeks, the lung has recovered its normal structure.

Table 5.2.3 Pneumonia as a cause of septic shock

	Number of patients	Source of infection (%)			
		Lung	Abdomen	Urinary tract	Other
Warren et al. 2001[34]	2314	34	27	7	31
Abraham et al. 2003[35]	1754	51	28	13	8

Complications

Lobar pneumonia may be complicated by dissemination of the pneumococci throughout the lungs and to other organs. In some patients acute pneumococcal bronchitis and foci of bronchopneumonia may be present in lobes other than that mainly involved. These accessory lesions, if severe, may exacerbate the disease by further impairing the respiratory exchange in the lungs. In many cases of lobar pneumonia there is a bacteraemia at the height of the infection. Acute endocarditis may then develop, and this is sometimes followed by the formation of an abscess in the brain after lodgement of an infected embolus. Pneumococcal meningitis, peritonitis and arthritis are rarer manifestations of the dissemination of the organisms by the blood but septicaemia with consequent septic shock are important complications in patients requiring hospital admission.[33] Pneumonia is the commonest cause of septic shock (Table 5.2.3).[34,35]

Although, in patients who recover, the area of lobar consolidation usually resolves completely, several complications may interfere with the healing process. Resolution may be delayed through incomplete digestion of the fibrin in the exudate within the alveoli, and organisation, followed by fibrosis ('carnification'), may develop. The fibrosis is essentially intraluminal, taking the form of micropolypoid buds of granulation tissue (Masson bodies) that largely fill alveoli and extend into alveolar ducts and respiratory bronchioles (organising pneumonia), as described above under bronchopneumonia (see Fig. 5.2.4). The contracting fibrous tissue may exert traction on the airways, leading to bronchiectasis, which may affect the whole or part of the lobe. Alternatively, part of the affected tissue may break down, especially in cases of infection by pneumococci of serotype 3, and a lung abscess may form.[36] On the pleural surface, the serofibrinous exudate may develop into empyema (see Fig. 13.6, p. 713) or be complicated by suppurative pericarditis.

STAPHYLOCOCCAL PNEUMONIA

Staphylococcus aureus pneumonia is a serious but relatively uncommon disease with a high case fatality rate. It often complicates influenza.

The special relationship of staphylococci and influenza virus has been dealt with on page 158. In children, staphylococcal pneumonia may follow measles or whooping cough. In infants a primary staphylococcal bronchopneumonia is known, with a case fatality rate as high as 80% in the pre-antibiotic era. The infection is generally endogenous, the bacteria frequently being derived from the patient's skin or nose and the infection air-borne. However, staphylococcal pneumonia or lung abscess sometimes follows bacteraemia or septicaemia,[37] particularly in drug addicts with right-sided bacterial endocarditis.

Although the mortality from most forms of pneumonia has been reduced by modern drugs, many strains of *Staphylococcus* now widely distributed in the population are resistant to the generally used antibiotics. Even relatively new antibiotics such as meticillin are inactive against some of these staphylococci, which have become known as meticillin-resistant *S. aureus* or MRSA. Such strains periodically become prevalent in hospitals,[15] carried in the nose by staff and patient, and fatalities from staphylococcal infection, often with pneumonia, have occurred among surgical patients who otherwise should have recovered from their operation. In addition, although MRSA is primarily viewed as the prototype of multiresistant nosocomial (hospital-acquired) infections, new lineages have emerged that cause community-acquired infections in individuals without risk factors, including rare cases of necrotising pneumonia.[38–40]

S. aureus owes its pathogenicity to a series of necrotising exotoxins that induce a marked neutrophil response resulting in suppurative tissue necrosis.[41] Particularly potent is a strain of meticillin-resistant *S. aureus* that secretes an exotoxin known as Panton–Valentine leukocidin. As well as complicating influenza,[42–44] this strain has resulted in fatal septic shock in previously healthy persons.[38]

At necropsy, the bronchi are acutely inflamed and the lungs contain many bright yellow centrilobular foci of suppuration (Fig. 5.2.7), which in the more advanced cases may have enlarged and coalesced to form abscesses 1 cm or more in diameter. Adjacent air spaces contain a purulent exudate. A superficial abscess may rupture into the pleura and cause empyema, which is a common complication of staphylococcal pneumonia. If the patient survives, there may be permanent damage to the lungs in the form of pulmonary fibrosis, bronchiectasis or large air-filled cysts known as pneumatoceles (Fig. 5.2.8).

Figure 5.2.7 Staphylococcal bronchopneumonia. The pneumonic foci show early suppuration.

STREPTOCOCCAL PNEUMONIA

In the pre-antibiotic era, up to 5% of all acute pneumonias were caused by group A β-haemolytic streptococci but *Streptococcus pyogenes* is now a rare cause of serious pulmonary infection; nevertheless, occasional cases of streptococcal pneumonia are still encountered,[45] and infective pulmonary embolism is recorded in streptococcal toxic shock.[46] Streptococcal pneumonia typically follows viral infections of the respiratory tract and is thought to have been a prominent bacterial superinfection during the 1919 influenza pandemic. Patients present with abrupt fever, dyspnoea and pleuritic chest pain. They often develop haemoptysis and cynosis. Death may take place within 2–3 days of the onset, in which case the lungs show haemorrhagic oedema and pneumonic consolidation is not well developed. In subacute cases there is bronchopneumonic consolidation, which is characteristically accompanied by early pleural involvement and effusion.

The anaerobic *Streptococus milleri* is now recognised to be an important cause of necrotising lung disease, causing lung abscess and empyema. Patients are often elderly men with periodontal disease, excessive alcohol consumption, malignant disease or recent thoracic surgery.[47]

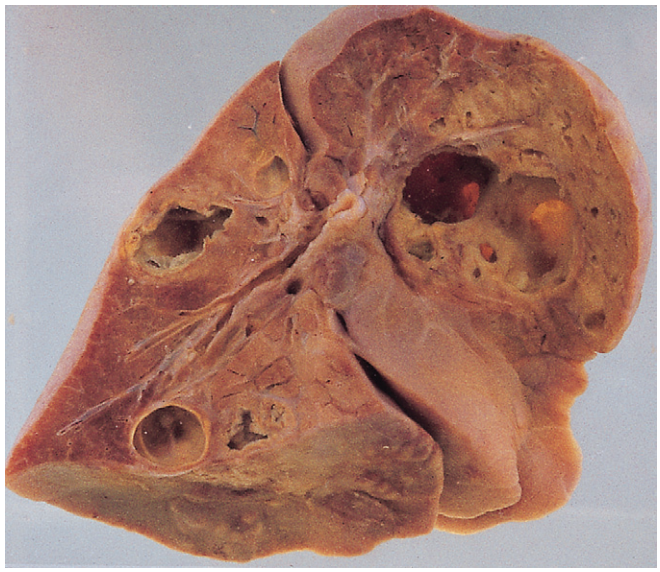


Figure 5.2.8 Pneumatoceles in a child's lung, the consequence of staphylococcal pneumonia.

HAEMOPHILUS PNEUMONIA

The Gram-negative bacillus *Haemophilus influenzae* is a frequent isolate from the upper respiratory tract of healthy individuals and can often be cultured from the sputum of patients with pneumonia due to other organisms, the true pathogen being identified by lung aspiration or blood culture. It was first isolated in the 1889–90 influenza pandemic and so named because its discoverer, Pfeiffer, recovered it from a large proportion of cases and mistook it for the cause of influenza. Occasionally however *H. influenzae* is itself the cause of pneumonia.[48] Patients are often elderly or predisposed to pneumonia by alcoholism or chronic bronchitis. The consolidation may take the form of either lobar pneumonia or bronchopneumonia. The changes in the lung are similar to those in pneumococcal pneumonia (see above). Pleural effusion is a common feature.

MORAXELLA PNEUMONIA

The Gram-negative diplococcus *Moraxella catarrhalis*, previously known as *Branhamella catarrhalis* or *Neisseria catarrhalis*, is usually a harmless pharyngeal commensal but in the immunodeficient it can cause many serious infections, including pneumonia.[49–51] *M. catarrhalis* is one of the bacteria that colonise the bronchi in chronic bronchitis and are responsible for acute exacerbations of this disease.[52] Chronic bronchitis and lung cancer both predispose to *M. catarrhalis* pneumonia.[53–55] Other conditions predisposing to *M. catarrhalis* infection include old age, heart failure, diabetes mellitus and corticosteroid treatment. The incidence of *M. catarrhalis* colonisation and infection is highest in winter. The pathological appearances are those of acute bronchitis and bronchopneumonia.

Acinetobacter is another genus belonging to the family Moraxellaceae, one species of which (*A. baumannii*) has emerged as a potential cause of pneumonia in intensive care units. *Acinetobacter* are generally regarded as harmless soil-living commensals but they may colonise hospitals and cause serious respiratory illness in severely immunocompromised patients. *Acinetobacter* species are innately resistant to many classes of antibiotics.

LEGIONELLA PNEUMONIA (LEGIONNAIRE'S DISEASE)[56–58]

Aetiology and epidemiology

The legionellae were only discovered after prolonged investigations into the deaths of 34 of some 4500 members of the American Legion attending a convention in a Philadelphia hotel in 1976.[59,60] The investigations took so long because the responsible bacterium, subsequently named *Legionella pneumophila*, is resistant to conventional stains and fastidious in its culture requirements. Once identified, it was possible to recognise retrospectively from stored sera that *Legionella* had been responsible for pneumonia in the past. Sporadic cases were subsequently recognised.[61,62] These are commoner than those encountered in epidemic outbreaks but nevertheless only form a small proportion of community-acquired pneumonia (see Table 5.2.2). In addition to causing pneumonia (legionnaire's disease), *Legionella* is responsible for a less severe, non-pneumonic, acute febrile illness known as Pontiac fever. The term 'legionellosis' embraces both diseases.

Although *Legionella* pneumonia occurs in epidemics, the bacterium is seldom transmitted from person to person. Spread is usually due to atmospheric contamination. It is ironic that a bacterium so hard to grow in the laboratory can succeed so well in air-conditioning plants. These provide the necessary warm, moist conditions that the bacterium requires, drawing it in from the outside, fostering its growth and dispersing it around a building. The contaminated buildings are therefore generally modern, but with neglected engineering plants. Colonisation of the plant by certain free-living amoebae may also promote the growth and survival of legionellae for these bacteria are resistant to amoebic digestion and may survive exposure to disinfectants when the amoeba encysts.[63]

Passers-by as well as those within the building may be infected. In 1985, the 2-year-old Stafford General Hospital in the UK was the setting of one of the biggest outbreaks: 46 people died there of legionnaire's disease, mostly patients rather than staff. It is no coincidence that outbreaks affect hospitals or conventions of ex-servicemen, for the old, the infirm, heavy smokers and those who drink to excess are at particular risk. Hospital-acquired infection is particularly likely to affect immunocompromised patients, such as transplant recipients.[62] Also, mixed infections involving legionellae may be commoner than previously thought.[64]

Bacteriology

Legionellae are aerobic, 1–2-μm, Gram-negative bacilli that differ from other such bacilli in the fatty acid profile of their cell wall. They fail to grow on standard media and require buffered charcoal yeast extract, which is also useful for isolating *Nocardia*. The number of species has been continually increasing since the original isolation of *L. pneumophila* and now exceeds 50, of which about half are pathogenic to humans. In the USA *L. pneumophila* accounts for about 85% of *Legionella* infections, *L. micadadei* for about 8% and *L. longbeachae* for 1–3%. The legionellae are facultative intracellular organisms that are able to proliferate within phagocytic cells. They are also able to invade and proliferate within alveolar epithelial cells.[65]

Host defence

Humoral mechanisms of defence appear to be limited to opsonic enhancement of phagocytosis. The role of neutrophils is unclear: neutropenic patients are not particularly susceptible to legionnaire's disease. Macrophages activated by T-cell lymphokines appear to be more important.[66]

Clinical features

Legionnaire's disease is heralded by a vague prodromal illness that lasts about 5 days. Malaise and muscle pain are followed by rapidly rising fever, rigors, cough, chest pain and dyspnoea. There may also be confusion, diarrhoea and proteinuria. There is usually a moderate leukocytosis. Thus, the clinical features of legionnaire's disease are similar to those encountered in other bacterial pneumonias. The radiographic findings are similarly non-specific but detection of *Legionella* antigen in urine provides a reliable diagnostic test.[67] Macrolides, fluoroquinolones and rifampin (rifampicin) are the most widely used drugs in treatment.

Pathology[56,57,61,68–72]

The gross appearances of the lungs are those of a confluent or multifocal lobular pneumonia with a fibrinous pleurisy and a serosanguineous pleural effusion. If confluent, the boundaries of the consolidation generally fail to match the interlobar fissures (Fig. 5.2.9). There may

be abscess formation[73] but this is not typical. A miliary distribution is another atypical manifestation.[74]

Microscopically, airways do not appear to be particularly involved in the inflammatory process, so the disease is not a bronchopneumonia. An acute, leukocytoclastic, fibrinopurulent pneumonia is characteristic (Fig. 5.2.10) but sometimes macrophages are more prominent than neutrophils. The legionellae resist digestion and multiply within the phagocytes, which they eventually destroy so that intense necrosis of the inflammatory cells is often observed. At low magnifications, alveolar walls may be difficult to recognise but even when there is extensive necrosis of the exudate, close inspection, perhaps aided by reticulin stains, shows that the alveolar architecture is generally intact. Occasionally however there are breaks in the alveolar walls or more widespread destruction may be seen. This may be due to vasculitis and thrombosis, which is sometimes evident in small blood vessels.

Demonstration of the organisms is difficult; the fickle and non-specific Dieterle silver impregnation method is the best of the non-immunological techniques used to stain the small coccobacilli. Fortunately the bacterial antigens withstand formalin fixation and routine processing, permitting immunostaining to be applied to paraffin sections.[75] Electron microscopy of the bacteria shows features that are indistinguishable from those of Gram-negative bacilli.[76] In practice, most cases are diagnosed without recourse to pathology.

The hilar lymph nodes are often infected and there is haematogenous dissemination to sites such as the spleen and bone marrow in 27% of cases.[61]

The process generally resolves completely but healing by organisation may be recognised in fatal cases as buds of connective tissue (Masson bodies) in the lumen of alveoli, alveolar ducts and respiratory bronchioles. Such postpneumonic fibrosis presumably accounts for the permanent impairment of lung function that has been noted in some patients.

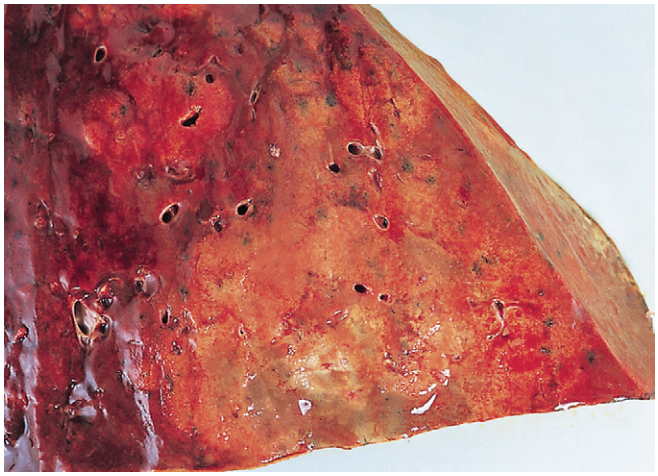


Figure 5.2.9 Legionnaire's disease, represented by a confluent lobular pneumonia that does not show the uniform involvement of the affected lobe seen in lobar pneumonia.

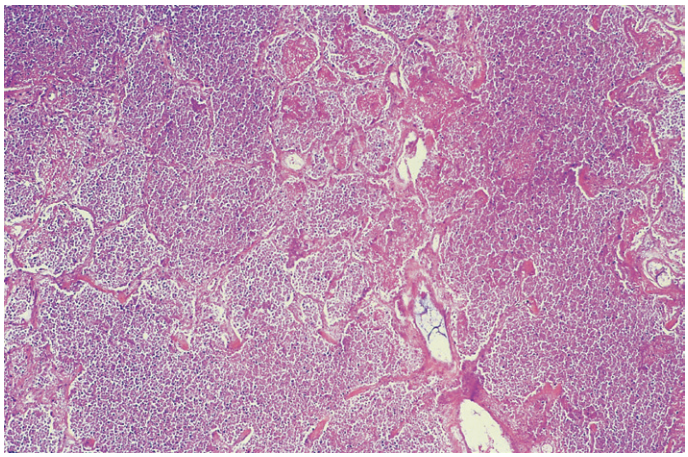


Figure 5.2.10 Legionnaire's disease, showing widespread alveolar filling by fibrin and necrotic neutrophils.

KLEBSIELLA PNEUMONIA

Klebsiella pneumoniae (Friedlander's bacillus) is a rare cause of community-acquired pneumonia but accounts for a higher proportion of pneumonia acquired in hospital, where patients are more likely to be treated with antibiotics that permit this bacterium to dominate the pharyngeal flora.[77] *K. pneumoniae* is also a particularly common inhabitant of the oral cavity in those with poor dental hygiene and such persons are accordingly at increased risk of *Klebsiella* pneumonia. Alcoholics are also particularly susceptible to *Klebsiella* pneumonia, constituting about half the patients dying of *Klebsiella* infection.[78] Others at particular risk are the elderly and diabetics. The mortality of *Klebsiella* pneumonia is much higher than that of pneumococcal pneumonia: 21% in the general population and 64% in alcoholics.[78,79] Bacteraemia is a particularly adverse prognostic factor.[78]

Klebsiella pneumonia has a predilection for the upper lobes. There is often uniform diffuse consolidation but, with only part of the lobe involved, a sharply demarcated edge abutting interlobular septa rather than interlobar fissures: the part of the lobe affected by such consolidation enlarges by the progressive involvement of adjacent lobules (Fig. 5.2.11). The abundant mucoid coat of the klebsiellae gives the pneumonic lesions a distinctively slimy appearance and feel. This material is mucicarminophilic, a characteristic that is often helpful in identifying the infection in histological sections. *Klebsiella* pneumonia is particularly liable to suppurate and form lung abscesses (Fig. 5.2.12). These may progress to massive pulmonary gangrene.[80] Chronic *Klebsiella* pneumonia may mimic tuberculosis by presenting with cavitating upper-lobe disease.

PSEUDOMONAS PNEUMONIA

The species of *Pseudomonas* involved in lung infections is usually *Pseudomonas aeruginosa*, which is the commonest bacterium isolated in hospital-acquired pneumonia.[15] Infection may be inhalational or blood-borne. Infection via the airways generally follows colonisation of the pharynx, especially in patients on antibiotics that destroy the normal flora of the upper respiratory tract. As with many bacterial infections, prior viral injury promotes adhesion to the bronchial mucosa,[81,82] for it is difficult for *P. aeruginosa* to adhere to normal epithelial cells. Adhesion of the bacteria is dependent upon the transient expression of a sialoganglioside at the apex of the regenerating epithelial cells.[83] Inhalational *Pseudomonas* pneumonia has also developed in patients treated by tracheostomy and mechanical ventilation due to contamination and inadequate disinfection of the ventilators.[19] Several outbreaks in the USA were attributable to faulty bronchoscopes.[84,85]

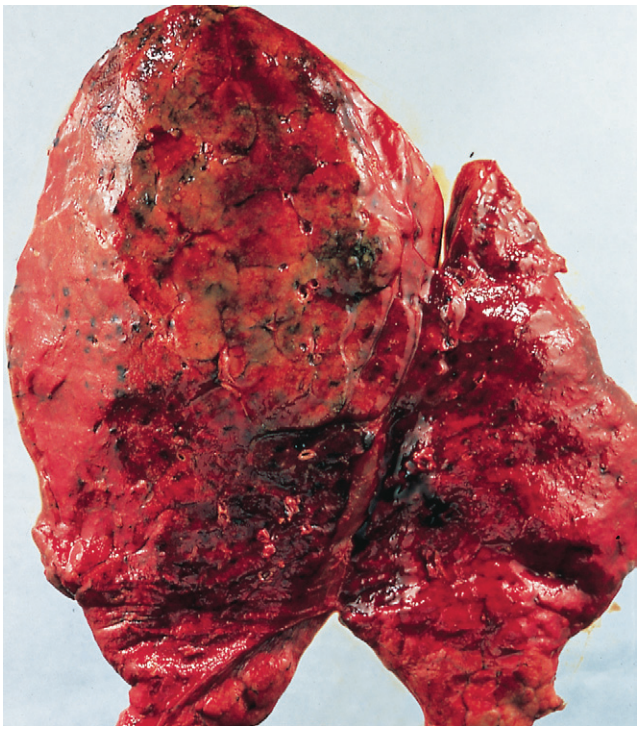


Figure 5.2.11 Friedlander's (*Klebsiella*) pneumonia showing diffuse consolidation of the upper part of the upper lobe. The unaffected lower portion has collapsed on slicing but the consolidated, airless upper portion has retained its shape.

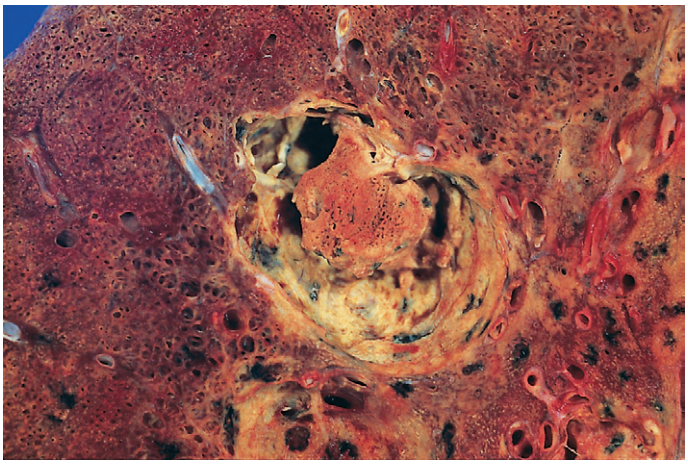


Figure 5.2.12 Abscess formation complicating Friedlander's (*Klebsiella*) pneumonia.

Pseudomonas pneumonia is often characterised by well-demarcated pale areas of necrosis, which histologically are composed of an amorphous coagulum containing many bacteria, the nuclear debris of necrotic neutrophils and small numbers of lymphocytes and macrophages.[86,87] *Pseudomonas* appears to be able not only to resist, but also to destroy neutrophils.[88] It is debatable whether the tissue necrosis is due to bacterial toxins or an immunological response.

Pseudomonas septicaemia may complicate *Pseudomonas* pneumonia[87] or abdominal infection. It results in further changes, notably prominent colonisation of blood vessels. So pronounced is this feature that the vessels exhibit a distinctive blue haze with haematoxylin, or a red one with a Gram stain.[89] The rod-like form of the bacteria is usually readily apparent at high magnification but the Sandiford modification of the Gram stain is especially useful for demonstrating Gram-negative bacteria in tissue sections (Fig. 5.2.13A).[90] The bacterial colonisation causes a vasculitis with resultant thrombosis and ischaemic necrosis (Fig. 5.2.13B). Such necrotising arteritis is not found in non-bacteraemic *Pseudomonas* pneumonia.[91] Meningitis, arthritis and jaundice are further manifestations of *Pseudomonas* septicaemia. There may also be striking skin lesions, including vesicles and sharply demarcated foci of cellulitis that enlarge rapidly and become haemorrhagic and necrotic.

BURKHOLDERIA INFECTION

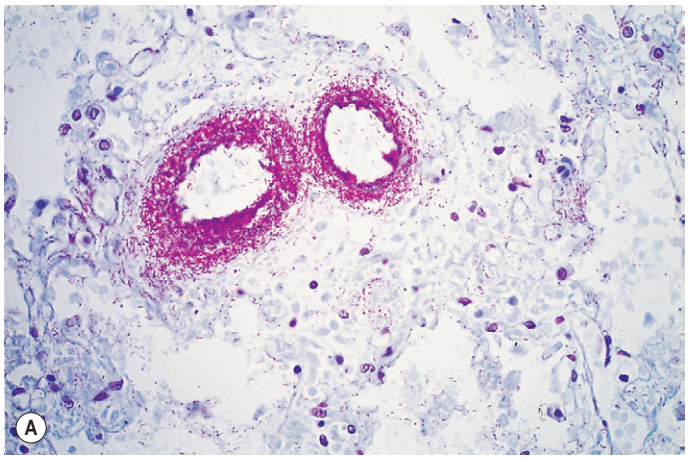
Acute melioidosis

Melioidosis is a generalised infection caused by *Burkholderia* (formerly *Pseudomonas) pseudomallei*, a Gram-negative bacillus found in watery environments in certain tropical areas, notably south-eastern Asia and northern Australia.[92] However, isolated cases have been described in many other countries.[93,94] The route of infection is most often through the skin but may be through the respiratory tract, where cystic fibrosis appears to be a predisposing factor.[95] Early studies were made during the British occupation of Burma, whilst French and American servicemen were infected in Vietnam.[96] The prognosis was initially thought to be very poor but improved serological testing indicated that subclinical and mild forms of the disease are common in certain tropical areas.[96] The bacterium may lie dormant in an infected person for many years before causing disease and it is estimated on the basis of high antibody titres that many thousands of American veterans of the Vietnam war are at risk. Acute and chronic forms are recognised, and, in both, lesions are commonest in the lungs. Melioidosis is very similar clinically (but not epidemiologically) to the equine disease, glanders, which is caused by infection with *Malleomyces mallei*, with which *B. pseudomallei* shares certain antigenic determinants. Chronic melioidosis is described on page 213.

Acute melioidosis is characterised by the sudden onset of severe diarrhoea, overwhelming pneumonia and septicaemia, and if untreated is rapidly fatal. Numerous abscesses are found throughout the body. In chest radiographs these are seen as disseminated nodules.[97] The early lesions take the form of small foci of neutrophils surrounded by haemorrhagic zones. As the abscess enlarges, fibrin becomes more prominent and necrosis ensues. Cases with prominent pulmonary features are characterised by a confluent necrotising pneumonia which has a bronchitis element that is not evident when there are only discrete abscesses. Vasculitis, a feature of *P. aeruginosa* pneumonia, is not seen in melioidosis. Bacilli are generally quite numerous and often form distinct collections within multinucleate macrophages that are scattered amongst the numerous neutrophils.[98] They have been shown to survive and multiply within cells, including neutrophils.[99] The bacteria are most easily identified by the Giemsa stain, which can then be supplemented by a Gram preparation. Staining is strongest at the ends of the bacilli, which therefore have a bipolar appearance that has been likened to that of a closed safety pin.

Burkholderia cepacia pneumonia

Burkholderia cepacia (formerly *Pseudomonas cepacia*) is an important pathogen in cystic fibrosis[100] but is seldom isolated in the immunocompetent. The few pathological studies of *B. cepacia* pneumonia have shown necrotising granulomatous inflammation merging with areas of more conventional necrotising bronchopneumonia, occasionally with necrotising granulomas in the mediastinal lymph nodes.[101]



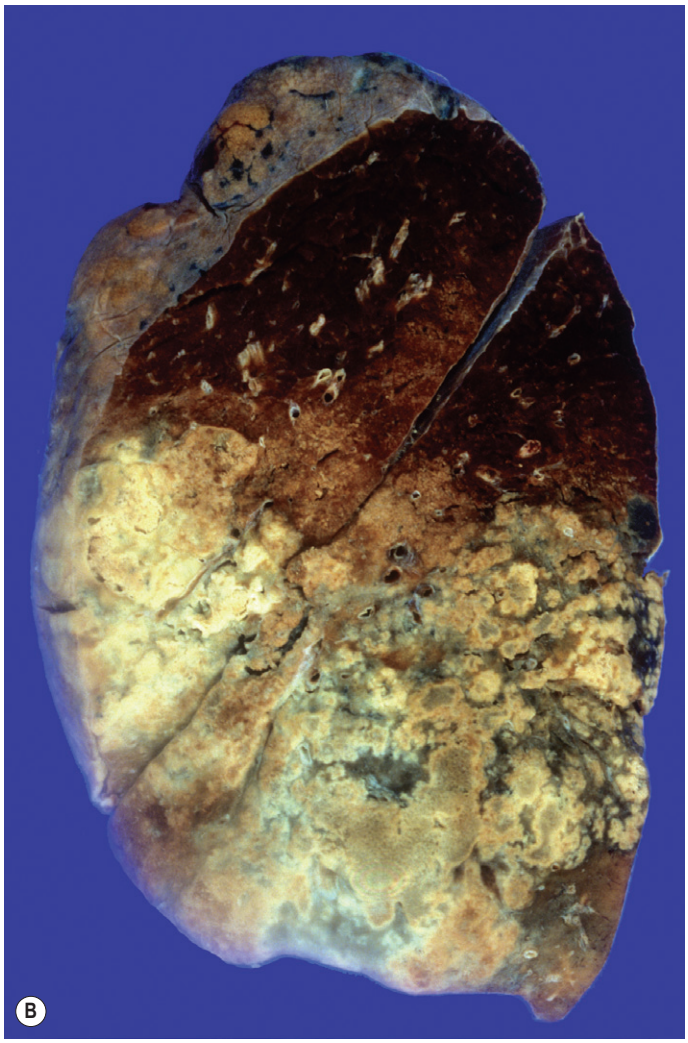


Figure 5.2.13 Blood-borne *Pseudomonas aeruginosa* pneumonia. (A) A Gram–Sandiford stain shows heavy colonisation of arterial walls by Gram-negative bacilli. (B) The consequent vasculitis has led to extensive infarction of the lower part of the lung.

PNEUMONIC PLAGUE

In humans, infection with the Gram-negative bacillus *Yersinia pestis* takes two main forms: bubonic plague, in which the bacillus is transmitted to humans by the bite of infected rat fleas, and pneumonic plague, in which the organism is usually spread from person to person by infected sputum droplets. Before the era of effective antibiotics both forms had a high case fatality rate: indeed, the plague bacillus has been the cause of some of the most widespread and devastating epidemics in human history.

In the pneumonic form the lungs show many areas of bronchopneumonia: these are sometimes confluent but the course of the untreated disease is generally too short for massive consolidation to develop. The pulmonary lesions are often haemorrhagic and they are usually accompanied by serofibrinous pleurisy and great enlargement of the hilar lymph nodes. Histologically the alveolar capillaries are engorged and the air spaces are full of fluid exudate containing few leukocytes but many bacilli. In successfully treated cases, progression to consolidation and rarely cavitation has been noted radiologically.[102]

TULARAEMIC PNEUMONIA

Tularaemia is caused by *Francisella* (formerly *Pasteurella*) *tularensis*, a Gram-negative coccobacillus that infects many wild animals in North America and, to a lesser extent, Scandinavia, Japan and elsewhere, including the UK.[103] The bacterium was named after Tulare county in California where human infection was first identified. The infected animals include rabbits, hares, muskrats and ground squirrels. Humans are infected when handling these animals or when bitten by ticks that act as vectors of the disease. Direct infection takes place through skin abrasions, mucous membranes, the conjunctivae, and, less commonly, the lungs. The bacterium is highly virulent and its handling poses an extreme hazard to microbiology staff. It is a facultative intracellular pathogen with its primary target being the macrophage.

Pulmonary involvement is usually by septicaemic spread from a lesion in the skin or eyes, via the local lymph nodes, but may be primary. Many patients show neither septicaemia nor pulmonary involvement but in fatal cases the incidence of pneumonia rises to 70%.

At necropsy, the lungs show necrotising bronchiolitis, bronchopneumonia, pleurisy and pleural effusions. The consolidation tends to become confluent and undergo necrosis.[104] The alveoli then contain abundant fibrin and necrotic macrophages, resembling the changes seen in *Legionella* pneumonia. Vasculitis and thrombosis may lead to necrosis of the alveolar walls. The bacteria are difficult to demonstrate in sections with conventional stains but can be identified by immunocytochemistry. Culture is important and the demonstration of a rising titre of antibodies is also helpful in establishing the diagnosis.

ANTHRAX PNEUMONIA (WOOLSORTER'S DISEASE)

Anthrax occurs in many species of domestic animals, especially herbivores. Spores of the causative organism, *Bacillus anthracis*, occasionally infect humans, most commonly by skin inoculation, where they cause a 'malignant pustule', least commonly by ingestion, or with devastating effect by inhalation, resulting in 'woolsorter's disease'.

Woolsorter's disease was formerly seen in the Yorkshire textile towns, where it was acquired by inhalation of dust from imported wool contaminated with anthrax spores. Others at risk include those exposed to infected hides, hair, bristle, bonemeal and animal carcasses. The spores are very resistant to drying but effective measures are now directed to their destruction by exposure of imported materials to antiseptics before they are handled; as a result anthrax is now very rare in Great Britain. In 1979 there was a major epidemic of anthrax resulting in over 60 deaths in a narrow corridor of land downwind of a military establishment near Sverdlovsk, Russia, which was suspected of conducting microbiological warfare research.[105,106] Anthrax spores were also used as a bioweapon by terrorists operating in the USA in 2001: of 11 people who were infected, 5 died. Screening procedures and plans to deal with the possibility of similar attacks have subsequently been put in place.[107–109]

If inhaled, the spores are rapidly transmitted to the mediastinal lymph nodes. It is here that the bacilli form and the disease starts. From the lymph nodes the bacilli reach the blood stream and are distributed in large numbers throughout the body. The septicaemia is often so severe that the organisms are recognisable in films of the circulating blood. Although the lungs may have provided the portal of entry, they are affected secondarily as part of a systemic blood-borne disease.[110,111]

The course of inhalational anthrax is dramatic. Non-specific influenza-like symptoms rapidly progress to cardiopulmonary failure and death within a few days.[112] Necropsy shows haemorrhagic necrosis of the infected tissues. The process is most advanced in the lymph nodes draining the site of primary infection.[106] Thus, in woolsorter's disease a haemorrhagic mediastinal mass is one of the principal findings at necropsy. Other changes commonly encountered at necropsy include a large, dark, soft spleen, haemorrhagic effusions, haemorrhagic intestinal ulceration, haemorrhagic meningitis (which is often limited to the top of the cerebral hemispheres in a so-called 'cardinal's cap'), haemorrhagic bronchitis and widespread, often confluent, areas of haemorrhagic pneumonia. As in other organs, the haemorrhagic inflammatory oedema that constitutes the exudate in the alveoli contains large numbers of the characteristic large Gram-positive bacilli, which are readily seen in haematoxylin and eosin preparations.[105,111,113] However, immunohistochemistry is proving more reliable than Gram staining in identifying the bacteria.[108,109]

LEPTOSPIRAL PNEUMONIA

Leptospirosis is a zoonosis of worldwide distribution with many wild and domestic animal reservoirs. Human infection occurs through direct contact with infected animals or, more commonly, through contact with water or soil contaminated with the urine of infected animals. Sewage workers, farmers, animal handlers and veterinarians are at particular risk. Pulmonary disease may be seen in cases of infection by leptospires of various serogroups: they are severest in cases of infection by *Leptospira icterohaemorrhagiae*, which is acquired from rats, but have been a conspicuous feature in a small proportion of cases of canicola fever (infection by *L. canicola*, acquired from dogs) and of infection by *L. bataviae*, which occurs in parts of south-eastern Asia. The spirochaetal leptospires can be demonstrated in the lesions by Levaditi's silver impregnation method, immunocytochemistry or in situ hybridisation.

Pulmonary involvement is manifest as cough and haemoptysis in association with patchy consolidation of the lungs.[114,115] Occasionally, severe pulmonary haemorrhage is the predominant or only manifestation of the infection.[116,117] but provided the disease is recognised, and treated early and efficiently, the case fatality rate is low.

The pulmonary lesions are foci of haemorrhagic pneumonia or, in some cases, of simple haemorrhage.[116] In the pneumonic foci there is a haemorrhagic fibrinous exudate that contains a few neutrophils and occasional macrophages; the exudate is most conspicuous within the alveoli but is seen also in the interalveolar septa, which are correspondingly thickened. Diffuse alveolar damage is occasionally observed. In cases of simple pulmonary haemorrhage, the bleeding is often associated with the profound thrombocytopenia that is an occasional accompaniment of leptospirosis but electron microscopy reveals that there is also profound capillary damage, culminating in endothelial necrosis[118]: a paucity of bacteria near the lesions supports the suggestion that they are due to toxins released elsewhere.[119]

CHLAMYDOPHILA PNEUMONIA (PSITTACOSIS, ORNITHOSIS)

The chlamydophilae, formerly known as the chlamydiae or bedsoniae and once considered to be viruses, are obligate, intracellular organisms, 0.25–0.50 μm in diameter, that are now classed as bacteria. The genus includes three species pathogenic for humans: *Chlamydophila psittaci*, *C. trachomatis* and *C. pneumoniae*.

C. psittaci pneumonia is contracted from infected birds, particularly parrots imported from South America, where the disease is enzootic. In contrast, *C. trachomatis* is almost exclusively confined to humans, causing trachoma, lymphogranuloma venereum and other genital diseases, and, in infants, pneumonia, which is usually accompanied by ocular infection.[120,121] *C. pneumoniae* was described as a separate pathogen in 1986 and in some communities is responsible for as many as 10% of pneumonia admissions to hospital,[122–125] although generally causing milder disease than *C. psittaci*.

Organisms similar to *C. psittaci* are found in many species of wild and domesticated birds in various parts of the world and at least some of these are pathogenic for humans. For this reason, the more generally applicable name, ornithosis, is more appropriate to this group of diseases rather than psittacosis (parrot's disease). Budgerigars are now the commonest source of ornithosis in the UK.[126] Outbreaks have also been associated with ducks, chickens and turkeys.[127,128]

Infected birds, which may show no signs of disease, excrete the organisms in droppings that eventually form a highly infected dust. It is usually through the inhalation of such dust while attending to the birds that individuals become infected, but the disease may also be contracted in poultry-processing plants or pillow-filling factories.[127] The infectivity of ornithosis is high and numerous instances have been recorded of nurses and relatives contracting the disease while caring for patients. The disease has also been acquired through exposure to the organism in the laboratory and in the performance of necropsies.

Clinical features

The clinical presentation of ornithosis varies from a mild influenza-like illness to fulminating pneumonia complicated by lesions in other systems. Fulminating cases carry a high mortality. Symptoms usually start within 1–2 weeks of exposure. The organism may be cultured from the patient's blood, but more usually the diagnosis is established by demonstrating a rising titre of complement-fixing antibodies. Cross-reactions with other organisms of the psittacosis–lymphogranuloma–trachoma group occur but should not be confusing in practice. Many patients with ornithosis give a positive skin reaction to Frei (lymphogranuloma venereum) antigen.

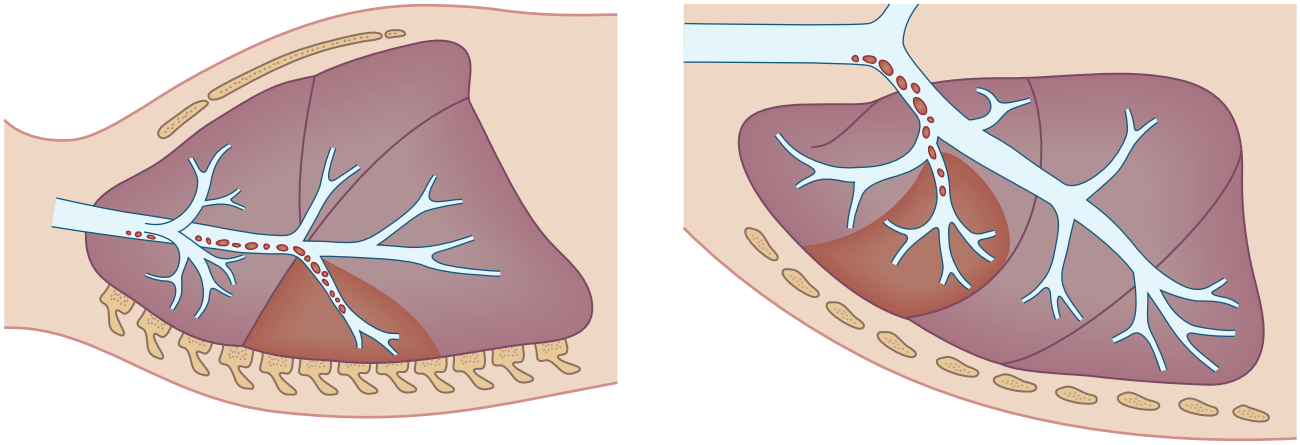


Figure 5.2.14 The effect of posture on the distribution of aspirated material. When the patient is fully supine (left) aspirated material is preferentially distributed by gravity to the apical segment of the lower lobe, whereas when tilted to one side (right) the lateral portions of the anterior and posterior basal segments of the upper lobe are affected. *(Reproduced from Brock et al. (1942)[139] courtesy of the Editor of* The Guy's Hospital Reports.*)*

Pathology

At necropsy, the lungs are bulky and patchily consolidated. The consolidated areas, which are usually haemorrhagic, are more numerous in the lower lobes than elsewhere. Where they abut the pleura there is local fibrinous pleurisy but pleural effusion is uncommon.

Microscopically, the changes are appropriate to a bacterial rather than to a viral pneumonia, for exudation within the alveoli is more marked than interstitial changes. However, the inflammatory cells are a mixture of those found in bacterial and viral pneumonia, macrophages predominating in the air spaces and a mixed lymphocytic and neutrophil infiltrate being seen in the interstitium. The changes are concentrated on the terminal bronchioles, from which they spread to involve adjacent alveoli and then the whole lobule, by which time there is often necrosis of the bronchiolar and bronchial epithelium.[129] There is engorgement and often thrombosis of capillaries that can result in foci of alveolar necrosis. Later, the alveoli develop a conspicuous lining of swollen epithelial cells. The chlamydophilae are just visible with the light microscope as cytoplasmic inclusion bodies (known as Levinthal–Coles–Lillie bodies, LCL bodies, or Levinthal bodies) that range from about 0.25 to 0.50 µm in diameter. They are to be seen in the cytoplasm of a variable proportion of the alveolar lining cells. They are basophilic and may most easily be found in preparations stained by the prolonged Giemsa method. As with many bacterial pneumonias, healing may be by repair rather than resolution, resulting in bronchiolitis obliterans organising pneumonia.[130]

C. pneumoniae pneumonia

C. pneumoniae is spread from person to person rather than from birds, infecting both upper and lower respiratory tracts and causing prolonged bronchitis and mild pneumonia of rather non-specific character, somewhat similar to that caused by *Mycoplasma pneumoniae*.[125] Retrospective studies of stored sera have shown that many patients diagnosed as having psittacosis on the basis of a positive serological test were actually infected with *C. pneumoniae*. Antibodies to *C. pneumoniae* have also been identified in many persons who give no history of respiratory disease.[131]

C. pneumoniae infection has a bimodal age distribution, affecting schoolchildren and the elderly. *C. pneumoniae* pneumonia is not fatal and there have consequently been few histopathological studies in humans. Experimental studies suggest that the bacterium causes a non-specific acute pneumonia.[125] *C. pneumoniae* has been linked to chronic obstructive lung disease[125,132,133] and an intriguing relationship between *C. pneumoniae* and atheroma has been identified.[124,134,135]

ASPIRATION PNEUMONIA[136]

Causes of aspiration pneumonia

Aspiration lesions include infective processes such as pneumonia and lung abscess, which are dealt with here, and non-infective processes such as exogenous lipid pneumonia and the chemical pneumonias or pulmonary fibrosis that result from the aspiration of gastric acid and other irritants. Aspiration is promoted by loss of consciousness and suppression of the cough reflex, particularly the latter.[137] It is therefore likely to complicate drunkenness, general anaesthesia, cerebrovascular accidents, drug overdosage or other causes of coma. Aspiration is also promoted by dysphagia, whether it be neurological or due to oesophageal diseases such as achalasia, stricture, diverticulum or involvement in systemic sclerosis.[138] Aspiration pneumonia and lung abscess are also promoted by poor oropharyngeal hygiene: they are rare in the edentulous.

Anatomical location

Aspiration lesions affect the dependent parts of the lungs so that their anatomical location is dictated by the position of the individual when aspiration occurs. Common sites of aspiration pneumonia include the apical segment of the lower lobe and the lateral parts of the basal segments of the upper lobe because gravity carries the aspirated material into these lung segments when the patient is in the prone and lateral positions respectively (Figs 5.2.14, 5.2.15).[139] Conversely, the right middle lobe is affected when gasoline is accidentally aspirated

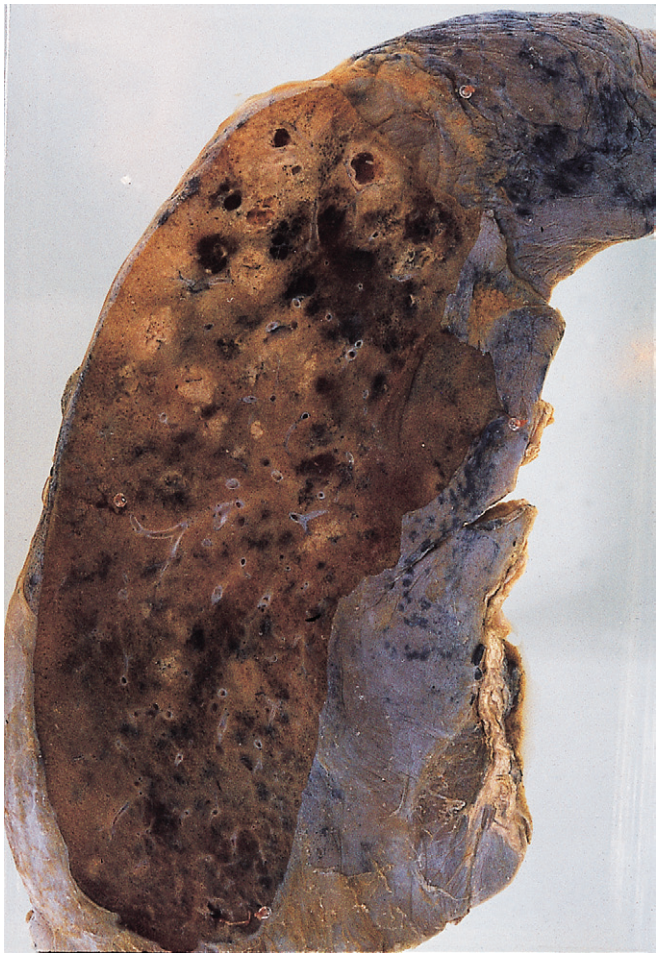


Figure 5.2.15 Aspiration pneumonia showing necrotizing foci of consolidation in the apical segment of the lower lobe.

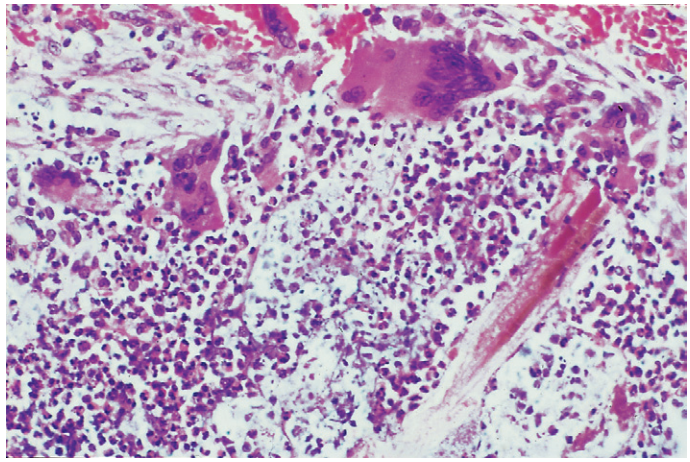


Figure 5.2.16 Aspiration pneumonia showing a bronchiole filled with pus in which there is a spicule of foreign material with attendant foreign-body giant cells.

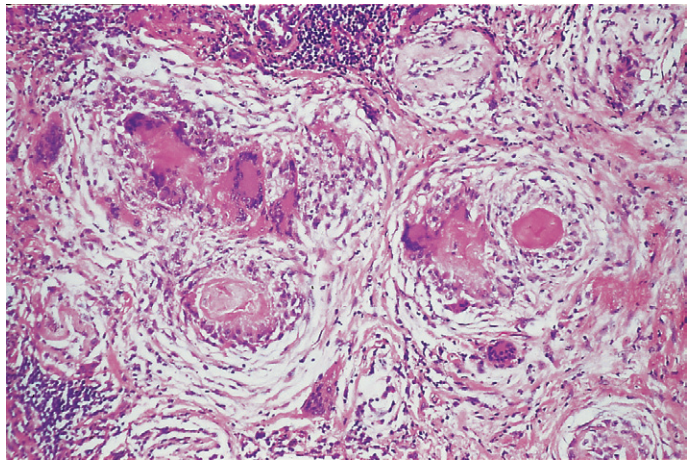


Figure 5.2.17 Aspiration pneumonia characterised by florid foreign-body granulomas.

while it is being syphoned from a motor vehicle, a procedure that necessitates the person bending forward so that the right middle lobe and the lingula become the most dependent parts of the lungs.[140]

Pathological findings

Aspiration pneumonia is a bronchopneumonia in that the conductive air passages as well as the alveoli are filled with pus and the consolidation is peribronchiolar. The consolidation is particularly florid; individual foci are often much larger than those encountered in the more usual type of bronchopneumonia. The lesions also tend to undergo necrosis (see Fig. 5.2.15). Microscopically, particles of undigested food may sometimes be observed in the pus. These are generally attended by foreign-body giant cells (Fig. 5.2.16) and a florid granulomatous reaction may be provoked, sometimes termed 'pulse granuloma' (Fig. 5.2.17).[141–143] In such cases, the surgeon palpitating the lung at thoracotomy may suspect metastatic carcinoma but the pathologist is more likely to mistake the microscopic changes for a specific infective granulomatous disease, such as miliary tuberculosis, if the aspirated debris goes unrecognised. Less frequently, the granulomas may contain components of pharmaceutical tablets such as starch, talc, microcrystalline cellulose and crospovidone used as fillers, or kayexalate, which is a polystyrene sulphonate used in the treatment of hyperkalaemia.[143] The fillers may also gain access to the lungs via the blood stream in intravenous drug abusers and are described in the section on foreign-body emboli on page 411.

Clinical features

Fever, consolidation of the lung and leukocytosis may develop soon after the aspiration. Alternatively, the precipitating episode may not be recognised and the onset of the pneumonia may be insidious. Cavitation and the production of foul purulent sputum are common late manifestations of aspiration pneumonia.

Bacteriology

The bacteria responsible for aspiration pneumonia are the dominant components of the indigenous flora of the upper respiratory tract and mouth. Because of this, specimen contamination bedevils the interpretation of sputum samples. Cultures of blood, pleural fluid or transcutaneous tracheal aspirates are more informative. Facilities for anaerobic culture are essential as anaerobes outnumber aerobes by 10

to 1, as they do in the mouth and pharynx. Mixed infections are the rule, comprising either a variety of different anaerobes or mixed anaerobes and aerobes. The commonest isolates are *Bacteroides melaninogenicus, Fusobacterium necrophorum*, anaerobic or microaerophilic cocci and *Bacteroides fragilis*.[144] It is fortunate that all except the last of these are sensitive to penicillin. *B. fragilis* is sensitive to the cephamycin, cefoxitin. A predilection for opportunistic mycobacteria to infect lungs containing aspirated lipids, such as those in milk, is referred to on page 212.

LUNG ABSCESS

An abscess is a focus of suppuration consisting of a collection of pus that is walled off by chronic inflammatory granulation tissue and fibrous tissue. Although abscesses are very familiar lesions, in the lung they are often confused with other pus-filled cavities, particularly those of bronchiectasis. Similarly, when a lung abscess discharges into the air passages, as it is prone to do, the air-filled space that results is often confused with an empty bronchiectatic cavity. Lung abscess and bronchiectasis are fundamentally different diseases. The essential structural difference between them is that several airways communicate with an abscess cavity, whereas if multiple airways are ectatic, they only communicate at their normal branching points (see Fig. 3.34, page 119). This is because the formation of an abscess entails 'cross-country' destruction of lung tissue, something that is unique to an abscess, regardless of its aetiology.

Spontaneous rupture of an abscess into a bronchus is a likely event and if the patient survives this by coughing up the pus instead of disseminating it throughout the bronchial tree, a marked improvement in the patient's general condition can be expected. With time, the granulation tissue bordering the now empty cavity may become epithelialised. Also, the many airways cut across when the abscess formed may be sealed off by scar tissue. The cavity may then resemble a congenital cyst. A congenital bronchogenic cyst is distinguished by the presence of cartilage and glands in its wall, but a simple congenital cyst may be indistinguishable morphologically from a cavity that started as an abscess. Other congenital cysts (dealt with in Chapter 2) have their own special features (see Table 2.2, p. 56).

Sometimes the airways leading into a postinfective cavity only open in inspiration so that they act as check valves. The fibrous wall is then stretched progressively, resulting in a very thin-walled air sac that is often termed a pneumatocele. This process is seen particularly after staphylococcal infection (see Fig. 5.2.8). Pneumatoceles resemble emphysematous bullae but, although they are often multiple, the remainder of the lung tissue is generally free of emphysema, something that is unlikely with bullae.

Secondary lung abscess

Abscesses develop in the lungs as a complication of several conditions. Pneumococcal pneumonia was formerly a common cause but pneumonia due to staphylococci, klebsiellae (see Fig. 5.2.12) and anaerobic bacteria is now more important in this respect.[145] Local predisposing conditions include bronchial cancer and the presence of a foreign body. Septic embolism and multiple pyaemic abscesses of the lung were formerly common complications of such staphylococcal infections as osteomyelitis and carbuncle but antibiotics have rendered these rare. Still seen on occasion is necrobacillosis (Lemierre's disease), a severe septicaemic illness in which pharyngitis caused by the anaerobe *Fusobacterium necrophorum* is complicated by thrombophlebitis of the internal jugular vein and multiple metastatic abscesses, particularly in the lungs.[146–149]

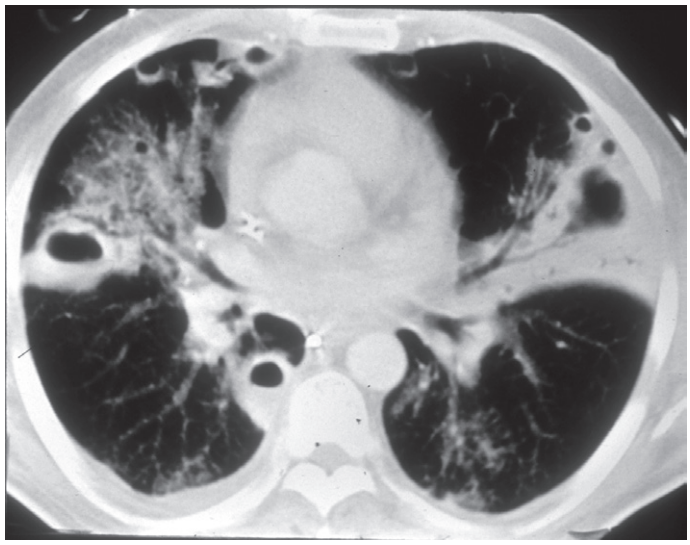


Figure 5.2.18 Bilateral aspiration abscesses. High-resolution computed tomography scan shows bilateral consolidation and cavitation. Culture grew anaerobic bacteria.

Primary lung abscess: an aspiration lesion

The development of a secondary lung abscess is easily understood and clearly dependent upon some other underlying disease. On occasion, however, a lung abscess has no apparent cause and is therefore termed primary. The available evidence indicates that primary lung abscesses are nearly always a consequence of the aspiration of infected oropharyngeal secretions. First, there is usually some condition predisposing to aspiration or impairing the cough reflex, for example, alcoholic stupor, general anaesthesia, head injury or neurological disease causing loss of consciousness, dysphagia or primary oesophageal dysfunction. Second, dental hygiene is usually poor, and there is often periodontitis or gingivitis. Third, primary lung abscesses are usually found in the dependent parts of the lungs. They are commoner on the right, probably because the right main bronchus is a more direct continuation of the trachea than the left, and in the apical segment of the lower lobe and the lateral parts of the basal segments of the upper lobe, these being the most dependent parts in the prone and lateral positions respectively (Figs 5.2.14, 5.2.18 and 5.2.19).[139] Fourth, the bacteria responsible are usually the mixed anaerobes that predominate in the oropharynx, particularly in people with bad teeth (*Fusobacterium*, *Bacteroides* and *Peptostreptococcus* species), and aerobes such as *Streptococcus milleri*.[47,150,151] Thus, primary lung abscess has much in common with aspiration pneumonia and it is for this reason that it is dealt with here, rather than in Chapter 5.3, the chapter on chronic bacterial infection, which its indolent nature would justify. The bacteriology of empyema is similar to that of aspiration pneumonia and primary lung abscess but this condition is dealt with in Chapter 13, the chapter on pleural disease.

BOTRYOMYCOSIS

The term 'botryomycosis' is used to describe colonies of pyogenic bacteria growing within tissues such as the skin, muscle, bone and various viscera, including the lungs.[152–154] The colonies generally exist within pus-filled cavities and are often enclosed within sheaths of eosinophilic hyaline material (Splendore–Hoeppli reaction – see p. 214) (Fig. 5.2.20). They are indistinguishable from the granules of

Figure 5.2.19 Primary lung abscess straddling the fissure and involving the lateral parts of the basal segments of the upper lobe and the apical segment of the lower lobe.

actinomycosis in sections stained by haematoxylin and eosin but Gram stains show cocci or bacilli rather than filamentous bacteria. The bacteria are viable but the growth of the colonies is slow and there is no invasion of the adjacent tissues: something approaching a state of balance exists between the body defences and the bacteria.

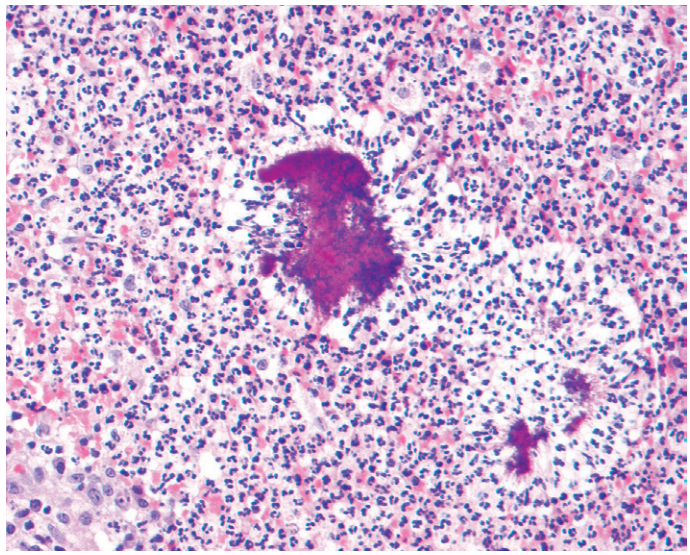


Figure 5.2.20 Botryomycosis. A colony of mixed bacteria is seen within a purulent exudate.

The size of the bacterial colonies varies. They may only be identifiable with the aid of a microscope or they may form visible flecks within the pus, similar to the sulphur granules of actinomycosis. Rarely the colonies are considerably larger; sometimes a single mass of bacteria may attain a size of 5 cm in diameter. One such colony simulated an aspergilloma and was called a 'botryomycoma'.[155]

The bacteria involved are often of mixed species but generally include anaerobes such as *Bacteroides* or peptostreptococci.[155] These are normal inhabitants of the pharynx and are generally found in aspiration pneumonia and primary lung abscess, thus relating botryomycosis to these aspiration lesions. Botryomycosis is also a complication of cystic fibrosis,[156] acquired immunodeficiency syndrome (AIDS)[157] and tracheopathia osteochondroplastica.[158]

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Chapter 5

5.3 *Chronic bacterial infections*

CHAPTER CONTENTS

TUBERCULOSIS

Bacteriology

Tuberculosis is caused by certain mycobacteria. In the laboratory these microbes are difficult to stain and in the body they are difficult to kill. Their comparative resistance to the normal body defences is due to an ability to inhibit phagosome–lysosome fusion, permitting them to survive within the host's phagocytes.[1,2] Their resistance to ordinary stains is attributed to their cell walls being rich in mycolic acid waxes. This necessitates the use of hot concentrated carbol fuchsin for their demonstration, as in the Ziehl–Neelsen stain. Once stained in this way, they are difficult to decolorise, even with strong acids and alcohol, hence references to the acid- and alcohol-fast bacilli. Mycobacteria also show some resistance to formalin: of 138 tissue specimens from autopsy lungs fixed in formalin and showing histological evidence of acid-fast bacilli, 12 grew mycobacteria, including three *Mycobacterium tuberculosis* isolates.[3]

The bacilli are normally scanty in tuberculous tissue and their identification with the Ziehl–Neelsen stain may require tedious examination of many sections.[4] They are easier to identify in rhodamine-auramine-stained sections examined by fluorescence microscopy.[5–7] Tissue containing necrotising granulomas is most likely to give positive results whereas specimens showing only non-necrotising granulomas, poorly formed granulomas or acute inflammation are less likely to reveal acid-fast bacilli.[8,9] Culture is no more likely to identify the mycobacteria than the examination of tissue sections.[9,10] Failure to demonstrate them does not exclude a diagnosis of tuberculosis. The future lies in immunohistochemistry[11] or molecular techniques such as the polymerase chain reaction, which can be adapted for application to paraffin sections.[12–15a] The detection of mycobacterial RNA indicates that the bacilli are viable and is therefore preferable to tests for mycobacterial DNA. Molecular techniques are also useful in identifying drug resistance, distinguishing mycobacterial species and identifying specific strains of *M. tuberculosis*.[16–18]

The mycobacteria that cause tuberculosis in humans are sometimes listed as *M. tuberculosis, M. bovis, M. africanum* and *M. microti*, the so-called tuberculosis complex, although these four organisms are probably just variants of a single species. The first two correspond to the human and bovine tubercle bacilli while *M. africanum* includes a heterogeneous group of strains, with properties intermediate between the former two, isolated from humans in equatorial Africa and from African immigrants in Europe. The features and management of tuberculosis in humans caused by these three variants are very similar. *M. microti*, the vole tubercle bacillus, is of attenuated pathogenicity for humans and has been used as a vaccine.

M. tuberculosis is largely responsible for the disease and the infection is predominantly pulmonary, acquired through inhalation of this

organism into the lungs. Formerly, intestinal tuberculosis, acquired by drinking milk infected with *M. bovis*, was much commoner, but the eradication of mycobacteriosis from cattle and the widespread pasteurisation of milk brought about a virtual disappearance of this form of disease in developed countries.

In addition to the human, bovine and vole types, the term 'tubercle bacillus' includes the avian and the 'cold-blooded' types. The avian tubercle bacillus is a distinct species, *M. avium*, while the 'cold-blooded' group includes the fish, turtle and frog tubercle bacilli, which are known as *M. marinum*, *M. chelonei* and *M. fortuitum* respectively. All these other 'tubercle bacilli' can cause opportunistic infections in humans and, together with a number of other opportunistic species, are often referred to as the atypical, anonymous or opportunistic mycobacteria. *M. intracellulare* is no longer distinguished from *M. avium*, and the collective *M. avium-intracellulare* is often used. Similarly, reference is sometimes made to *M. fortuitum-chelonei*. The opportunistic mycobacteria are dealt with separately later in this chapter (see p. 211).

Route of infection in pulmonary tuberculosis

In the past, there was much speculation about the possible routes of infection in tuberculosis. Today, there is little doubt that when the lesions are present in the lungs the infection has taken place as a result of inhalation of tubercle bacilli. That the respiratory tract should be the chief portal of entry is scarcely surprising in view of the great preponderance of the pulmonary form of chronic tuberculosis in humans and of the enormous numbers of tubercle bacilli that are eliminated daily in the sputum of most untreated active cases. Those in close contact with such patients are liable to inhale the bacilli and acquire the infection in their lungs. Although the smaller droplets of expectorated sputum, which may remain for many minutes suspended in the air after a cough, are probably the chief vehicle for the transmission of tubercle bacilli, it should be realised that the organisms are resistant to desiccation, and that in consequence, dried 'droplet nuclei', or the dust that they ultimately contaminate, may long remain as potential carriers of the infection. Tuberculosis transmission can be reduced however by hospitalising patients with positive sputa in isolation rooms equipped with ultraviolet light and exhaust ventilation.[19]

Other routes of infection which may have operated in pulmonary mycobacteriosis in the past include haematogenous dissemination from a primary focus of *M. bovis* infection in the intestine, acquired by drinking infected milk, and similar spread from a primary focus in the skin acquired by traumatic inoculation (a rare occupational hazard of pathologists and butchers, hence the old term 'butcher's wart'), but these have never been as important as droplet spread.

Epidemiology

In most developed countries there has been a considerable fall in the incidence of tuberculosis and its mortality over the last century (Fig. 5.3.1). This is attributable to a variety of factors that began to operate among the prosperous classes and subsequently extended to all strata of society. During almost the whole of this period an amelioration in social conditions took place in an almost uninterrupted, unspectacular manner and it is to these unspecific factors that for many years the progressive fall in mortality was essentially due, although it was aided by public health measures such as the eradication of tuberculous cattle and mass radiography screening. After 1950, the decline in mortality from tuberculosis was hastened by the introduction of effective antituberculosis drugs. By bringing about a great fall in the number – often even the complete disappearance – of bacilli in the sputum in cases of active respiratory tuberculosis, these drugs have much reduced the hazard of infection that was formerly incurred by those who inadvertently or by obligatory associations were brought into contact, at work or at home, with an infectious case of the disease.

The reduced incidence of the disease in developed countries led to changes in the ages of the affected patients. Whereas it was formerly a disease of the young, tuberculosis came to be largely limited to the elderly in these countries, the disease representing recrudescence of quiescent infection acquired in youth. Many of these elderly patients suffered from an insidiously progressive form of the disease and this is still the case today (see p. 210).

The situation remained very different elsewhere. Much of the world has still not shared the economic and health benefits enjoyed in the west and in many countries tuberculosis remains one of the most important specific communicable diseases. Furthermore, the considerable gains that have slowly been achieved are now in peril because of the acquired immunodeficiency syndrome (AIDS) and other factors.

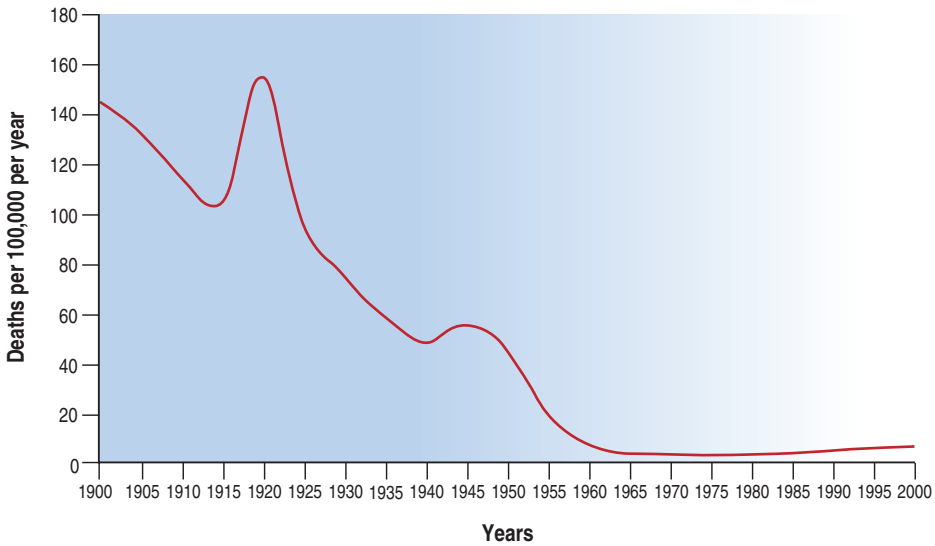

Figure 5.3.1 Deaths from tuberculosis in England and Wales in the twentieth century. The decline in mortality, temporarily checked by two world wars, was established well before specific chemotherapy became available, and is largely attributable to improved living standards.

There has been a resurgence of tuberculosis recently, even in groups where AIDS has yet to make a major impact, possibly due to new levels of urban deprivation and the influx of immigrants and refugees from countries with a high incidence of the disease.[20] In the UK, for example, immigrants from the Indian subcontinent have rates of tuberculosis about 25 times as high as that of the white population.[21] The decline in the incidence of tuberculosis in the UK slowed towards 1987 and has subsequently reversed: since that date case numbers have risen, particularly in inner London. The situation is similar in many other developed countries. Tuberculosis can therefore be regarded once more as a worldwide problem. It is estimated that about one-third of the world's population (approximately 2000 million people) have latent tuberculosis while the prevalence of active disease is put at more than 20 million worldwide. In 2006 there were 9.2 million new cases and 1.7 million deaths, which makes tuberculosis the largest cause of death from a single pathogen in the world.

Despite the prevalence of tuberculosis, the human response to infection is good. In the absence of immunosuppressive disorders such as human immunodeficiency virus (HIV) infection, only about 10% of those infected develop clinically evident disease. The basis of these patients' susceptibility is not well understood but tobacco smoking is a predisposing cause[22] and genetic factors appear to be involved.[23]

The impact of HIV infection

Following the advent of AIDS the downward trend in tuberculosis stabilised or was reversed.[24,25] An alarming resurgence of the disease is being witnessed, particularly in the poorer communities where drug abuse is prevalent (Table 5.3.1).[26–28] Furthermore, multidrug-resistant strains have emerged and now represent a global problem.[29–33] The mortality is high with such strains, even in patients who are not immunodeficient, but it is particularly high in AIDS.

It is estimated that worldwide more than 6 million people are dually infected with the tubercle bacillus and HIV, the majority in 10 sub-Saharan African countries. In 2007, there were an estimated 1.37 million new cases of tuberculosis among HIV-infected people and 456 000 deaths, one in four deaths from tuberculosis being HIV-related.[34] In sub-Saharan Africa, the AIDS epidemic is having a devastating effect on tuberculosis control programmes, with up to 100% increases in reported tuberculosis cases. The annual risk of active tuberculosis in those who are doubly infected is 10%, compared with a 10% lifetime risk in those who harbour the tubercle bacillus but are HIV-negative.[35] The situation in richer countries may not be so bad because HIV-infected persons tend to be young and those harbouring tuberculosis old, rendering recrudescence unlikely.[35] However, within HIV units, cross-infection is being reported.[31] Such nosocomial transmission has involved patients and hospital staff who are immunocompetent as well as other HIV-positive patients.[36]

The mechanism whereby HIV infection promotes tuberculosis is probably related to the pattern of cytokines produced by T-lymphocyte subsets. T-helper-1 lymphocytes produce interferon-γ and are central to antimycobacterial immune defence. However, when peripheral blood lymphocytes from HIV-infected patients with tuberculosis are exposed to tubercle bacilli in vitro they produce less interferon-γ than lymphocytes from HIV-negative patients with tuberculosis, suggesting that a reduced T-helper-1 response contributes to HIV-infected patients' susceptibility to tuberculosis.[37] It is also noteworthy that there is a reciprocal relationship between tuberculosis and HIV infection: tuberculosis appears to promote the course of HIV infection, probably by inducing macrophages to secrete cytokines that increase HIV replication.[38–40]

Not surprisingly in view of the interrelationship of HIV and the tubercle bacillus, the tuberculosis associated with HIV infection is particularly aggressive, being characterised by widespread dissemination throughout the body and a poor host response.[41] This non-reactive form of tuberculosis is similar to the insidious disease of elderly patients referred to above and described on page 210.

Table 5.3.1 The effect of human immunodeficiency virus (HIV) infection on the global toll of tuberculosis[27,28]

Region	People infected (millions)	New cases	Deaths	HIV-attributed
Western Pacific[a]	574	2 560 000	890 000	19 000
South-East Asia	426	2 480 000	940 000	66 000
Africa	171	1 400 000	660 000	194 000
Eastern Mediterranean	52	594 000	160 000	9000
The Americas[b]	117	560 000	220 000	20 000
The industrialized countries[c]	382	410 000	40 000	6000
Total	1722	8 004 000	2 910 000	315 000

[a]Excluding Japan, Australia and New Zealand.

[b]Excluding USA and Canada.

[c]Western Europe, USA, Canada, Japan, Australia and New Zealand.

Primary and postprimary types of tuberculosis

Although the morbid anatomical changes that develop in tuberculosis assume a variety of forms, the great majority of cases fall into one or other of two distinctive types. The first type was formerly found mainly in children and became known as the 'childhood type' of tuberculosis. Further experience has shown that it is not so much the youth of these patients as the fact that they are infected for the first time that accounts for the distinctive structural features of their lesions. In consequence, this form of tuberculosis is now known as the 'primary type', and as the incidence of the disease in the general population has declined and the age of first infection has correspondingly risen, it is now met with increasing frequency in adults. The second morphological form – previously known as the 'adult type' of the disease – occurs in those patients who have been sensitised by an earlier exposure to tuberculosis: this type of disease is now generally termed 'postprimary tuberculosis'. Postprimary tuberculosis is due to either fresh infection or reactivation of a dormant primary lesion (Fig. 5.3.2). Reinfection is common in countries in which tuberculosis is prevalent but in the developed countries reactivation of infection acquired decades earlier is commoner. The various patterns of tuberculous infection are summarised in Box 5.3.1.

Primary tuberculosis

The very early stages of a tuberculous lesion in the human lung have seldom been seen, and our ideas on its pathogenesis have been derived almost wholly from study of lesions in experimental animals.[42] Initially, the presence of tubercle bacilli in an alveolus excites little immediate reaction, and for the first day or two the only change may

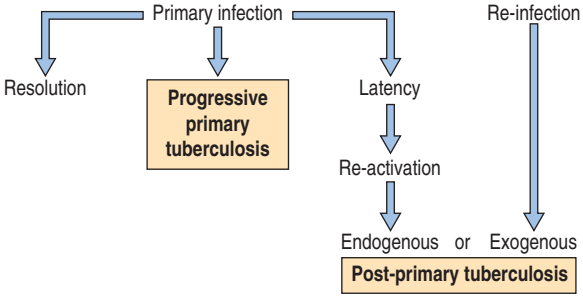

Figure 5.3.2 Possible events following infection by tubercle bacilli.

Box 5.3.1 **Summary of patterns of tuberculous infection of the lungs**

Primary tuberculosis[a]

Ghon focus + regional lymph node = primary complex

Reparative

Quiescent

Progressive

Pleural involvement

Airway dissemination (tuberculous bronchopneumonia, laryngeal lesions)

Epituberculosis (segmental tuberculosis)

Haematogenous (miliary tuberculosis, meningitis, solitary lesions in organs with a rich systemic blood supply and therefore a high oxygen tension, e.g. kidney. Also the lung apices because of their high ventilation/perfusion ratio)

Postprimary tuberculosis[a] **(reactivation or reinfection)**

Fibrocaseous apical cavitation (high oxygen tension)

Reparative

Quiescent

Progressive

Local extension

Pleural involvement

Airway dissemination (tuberculous bronchopneumonia)

Haematogenous (miliary tuberculosis)

Non-reactive tuberculosis (immunocompromised or elderly)

[a]Primary tuberculosis usually heals but if it progresses there is a greater chance of widespread dissemination than in postprimary disease, in which progression is more often local.

be a small amount of exudate and a few neutrophils round the organisms. Within the next few days, macrophages collect in increasing numbers, and ingest most of the bacilli.

Gradually, the macrophages, with living bacilli in their cytoplasm, aggregate to form microscopical nodules. The macrophages also develop an abundant eosinophilic cytoplasm and are described as 'epithelioid'. This represents a switch from their basic phagocytic function to a secretory one (see sarcoidosis, p. 286), modulated by lymphokines from T lymphocytes, notably interferon-γ.[23,43,44] This change promotes the antibacterial properties of the macrophage but also contributes to tissue necrosis, as outlined below. After about 2 weeks some of the more centrally placed macrophages fuse to form multinucleate cells of Langhans type. Small numbers of lymphocytes

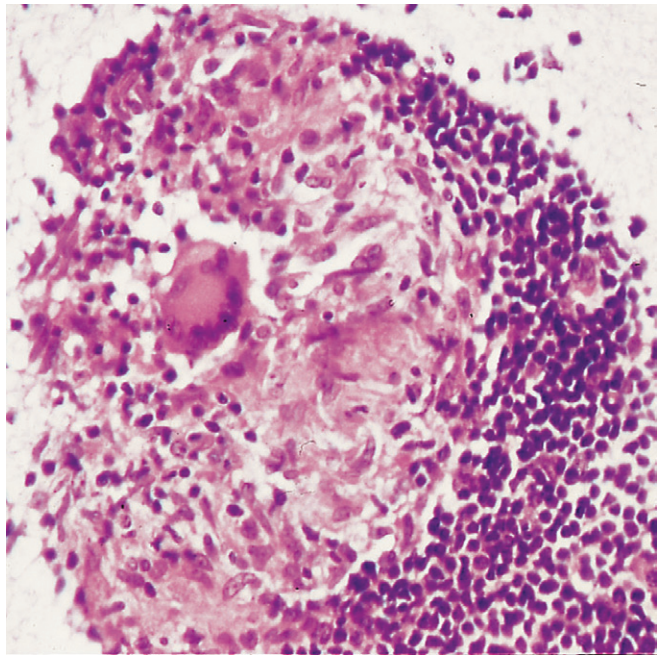

Figure 5.3.3 A tuberculous granuloma consisting of a central collection of epithelioid macrophages surrounded by lymphocytes. A Langhans giant cell is seen amongst the epithelioid cells.

are mixed with the epithelioid and giant cells and outside these, further lymphocytes form a dense outer mantle. This localised collection of epithelioid macrophages, Langhans giant cells and lymphocytes constitutes a tuberculous granuloma (Fig. 5.3.3). Immunocytochemistry shows that the lymphocytes in the inner zone of the granuloma are mainly T-helper (CD4) and memory (CD45RO) cells whereas the outer zone includes both CD4 and CD8 (T-suppressor) lymphocytes, while immediately adjacent to the outer zone and difficult to distinguish from it without immunocytochemistry there is a secondary centre composed of B lymphocytes and active (Ki-67+) antigen-presenting cells (Fig. 5.3.4).[45]

By the third week, the granuloma has usually grown sufficiently to be visible to the naked eye as a small, grey nodule, or tubercle, which gives the disease its name. As the tubercle enlarges, its centre turns yellow. Microscopical examination at this stage shows that the granuloma has undergone necrosis (Fig. 5.3.5). A ring of satellite tubercles then develops and as these undergo central necrosis they fuse together (Fig. 5.3.6). In this way the original granuloma gradually increases in size. The growth of a tuberculous lesion by the progressive development and subsequent incorporation of satellite tubercles is also seen in postprimary tuberculosis (see Fig. 5.3.19, p. 210).

It is characteristic of the classic active tuberculous lesions that the tubercle bacilli are scanty, probably reflecting a state of relatively strong immunity/hypersensitivity (see below). Also characteristic of tuberculosis is prolonged survival of the tubercle bacilli within the tissues, despite a vigorous host reaction. This is attributable to the tubercle bacillus inhibiting the fusion of macrophage lysosomes and phagosomes and so avoiding the bactericidal contents of the lysosomes.[1,2]

The type of necrosis found in a classic tuberculous lesion is distinctive, being dry, crumbling and cheesy (hence the term 'caseous' as a macroscopic description). It is of the coagulative rather than liquefactive type, probably because of the relative dearth of polymorphonuclear leukocytes. The necrosis is a hypersensitivity phenomenon; no

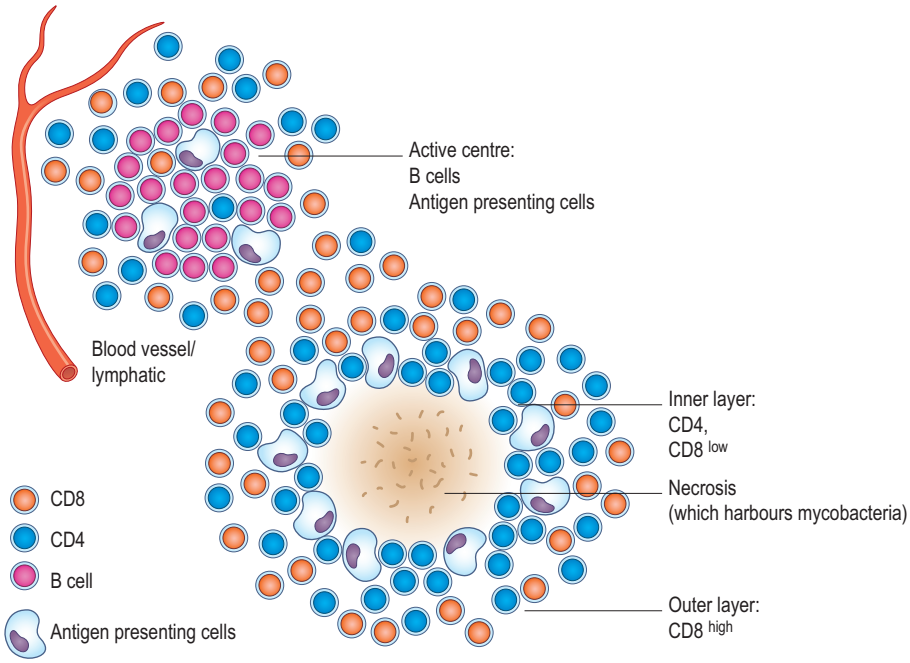

Figure 5.3.4 Diagrammatic representation of a tuberculous granuloma. The central necrosis, which harbours mycobacteria, is surrounded by an inner layer of antigen-presenting cells and CD4+ T lymphocytes, within which CD8+ cells are scarce. The outer lymphocyte infiltrate contains large numbers of CD8+ T cells and active (Ki-67+) centres with mycobacteria-containing antigen-presenting cells and B cells surrounded by both CD4+ and CD8+ T cells. *(Redrawn from Ulrichs et al.[45] by permission of the* Journal of Pathology.*)*

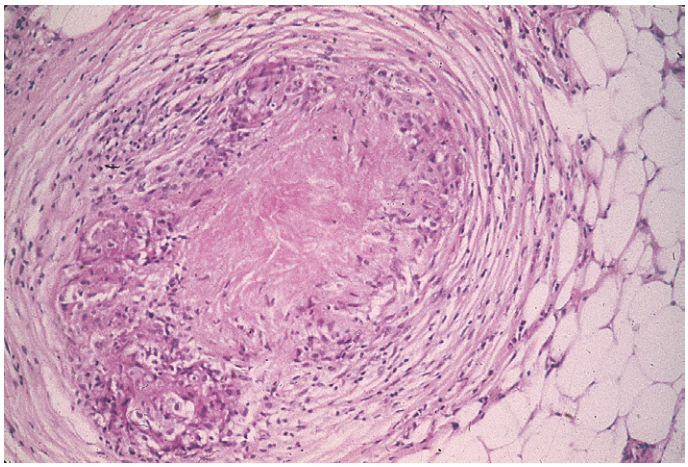

Figure 5.3.5 A tuberculous granuloma showing central caseous necrosis.

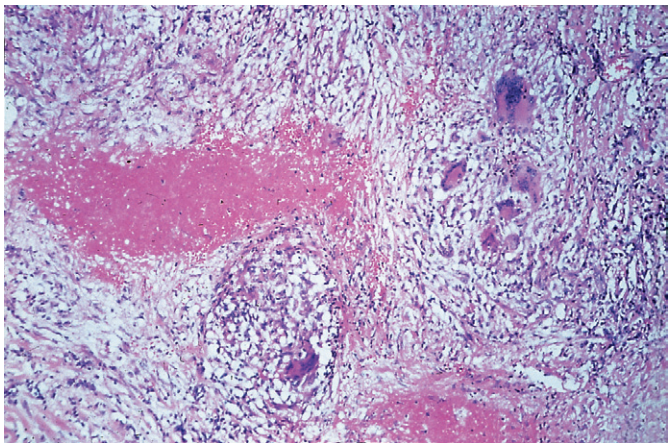

Figure 5.3.6 Tuberculous granulomas clustered around more extensive areas of coagulative necrosis.

mycobacterial toxins have been identified. It represents apoptosis brought about by cytotoxic T cells and macrophages activated by subsets of T-helper cells. The epithelioid cells show strong immunoexpression of the proapoptotic proteins Bax and Fas, with the anti-apoptotic protein Bcl-2 being notably absent.[46,47]

The elastic tissue of the lung persists for a long time in necrotising tuberculous lesions. When stained appropriately, its distribution and pattern give information about the position of blood vessels and of alveolar walls within the necrotic centre that cannot be recognised clearly, if at all, in haematoxylin and eosin preparations. Ultimately, however, all trace of the lung's elastin framework is lost.

In the comparatively small number of human cases in which there is an opportunity to examine the lungs while the lesion of primary tuberculosis is still active, the latter – often known as the 'Ghon focus'[48] – is generally visible as a pale yellow, caseous nodule, a few millimetres to a centimetre or two in diameter. Characteristically, it is situated in the peripheral part of the lung underlying a localised area of chronic inflammation and thickening of the pleura. Usually, only one such focus is present, but if the lungs are searched carefully, preferably with the help of postmortem radiography, it will be found that there is more than one focus in a small proportion of cases. It is a point of importance in the distinction between primary and post-primary tuberculosis of the lungs that in the latter the lesions are almost invariably in the apical region of an upper lobe, whereas in the former they are found most frequently in the periphery of the lower lobes, where airflow is greatest.

Studies on primary tuberculosis in both humans and experimental animals show that within a few days of their deposition in subpleural alveoli some of the bacilli are carried centripetally in the lymphatics to establish infection in hilar lymph nodes. Thereafter, the granulomatous changes in the lung and lymph nodes, and the smaller foci that may have formed along the course of the intrapulmonary lymphatics, all develop at about the same rate but the caseating lesions in the lymph nodes tend to be larger than the primary focus in the lung. This combination of a peripheral Ghon focus with the corresponding focus of caseation in the regional lymph nodes is known as the primary complex of Ranke (Figs 5.3.6 and 5.3.7). The complex is the typical result of a primary tuberculous infection of the lungs.

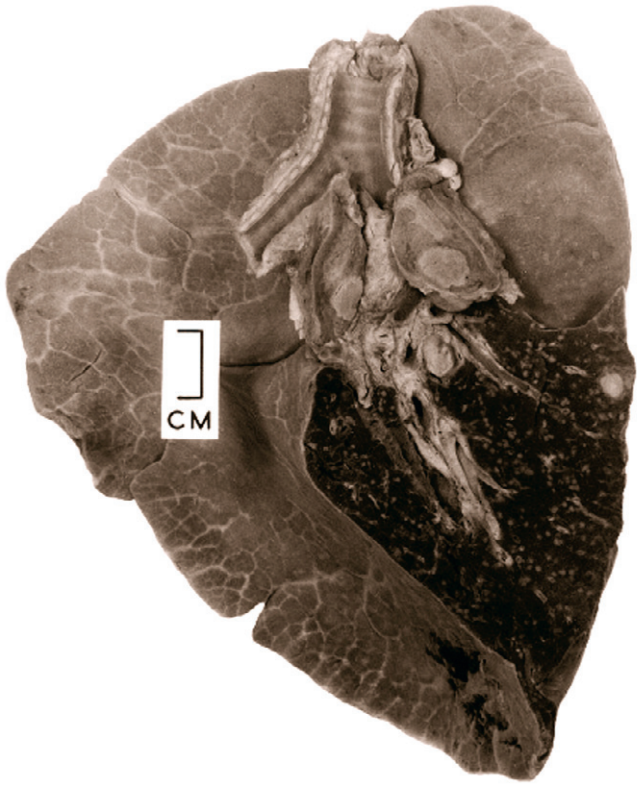

Figure 5.3.7 Primary complex of tuberculosis with miliary spread. A small Ghon focus in the lower lobe of the lung is accompanied by prominent caseating tuberculous lymphadenitis. The infection has spread from one of the lymph nodes into a branch of a pulmonary artery, resulting in miliary haematogenous tuberculosis of the lower lobe. *(Courtesy of the Curator of the Pathology Museum, Charing Cross and Westminster Medical School,*

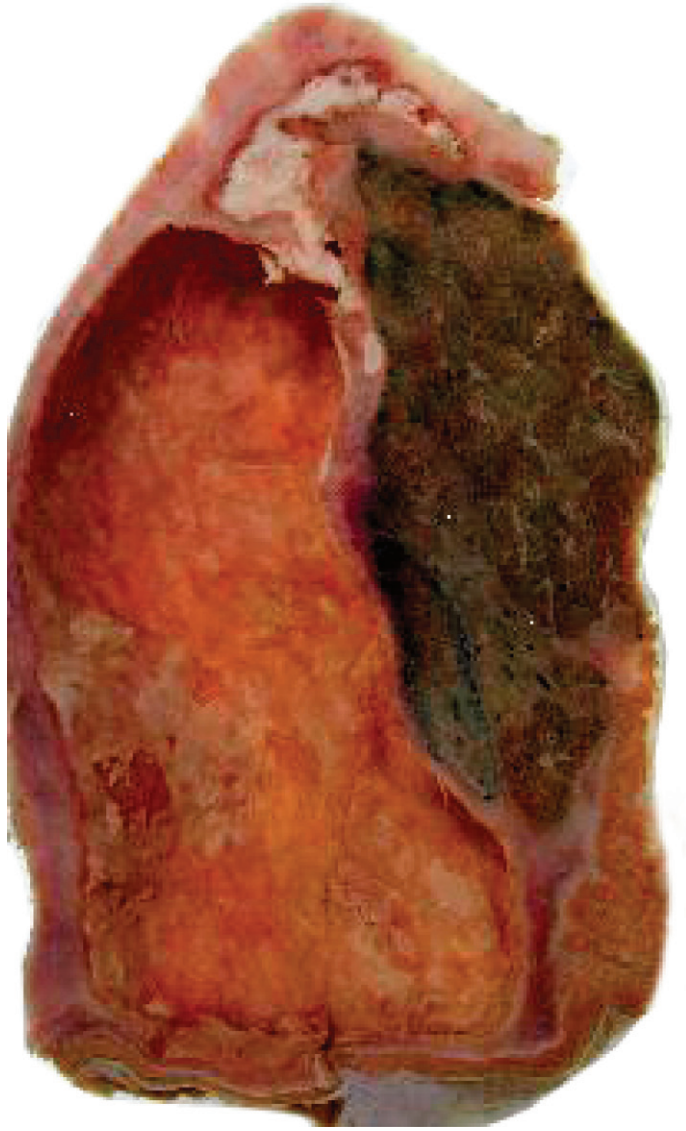

Figure 5.3.8 Tuberculous empyema. The lung is compressed by a large cavity that was originally filled by caseous material, loculated collections of which persist at the apex. The walls of the cavity are formed by the thickened parietal and visceral layers of the pleura. *(Courtesy of the curator of the Gordon Museum, Guy's Hospital, London, UK.)*

The primary complex may undergo a series of reparative changes, or it may continue to enlarge and in so doing implicate further structures and thus promote dissemination of the infection. The pathological features of healing and progressive primary complexes and the relative frequency of these processes will be considered next.

Reparative changes

The slow enlargement of the caseating primary complex is accompanied by the development of a fibrous capsule that impedes further centrifugal dispersal of the bacilli should any still remain alive. Later, there is often dystrophic calcification and even ossification, within which fatty and sometimes haemopoietic marrow may form. Diffuse racemose (dendriform) ossification (see p. 149) has also been reported in association with pulmonary tuberculosis.[49]

These old foci of caseous necrosis, walled off by fibrous tissue, may contain viable bacilli, despite an absence of inflammation. Such latent lesions, which are known as quiescent tuberculosis, are potential sites of recrudescence. Active disease is denoted by granulomatous inflammation.

Progressive changes

In a small proportion of cases of primary tuberculosis, the reparative changes fail to stem the progress of the disease. As the infected tissues undergo caseation, the bacilli tend to die in the central areas but to survive and multiply in the surviving zone of granulation tissue that borders the lesion, leading to its peripheral extension. As a result of this, a caseous mass, several centimetres in diameter, may form either in the lung itself or in the now much enlarged and generally matted regional lymph nodes. If the lesion erodes into a bronchus, loss of the necrotic material through the airway leads to the creation of a cavity, often of a size little less than that of the parent caseous mass, and surrounded by a ragged lining of partly necrotic tuberculous granulation tissue. If the necrotic focus breaks through the pleura, the result is pleural effusion, pneumothorax, tuberculous empyema (Fig. 5.3.8) or pyopneumothorax. Sometimes this is the presenting manifestation of the disease, and occasionally the only clinical evidence of the disease. In tuberculous empyema the matter in the pleural sac is caseous and not purulent, despite the traditional terminology, unless there is a secondary infection by pyogenic organisms.

Figure 5.3.9 Primary complex of tuberculosis comprising a large caseating Ghon focus and marked enlargement of the infected mediastinal lymph nodes. A caseating lymph node to the right of the lower end of the trachea has become adherent to the latter, and the tuberculous process has extended through the tracheal wall to form a sinus. Aspiration of infective material from this sinus has led to the development of the tuberculous bronchopneumonia, represented by multiple small foci of consolidation scattered throughout the lung. *(Courtesy of the curator of the Gordon Museum, Guy's Hospital. London, UK.)*

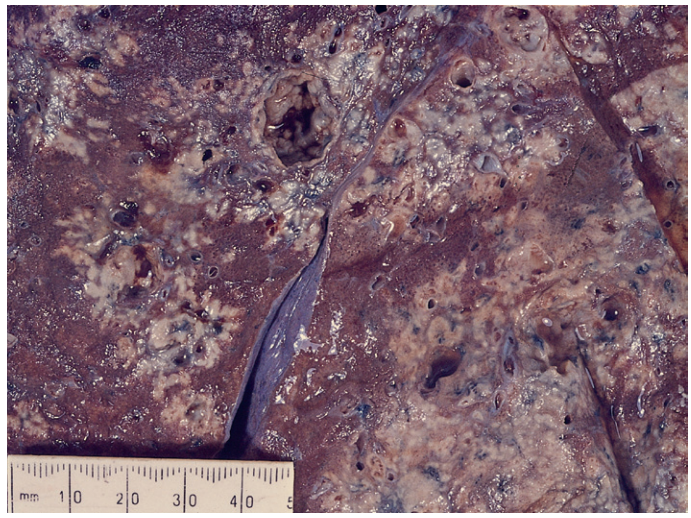

Figure 5.3.10 Dissemination of caseous material via the airways has led to widespread focal consolidation. *(Courtesy of Dr Max Millard, formerly of Florida, USA.)*

Dissemination through the airways

Caseous material that enters the main respiratory passages is largely expectorated but some is dispersed to other parts of the lungs by the deep inspiration that usually accompanies coughing. Such dispersion of large numbers of organisms within the bronchial tree may lead to widespread tuberculous bronchopneumonia ('galloping consumption'), an often fatal condition (Figs 5.3.9–5.3.11). Smaller numbers of bacilli may infect the bronchial, tracheal or laryngeal mucosa, or, by being swallowed, the intestine. Infection of a bronchus causes ulceration, mucosal thickening or concentric scarring which may be complicated by collapse of the distal lung.

Caseous hilar nodes may compress a bronchus and lead to absorption collapse (see middle-lobe syndrome, p. 92).[50–52] Partial

Figure 5.3.11 Tuberculous bronchopneumonia. Almost the whole of the lung shows pale, confluent areas of caseation. *(Courtesy of the curator of the Gordon Museum, Guy's Hospital. London, UK.)*

obstruction may lead to air trapping and severe distension of a lobe, proper ventilation of which may be obtainable only by surgical evacuation of the caseous contents of the nodes responsible. Massive enlargement of paratracheal nodes, particularly those of the right side, may result in compression of the trachea, causing stridor and sometimes cyanosis.

A caseating hilar lymph node may also erupt into a bronchus. Very rarely, so much matter escapes suddenly that the patient, usually a child, is quickly asphyxiated. More often there is progressive change in the affected segment. This is the condition known as epituberculosis.

Epituberculosis (segmental tuberculosis)

This condition[53] is a fairly frequent radiological finding in cases of primary pulmonary tuberculosis. The radiographic picture is that of a segmental opacity. It is associated with little clinical disturbance and usually resolves completely over a period of months. It was once commonly assumed to represent absorption collapse due to compression of the segmental bronchus by the lymph node component of the primary complex, but this explanation is now recognised to be inadequate in many cases. The great majority of these lesions represent inflammatory consolidation caused by the lymph node component of the complex perforating into the segmental bronchus so that infected caseous material is disseminated throughout the distal air passages.

The affected segment is pale grey and the lobular markings are accentuated by thickening of the interlobular septa. There is exudation of both fluid and macrophages into the alveoli, and lymphocytic infiltration of the alveolar walls. That the lesion is not merely a non-specific obstructive pneumonitis is clear from the constant presence of numerous epithelioid cell granulomas. Initially the granulomas are non-necrotising but quite extensive caseation may develop. Tubercle bacilli are to be found in the caseous node but are usually very sparse in the consolidated lung.

The lesion can be reproduced experimentally by introducing either killed tubercle bacilli or the purified protein derivative of tuberculin into previously sensitised animals. The condition is therefore considered to represent a local hypersensitivity reaction to the aspiration of caseous material from the perforated hilar nodes. This is supported by the acceleration of the resolution that is achieved by adding corticosteroids to the usual specific antituberculous drugs, and by the dramatic reappearance of the disease if the corticosteroids are withdrawn.

The natural outcome of epituberculosis is variable. There may be complete resolution or patchy fibrosis with contracture and perhaps bronchiectasis. The perforation of the bronchus usually heals with only minor scarring, but occasionally it causes fibrous constriction of the bronchus similar to that caused by aerogenous spread to the bronchus from a lesion in the lung, as described above. A rare sequel, comparable in pathogenesis to the traction diverticula of the oesophagus, is the formation of a bronchial diverticulum.

Haematogenous dissemination

Tuberculous bacillaemia is a common early event in primary tuberculosis. Strom provided evidence of this when he used radiolabelled tubercle bacilli to induce the disease experimentally.[54,55] The bacilli are generally destroyed by phagocytes throughout the body but occasional organisms may escape this fate and – after their lodgement in a kidney, bone or joint, the central nervous system, an adrenal gland or some other organ favourable to their growth – set up an isolated focus of tuberculosis that may either remain latent for years or progress. The apices of the lungs are amongst the tissues that favour the establishment of blood-borne tuberculosis. The reason for this is described below under 'Postprimary tuberculosis'.

When many bacilli enter the circulation simultaneously and a massive haematogenous dissemination ensues, generalised miliary tuberculosis develops. In this condition, as in all forms of bacteraemia, the organisms are removed from the circulating blood by phagocytic cells lining sinusoids in the liver, spleen, bone marrow and elsewhere. Although, to judge from experimental tuberculous bacillaemias, most of the circulating bacilli are promptly destroyed by the phagocytes, enough survive ingestion to set up innumerable small metastatic foci of infection.

The massive blood stream invasion by tubercle bacilli necessary to produce miliary tuberculosis is often brought about by a caseating tuberculous focus involving the wall of a neighbouring blood vessel. This is particularly likely to complicate the hilar lymph node component of a primary complex, for these caseous masses are not only larger than those in the lungs, but they develop in proximity to the large veins in the mediastinum (see Fig. 5.3.7). The wall of the affected blood vessel becomes replaced by tuberculous granulation tissue. In time, caseation develops, the lesion ulcerates through the intima and tubercle bacilli escape into the blood stream. In exceptional cases, the aorta may be eroded, with consequent rupture and rapidly fatal bleeding. However, it is not always possible to demonstrate vascular erosion and it seems likely that the organisms may on occasion reach the blood by way of the lymphatics.

Generalised miliary tuberculosis is usually fatal unless treated quickly and appropriately, particularly if the infection has involved the central nervous system and given rise to tuberculous meningitis. Necropsy in such cases shows enormous numbers of small, grey tubercles, a millimetre or less in diameter, most notably in the liver, spleen, bone marrow, lungs and meninges, and more sparsely in other organs (Fig. 5.3.12). The term 'miliary' derives from a supposed likeness of the tubercles to millet seeds. The preponderant distribution and typically uniform dispersal of tubercles in the parts affected may be ascribed partly to the particularly large number of phagocytic cells in the walls of the blood sinusoids of the tissues, and partly to the situation of the vessel invaded: if it is a systemic vein in the mediastinum, or the main thoracic duct, the bacilli are first carried to the lungs, where many are filtered out in the pulmonary capillaries to give origin to a preponderance of the miliary tubercles in the lungs; if it is a tributary of the pulmonary veins, they are carried to other organs in the systemic arterial circulation.

Histologically, miliary tubercles have a characteristic structure. A Langhans multinucleate giant cell commonly forms the centre and is enclosed by a zone of epithelioid macrophages and an outer shell of lymphocytes. If the patient survives for a month or more, the tubercles will be larger and their centres show early caseation. These more advanced lesions consist of small groups of satellite tubercles that have a general resemblance to the original one and surround the central caseous area that has taken its place.

Today, when many of those patients who develop generalised haematogenous dissemination of the infection are successfully treated, the progressive changes in the tubercles in the lungs can sometimes be followed in serial radiographs and the findings compared with those in histological preparations of the lungs of patients who died at the corresponding stage. Gradually, during the weeks following the institution of the treatment the finely dispersed opacities can be seen to regress until their presence is no longer detectable radiologically. At this stage, microscopical examination of the tubercle shows merely a minute scar composed almost wholly of hyaline collagen with no trace of the former distinctive cellular structure. If a cure follows at a more advanced stage of the disease, after caseation has occurred, the caseous material becomes calcified. This results in a fine mottling of the lung fields that may be seen radiologically for years after.

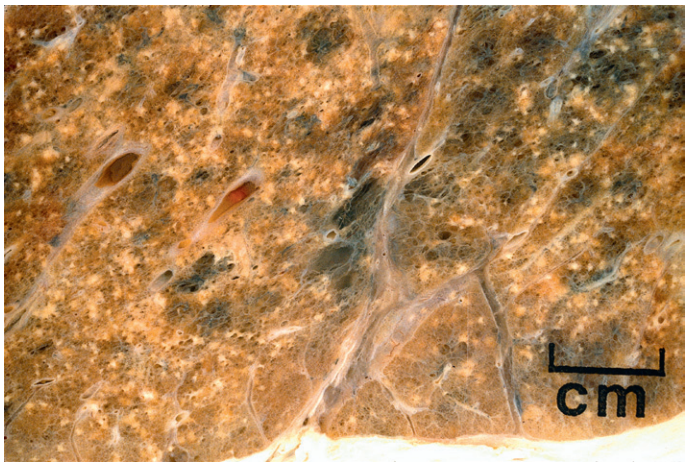

Figure 5.3.12 Miliary tuberculosis. The lung is studded with numerous tubercles, each the size of a millet seed. *(Courtesy of Dr M Kearney, Tromso, Norway.)*

Subclinical primary tuberculosis

The true prevalence of tuberculous infection in the general population is very much higher than overt clinical manifestations suggest. This inference is based on two main sources of evidence: first, identification of healed tuberculous lesions in necropsy studies on long series of consecutive cases of patients dying from all causes in large general hospitals; and second, immunological surveys on large samples of the population employing the tuberculin skin test as an indicator of previous infection.

The realisation that primary tuberculosis is followed by recovery in the great majority of those infected was the most important outcome of a pioneer study by Naegeli at the end of the nineteenth century in the postmortem room of the Zurich General Hospital. Employing acceptable anatomical criteria for the identification of healed and active tuberculous lesions, he reached two very significant conclusions: first, that practically all the adults who had died in that hospital from diseases of all kinds had, at some site in their body, recognisable tuberculous foci that, in the great majority, had healed; and second, that in only a minority of these patients could death be attributed to tuberculosis. Forty years later, a similar study was made at the same hospital, and again traces of a previous tuberculous infection were detected in the bodies of 80–90% of all adult patients.

The interest and surprise aroused by Naegeli's work stimulated numerous similar studies elsewhere: his general conclusions were fully confirmed and it was recognised that signs of past tuberculous infection, notably calcified mediastinal and mesenteric lymph nodes, were common in any population studied. Although in elderly people the frequency of evidence of such healed infections changed little over the ensuing half-century, in children and young adults it showed a decline that reflected the diminished incidence of clinical tuberculosis in western countries. A much larger fraction of the population than formerly became liable to reach adult life without a primary infection and, as a corollary, also without the valuable, if partial, immunity that results from an infection that has been overcome. Prophylactic immunisation in childhood was therefore instituted and is now widely practised.

The tuberculin skin test

As well as first identifying the tubercle bacillus in 1882, Robert Koch went on to develop a vaccine against the disease based upon the subcutaneous injection of a sterilised extract of the bacteria. It was not successful therapeutically but von Pirquet used Koch's 'old tuberculin' as a skin-testing agent after showing that reactivity to it indicates that a person has been infected by the tubercle bacillus. In the original test, a drop of old tuberculin was placed on the skin and a scratch was made through the drop, but reagents are now administered by intradermal injection (the Mantoux method) or by use of multiple-pronged devices (Heaf and tine tests). Old tuberculin has given way to purified protein derivative but the principle of the test remains unchanged and it provides a useful indication of the extent of transmission of tuberculosis in countries where tuberculin reactivity has not been artificially induced by bacillus Calmette–Guérin (BCG) vaccination (see below) or there is not heavy exposure to the opportunistic environmental mycobacteria. To circumvent the problem of opportunistic mycobacteria causing such spurious reactions, blood tests have been developed that measure T-cell interferon release in vitro in response to antigens unique to the tubercle bacillus.[56]

The tuberculin skin test becomes positive within a few weeks of tuberculous infection being acquired and remains so in the great majority for many years. Confidence in the reliability and specificity of the test is based mainly upon evidence from two sources. The first comes from surveys made on cattle just before slaughter: the result of the test correlated very closely with the presence or absence of tuberculous lesions in the carcass. The second is derived from tests on clinically tuberculous and clinically non-tuberculous children under 5 years of age: 94% of the former, and only 12% of the latter, were positive.

Tuberculin surveys have given incontestable support to the general conclusion drawn from necropsy studies that tuberculosis has been widespread in urban populations. In a tuberculin survey in London between the two world wars the percentage of positive reactors was found to rise progressively from well below 10 in children under 2 years to 90 in adults. Yet despite the great frequency of infection and the large number of deaths from the disease, the case fatality rate – the only numerical indicator of the probable outcome of an infection – is comparatively low. This is exemplified by the figures set out in Table 5.3.2, which shows that even in 1931 only one out of several thousand children who became infected actually died from the disease: a fatal outcome is even less frequent today.

The immunity and hypersensitivity that result from tuberculous infection

The frequency with which a primary tuberculous infection is overcome, usually without the patient being aware of its presence, roused interest in the possibility that in tuberculosis, as in many other infectious diseases, recovery from an attack might leave a heightened resistance to infection in the event of subsequent exposure to the same organism. Further, as some degree of immunity generally results from a natural infection, the question was raised whether similar protection could be conferred by some controllable prophylactic procedure. An affirmative answer has been given to both these questions.

The first study that disclosed convincingly that a primary infection conferred some protection was made by Heimbeck in Oslo. His conclusions were based on studying follow-up records of positive and negative tuberculin reactors among probationer nurses entering the municipal hospital in that city. Through a comparative study of the findings on enrolment and the subsequent medical history while nursing, it became apparent that, although all were equally exposed to the same general hospital environment and its hazards, the incidence of overt tuberculosis was significantly less in those girls who were positive reactors at the time of their entry.

Heimbeck's conclusions have since been scrutinised and confirmed in many studies elsewhere. The most extensive of these – the Prophit

Table 5.3.2 Comparison by age of positive tuberculin reactors in a sample London population with deaths from tuberculosis for England and Wales in 1931

Age group (years)	Positive reactors (%)	Deaths from tuberculosis (%)
0–5	12	0.076
6–10	30	0.026
11–20	61	0.060

Table 5.3.3 Incidence of clinical tuberculosis among positive and negative reactors to tuberculin in London, 1934–44[57]

Tuberculin reaction at outset	Number of people examined	Cases of tuberculosis recorded	Incidence (%)
Positive	7130	95	1.33
Negative	1745	69	3.95

Fund Tuberculosis Survey – was carried out on nearly 10 000 young people, mainly nurses and medical students, in London over the period from 1934 to 1944.[57] The results of this investigation are summarised in Table 5.3.3, which shows that there was about three times as high an incidence of clinical tuberculosis among young adults who were negative reactors at the start of the study as among similarly exposed positive reactors in London. This is almost the same as the average ratio derived from nearly 30 comparable surveys elsewhere in Europe and in America. It establishes the conclusion that, although a primary infection does not confer absolute immunity, it does give a valuable degree of protection against developing the disease in a clinical form after subsequent exposure to the same organism.

Specific prophylactic immunisation

Numerous efforts have been made to confer immunity to tuberculosis through prophylactic inoculation, many by veterinary surgeons who hoped to free cattle from the disease. The most significant conclusion from their work was that, unlike what had been found for many other infectious diseases, killed organisms were relatively impotent as immunising agents. Protection could be conferred only through an infection that had been overcome. In consequence of this, the search for an effective prophylactic agent became one for strains of the bacillus that were of such low natural virulence, or that had been so attenuated by appropriate methods of culture, that they could be inoculated safely while still alive. Such strains, it was hoped, would produce only a self-limiting infection. Of those that have been found, the organism now widely known, after those who developed it, as bacillus Calmette–Guérin or BCG has established itself as the agent of choice, and is now widely employed in antituberculosis schemes in many parts of the world. Yet, although the effectiveness of BCG has been demonstrated on many occasions (Table 5.3.4), in other studies it appears to have conferred no protection whatsoever.[58] The reason for these marked differences is poorly understood but may be connected with the fact that, since its introduction, numerous daughter strains of varying antigenicity have developed, which is not surprising as being a live bacterium it has had to be passaged in vitro over 1000 times.[59] Another possible reason is the variable prevalence of other mycobacteria in the environment as these confer some protection against tuberculosis but also reduce the effectiveness of BCG.[59a] Table 5.3.4 shows that BCG is most effective when administered soon after birth, i.e. to the immunologically naïve.

In developing countries, where the prevalence of tuberculosis is high, BCG immunisation of the newborn is recommended to prevent the dangerous forms of childhood tuberculosis, but elsewhere it is only recommended for the Mantoux-negative members of certain high-risk groups – health workers, including mortuary and laboratory staff, veterinarians, case contacts, immigrants from countries with a high prevalence of tuberculosis together with their children and infants wherever born, and those intending to stay in Asia, Africa or Central or South America for longer than a month.

Although BCG inoculation is generally harmless, disastrous dissemination of the infection has been known to occur.[60] Impaired host immunity may be presumed to account for these rare instances as the dose and batch of the vaccine used in these exceptional cases have not differed from those used successfully in other children. Cases have been reported in the context of AIDS and inherited immunodeficiency states such as severe combined immunodeficiency and chronic granulomatous disease. However, in half the cases reported no well-defined inherited immunodeficiency state has been recognised. Some of these patients have been able to mount a good granulomatous response against the infection but others have developed disease similar to lepromatous leprosy, characterised by florid proliferation of the bacilli and an apparently ineffective non-granulomatous macrophage response.[61] It follows that any form of immunosuppression is a contraindication to BCG immunisation: this includes corticosteroid treatment and HIV infection.

BCG immunisation confers advantages other than protection against tuberculosis as it has heterologous effects on the immune response to many organisms and thereby exerts a beneficial influence on several human infections.[61a] It has also been suggested that children so immunised suffer less leukaemia and other malignancies but such claims are somewhat tenuous.[62] However, BCG has been injected into the pleural cavity or the bladder of patients with inoperable cancer of these regions in the hope that it would have a non-specific adjuvant effect on the immune reaction to the cancer and, as with its use in preventing tuberculosis, there are rare instances of the bacillus being disseminated widely throughout the body.[63,64]

The relationship of immunity to hypersensitivity in tuberculosis

The rapid translocation of tubercle bacilli to the regional lymph nodes, and perhaps beyond, on first infection, is less likely in post-primary tuberculosis, indicating some degree of acquired immunity, while the development of caseation at a time when cellular immune mechanisms may be expected to take effect suggests that hypersensitivity accompanies the immunity. Long ago, Rich showed that guinea pigs made allergic by the injection of non-virulent tubercle bacilli still retained resistance after gradual desensitisation with tuberculin, suggesting that hypersensitivity and immunity were distinct,[65] a proposition for which there is now considerable support.[66,67] Hypersensitivity and specific acquired immunity are both cell-mediated, but T-cell characterisation indicates that different T-cell subsets are involved.

Antigens are processed by specific cells, such as dendritic cells, and are presented in association with products of the major histocompatibility complex genes to T lymphocytes. Cytotoxic (CD8-positive) T cells are activated by products of the class I major histocompatibility genes (HLA-A and -B), which are expressed on the surface of antigen-presenting cells if microbial proliferation proceeds unchecked within phagocytes, the bacteria-containing phagocytes then being eliminated

Table 5.3.4 The protective effect of bacillus Calmette–Guérin (BCG) found in nine major studies[58]

Group studied	Date of commencement	Duration (years)	Age range	Protection (%)
Native North American	1935–38	9–11	0–20 years	80
Chicago, USA	1937–48	12–23	3 months	75
Georgia, USA	1947	20	6–17 years	0
Illinois, USA	1947–48	19–20	Young adults	0
Puerto Rico	1949–51	5–7.5	1–18 years	31
Georgia/Alabama, USA	1950	14	Over 5 years	14
Great Britain	1950–52	15	14–15 years	78
South India (Bangalore)	1950–55	9–14	All ages	30
South India (Madras)	1969–71	7.5[a]	All ages	0

[a]15-year follow-up has revealed some protection amongst those administered BCG as neonates.

by the T cells. On the other hand, effective processing of the bacteria results in the antigen-presenting cells expressing class II major histocompatibility genes (HLA-D), the products of which activate (CD4-positive) T-helper cells, so enhancing bacterial elimination.[68]

Two types of T-helper cells are recognised, one concerned mainly in immunity and the other with hypersensitivity. Type 1 T-helper lymphocytes (Th1) secrete interleukin-2 and the macrophage-activating cytokine interferon-γ, resulting in enhanced bacterial elimination; however, it also results in the secretion of tumour necrosis factor by the macrophage, which contributes to the hypersensitivity that derives from the activation of type 2 helper T cells (Th2).[69] Th2 cells secrete interleukins-4, -5, -6 and -10, which prime tissue cells to the necrotising action of tumour necrosis factor secreted by macrophages activated by Th1 cells. Thus, type 1 reactions are essentially protective but also contribute to the type 2 cell-mediated hypersensitivity (Fig. 5.3.13).[43,44,68,70] Many chronic infections are first characterised by a Th1 response which then shifts to a Th2 response, with detriment to the host. Animal models suggest that necrosis occurs in T-cell-dependent granulomas when Th2 involvement is superimposed on a Th1 reaction.[71]

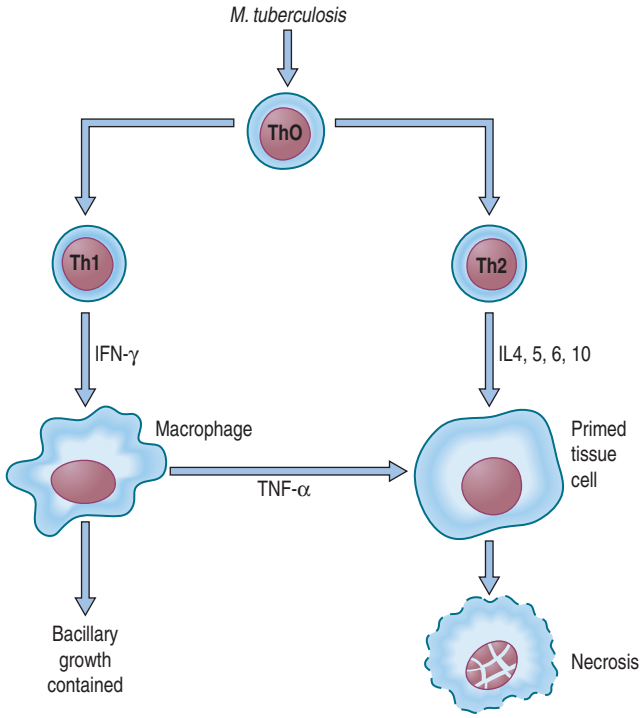

Figure 5.3.13 Types of T-helper cell (Th-) reactions. IFN, interferon-γ; IL, interleukin; TNF-α, tumour necrosis factor-α. *(Redrawn after Grange.[68])*

Postprimary tuberculosis

In contrast to primary tuberculosis of the lungs, where the Ghon focus may develop in any lobe, the early lesions in the postprimary disease are almost invariably found near the apex of one of the upper lobes. Postprimary pulmonary tuberculosis obviously involves considerable spread of the infection. The dissemination is believed to be blood-borne. Using radiolabelled bacilli, Strom provided experimental evidence that tuberculous bacillaemia is a common and early event in primary tuberculosis.[54,55] In the great majority of people, both the primary complex and its haematogenous dissemination are quickly overcome, but in some the distant foci progress or remain latent. If tributaries of the pulmonary veins are involved in the spread of the infection, the bacilli pass out of the thorax, but if the blood stream is colonised via the lymphatics, the pulmonary capillaries are the first to be reached, and so the infection returns to the lungs.

Oxygen tension governs the predilection for blood-borne tuberculosis to favour the apical regions of the lungs and also sites such as the kidneys, meninges and metaphyses. These extrapulmonary sites are well vascularised and therefore have a relatively high oxygen tension. The tubercle bacillus is a strict aerobe and thrives in such organs. In the lung, more complex factors govern oxygen tension. The apices of the lungs are poorly perfused, but the pulmonary arteries bring deoxygenated blood. Ventilation on the other hand promotes oxygen tension, but the apices are also the most poorly ventilated parts of the lungs. The oxygen tension in the lungs is in fact dependent upon the ventilation/perfusion ratio. In the upright position, this declines from the apices to the bases of the lungs (Fig. 5.3.14),[72–75] and the oxygen tension is therefore highest at the top of the lungs, thus favouring the development of postprimary tuberculosis at the apices.

If the disease progresses, radiological opacities appear in the apex of one or both of the upper lobes. They may resolve or progressively enlarge and ultimately cavitate. Necropsy studies indicate that such lesions represent areas of caseating granulomatous inflammation that

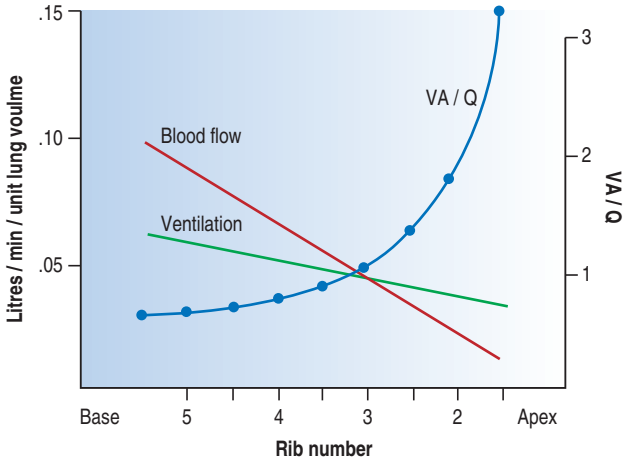

Figure 5.3.14 Regional differences in pulmonary blood flow, ventilation and ventilation/perfusion ratios (VA/Q), consequent upon gravitational forces. These result in a higher oxygen tension and poorer lymphatic drainage at the apices, thereby promoting the development of tuberculosis at this site. *(Redrawn after West.[74])*

ultimately develop large central areas of necrosis. It is through the expulsion of this dead tissue through the regional bronchi that the cavities so typical of the advanced lesions originate.

If the liquefying contents of a cavity escape into the bronchial tree, the bacilli become widely dispersed to other parts of both lungs, as in progressive primary tuberculosis. This diffuse bronchogenic infection gives rise to innumerable small areas of caseous pneumonia, mostly in the lower lobes, and occasionally, a rapidly developing confluent tuberculous bronchopneumonia involves almost the whole lower lobe. Microscopical examination may show tubercle bacilli and macrophages in very large numbers in the consolidated areas. Occasionally, such regions undergo caseation. They may become so confluent as to involve a whole lobe.

At necropsy, the lungs of a patient with long-standing, progressive, postprimary tuberculosis have a characteristic appearance. Large cavities may replace much of an upper lobe and one or more smaller, but otherwise similar, cavities may be present in the apical part of the lower lobe. The cavities may be filled with caseous material (Fig. 5.3.15) or the contents may have been evacuated through communicating bronchi (Figs 5.3.16–5.3.18). The cavities may be several centimetres in diameter, with walls formed by tuberculous granulation tissue in which the fibrotic remains of the larger bronchi and of branches of the pulmonary arteries form coarse, irregular bands. Usually the disease is bilateral, with similar, but often less advanced, changes in the opposite lung. As in progressive primary tuberculosis, satellite nodules are evident at the advancing edge (Fig. 5.3.19).

The hilar lymph nodes are less obviously involved in the postprimary form of tuberculosis than in the primary form of the disease but, on histological examination, tuberculous foci, often with small areas of caseation, can generally be seen in them.

Histological examination of the wall of a cavity usually discloses several zones, each grading into the next. The yellowish-grey lining is formed largely of granulation tissue that has undergone caseation but not yet liquefied. Acid-fast bacilli can generally be seen in this zone: their multiplication there and subsequent escape into the cavity largely account for the high infectivity of the sputum expectorated by patients with advanced pulmonary tuberculosis. Just deep to this is a zone of granulation tissue containing a profusion of macrophages and lymphocytes and occasional multinucleate giant cells. If the cavity has been infected secondarily by other organisms, as often happens, this

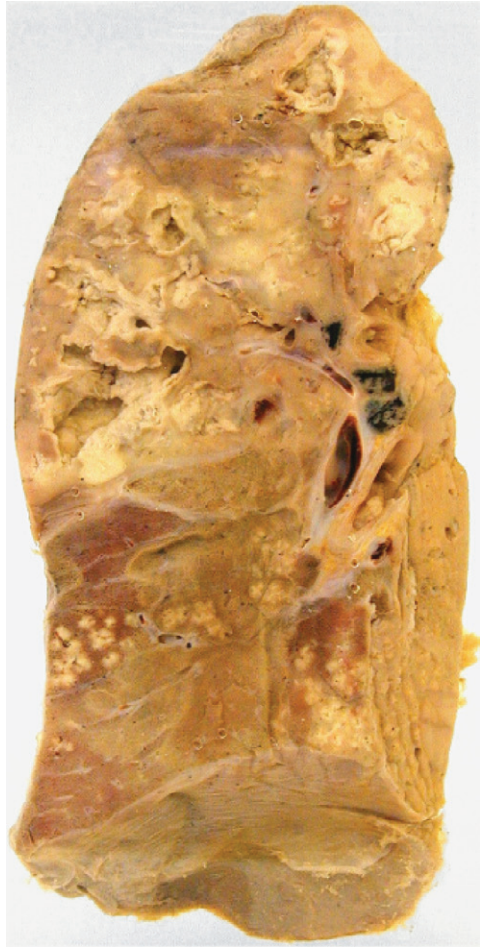

Figure 5.3.15 Postprimary tuberculosis. The upper lobe is consolidated and several large foci of caseous necrosis are evident. Smaller foci are also seen in the lower lobe. *(Courtesy of the Curator of the Gordon Museum, Guy's Hospital, London, UK.)*

zone may also contain many neutrophils. Outside this zone there is generally a mantle of satellite tubercles. Still deeper in the wall are traces of residual parenchyma, often with alveoli obliterated by compression and fibrosis. The cavities enlarge by incorporation of the satellite tubercles, more of which are constantly forming more peripherally (see Fig. 5.3.19). In this way tuberculous granulation tissue extends into the surrounding lung substance as its lining progressively caseates, liquefies and is expectorated. Eventually the process of cavitation may reach the pleura, but perforation into the sac hardly ever takes place, for the chronic pleurisy that accompanies the changes within the lungs results in the formation of firm adhesions between the visceral and parietal layers, with obliteration of the pleural sac.

Although the formation of a cavity is a serious development in the progress of a postprimary tuberculous infection of the lung, it does not represent an irreversible stage in the course of the disease. As long as it is small, a cavity may heal by scarring. Ultimately, such a lesion may only be recognisable as an area of fibrosis that stands out from the surrounding parenchyma because of its black pigmentation and the radiating pale strands of fibrous tissue that pucker the neighbouring lung substance. Alternatively, a balance may be achieved whereby the tubercle bacilli are not destroyed but their spread is halted and the process is held in check, typically by a fibrous capsule forming. Such an encapsulated mass of caseous material is sometimes termed a tuberculoma (Fig. 5.3.20). In such quiescent tuberculosis there is no

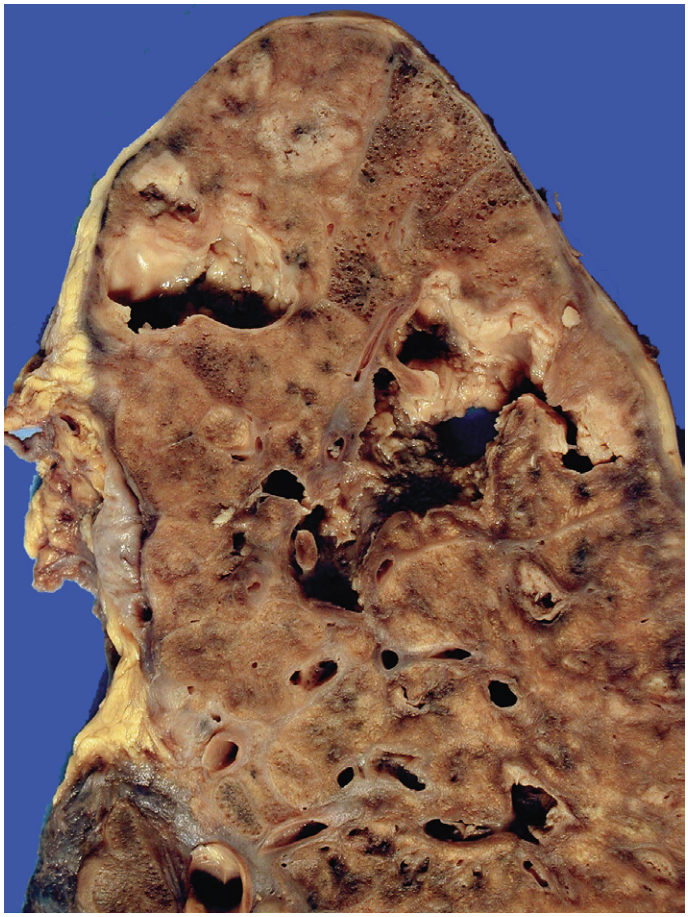

Figure 5.3.16 Postprimary tuberculosis. The caseous contents of this cavitating upper-lobe lesion have been partially evacuated through communicating airways. *(Courtesy of Dr M Kearney, Tromso, Norway.)*

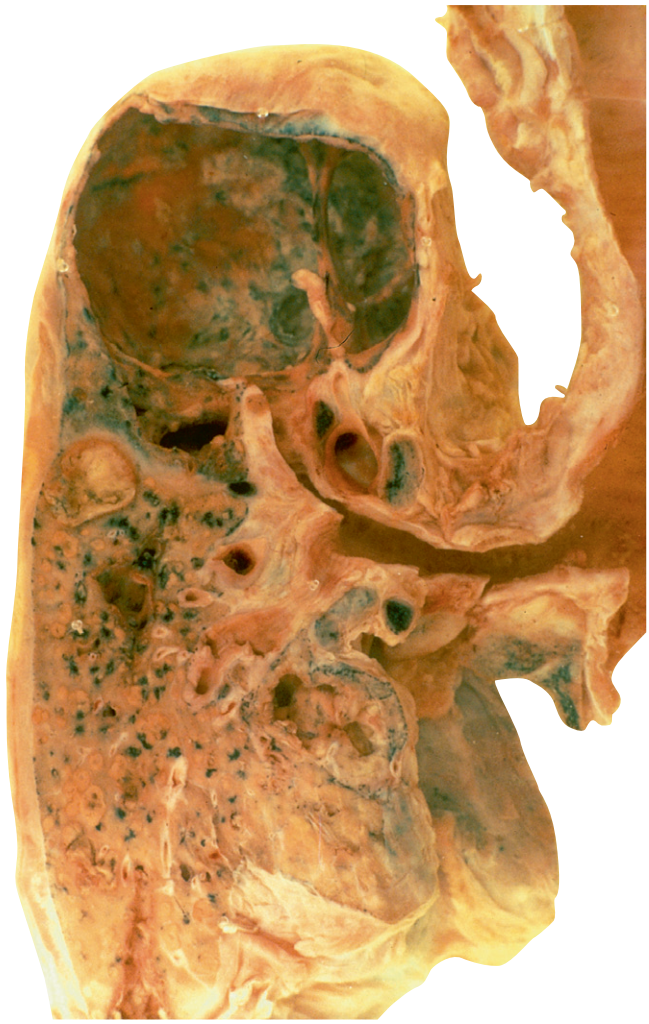

Figure 5.3.17 Postprimary tuberculosis. The upper lobe is replaced by a large air-filled cavity, its caseous contents having emptied into the lobar bronchus with which the cavity communicates.

inflammation but viable bacilli may survive in the central caseation, ready to reactivate the disease should host defence weaken. Any granulomatous inflammation in the vicinity of such a lesion indicates active tuberculosis.

Local complications of postprimary pulmonary tuberculosis

Pulmonary tuberculosis is often attended by minor episodes of haemoptysis. That the involvement of blood vessels is not more frequently accompanied by haemoptysis is accounted for by the fact that the destructive process usually advances slowly, so that obliterative endarteritis leads to the closure of the lumen of the pulmonary and bronchial arteries before their walls have been penetrated. However, caseation sometimes advances too quickly for the artery to become completely blocked, and an aneurysm may form where the muscular and elastic coats are destroyed on the side nearer the cavity. It is through the rupture of such aneurysms (Rasmussen's aneurysms) that sudden and sometimes fatal haemorrhages occur.

Large tuberculous cavities may persist indefinitely once the tuberculous infection has been overcome. If the cavity is not able to drain freely into the bronchial tree, secretion may accumulate in it and predispose to secondary bacterial infection, sometimes with the formation of a lung abscess. Fungal colonisation may also take place, leading to the formation of an aspergilloma or other variety of intracavitary ball colony[76] (see p. 231).

In some cases the cavity acquires an epithelial lining: the epithelial lining may be of modified respiratory type or squamous. A squamous lining may be simple or stratified; sometimes keratinisation develops, and the lumen of the cavity may become filled by compressed desquamated cells, the appearances then being reminiscent of an epidermoid cyst. Squamous carcinoma occasionally arises from such areas of metaplasia.

Chronic tuberculosis of the lungs is usually accompanied by pleurisy. Although this begins in the neighbourhood of the most active lesions, in time it may extend to involve the whole surface of the lung. The condition advances slowly, generally without the formation of much exudate; by the time of necropsy the pleural lesions have usually undergone fibrosis. The damaged lung becomes firmly attached to the chest wall – indeed, the fibrosis may be so firm and extensive that the lung can be removed from the body only by dissection outside the parietal pleura. Occasionally, the entire lung may be enclosed by a dense white layer of hyaline connective tissue, several millimetres thick.

Extrapulmonary complications of postprimary respiratory tuberculosis

The proliferation of tubercle bacilli that takes place in the caseating lining of cavities in the lungs is often so great that it leads to heavy

Figure 5.3.18 Postprimary tuberculosis. Tuberculous bronchopneumonia is seen throughout the lower lobe, the result of aerogenous dissemination of infection from the cavitating focus at the apex of this lobe. A further focus of cavitating tuberculosis is seen in the midzone of the upper lobe.

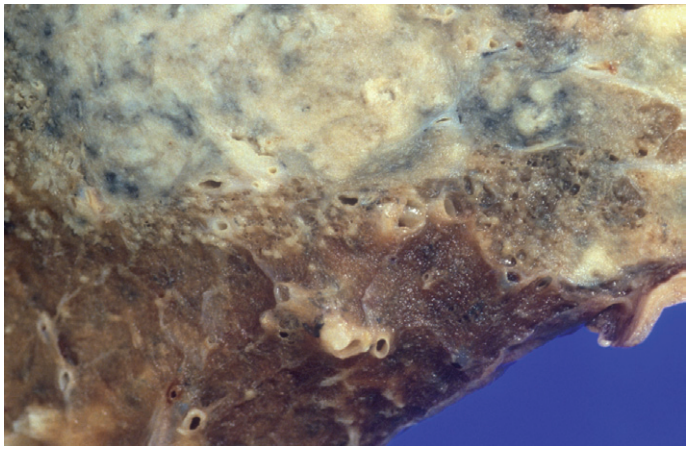

Figure 5.3.19 Postprimary pulmonary tuberculosis progressing by the incorporation of satellite tubercles. Satellite tubercles are evident at the advancing edge of a chronic caseating focus of infection.

infection of the exudate and secretions, most of which are expelled by coughing, sometimes aided by the adoption of a posture that promotes gravitational drainage. These organisms form a potent reservoir for infection of the upper respiratory tract and of the alimentary canal.

In advanced cases of chronic respiratory tuberculosis small ulcers, each a few millimetres in diameter, often develop in the tracheobronchial mucosa,[77] as described above under the dissemination of primary

Figure 5.3.20 Quiescent tuberculosis forming a 'tuberculoma'. Growth of this apical focus of tuberculosis has been halted and its caseous contents walled off by a fibrous capsule. However, the infection has not necessarily been overcome as viable bacilli may persist in the caseous material and reactivate the disease if immunity wanes.

pulmonary tuberculosis via the airways. Occasionally it may mimic a neoplasm but generally there is just slight destruction of tissue and the ulceration amounts to little more than loss of epithelium; occasionally, it may extend more deeply and expose one or more rings of tracheal cartilage. Such tracheobronchial disease was identified in 42% of cases in the preantibiotic era.[77] Subsequently, it was rarely encountered, until AIDS appeared, since when there have been several reports of endobronchial tuberculosis.[78–81] Similar infection may involve the larynx, particularly the glottis and the aryepiglottic folds; the subsequent injury to the vocal cords leads both to hoarseness and to frequent stimulation of the cough reflex.

The passage through the mouth of sputum teeming with tubercle bacilli may also lead to infection of the oral mucous membrane. Most commonly, the lesions appear as ulcers on the margin of the tongue: these are probably initiated by some minor damage to the mucosa such as results from abrasion by a nearby carious tooth, the resulting breach in the epithelial surface giving access to the organisms. Once these ulcers form, they may penetrate deeply into the muscle. Sometimes, the organisms gain entry to the tonsils and there produce typical changes.

Unless trained not to do so, many patients with respiratory tuberculosis swallow much of their sputum and thus maintain a constant infection of the alimentary canal. Since tubercle bacilli are relatively resistant to acid in the concentrations found in gastric juice, they escape destruction in the stomach and enter the small intestine. The most typical lesions occur in the lowest 2 m of the ileum; these are chronic, circumferentially oriented ulcers that begin in, and finally destroy, Peyer's patches, and then extend towards the mesentery along the mucosal lymphatics.

Amyloidosis is prone to develop in many cases of slowly progressive pulmonary tuberculosis. Although many organs become infiltrated with the amyloid material, renal involvement is the commonest serious manifestation and the lungs are seldom involved. As in other forms of secondary amyloidosis, the amyloid is a polymer of the hepatic acute-phase protein A.

Tuberculosis in the elderly and immunodeficient: non-reactive tuberculosis

In developed countries, miliary tuberculosis is now a commoner cause of death in the elderly than the young.[82] It is thought to result from

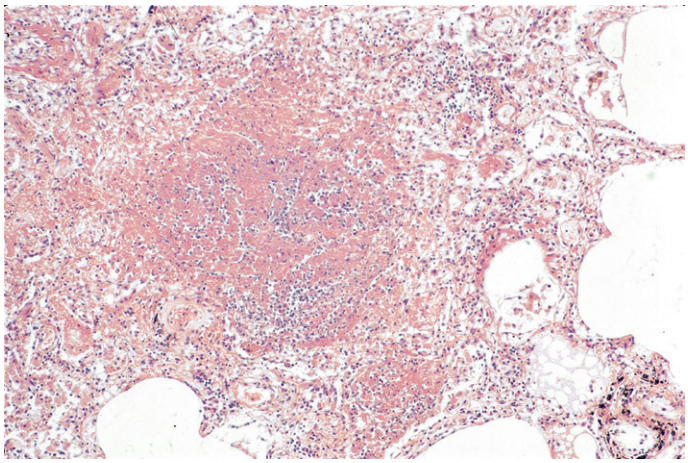

Figure 5.3.21 Non-reactive tuberculosis in acquired immunodeficiency syndrome (AIDS). There is extensive necrosis but no granulomatous reaction. Such lesions teem with tubercle bacilli.

activation of old tuberculous foci, primary or postprimary, as a consequence of waning of the immunological defences. In many cases the disease takes a 'cryptic' form,[82–84] characterised by insidious onset and progression, and often lacking any evidence of miliary mottling in the chest radiograph. The diagnosis is usually not made until necropsy. Both cryptic and overt miliary tuberculosis in the elderly may be accompanied by changes in the blood, including pancytopenia and leukaemoid reactions: these may be the first manifestation of the illness, and their significance in such cases is sometimes overlooked. In the elderly, and especially in the immunodeficient, the disease may be non-reactive. Non-reactive tuberculosis differs from ordinary tuberculosis in lacking the usual giant cell granuloma formation.

At necropsy, disseminated miliary tuberculous lesions are found to be widespread. Microscopy shows that the lesions comprise foci of virtually structureless necrotic matter, sharply defined from the surrounding tissue, which shows little or no abnormality (Fig. 5.3.21). There is little or no granulomatous response. Appropriate staining shows that they teem with tubercle bacilli, and, unlike the caseation of classic tuberculosis, the necrotic material may contain much nuclear debris.[41,85,86] Neutrophil polymorphonuclear leukocytes are commonly seen.

Other forms of non-reactive tuberculosis include diffuse alveolar damage and vasculitis. In the former tubercle bacilli are generally demonstrable in the hyaline membranes[86] while in the latter they teem within the vessel walls.

Non-reactive tuberculosis is the result of a deficiency in the body's cellular defences. In some cases it develops as a complication of lymphoid neoplasia, particularly Hodgkin's disease and leukaemia. In other cases it has followed treatment with immunosuppressant drugs. More recently it has been seen in patients suffering from AIDS.[41,87] Often, however, no predisposing cause is found; such patients are generally elderly.

If the diagnosis of non-reactive tuberculosis is suspected during life, tubercle bacilli should be looked for in films of bone marrow. Biopsy may be helpful; any suggestion of a tuberculous reaction is potentially an important diagnostic guide. When any biopsy section includes unexplained areas of necrosis, particularly when there is little in the way of a related cellular reaction, it is imperative to look for tubercle bacilli.

It is to be remembered that the tissues in this form of tuberculosis are highly infective. Several cases of tuberculous infection in laboratory staff, including those working in mortuaries, have been traced to this source.

Postmortem recognition of pulmonary tuberculosis

It is estimated that many cases of active tuberculosis of the lungs go unrecognised until necropsy. This is particularly true of the elderly, whose resistance to the infection is lowered as an accompaniment of ageing: dormant lesions become active, and spread of the disease follows, often with little in the way of clinical manifestations to indicate the seriousness of the danger. Similarly, at any age, patients, whose resistance is lowered by conditions such as lymphoma and poorly controlled diabetes mellitus, are prone to reactivation of dormant tuberculosis and vulnerable to exogenous reinfection: often the presence of the infection is overlooked, even when it is the immediate cause of death, until disclosed in the postmortem room. Now that the necropsy rate is falling markedly in so many countries, many cases of active tuberculosis must go unrecognised. The danger that persists after the patient's death is that the infection may have been passed to relatives or associates without awareness of the need for treatment.

Treatment of tuberculosis

The treatment of tuberculosis is based on a combination of drugs (classically triple therapy) but is bedevilled by the emergence of drug-resistant strains, an inability of many countries to provide the drugs and poor compliance on the part of the patient.[88–91]

INFECTION BY OPPORTUNISTIC MYCOBACTERIA

Bacteriology

The organisms responsible for tuberculosis and leprosy are only two of about 40 species of mycobacteria, most of which live freely in the environment, particularly where water abounds, and seldom infect humans. Occasionally, however, especially when resistance is low, several of these environmental mycobacteria cause serious disease.[92,93] Their distinction from *M. tuberculosis* is important because they require special drug regimens; they do not respond to antituberculosis treatment. Formerly dismissed as 'atypical' or 'anonymous', these species are better described as the opportunistic mycobacteria. They include *M. marinum* and *M. ulcerans*, the causes of swimming-pool granuloma and Buruli ulcer respectively, and a group that causes disease that is very like tuberculosis. In infection by members of the latter group, as in tuberculosis itself, the lungs are the organs most often involved and there may be spread to lymph nodes, bone, meninges, kidneys and elsewhere, or massive dissemination throughout the body akin to miliary tuberculosis. The similarity to tuberculosis is also seen in that the gastrointestinal tract is another important portal of entry.[94]

The commonest opportunistic mycobacteria infecting the lungs are *M. avium-intracellulare*, *M. kansasii* and *M. xenopi*. Less frequent causes of tuberculosis-like disease are *M. scrofulaceum*, *M. malmoense*, *M. szulgai*, *M. simiae*, *M. chelonei*, *M. fortuitum* and *M. gordonae*. *M. avium-intracellulare* and *M. scrofulaceum* are often said to comprise the MAIS complex. They are all acid-fast but, unlike *M. tuberculosis*, many of them can also be demonstrated with periodic acid–Schiff and Grocott's stains. *M. kansasii* has a distinctive shape, being long, broad, beaded and bent.[95] Species-specific probes are available.[96,97]

Infection with these organisms comes from the environment, in contrast to tuberculosis, which is always transmitted from an infected individual. The infection rate of tuberculosis in the community bears a direct relation to the number of infectious cases but this is not the case with the opportunistic mycobacteria. The prevalence of opportunistic mycobacterial infection in a community is independent of that of tuberculosis and is not controlled by public health measures aimed at reducing the spread of tuberculosis.

Interpretation of cultured isolates

The interpretation of cultured isolates must always take account of the possibility that specimens may be contaminated with opportunistic mycobacteria from the environment. Whereas *M. tuberculosis* is an obligate parasite and its isolation indicates tuberculosis, the culture of opportunist mycobacteria does not necessarily indicate that they are the cause of the disease being investigated. Their isolation from granulomatous tissue strongly suggests that they have played a causative role, but sputum isolates need to be obtained consistently over a period of weeks, and other causes of granulomatous disease, especially tuberculosis, thoroughly excluded before a clinical diagnosis of opportunistic mycobacterial infection can be advanced with confidence.

Predisposing causes

Factors predisposing to opportunistic mycobacterial infection may be general or local.[98] General factors include any congenital or acquired immunodeficiency, but especially AIDS,[94,99,100] therapeutic immunosuppression and autoimmune disease. Local factors include pneumoconiosis, chronic bronchitis, cystic fibrosis, bronchiectasis and old tuberculosis. The virulence of mycobacteria is enhanced by lipid[101] and the growth of opportunistic mycobacteria, especially *M. fortuitum-chelonei*, appears to be promoted by lipid pneumonia.[102–104] The aspiration of milk may explain an observed association between achalasia and *M. fortuitum-chelonei* infection.[105,106]

Only rarely is no predisposing cause recognised.[107,108] Although some impairment of host defence is generally necessary for these bacteria to establish themselves in humans, heavy exposure may result in healthy individuals being infected. An example of this is the increasingly frequent presentation in affluent, non-immunocompromised individuals of diffuse lung disease due to the inhalation of aerosols from hot tubs and showers heavily infected by these bacteria. However, there are suggestions that this may represent extrinsic allergic alveolitis rather than infection.[96,109–114]

Despite the above, there appears to be an increasing incidence of infection by opportunistic mycobacteria in persons who are not obviously immunodeficient or heavily exposed. These individuals are often women and it has been suggested that their infection may be due to them suppressing their cough reflex for reasons of societal etiquette, an unlikely scenario but one that has nevertheless entered the medical argot as the Lady Windermere syndrome, a term taken from the fastidious character of the same name in Oscar Wilde's play *Lady Windermere's Fan*.[115] A survey of such patients found that they were taller and leaner than controls, had high rates of scoliosis, pectus excavatum, mitral valve prolapse and mutation of the cystic fibrosis transmembrane conductance regulator gene. This categorised the condition as one of women with a complex pre-existing morphotype, suggesting that there was an underlying genetic defect.[116]

Pathological changes

The pathological changes produced by opportunistic mycobacteria are generally very similar, if not identical, to those of tuberculosis (Fig. 5.3.22), but there is more airway involvement leading to bronchiectasis[117–119] and a higher proportion of cases that lack the classic granulomatous response.[120] In one study, four histological features were identified that favoured non-tuberculous mycobacterial infection: the presence of microabscesses, the granulomas being ill defined, an absence of necrosis and a comparatively small number of giant cells,[121] but these are not absolute points of distinction.

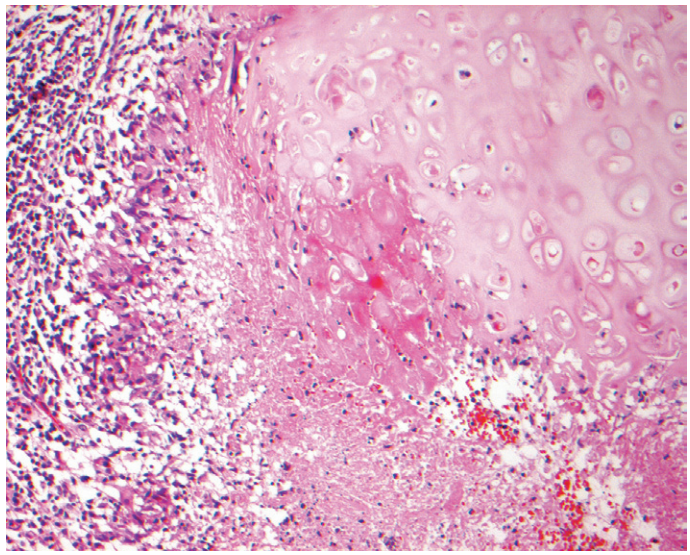

Figure 5.3.22 *Mycobacterium avium-intracellulare* infection. There is necrotising granulomatous inflammation similar to that seen in tuberculosis.

Granulomatous disease indicates a strong immune response and the mycobacteria are then scanty, as in classic tuberculosis. However, in very severe immunodeficiency, as for example AIDS, the lesions may consist of numerous swollen macrophages, all of which contain large numbers of acid-fast bacilli (Fig. 5.3.23). Necrosis is not seen and granulomas are poorly formed or absent. The changes then resemble those of lepromatous leprosy[94] or, if the macrophages are spindle-shaped, inflammatory myofibroblastic tumour (see p. 620).[122–125] A leproma-like pattern has also been described in disseminated BCG infection but is unusual in non-reactive tuberculosis[126] which is characterised by sheets of necrosis unattended by the usual granulomas, the tubercle bacillus being more toxic to the macrophage than the opportunistic mycobacteria.[127]

Treatment

The treatment of opportunist mycobacteriosis is less well defined than for tuberculosis, there being few large clinical trials. However, the British Thoracic Society has published a set of guidelines.[97]

BRUCELLOSIS

Pneumonia is a rare form of brucellosis but has been reported in countries such as Kuwait and Arabia[128,129] where this zoonosis is endemic, and in farmers and meat packers in North America and Europe.[130,131] Cattle, sheep, goats and camels are common sources of infection, which is usually acquired by consuming unpasteurised milk or milk products. Close contact with infected animals or their carcasses may also be responsible for transmission of the disease to humans, either orally or, in the case of pneumonia, by inhalation.

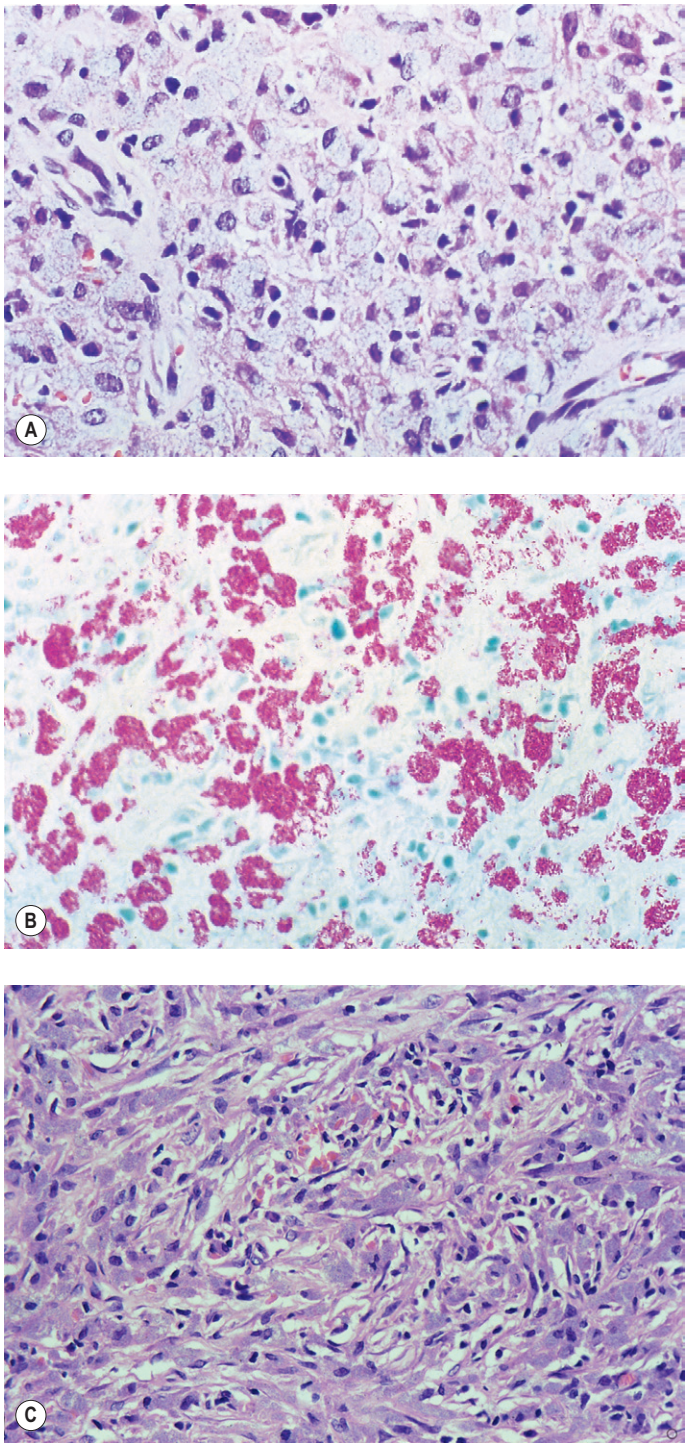

Figure 5.3.23 *Mycobacterium avium-intracellulare/M. scrofulaceum* (MAIS complex) infection in a patient with acquired immunodeficiency syndrome (AIDS). Whereas the tissue reaction to opportunistic mycobacteria is usually identical to that seen in tuberculosis, in the immunodeficient it resembles the lepromatous form of leprosy, consisting of numerous macrophages with abundant pale cytoplasm (A); Ziehl–Neelsen staining demonstrates that this contains innumerable acid-fast bacilli (B). (C) Alternatively, the macrophages may be spindle-shaped and the cytoplasm eosinophilic, resulting in an appearance simulating inflammatory myofibroblastic tumour.

Patients with *Brucella* pneumonia develop a cough productive of mucopurulent sputum or present with fever of unknown cause.[132] Perihilar or peribronchial infiltrates, or less frequently coin lesions, are evident radiographically. Pleural effusion with a predominance of monocytic or lymphocytic infiltrates is also described.[133]

Histology shows necrotising epithelioid and giant cell granulomas, very similar to those of tuberculosis.[128,134,135] Diagnosis is dependent upon excluding tuberculosis and identifying brucellae by culture or brucellar DNA by polymerase chain reaction in blood or tissue.[135] Examination of sputum and bronchial washings is generally unrewarding.

CHRONIC MELIOIDOSIS

The general features and acute form of melioidosis have been described on page 186. Chronic melioidosis is acquired in the same way as the acute form and may represent persistence or recrudescence of acute disease or arise insidiously in someone unknown to have had acute disease. The disease progresses gradually over months or years. It takes the form of localised lesions that may affect any organ but most commonly involve the lungs, where chronic cavitatory melioidosis may closely mimic tuberculosis apart from relative sparing of the apices.[136–138] Pleural effusion and empyema are less common in chronic than acute disease. Before cavitation takes place, microscopy shows areas of necrosis surrounded by granulomatous inflammation. The central necrotic zones are often stellate, and may be suppurative or caseous. The surrounding granulomatous reaction consists of epithelioid and Langhans giant cells and is itself encompassed by a fibrous mantle. When necrosis is suppurative, the histological features mimic those of cat scratch disease or lymphogranuloma venereum, and, especially in the lungs, tularaemia (see p. 187) or sporotrichosis (see p. 244). When the necrosis is caseous, the histological picture is very similar to that of tuberculosis. In contrast to the acute form of the disease, the causative bacterium (*Burkholderia pseudomallei*) can be difficult to demonstrate in tissue sections (see p. 186 for staining methods). The diagnosis is then largely dependent upon serological techniques.

ACTINOMYCOSIS

Bacteriology

Actinomycetaceae (which include the genera *Actinomyces*, *Nocardia* and *Rhodococcus*) and Mycobacteriaceae (which include the genus *Mycobacterium*) are both families of the order Actinomycetales. Although Actinomycetales are classed as bacteria and mycobacterial diseases are invariably considered among bacterial infections, some of the pathogenic Actinomycetaceae are often mistakenly referred to as fungi and the diseases they cause are commonly grouped with those caused by the true fungi under the general heading of mycoses. It will be difficult to correct this misconception, particularly in view of such entrenched nosological nomenclature as actinomycosis, which by virtue of the ending '-mycosis' – its etymology is usually misinterpreted – is unlikely to be displaced from its common association with the true mycoses, in spite of other well-understood terminological paradoxes and pitfalls such as mycosis fungoides and mycotic aneurysm. However, as well as differing from fungi in size, structure and metabolism, the Actinomycetaceae are susceptible to antibacterial agents and resistant to specifically antifungal drugs.

Actinomyces israelii is by far the most frequent cause of actinomycosis in humans. *A. bovis*, the cause of actinomycosis in cattle, is an

exceptionally rare cause of the disease in humans. Other species that occasionally cause actinomycosis in humans include *A. eriksonii*, *A. meyerii* and *A. naeslundii*. *A. propionicus (Arachnia proprionica)*, an organism closely related to *Actinomyces israelii*, also causes disease indistinguishable from actinomycosis.

A. israelii is a strictly anaerobic, Gram-positive bacterium, formed of branching filaments 0.5–1.0 µm wide. The filaments readily break into bacillus-like fragments. They are not acid-fast. Like those of the nocardiae (see below), fragments of the *Actinomyces* may be mistaken for contaminant corynebacteria.

A. israelii is a common commensal or saprophyte in the human mouth and intestine and it is probable that most infections by this organism are endogenous. About 60% of cases of actinomycosis present with lesions in the region of the mouth, face or neck, the portal of entry being dental or tonsillar. About 25% of cases of actinomycosis involve the ileocaecal region and in the remaining 15% of cases the infection is in the lungs. It is presumed that pulmonary actinomycosis is the outcome of aspiration of infected matter from the tonsillar crypts or mouth, apart from the very small proportion of cases in which the disease has extended from known foci of infection in the abdomen. The diagnosis should therefore be particularly suspected in patients with dental caries or a history of unconsciousness with aspiration. The incidence of actinomycosis is in decline, probably due to a combination of improved dental hygiene and the early initiation of antibiotic therapy, the bacterium being highly sensitive to penicillin.

Most cases of actinomycosis are of mixed microbial aetiology, the pathogenicity of *Actinomyces* being enhanced by the synergistic action of other bacteria, notably microaerophilic streptococci, other anaerobes such as *Bacteroides* and *Fusobacterium*, and aerobic streptococci and staphylococci. *Actinobacillus actinomycetem comitans* is another constituent of the mouth flora – one that is seldom recovered in pure culture[139] but is often found in association with *Actinomyces israelii* in actinomycotic lesions. It secretes a powerful leukotoxin which probably contributes to the virulence of these mixed infections.

Clinical features

Pulmonary actinomycosis is promoted by poor dental hygiene, smoking and heavy drinking[140] and is recorded in AIDS.[141] It is usually a disease of adults, though may rarely occur in children.[142,143] It is characterised by fever and expectoration of mucopurulent sputum. Contrary to a common belief, 'sulphur granules' – the yellow colonial granules of the organisms – are not often to be found in the sputum. Haemoptysis is a significant complication and may require surgical treatment.[144] The diagnosis depends on recognition of the fine, Gram-positive, sometimes branching filaments in films, and isolation of the organism. It has to be remembered that the organism may be present in sputum only in short bacillary forms that are liable to be misinterpreted. The chest radiograph may show opacities of various sizes scattered through both lungs, particularly in the middle and lower zones. Alternatively, there may be a large pneumonic area, sometimes associated with an empyema: this type of disease may be accompanied by new bone formation on the inner aspects of several contiguous ribs due to elevation of the periosteum by the inflammatory infiltrate. Occasionally, infiltration of the chest wall suggests malignancy (Fig. 5.3.24). The presence of discharging sinuses on the chest wall is characteristic of advanced thoracic actinomycosis[145] but this stage is seldom encountered today.[146,147] It is in the pus discharging from these sinuses that the 'sulphur granules' referred to above are to be found. Recent series have been characterised by less specific features that have suggested tuberculosis or cancer.[140,141,148] The diagnosis has often been made only after lung tissue has been resected, but may be possible by biopsy, particularly when the process involves major airways.[141,149] It should be confirmed by culture and, because *A. israelii* is a strict anaerobe and will die on exposure to atmospheric oxygen, prompt delivery to the laboratory for appropriate processing is imperative.

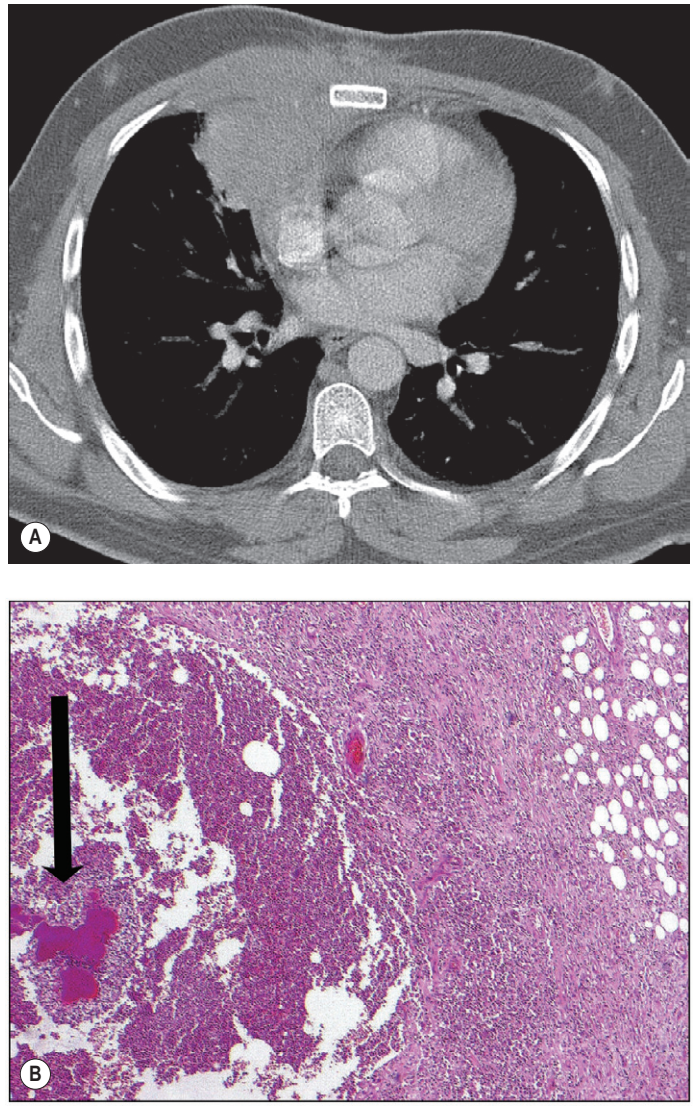

Figure 5.3.24 Actinomycosis. (A) Computed tomography shows a mass in the right middle lobe extending through the chest wall and mimicking an invasive carcinoma. (B) The lobectomy specimen shows colonies of *Actinomyces* (arrow) within abscesses that extend into the fat of the chest wall.

Pathological findings

Actinomycosis of the lungs typically affects the lower lobes but may involve any part. Characteristically, the affected tissue is riddled with chronic abscesses that range in diameter from a few millimetres to 3 cm. These lesions may communicate with one another, drain into the bronchial tree or extend to the pleural surface and open into the pleural sac. 'Sulphur granules' are often to be found within the abscesses. These colonies of *Actinomyces* consist of numerous radiating bacterial filaments that often terminate in a prominent cap of eosinophilic material that represents immune material, a reaction known as the Splendore–Hoeppli phenomenon (Fig. 5.3.25). Fibrosis surrounds the suppurative foci and extends more widely through the lungs, particularly involving the septa. The infection may spread to

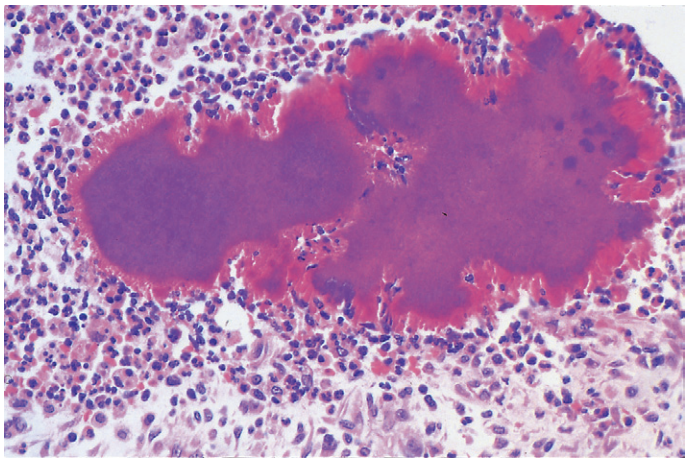

Figure 5.3.25 Actinomycosis. Pus containing a colony of *Actinomyces* surrounded by an eosinophilic mantle of immune material. The eosinophilic mantle is known as the Splendore–Hoeppli phenomenon, although neither of these workers recognised its true nature. Splendore described the eosinophilic material around *Sporotrichum* in 1908 and erroneously assumed that it was a new species, while Hoeppli described the same material around schistosomes in 1932 and erroneously suggested that it was secreted by the parasite. The material is now considered to consist of immunoglobulin, complement and cellular debris. It is especially striking in actinomycosis, botryomycosis and various fungal infections, but may also be seen around parasites such as schistosomes and helminths, and even around foreign material.

the pleura and on into the spine and ribs, whether or not there is an actinomycotic empyema: the latter may be loculated or involve the entire pleural sac. Obliteration of the sac prevents empyema formation but does not present a barrier to the infection as it spreads outwards to involve not only the thoracic skeleton but also the soft tissues and skin of the chest wall, often with the establishment of the draining sinuses that are a classic, if rare, feature of the disease. Actinomycotic bacteraemia is uncommon but arises more frequently from pulmonary foci than from any other form of actinomycosis; it may give rise to metastatic abscesses in other viscera, the skeleton or soft tissues. Actinomycosis is occasionally complicated by amyloidosis.

NOCARDIOSIS

Bacteriology

Nocardiosis is caused by several genera of aerobic Actinomycetaceae. *Nocardia asteroides* is the usual cause: *N. brasiliensis* and *N. caviae* are less common human pathogens. None of these is part of the normal human flora. They are soil saprophytes that are often found in decaying organic matter and human infection is exogenous. *Nocardia* were first identified in cattle suffering from farcy in 1888.[150] Human disease was described shortly afterwards.[151,152]

In contrast to *A. israelii*, *N. asteroides* is an aerobic bacterium. It is formed of filaments measuring 0.5–1.0 µm in width, which are so highly branched that they have been likened to Chinese characters. They often break into bacillus-like fragments during preparation of films of infected exudate. They are Gram-positive but often weakly so, and although commonly acid-fast, they are seldom as strongly so as tubercle bacilli and they are not alcohol-fast; silver impregnation methods offer the best means of demonstrating this organism in tissue sections. In contrast to *A. israelii*, and to *N. brasiliensis* and *N. caviae*, *N. asteroides* does not form macroscopically evident colonial granules in infected tissues.

Clinical features

Nocardiosis is typically acquired by inhalation but may extend beyond the respiratory tract. Infection may develop in a previously healthy person,[153] but in most cases there are predisposing factors, particularly those that compromise cellular immunity.[154–157] The disease is ordinarily chronic but may progress rapidly in the severely immunocompromised. Predisposing factors include diseases such as leukaemia and AIDS that interfere with resistance, therapeutic agents such as corticosteroids and cytotoxic drugs that similarly suppress immunity and underlying pulmonary diseases, including alveolar lipoproteinosis.[158,159] The overall incidence of nocardiosis appears to be rising, probably in the main because of the increasing use of the drugs that predispose to its occurrence. The disease is commoner in adults than children.

Pulmonary nocardiosis causes fever and cough productive of thick, sticky, purulent sputum that may be streaked with blood. The radiological findings vary from minor infiltrates to extensive consolidation, sometimes with abscess formation or empyema.[160,161] Less commonly, nocardiosis results in bronchial obstruction.[162–164]

Pathological findings

In general, the picture of nocardiosis is that of suppuration, with the development of multiple abscesses. The lesions have a notable tendency to confluence. Pulmonary nocardiosis may affect one or both lungs widely, with extensive consolidation round the suppurative foci: the exudate in the alveoli of these pneumonic foci initially contains much fibrinogen, and a fibrin coagulum forms, often with relatively little leukocytic involvement. The organisms are present in the exudate, and may be very numerous. Their number is often only inadequately disclosed by Gram or Ziehl–Neelsen stains: the Grocott–Gomori method is generally more reliable (Fig. 5.3.26).[165] Healing may result in extensive organising pneumonia.[166] Rarely, pulmonary nocardiosis may take the form of an intracavitary nocardioma[167] or invade contiguous vertebrae and compress the spinal cord.[168] *N. asteroides* has a particular affinity for the central nervous system; nocardial brain abscess and nocardial meningitis are frequent complications of pulmonary infection. Coexisting microbial agents are commonly identified. Treatment of nocardiosis is generally medical, typically employing sulphonamides or co-trimoxazole. Abscesses and empyema may require additional surgery.

RHODOCOCCUS PNEUMONIA

Rhodococcus equi (formerly *Corynybacterium equi*) is an aerobic, Gram-positive and acid-fast bacillus belonging to the order Actinomycetales, and is therefore closely related to the mycobacteria and *Nocardia*. Its natural habitat is the soil and its transmission is aerogenous. It is best known as a pathogen in foals, cattle, swine and sheep, where it is a lethal cause of suppurative granulomatous pneumonia, lymphadenitis, mediastinitis and pyometra. It has only recently been recognised as pathogenic to humans. Human infection often follows exposure to farm animals or to stockyards contaminated with animal excreta. Virtually all *Rhodococcus*-infected patients have been severely immunocompromised, typically suffering from AIDS, of which it is an infrequent complication.[169] The clinical presentation is often insidious, consisting of fatigue, fever and a non-productive cough.

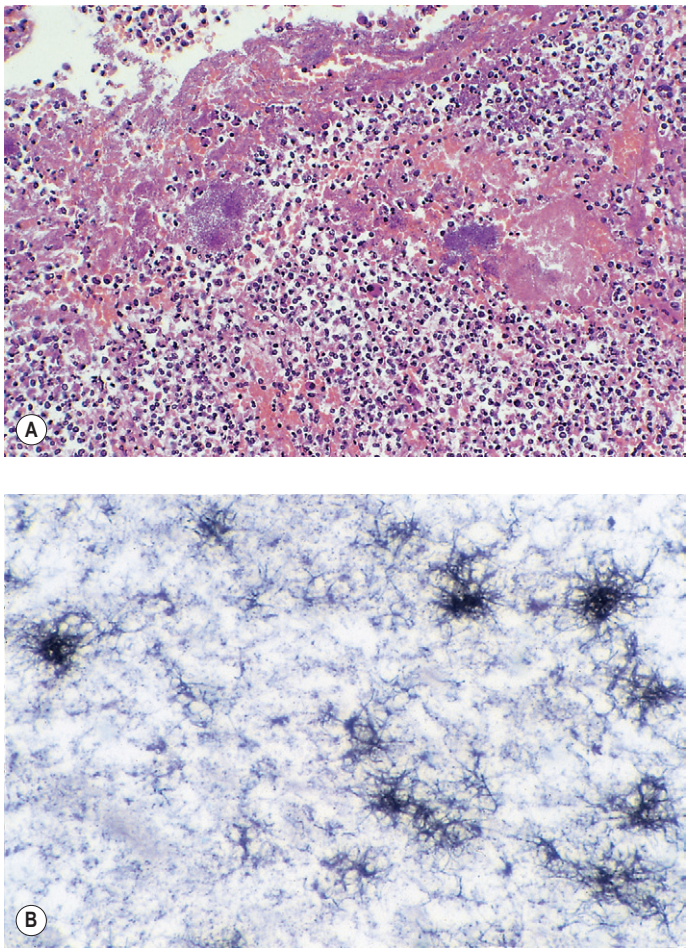

Figure 5.3.26 Nocardiosis. Pus containing colonies of basophilic nocardia (A), which are better demonstrated by Grocott staining (B).

R. equi infection causes pneumonic consolidation with abscesses. The disease typically affects the upper lobes and may simulate tuberculosis radiologically.[170–172] Spread to sites such as the brain and bone may occur. The inflammation is histiocytic in nature and may result in pulmonary malakoplakia.

Malakoplakia

Malakoplakia is a rare inflammatory disorder characterised by tumour-like accumulations of swollen macrophages. It usually affects immunocompromised persons and is due to a defect in macrophage function.[173] Bacteria are ingested normally but are not killed within the cell, suggesting that the fault lies in the lysosomes. Malakoplakia usually affects the lower genitourinary or gastrointestinal tracts and until recently few cases had been described with lung involvement. However, several cases of malakoplakia confined to the lungs have now been described, chiefly in the setting of AIDS but also associated with general debilitation, organ transplantation, haematopoietic malignancy and alcoholism.[170,171,174–183]

Bacteriology

Malakoplakia is associated with infection by various bacteria and fungi. In the urinary tract the organism is usually *Escherichia coli* but in the lungs *Rhodococcus equi* (formerly *Corynebacterium equi*) is generally involved, although rare cases associated with other infections are described.[184] Rhodococci are Gram-positive coccobacilli that may be mistaken for commensal diphtheroids in sputum. They are sometimes acid-fast. *R. equi* has been recognised as an agent causing bronchopneumonia in horses and other domesticated animals since its first isolation from infected foals in 1923. Its habitat is the soil. Infection of both humans and beasts is thought to be acquired through the lungs. Human infection almost always involves patients who have defects in cell-mediated immunity. A history of exposure to animals is not invariably obtained.

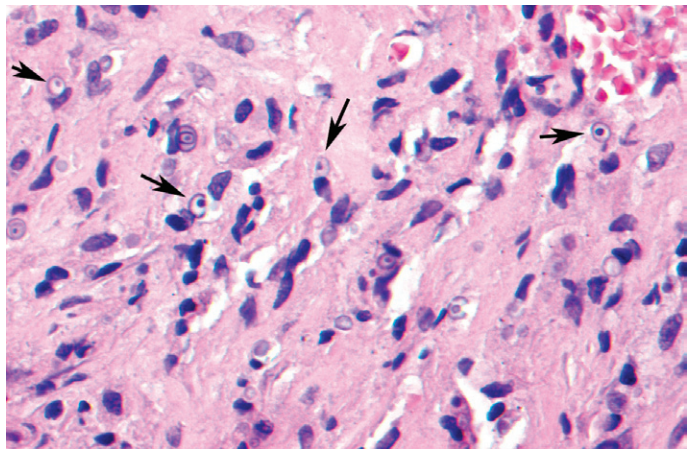

Figure 5.3.27 Malakoplakia. A mass lesion composed of histiocytes with abundant eosinophilic cytoplasm. Occasional Michaelis–Gutman bodies are evident (arrows).

Pathological and clinical features

Malakoplakia of the lungs may form solitary or multiple bilateral lesions, mimicking either primary or metastatic neoplasms radiologically. The gross appearances also mimic neoplastic disease. The lesions are well demarcated, firm and either solid or cavitating. Microscopically, the lung tissue is replaced by sheets of swollen macrophages with abundant eosinophilic, granular or vacuolated cytoplasm that stains well with periodic acid–Schiff reagents and is diastase-resistant. The appearances may suggest a granular cell tumour (see p. 640). A characteristic feature is the presence of Michaelis–Gutman bodies in the macrophage cytoplasm or free between the cells. These are faintly basophilic, round, target-like structures that measure up to 20 µm diameter (Fig. 5.3.27). They contain calcium and are therefore well shown by von Kossa's stain. The Michaelis–Gutman bodies represent mineralised bacteria-containing phagolysosomes.[183] Aggregates of bacteria can sometimes be demonstrated within macrophages by Gram stains.

SYPHILIS

Syphilitic lesions have never been particularly frequent in the lungs, and congenital pulmonary syphilis ('pneumonia alba') has probably always been the commonest manifestation. However, there has recently been an increase in syphilis and its protean manifestations should not be forgotten.[185,186]

Congenital pulmonary syphilis

The pallor and firmness of the lungs, which are larger than normal, account for this condition's old name, pneumonia alba. It is usually seen in stillborn syphilitic babies or those who die within a few hours of birth: in the latter, the aerated lobules stand out above the indurated parts. Microscopically, there is widespread thickening of the alveolar walls by fibroblastic connective tissue accompanied by an accumulation of plasma cells with some lymphocytes. In places there are microscopical foci of necrosis, maybe with histiocytic proliferation round them, as well as some accumulation of neutrophils: these lesions occasionally merge to form gummatous foci that may be evident macroscopically. Usually there is a conspicuous lining of cuboidal type II alveolar epithelial cells and many alveoli may be filled with macrophages. Silver impregnation methods show the presence of great numbers of treponemes in the tissues. The bacteria may also be demonstrated immunohistochemically.[187] Imaging may show diffuse pulmonary infiltrates, which persist long after adequate antibiotic treatment.[188]

Somewhat similar macroscopical and microscopical changes may result from viral infections in the neonatal period. Also, *Pneumocystis* pneumonia may be mistaken for syphilitic pneumonia in those cases in which interstitial accumulation of plasma cells is particularly marked (see p. 226).

Acquired pulmonary syphilis

Gummas and interstitial fibrosis are the manifestations of acquired syphilis in the lungs. The gummas may be solitary or multiple, and small or large. They may occur in the trachea and bronchi as ulcerative lesions, with a tendency to destroy the cartilage of the wall. These cause cough and haemorrhage whereas gummas in the lung substance may be clinically silent.

Bronchopulmonary gummas have the structure that is common to these lesions wherever they occur in the body. They consist of a necrotic core surrounded by granulation tissue that is heavily infiltrated by plasma cells and lymphocytes with scanty giant cells. Satellite lesions, as seen in tuberculosis, are not a feature. As elsewhere, gummas tend ultimately to produce dense scars that contract and produce deep cicatricial fissures in the surface of the lungs, an appearance comparable to that of the classic hepar lobatum of tertiary syphilis.

It is very important to consider and exclude other types of infection, particularly mycobacterioses and mycoses, before a diagnosis of gumma can be sustained, even when the patient's serological tests indicate the presence of syphilis. Moreover, primary and secondary tumours are commoner causes of discrete shadows in chest radiographs than gummas, even in patients with syphilis. The necrotic pulmonary lesions of Wegener's granulomatosis and even pulmonary infarcts are among other conditions to be considered in the differential diagnosis.

Other thoracic manifestations of acquired syphilis include diffuse pulmonary fibrosis of non-specific character, hilar lymphadenopathy and pleural fibrosis.[185,186]

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Chapter 5

5.4 *Fungal infections*

CHAPTER CONTENTS

In certain regions of the world, environmental soil conditions support the saprophytic phase of pathogenic fungi such as *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis* and *Paracoccidioides brasiliensis* that are able to cause disease in previously healthy people. Other fungi invade the tissues only because of lowering of the patient's resistance by some other disease or as a side-effect of treatment. Some of the fungi that cause these so-called opportunistic infections are seldom, if ever, responsible for illness in healthy individuals: this is particularly so of mucormycetes. Others cause disease in healthy individuals of a type very different from the progressive, destructive, disseminated infection that they set up in those whose resistance has been reduced: asthma from sensitisation to aspergilli and saprophytic growth in previously formed cavities are examples of such disease.

Many fungi that infect humans are dimorphic – that is, they grow as yeast-like organisms at certain temperatures and in mycelial form at others. Sporulating conidiophores (or 'fruiting heads') form on the mycelial hyphae when oxygen is plentiful and release spores into the atmosphere. The spores are particularly likely to be inhaled and germinate into hyphae in the lungs. The size and shape of the fungus in its various forms often enable the histopathologist to identify the genus (Box 5.4.1) but speciation generally requires culture.

Box 5.4.1 Microscopical differentiation of common fungi in lung tissue

Yeasts

Small

Pneumocystis
Histoplasma
Torula

Medium-sized

Candida
Cryptococcus
Blastomyces
Paracoccidioides

Large

Coccidioides

Hyphae

Short

Candida (pseudohyphae)

Long and regular

Aspergillus

Long and irregular

Mucormycetes

The ease and frequency of international travel make many hitherto 'exotic' diseases the immediate practical concern of doctors who have no personal experience in their recognition and management. The fact that fungi which are frequently the cause of disease in other parts of the world are not indigenous where the doctor is in practice is no longer an excuse for not considering the possibility that a patient may have acquired infection while visting another country or through exposure to contaminated, imported materials. Neither histoplasmosis nor coccidioidomycosis, for instance, occurs naturally in western Europe, yet every year in countries such as the UK patients are seen whose symptoms are due to these diseases: the cardinal importance of the patient's geographical history, and of the doctor's knowledge of geographical medicine, is self-evident.

PNEUMOCYSTOSIS[1,2]

Microbiology

Pneumocystosis is caused by organisms discovered in the early twentieth century by Chagas and soon after by Carini. They both thought the organism to be a stage in the life cycle of trypanosomes as they found it in the lungs of rats experimentally infected with trypanosomiasis. The Delanoës recognised that it was a distinct species, *Pneumocystis carinii*. *Pneumocystis* organisms were first identified as a cause of human disease in 1942, in Belgium, in association with cases of the condition, previously of unknown causation, that had been described in 1937 as interstitial plasma cell pneumonia. Outbreaks of the latter occurred during the Second World War, and for some years after, in orphanages and other institutions that housed malnourished children, particularly in eastern Europe and the Middle East.[3] The causative role of the *Pneumocystis* in this type of pneumonia in young children was generally recognised following work of Jirovec in Czechoslovakia in the years immediately after the war.[4,5] Subsequently it has been recognised that the human pathogen is a separate species, *P. jirovecii*. Although pneumocysts were long thought to be protozoal, they are now regarded as a primitive fungus in which the mycelium is reduced to a unicellular state but is still able to sporulate.[6–8] Despite this, various forms of the fungus are still referred to as sporozoa or trophozoites, as if it was a protozoa.

Electron microscopy[6,9–12] provides an insight into the structure of the organism and the pathogenesis of *Pneumocystis* pneumonia. It shows that the organism forms cysts measuring 3–6 μm in diameter, which have a thick wall or pellicle (Fig. 5.4.1). The pellicle is particularly thick at one point, a feature that is evident by light microscopy in silver-stained preparations as a peripheral dot on the cyst wall. The pellicle is triple-layered, consisting of an outer electron-dense zone about 75 nm thick, an electron-lucent intermediate zone 250 nm thick and an inner 7-nm membrane. Numerous small tubular structures are associated with the inner layer. Up to eight nucleated intracystic bodies or sporozoa are also probably derived from this membrane. These are released when the cyst ruptures (Fig. 5.4.2). Collapsed cysts are largely empty and the innermost membrane of the wall is either detached or absent. The released sporozoa grow from about 1.5 to 6 μm, have a thin pellicle and are highly irregular in shape (Fig. 5.4.3). They are now known as trophozoites and possibly undergo binary fission before entering a precyst stage in which their pellicles thicken (Fig. 5.4.4).

Cysts tend to be sparse near the alveolar walls, which are bordered chiefly by trophozoites, suggesting that limitation of some nutritional factor promotes cyst formation. In successfully treated cases only empty cysts are found, indicating that all viable forms of the parasite, whether free-living or encysted, are vulnerable to chemotherapy. Although there is not a heavy cellular reaction within the alveoli, cysts and trophozoites may fill these air spaces.

Electron microscopy also shows that the trophozoites attach to type I alveolar epithelial cells, eventually causing these cells to slough away from the alveolar walls.[13] Tracer studies show that there is increased permeability in the lung, even before epithelial cells are lost.[14] In severe cases, trophozoites are observed within the alveolar interstitium. From here they may gain access to the blood stream and disseminate widely.[15]

Epidemiology

The epidemic *Pneumocystis* pneumonia mentioned above as a feature of malnourished children is no longer seen in Europe but is still encountered in parts of the world where poverty and malnutrition are rife. *Pneumocystis* pneumonia is also recognised as a complication of immunodeficiency states, both congenital and acquired. Until the appearance of the acquired immune deficiency syndrome (AIDS), such immunodeficiency was generally due to lymphoproliferative disease or immunosuppressive therapy but interest now centres on *Pneumocystis* pneumonia as being by far the commonest opportunistic infection in AIDS (see Table 5.1.1, p. 167). *P. jirovecii* is kept in check by T lymphocytes and suppression of these cells, as in AIDS, allows the parasite to proliferate and cause pneumonia. In very severe T-lymphocyte depletion extrapulmonary dissemination is found (see below). Patients who have undergone heart/lung transplantation are also at risk of developing *Pneumocystis* pneumonia,[16] as are those with cancer.[17] Whatever the cause of the immunoparesis, *Pneumocystis* pneumonia in immunodeficient individuals lacks the intense plasma cell infiltration seen in malnourished children.

Antibodies to *P. jirovecii* can be detected in most of the population by the age of 4 years[18] but the absence of the organism from normal lungs suggests that the pneumonia represents reinfection rather than

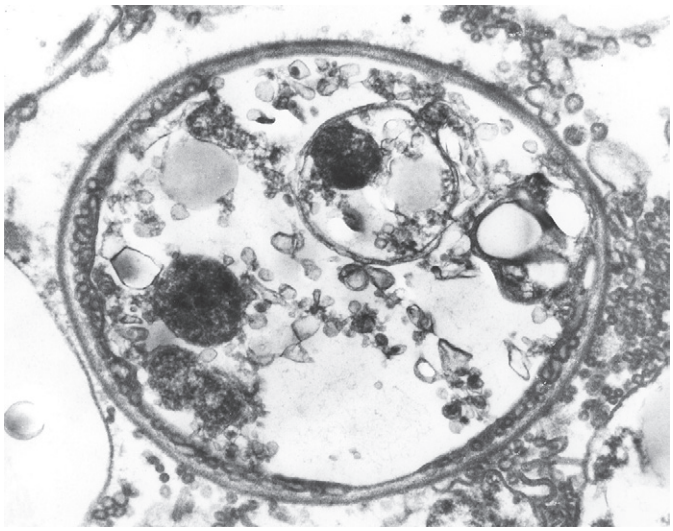


Figure 5.4.1 *Pneumocystis jirovecii*. Cyst form. The cyst wall has three layers: an outer electron-dense zone about 75 nm thick, an electron-lucent intermediate zone 250 nm thick and an inner 7-nm membrane. Numerous small tubular structures are associated with the inner layer, which also spawns up to eight intracystic bodies or sporozoites, one of which is visible here. Electron micrograph. *(Reproduced from Corrin & Dewar (1992).[12])*

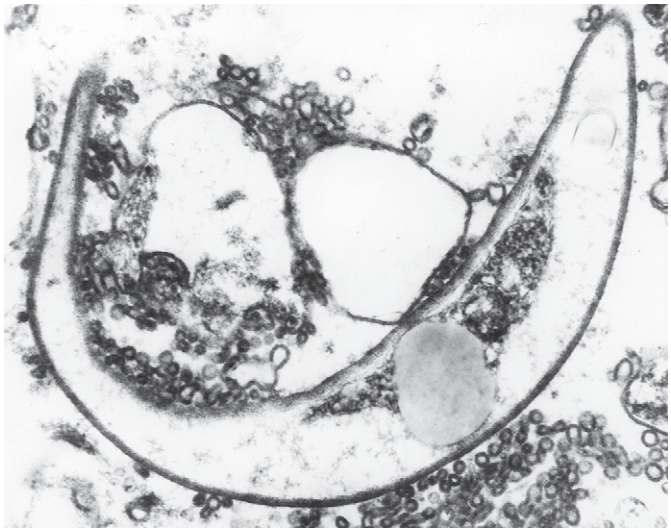


Figure 5.4.2 *Pneumocystis jirovecii*. Collapsed cyst releasing its contents. Electron micrograph *(Reproduced from Corrin & Dewar (1992).[12])*

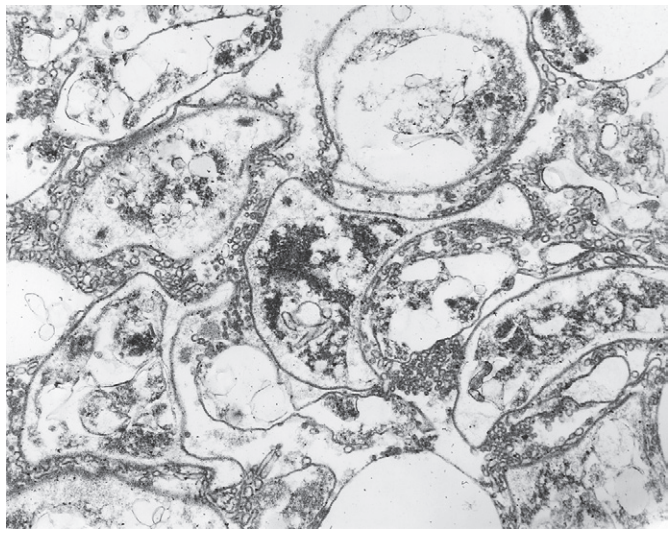


Figure 5.4.3 *Pneumocystis jirovecii*. Trophozoites. These are irregular in shape and have a thin unit membrane wall. Electron micrograph. *(Reproduced from Corrin & Dewar 1992.[12])*

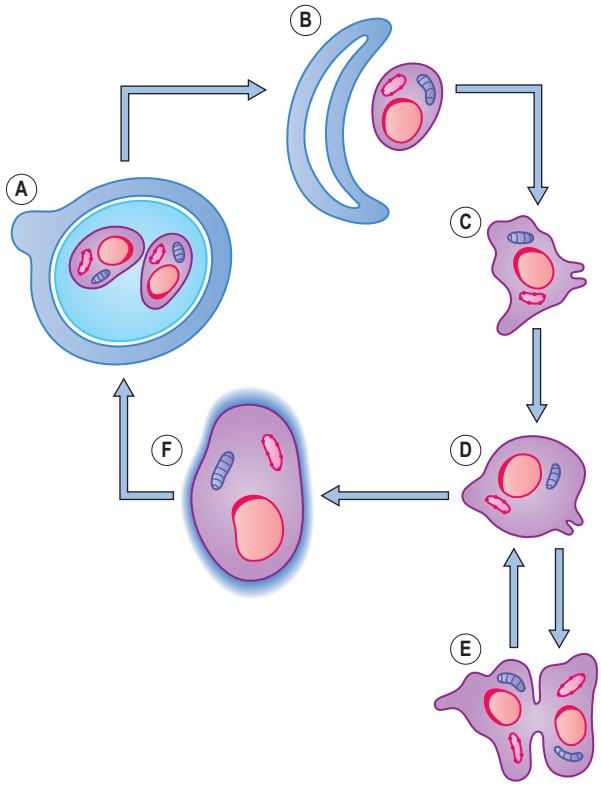


Figure 5.4.4 Proposed life cycle of *Pneumocystis jirovecii*. (A) Cystic form containing two intracystic bodies. Note the focal thickening of the pellicle. (B) Discharge of cyst contents and collapse of the cyst. (C–E) Trophozoites, which possibly undergo binary fission. (F) Trophozoite in precystic stage.

reactivation.[8,19,20] Infection is presumed to be by inhalation from an as yet poorly characterised environmental source. Although *P. jirovecii* has been found in a wide range of animals it shows host specificity and is the species prevalent in humans.

Autopsy in cases of *Pneumocystis* pneumonia presents no danger except in AIDS where there is a possibility of mortuary staff being infected by the HIV virus.

Clinical features

Pneumocystis pneumonia is characterised by breathlessness, cough and fever, generally of insidious onset. Untreated, the disease progresses with mounting tachypnnoea, hypoxaemia and cyanosis. Radiographs typically show widespread bilateral opacification. Late features include calcification, cavitation and pneumothorax. Diagnosis requires demonstration of the organisms, for which sputum production is generally induced by the inhalation of a saline aerosol or bronchoalveolar

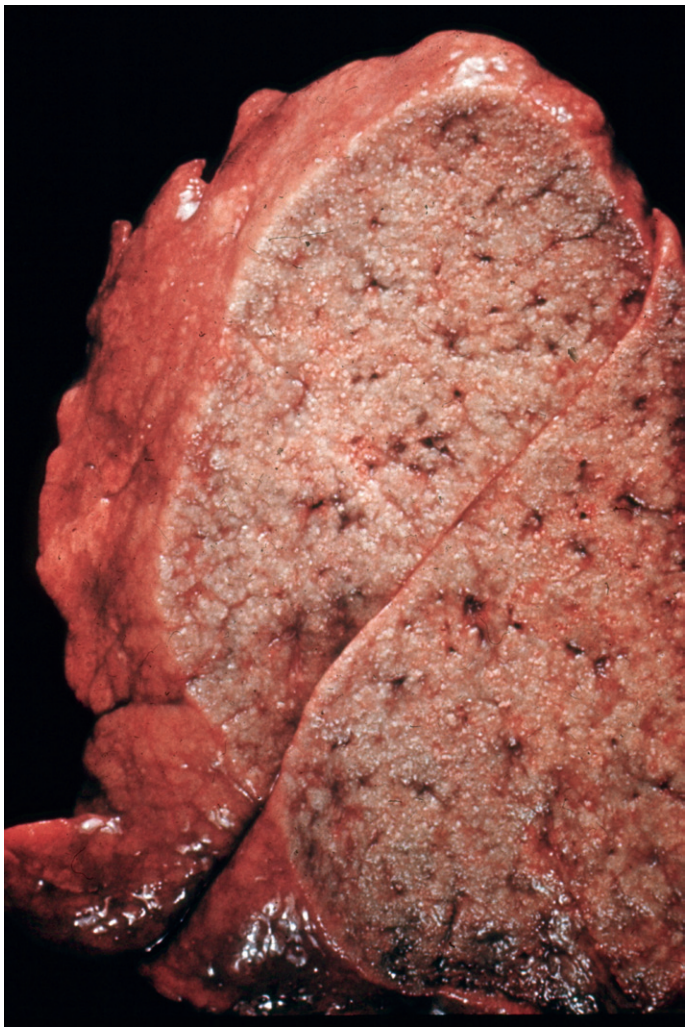


Figure 5.4.5 *Pneumocystis jirovecii* pneumonia. The lung shows diffuse consolidation. *(Courtesy of the late Dr AA Liebow, San Diego, USA and Dr T Jelihovsky, Sydney, Australia.)*

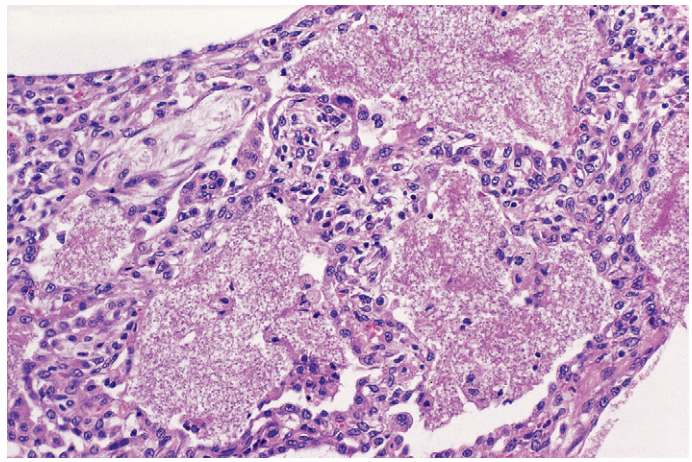


Figure 5.4.6 *Pneumocystis jirovecii* pneumonia. The alveoli are filled by a foamy exudate and the alveolar walls are thickened by a lymphoid infiltrate.

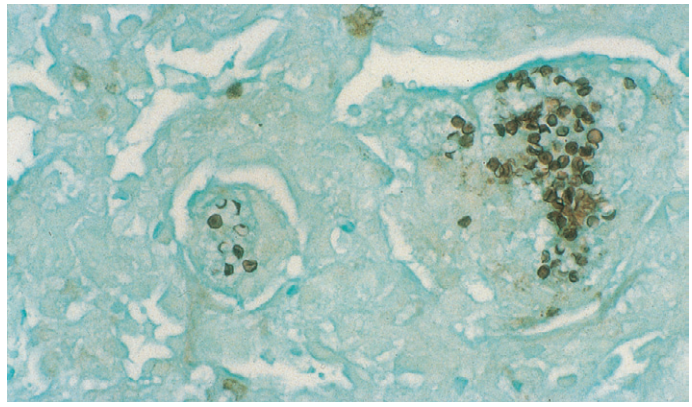


Figure 5.4.7 *Pneumocystis jirovecii* demonstrated by Grocott's methenamine silver stain. The smaller group includes crescentic forms representing collapsed cysts and other cysts that show a characteristic dot representing focal thickening of the cyst wall.

lavage is undertaken.[21] The organisms may be demonstrated with toluidine blue, Giemsa stain, Grocott's methenamine silver stain or by immunofluorescence, but detection of *Pneumocystis* DNA by the polymerase chain reaction is much more sensitive.[22–28]

Morbid anatomy

Fatal *Pneumocystis* pneumonia is generally characterised by widespread bilateral consolidation with relative sparing of the bases and apices of the lungs (Fig. 5.4.5). Rarely, the disease takes the form of solid or cavitating pulmonary nodules.[29,30]

Histological appearances

Microscopically, the alveoli are filled by a foamy, pale, eosinophilic exudate (Fig. 5.4.6). The parasite is unstained in haematoxylin and eosin preparations but with Grocott's methenamine silver stain the alveoli are seen to contain numerous round cysts that measure about 5 µm across. Crescent-shaped forms (Fig. 5.4.7) represent collapsed cysts and their presence is helpful if there is concern that erythrocytes have not been successfully differentiated in the staining procedure, especially if bronchial washings or bronchoalveolar lavage fluids are being examined and the topographical features provided by a biopsy cannot be studied. Another helpful feature is a dot, generally seen on the edge of the cyst (see Fig. 5.4.7); this represents a focal thickening of cyst wall.[31] Various quick modifications of fixation and processing and of the Grocott stain have been introduced to speed the diagnosis,[32–34] but the importance of fixation in killing any concomitant human immunodeficiency virus (HIV) should not be overlooked. Other special stains that find favour include the Gram Weigert and Giemsa methods[35,36] and those using monoclonal antibodies (Fig. 5.4.8).[22] The last two methods stain the trophozoite as well as the encysted form of the parasite, but as the cysts are invariably present in *Pneumocystis* pneumonia (and are shown by Grocott's stain), this is a dubious advantage: the Grocott stain is clearer and has the advantage of staining any other fungi that may also be present.[37] However, in sputa and other cytological specimens where the pneumocysts may be sparse the greater sensitivity of immunochemical stains and molecular techniques is advantageous.[23–27] In situ hybridisation has also been used to demonstrate pneumocysts in tissue sections.[38]

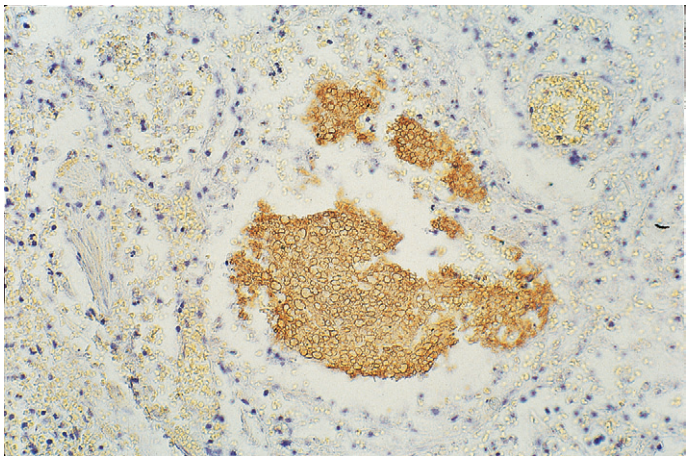


Figure 5.4.8 Immunocytochemical staining of *Pneumocystis jirovecii* demonstrates the trophozoites as well as the cysts.

Table 5.4.1 ***Pneumocystis jirovecii*** **pneumonia: atypical histological features**[43]

	No. of cases	%
Fibrosis	77	63
Interstitial	44	36
Intraluminal	23	19
Absence of typical exudates	11	9
Numerous alveolar macrophages	6	5
Granulomatous inflammation	5	4
Hyaline membranes	4	3
Marked interstitial pneumonitis	3	2
Parenchymal cavities	3	2
Interstitial microcalfication	2	2
Minimal histological reaction	1	1
Vascular permeation	1	1

The alveolar exudate in which the parasites are found is virtually free of host cells except for a mild increase in the number of alveolar macrophages. The reaction to the parasite is largely an interstitial infiltrate of lymphocytes and plasma cells (see Fig. 5.4.6). In most immunodeficient patients the infiltrate is generally mild but in malnourished children it is intense, warranting the original descriptive term interstitial plasma cell pneumonia.

Changes other than the classic one of foamy alveolar exudates may be found in *Pneumocystis* pneumonia, particularly in AIDS (Table 5.4.1 and Fig. 5.4.9),[29,30,39–46] demonstrating that pathological changes in infective disorders are dependent on host factors as well as the parasite. In addition to the cavitating nodules mentioned above,[29,30] necrotising granulomatous inflammation,[26,39,42–44,47] diffuse alveolar damage,[41] calcification,[40,45,48] lymphoid interstitial pneumonia (particularly in children)[49–51] and interstitial[52,53] and vascular invasion have been described, the latter sometimes resulting in a necrotising vasculitis.[30] The invasion of the interstitium and pulmonary blood vessels probably causes the necrosis that underlies the cavitating nodules.[30,53,54] The cavities develop into air cysts, which are prone to rupture into the pleural cavities, resulting in both pneumothorax and *Pneumocystis* infection of the pleura.[55,56] Alternatively, there may be interstitial spread and infection of the pleural cavities in the absence of any direct fistulous communication.[52]

In view of the vascular invasion it is not surprising that widespread blood-borne dissemination is also reported, particularly in AIDS.[15,39,57–61] The fact that this sometimes develops in the absence of obvious pneumonia has been attributed to the prophylactic use of inhaled pentamidine which reduces the risk of *Pneumocystis* pneumonia but does not prevent the organism spreading to other organs. Restitution of the immune response following effective antiviral therapy is sometimes accompanied by an 'immune reaction inflammation syndrome' (IRIS)[62] and this may ultimately result in widespread interstitial pulmonary fibrosis.

Although opportunistic infections are often multiple, there appears to be a special relationship between *P. jirovecii* and cytomegalovirus because these two organisms coexist particularly frequently in the infected lung (Fig. 5.4.10). It has been suggested that *P. jirovecii* acts as an intermediate host for cytomegalovirus.[63]

Differential diagnosis

The differential diagnosis of classic *Pneumocystis* pneumonia is from pulmonary oedema and alveolar lipoproteinosis. These three conditions are all characterised by the alveoli being filled by a largely acellular material, but whereas in oedema the material is amorphous, in lipoproteinosis it is granular and in *Pneumocystis* pneumonia it has a foamy appearance. Alveolar lipoproteinosls is further distinguished from *Pneumocystis* pneumonia by the presence of cholesterol crystal clefts and a few foamy fat-filled macrophages in the alveolar deposit and by the strong periodic acid–Schiff-positivity of the deposit (compare Fig. 5.4.6 with Fig. 6.2.18A, p. 319).

ASPERGILLOSIS

Mycology

Aspergilli are common saprophytes found throughout the world in decaying organic matter where their spores may be so numerous that they can be seen as a dense dust cloud when piles of such material are disturbed. Several species have been identified as causes of human disease but *Aspergillus fumigatus* is by far the most frequent, particularly in European cases of pulmonary disease and septicaemia. Other species responsible for disease in humans include *A. flavus* and *A. niger*, the latter more common in the USA.

Definitive diagnosis requires culture but this is not always successful. In histological preparations an aspergillus has a characteristic appearance and can be generically identified by the morphology of its hyphae (Fig. 5.4.11). *Aspergillus* hyphae are usually visible in haematoxylin and eosin preparations, and sometimes are so intensely haematoxyphil that they are immediately evident at low magnifications. Although the periodic acid–Schiff stain and the Gridley stain for fungi facilitate their recognition, the Grocott–Gomori methenamine silver nitrate method is very much more reliable. The hyphae are septate and their hyphal diameter, which varies from 3 to 6 µm, is fairly regular. Typically, the hyphae branch dichotomously at relatively narrow angles (35–45°), the branches then tending to orient themselves parallel to each other. Rare fungi of similar morphology, such as

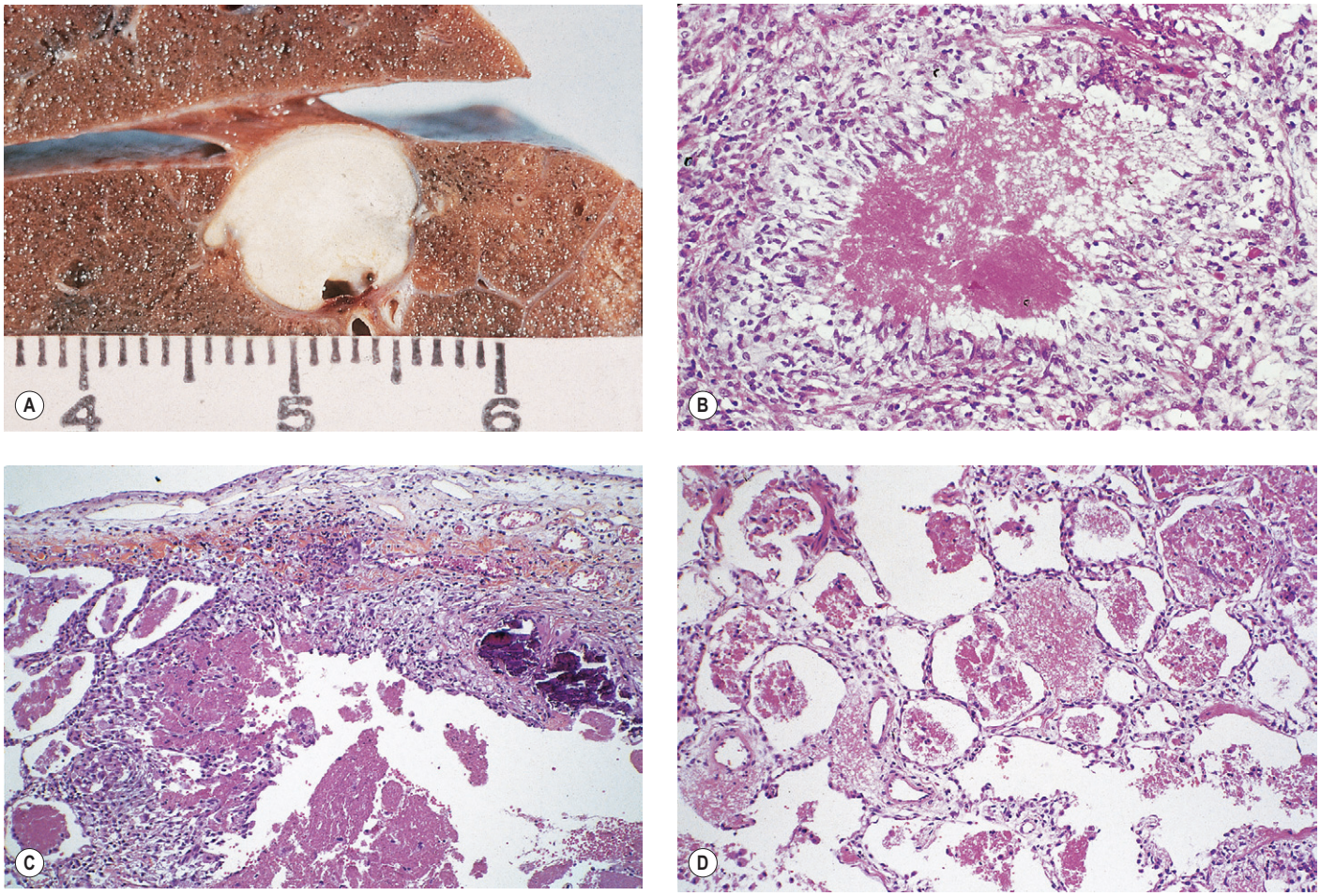


Figure 5.4.9 Atypical reactions to *Pneumocystis jirovecii* in severely immunodeficient patients. (A, B) Necrotising, granulomatous inflammation. (C) Necrosis, cavitation and dystrophic calcification. (D) Invasion of the interstitium, evident from the foamy exudate expanding alveolar walls as well as occupying alveoli. *(Courtesy of Dr R Steele, Brisbane, Australia; and Professor F Capron and Dr I Abdalsamad, Paris, France.)*

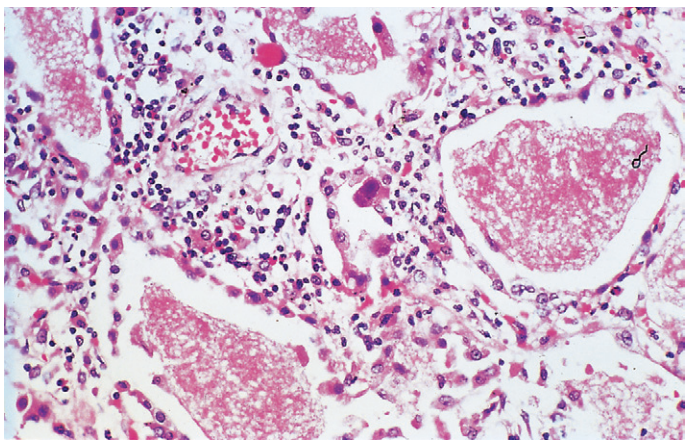


Figure 5.4.10 *Pneumocystis jirovecii* and cytomegalovirus pneumonia. As well as the foamy exudate of *Pneumocystis* pneumonia there are prominent viral inclusions (centre).

Chaetomium globosum, can be distinguished by immunocytochemistry, culture or molecular methods.[64–67]

The conidiophores (or fruiting heads), that are so striking a feature of aspergilli when growing as saprophytes, are seen in infected tissues only when the fungus is exposed to air: they are never found within the solid structure of colonised organs and tissues, but may occasionally be seen in the lung if the lesion communicates with a bronchus (Fig. 5.4.12). Species identification is based on colonial characteristics and on the structure of the conidiophores, which is best studied in culture (Figs 5.4.13 and 5.4.14).

Oxalate crystal deposition

Crystals of calcium oxalate have been identified in tissues infected by aspergilli, particularly *A. niger*, of which oxalic acid is a fermentation product. In some cases local tissue injury and even generalised acute oxalosis and renal failure have resulted from the production of oxalic acid by the fungus.[68,69] Its widespread deposition as insoluble calcium oxalate may be accompanied by sudden hypocalcaemia.[70] Tissue toxicity is attributed to calcium oxalate complexing with iron, resulting in the production of free oxidants.[71] Oxalosis is commonest with saprophytic aspergillosis but is also recorded with the allergic and

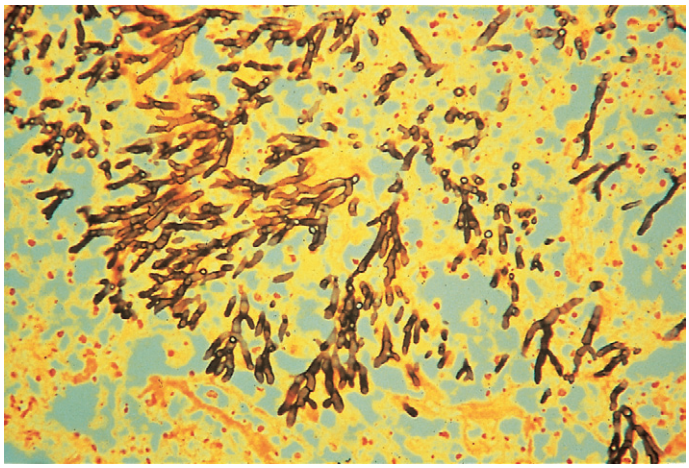


Figure 5.4.11 *Aspergillus* hyphae are septate, of fairly uniform thickness (3-6 µm diameter) and branch dichotomously. Grocott's methenamine silver stain.

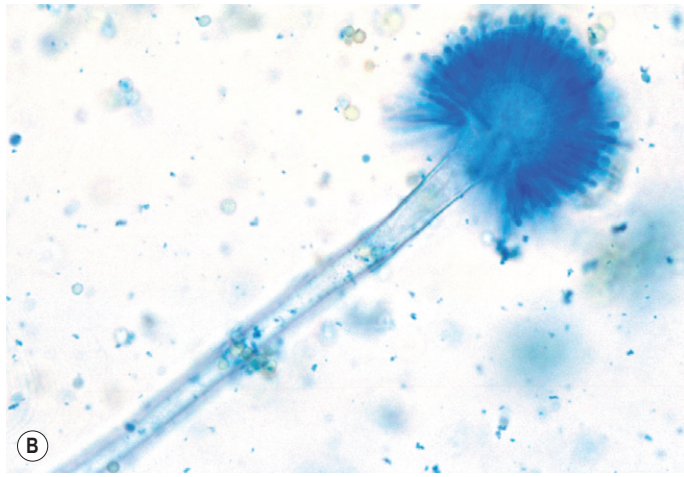


Figure 5.4.12 The fruiting heads or conidiophores of *Aspergillus* in a pulmonary cavity that communicated with the bronchi, so affording the fungus the oxygen that stimulates this form of reproduction. (A) Grocott's methenamine silver stain; (B) lactophenol cotton blue stain.

invasive varieties of the infection (described below). The demonstration of oxalate crystals in biopsy and cytology specimens can be a useful aid in the diagnosis of pulmonary aspergillosis.[72–74] The crystals are birefringent (Fig. 5.4.15), stain with alizirin red[75] and can be confirmed as oxalate by crystallography and X-ray diffraction.[76]

Predisposing causes and types of pulmonary aspergillosis[77,78]

Although exposure to *Aspergillus* spores is common, the fungus is not a frequent pathogen. Only if the individual is atopic, or the lungs have been previously damaged, or general resistance is lowered by other conditions are ill-effects likely to occur. Bronchopulmonary disease caused by aspergilli may accordingly be classified respectively as allergic, saprophytic and invasive.[77,79] Rarely, different forms of pulmonary aspergillosis occur in the same patient. For example, an aspergilloma may be complicated by allergic aspergillosis,[80,81] even in a non-atopic patient, whilst an aspergilloma may develop within the bronchiectasis resulting from allergic aspergillosis.[82,83]

Allergic bronchopulmonary aspergillosis

Persons suffering from this form of aspergillosis are generally atopic and give a history of asthma.[84–87] There is also an increased incidence of allergic aspergillosis in patients with cystic fibrosis, but nearly half those so affected are also atopic.[88] It is important to reiterate that this form of aspergillosis is not characterised by invasion of the tissues by the fungus: it is an allergic response to *Aspergillus* that remains confined to the airways. Furthermore, as the disease is a hypersensitivity phenomenon, hyphae are very sparse and have to be searched for diligently, in contrast to both the other main forms of aspergillosis (saprophytic and invasive) in which hyphae are numerous.

The allergic reaction in the lung is frequently reflected in a raised blood eosinophil count: eosinophilia is also seen in lung tissue and sputum. Circulating precipitating antibodies to *Aspergillus* antigens may be demonstrable and immunoglobulin E, both total and specific, is generally raised; indeed, these immunological tests, together with the demonstration of immediate (and late) skin reactions to *Aspergillus* antigens, are now the main means of confirming the clinical diagnosis of allergic aspergillosis. There is, however, a wide range of specific antibodies to various antigenic components of the fungus, and concentration of the serum may be necessary to detect them for they are often not present in the high concentrations found in association with an aspergilloma. Poor antigens may give false-negative results and corticosteroids may depress the antibody response and thus both skin and serological reactions. Culture of the sputum is not always positive and on occasion the diagnosis of allergic bronchopulmonary aspergillosis is first made by the histopathologist after surgery has been undertaken for a suspected malignancy (Fig. 5.4.16 and see Fig. 9.8, p. 464).[89]

The term 'allergic bronchopulmonary aspergillosis' is generally limited to a syndrome that is chiefly characterised by the expectoration of mucous plugs or the impaction of such plugs and the consequent development of bronchiectasis. However, allergy to *Aspergillus* may have further bronchopulmonary consequences, notably bronchocentric granulomatosis and eosinophilic pneumonia, both of which are dealt with elsewhere (see pp. 461 and 464). Attention here will be limited to mucoid impaction.

Mucoid impaction

In some asthmatic individuals particularly large mucous plugs develop, typically 1–2 cm thick and 2–5 cm long. They generally form in proximal bronchi (see Fig. 5.4.16) and can be clearly seen in plain

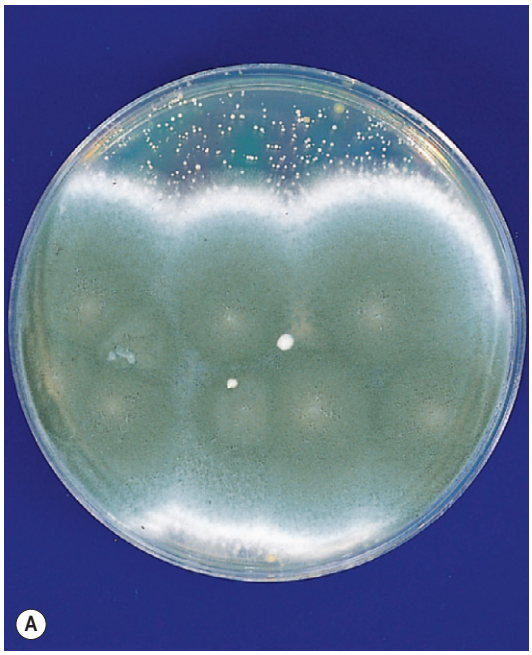


Figure 5.4.13 *Aspergillus* colonies in culture. The hyphal mycelium is white in all species but the conidiophores' colour is distinctive. (A) *A. fumigatus*; (B) *A. niger*.

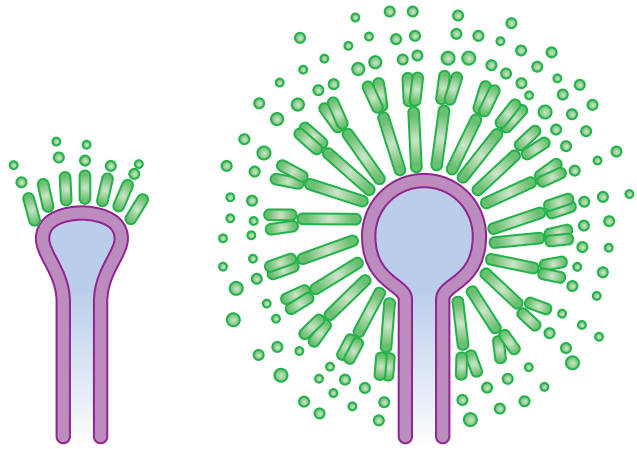
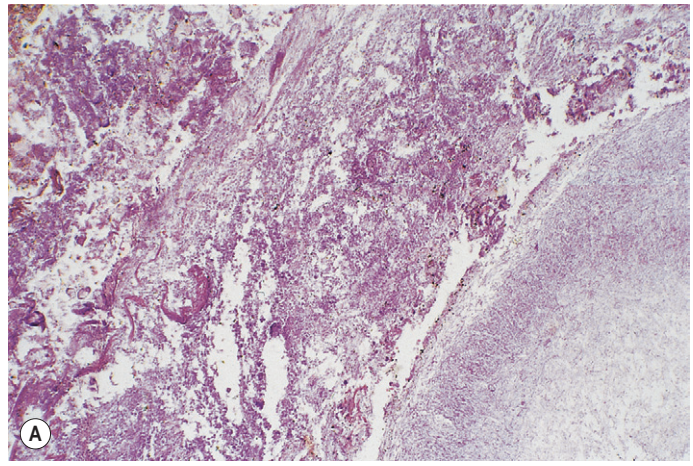


Figure 5.4.14 *Aspergillus* conidiophores. The structure of the conidiophores shows marked species variation. (A) Diagrammatic appearances of *A. fumigatus* on the left and *A. flavus* on the right. (B) A conidiophore in culture.



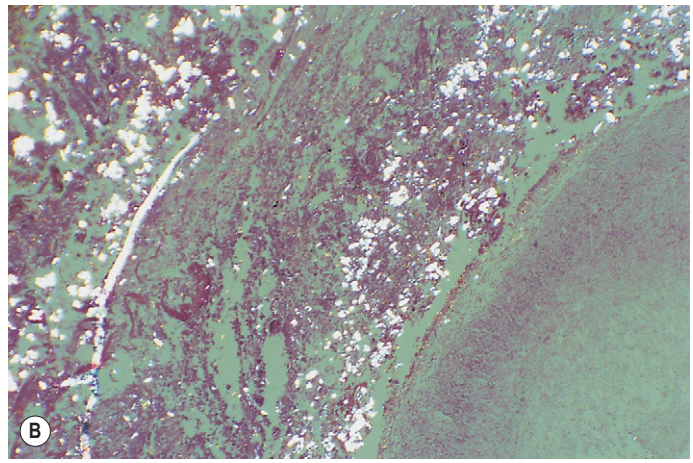
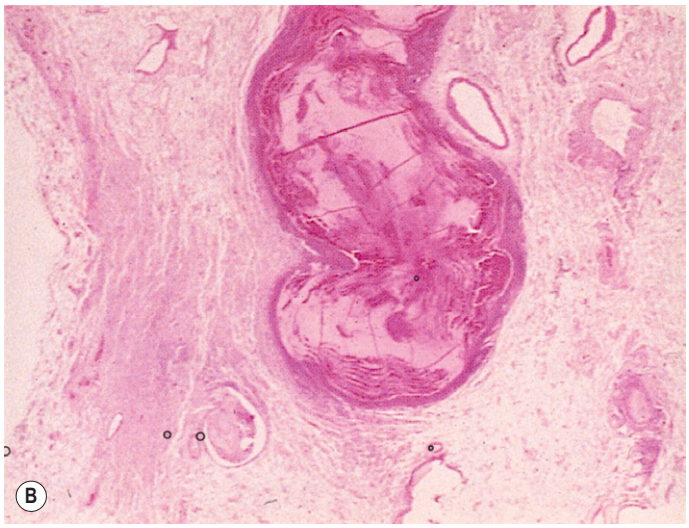


Figure 5.4.15 Calcium oxalate crystal deposition in the tissues bordering an aspergilloma viewed with (A) non-polarised and (B) polarised light. As is usually the case, much of the fungal colony is dead but here the adjacent host tissue is also necrotic; this change is attributable to oxalic acid secretion by the fungus. The oxalic acid combines with free calcium ions in the tissues to precipitate as insoluble, birefringent crystals.

radiographs as finger-like opacities near the hilum of the lung. They are frequently expectorated spontaneously (Fig. 5.4.17). The airway involved is dilated and its wall shows non-specific chronic inflammatory changes which vary from a mild infiltrate to a severe reaction that includes many eosinophils. The affected airway may be merely distended and therefore returns to normal after the plug is expectorated, or its wall may be largely destroyed by the inflammation so that there is permanent bronchiectasis (Fig. 5.4.18). The proximal distribution of this form of bronchiectasis contrasts with that of the postinfective form, which generally affects the bases.



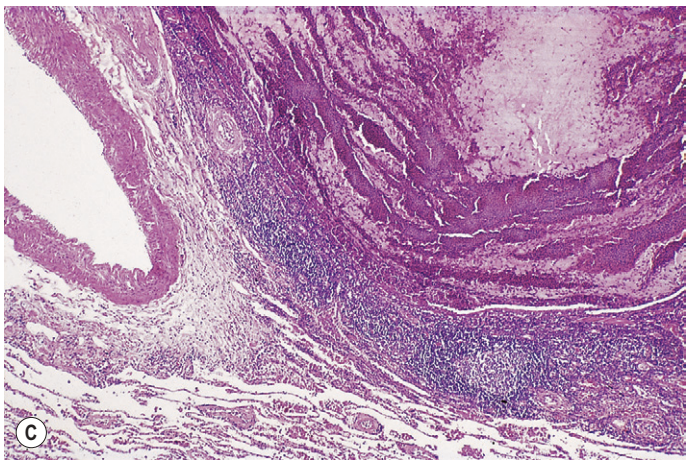


Figure 5.4.16 Allergic bronchopulmonary aspergillosis identified as the cause of a pulmonary opacity thought to be neoplastic. (A) Several bronchi are distended by plugs of viscous mucus. (B, C) Microscopy shows alternating eosinophilic bands, the pink ones representing mucus and the red conglomerations of eosinophils. In (C) the walls of the bronchi also show chronic inflammation, which weakens them and leads to proximal bronchiectasis. *(Courtesy of Professor DH Wright, Southampton, UK.)*

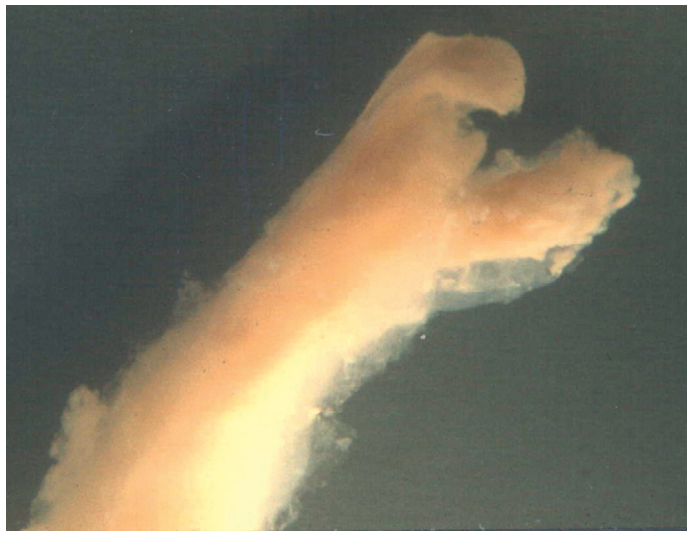


Figure 5.4.17 A mucous plug spontaneously expectorated by a patient with allergic bronchopulmonary apergillosis. Such plugs are short and stubby, very different from the long, many-tailed plugs expectorated in plastic bronchitis (compare with Fig. 3.20, p. 109). *(Courtesy of Dr T Jelihovsky, Sydney, Australia.)*

The mucous plugs undergo inspissation and often have the consistency of hard rubber. Although they may form casts of several generations of bronchi, they tend to be shorter and stubbier than the long stringy casts expectorated in plastic bronchitis (see p. 109). The microscopic appearances also differ. Mucous plugs characteristically consist of bands of agglutinated eosinophils alternating with layers of mucus (see Fig. 5.4.16). The bands of eosinophils are arranged parallel to the airway wall and frequently diminish in length towards the centre of the lumen so that wedges of alternating cellular and mucous bands point inwards, presenting an appearance that has been likened to fir trees.[90] Sparse *Aspergillus* hyphae are generally to be found in the mucous plugs.

In exceptional cases other fungi are responsible for similar changes, resulting in reports of allergic bronchopulmonary stemphyliosis, curvulariosis, drechsleriasis, candidosis, helminthosporiosis, penicilliosis, torulopsosis, fusariosis and pseudallescheriosis.[91–96] and the term 'allergic bronchopulmonary fungal disease' is therefore sometimes preferred.[97]

Extrinsic allergic alveolitis

Extrinsic allergic alveolitis may also be a manifestation of allergy to *Aspergillus*, but here it is heavily exposed non-atopic individuals who are affected. One example is 'malt worker's lung', which occurs in

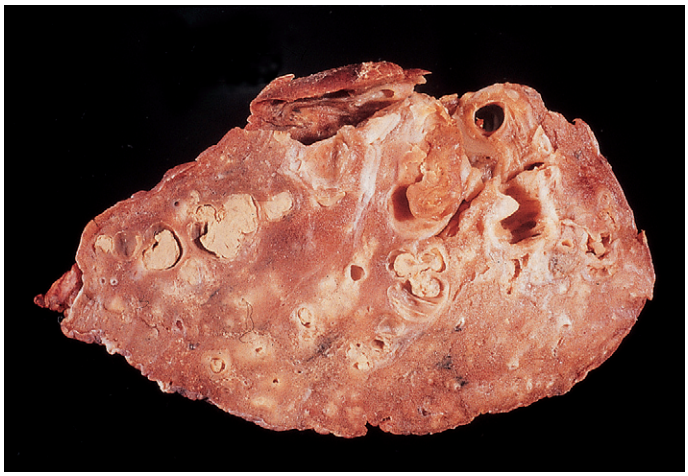


Figure 5.4.18 Allergic bronchopulmonary aspergillosis. The proximal bronchi (top) are dilated and some contain mucous plugs. More peripherally there is coagulative necrosis representing bronchocentric granulomatosis and beyond that pale foci of eosinophilic pneumonia are seen. *(Courtesy of the late Dr AA Liebow, San Diego, USA.)*

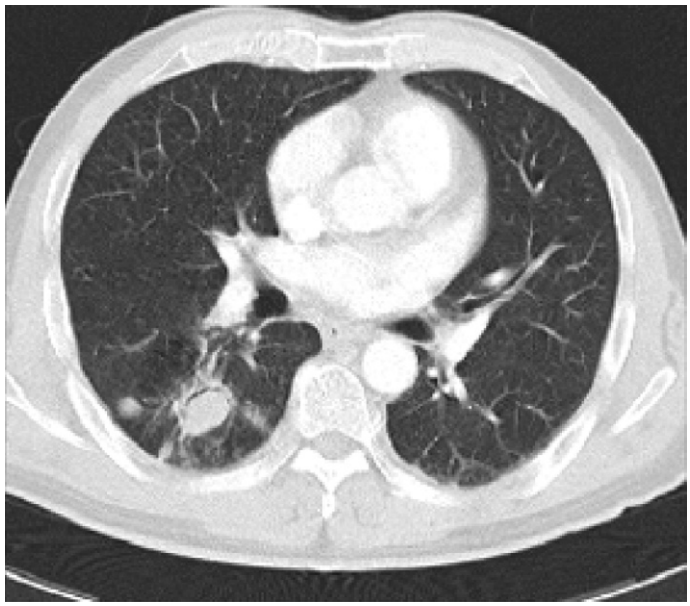


Figure 5.4.19 Aspergilloma. Computed tomography shows a cavity in the apical segment of the right lower lobe, containing an intracavitary body consistent with an aspergilloma, which was confirmed following lobectomy.

brewery staff working with mouldy barley; the species of *Aspergillus* involved here is usually *A. clavatus*. Extrinsic allergic alveolitis may also develop in patients harbouring an aspergilloma.[81] These forms of allergy to *Aspergillus* are similar, both clinically and pathologically, to the extrinsic allergic alveolitis that develops in response to other allergens (see p. 279).

SAPROPHYTIC ASPERGILLOSIS

Aspergilli may grow saprophytically within stagnant secretions in the bronchi in cases of chronic bronchitis and, less often, bronchiectasis. In certain circumstances this may be very marked, resulting in obstructive aspergillosis (see below). Other varieties of saprophytic aspergillosis include the colonisation of an infarct,[98] a tumour,[99] the bronchial anastomosis following transplantation[100,101] and a preformed cavity, resulting in the last case in the formation of an aspergilloma (intracavitary *Aspergillus* ball colony).[102]

Aspergilloma

In an aspergilloma the fungus grows in the lumen of a cavity in the lung without invading the tissues to any appreciable extent, drawing its nutriment from such exudate as may be present. The ball usually forms in an existing cavity, particularly an old tuberculous cavity,[102] but sometimes in a cavity resulting from conditions such as sarcoidosis (see Fig. 6.1.37, p. 289), bronchiectasis, abscess or emphysema, or in a congenital cyst. Aspergilloma formation has been observed both in the bronchiectatic lung distal to an obstructing carcinoma and within the cavity resulting from necrosis at the centre of a peripheral carcinoma.[103] Although usually single, aspergillomas may be present in cavities in both lungs, and in some cases there are several such lesions.

The term 'mycetoma' is frequently misapplied to intracavitary fungal balls, such as aspergillomas. The term is correctly limited to a type of fungal granuloma that is characterised by the formation of multiple sinuses and is usually the outcome of penetration of the soft tissues by a thorn, or the like, contaminated by the causative organism. Such lesions are most frequent on the extremities and 'Madura foot' is the type example. In this sense a mycetoma represents a lesion caused by invasion of the tissues by the organism concerned, in contrast to an intracavitary fungal ball, which is essentially outside the tissues and does not, except in unusual circumstances, lead to extension of the infection into the wall of the cavity itself. Many varieties of fungus cause mycetomas: most of them seldom, if ever, cause other disease.

While most intracavitary fungal ball colonies are formed by *A. fumigatus*, other species of *Aspergillus* have been identified in some cases and, exceptionally, fungi such as *Pseudallescheria (Petriellidium) boydii*,[104] *Cladosporium cladosporidioides*[105] and species of *Penicillium*, *Candida* or *Syncephalastrum*[106] have been responsible. Also, ball colonies similar to an aspergilloma may on rare occasions consist solely of bacteria (see nocardioma on p. 215 and botryomycoma on p. 192).

Radiology

The radiological appearances of an aspergilloma are often characteristic. The fungal ball appears as a sharply demarcated radiopaque spheroid that rests on the wall of the dependent part of the cavity and is separated from it elsewhere by a crescent of air (Fig. 5.4.19). In cases of long standing the colony may fill the cavity completely but the fungal ball is often able to move within the cavity in accordance with the patient's posture. However, although these features are characteristic of an aspergilloma, they may also be given by an indolent necrotising form of invasive aspergillosis which is considered below. A true aspergilloma is often demonstrated in radiographs over a period of several years, sometimes with little or no detectable change in its

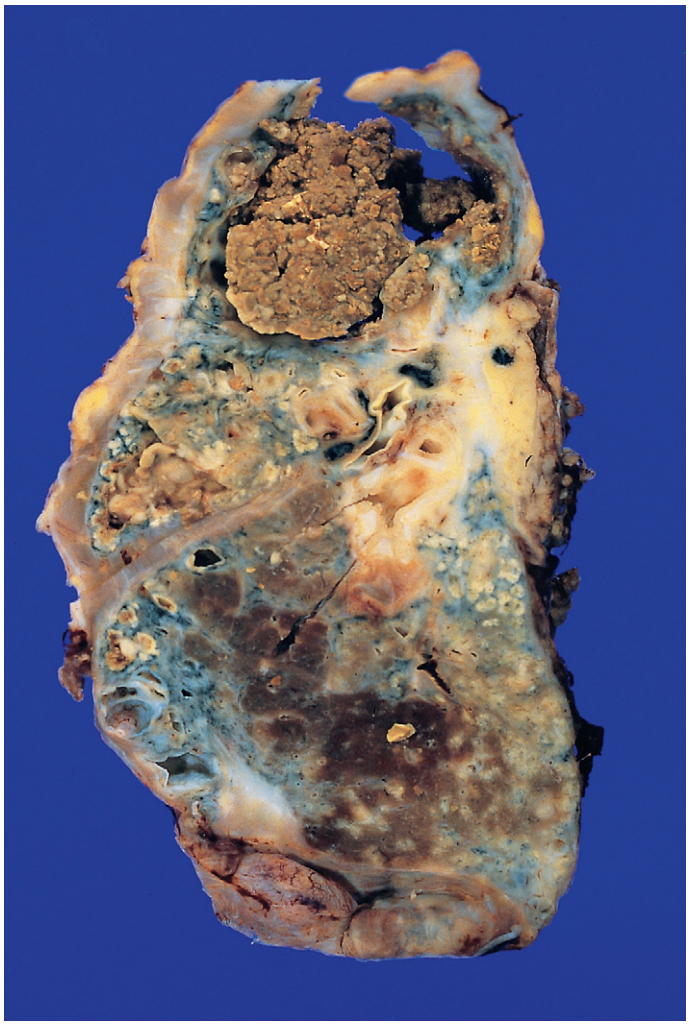


Figure 5.4.20 An *Aspergillus* fungal ball (an aspergilloma) filling an apical cavity. In its fresh state the fungal ball forms a soft, brown, pultaceous mass but as seen here after fixation, it is more friable.

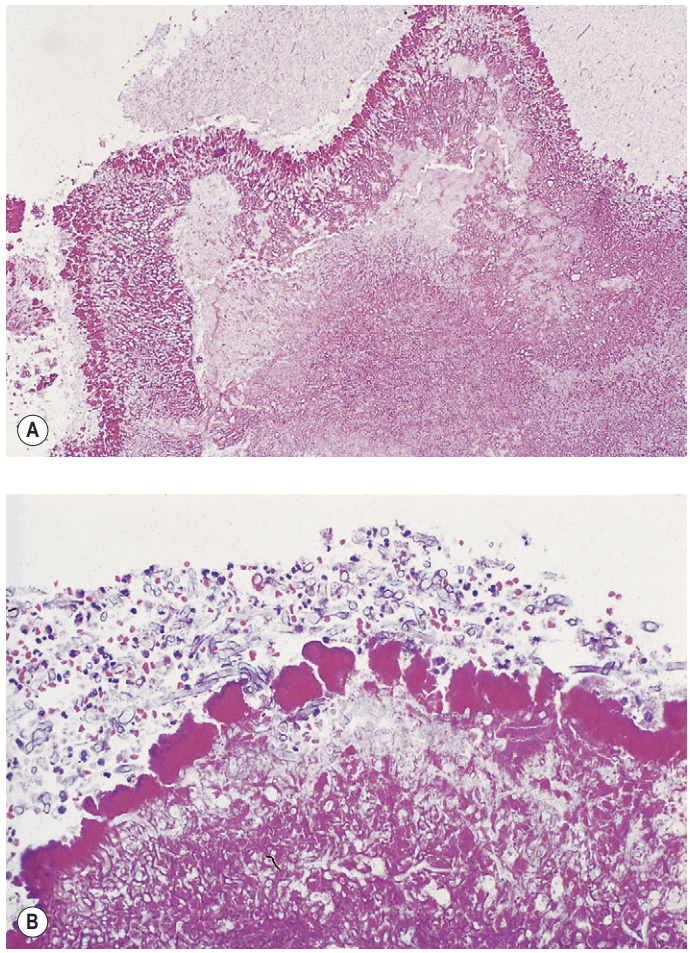


Figure 5.4.21 Aspergilloma. (A) The centre of the fungus ball consists of a dense feltwork of dead fungal hyphae. Only at the periphery is the fungus viable. (B) The edge of the fungus ball is coated by a layer of eosinophilic immune material (Splendore–Hoeppli phenomenon).

appearance, sometimes with appreciable phases of shrinkage and enlargement.

Antibody production

Most patients with an aspergilloma have strong serum precipitins against *Aspergillus* antigens but, unless allergy with asthma has developed, skin tests against extracts of the fungus are negative. Occasionally the circulating precipitins combine with fungal antigen disseminated via the airways to produce the changes of extrinsic allergic alveolitis elsewhere in the lung or there may be immune complex-mediated vasculitis elsewhere in the body.

Morbid anatomy

The fungal colony appears macroscopically as a grey or reddish brown, rarely white or green-tinged mass, sometimes firm or rubbery in consistency but often friable or pultaceous (Fig. 5.4.20). Old colonies may have a gritty feel, from deposition of calcium salts, and exceptionally there may be so much calcification that the ball becomes stony and may be classified among the so-called 'pneumonoliths'.

Histological appearances

Microscopically, an aspergilloma consists of a dense feltwork of hyphae, most of which are dead. Only the hyphae at the surface are well preserved. The tips of these may be abundantly coated with hyaline eosinophilic material of probable immune origin (Splendore–Hoeppli phenomenon; see Fig. 5.3.25, p. 215), giving the edge of the aspergilloma a distinctive appearance (Fig. 5.4.21). The lining of the cavity that contains an aspergilloma varies according to the nature of the condition that has given rise to it. The wall of an old tuberculous cavity may consist of dense, hyaline fibrous tissue, sometimes devoid of an epithelial covering; in other cases there may be a lining zone of chronic inflammatory granulation tissue, which usually is without specific features of tuberculosis or other former disease. When present, an epithelial lining may be of either respiratory or squamous type.

Chronic inflammatory changes in the lining of the cavity that are attributable to the fungal ball are variable but their presence underlies any enlargement of the cavity. It is mentioned above that numerous calcium oxalate crystals are occasionally present. These are found in

the cavity lining, particularly near the surface and in relation to the sides of blood vessels that face the fungus ball (see Fig. 5.4.15). The toxic nature of oxalic acid contributes to the progressive enlargement of the cavity but proteinases secreted by the fungus are probably more important in this respect.[107] Sometimes non-specific chronic inflammation is due to secondary bacterial infection.

It is exceptional for the fungus to invade the tissues, although this has been observed. Such a change from saprophytosis to invasive growth is more likely to occur when the patient's resistance is lowered, particularly by immunosuppressant and cytotoxic therapy and less often by administration of corticosteroids.

Haemorrhage

Haemoptysis is a common feature of aspergilloma. Usually it causes no more than anaemia, but in some cases it has been massive and death has resulted. It often accompanies the development of further excavation of the lung tissue round the colonised lesion. The rich capillary bed of a granulation tissue lining is generally the source of the haemorrhage,[108] but larger vessels are occasionally involved; the endarteritis obliterans usually found in chronic inflammation fails to seal them completely. The blood supply to the wall of an aspergilloma cavity ultimately derives from the bronchial circulation and the haemoptysis can sometimes be controlled by cannulation of the bronchial arteries concerned under radiographic control and the introduction of occlusive synthetic emboli (see Fig. 8.1.15, p. 412).

Obstructive aspergillosis

This form of aspergillosis was first described in patients with AIDS[109] and subsequently in the recipients of organ transplants.[110] It is characterised by a progressive cough, which is sometimes productive of bronchial casts composed entirely of *Aspergillus* hyphae, in contrast to the mucous plugs of allergic bronchopulmonary aspergillosis in which hyphae are scanty. There is no wheezing or eosinophilia but the patient rapidly develops hypoxaemia. Chest radiographs show areas of collapse and at bronchoscopy some airways are found to be completely obstructed by fungal casts. When these are removed the bronchial mucosa appears normal. The condition therefore represents saprophytic infection. Nevertheless, it is probably a precursor of the locally invasive pseudomembranous *Aspergillus* tracheobronchitis, described below.

INVASIVE AND SEPTICAEMIC ASPERGILLOSIS

Excluding saprophytic colonisation of pulmonary infarcts and superficial invasion round an aspergilloma – each a relatively rare occurrence – most instances of *Aspergillus* pneumonia are due to the patient's resistance being undermined by factors that cause prolonged granulocytopenia, such as lymphoproliferative disease, leukaemia and corticosteroid therapy.[111–115] Less often, invasive pulmonary aspergillosis complicates influenza or other viral infection[116,117] or chronic obstructive pulmonary disease.[117a,118] AIDS is another predisposing cause[119–121] but the incidence of invasive aspergillosis is nevertheless lower than that of many other opportunistic infections in this group of patients,[109,122,123] probably because the HIV attacks lymphocytes rather than granulocytes. Rarely, the patient is apparently immunocompetent.[124] In severely immunodeficient patients the infection spreads quickly and often disseminates via the blood stream, whereas in less debilitated patients infection results in more indolent localised lesions.

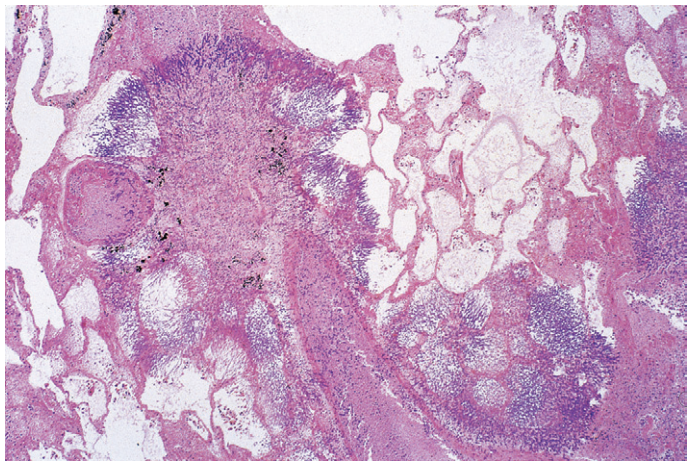


Figure 5.4.22 Invasive aspergillosis. The fungal hyphae grow through all constituents of the lung tissue, including blood vessels, which thrombose, resulting in infarction.

Invasive aspergillosis

In neutropenic patients invasive aspergillosis is characterised by star-like clusters of radiating hyphae that extend widely throughout the lung tissue (Fig. 5.4.22). There is vascular invasion leading to thrombosis, infarction and generalisation of the infection through the body. Non-neutropenic patients are more likely to show neutrophilic and monocytic exudates and inflammatory necrosis.[125]

Septicaemic aspergillosis

Septicaemic aspergillosis is commonly first recognised at necropsy, and often not until the tissues are examined with the microscope. In many cases the portal of invasion of the blood stream by the fungus is not apparent. In others it is a recognisable local infection such as *Aspergillus* pneumonia. There may be a rapidly overwhelming septicaemia, with little to show in the way of focal lesions, or there may be many large foci of necrosis, most frequently in the brain, heart and kidneys. The lesions are often so heavily colonised by the *Aspergillus* that, very soon after exposure to the air at necropsy, condiophores develop and colour the necrotic tissue – green in the case of *A. fumigatus* and *A. flavus* and black if the fungus is *A. niger*. There may even be an obvious growth of the pigmented mould on the surface. Microscopical examination often shows that the hyphae of the invading fungus are surrounded by a spreading zone of necrosis in advance of their progress through the tissues: this is probably a result of diffusion from the infected part of toxins and degradative enzymes produced by the *Aspergillus*.[68,107] Occasionally, the lesions are suppurative. Infection by other fungi may be present at the same time.

Chronic necrotising *Aspergillus* pneumonia (acute cavitary pulmonary aspergillosis)

This is a localised form of invasive aspergillosis in which the necrotic lung tissue may separate away as a sequestrum and mimic an aspergilloma both radiographically and macroscopically (Fig. 5.4.23)[126–134]; microscopically, however, infected lung tissue is easily distinguishable from an intraluminal ball colony of fungus, even though both are largely necrotic.

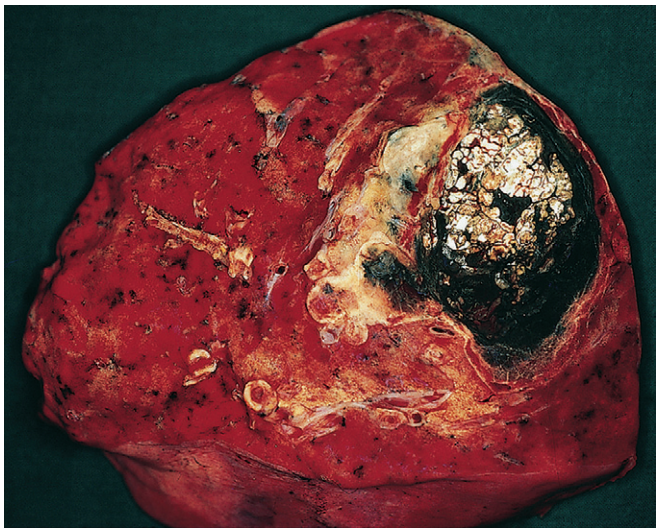


Figure 5.4.23 Chronic necrotising *Aspergillus* pneumonia. The lung contains a cavity partly lined by a plaque of *Aspergillus nigra*. The appearances simulate those of an aspergilloma but the cavity is newly formed and its contents consist of necrotic lung tissue heavily infiltrated by the fungus. Compare the colour of this non-sporing mycelium with the cultured colony of the same species, which is exposed to oxygen and is therefore producing black conidiophores (Fig. 5.4.13b). *(Reproduced from Wiggins et al. (1989) by permission of the editor of* Thorax.[130]*)*

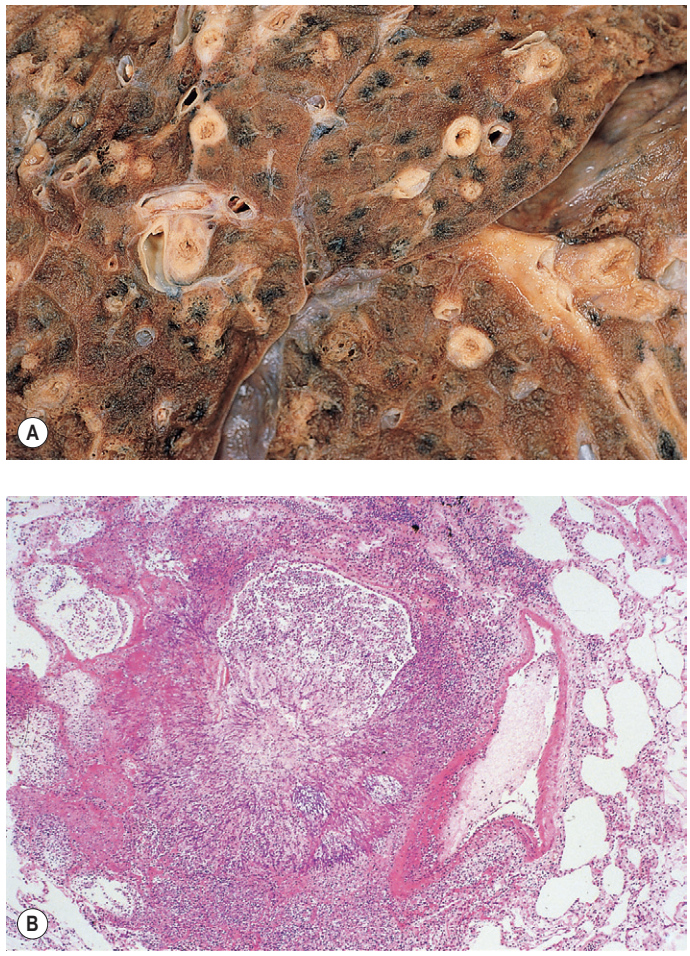


Figure 5.4.24 Pseudomembranous *Aspergillus* bronchitis. Many airways are plugged by fungal hyphae and necrotic debris. Invasion is generally limited but in this patient the process has already affected the adjacent pulmonary artery. (A) Gross appearances; (B) microscopy.

Pseudomembranous *Aspergillus* tracheobronchitis

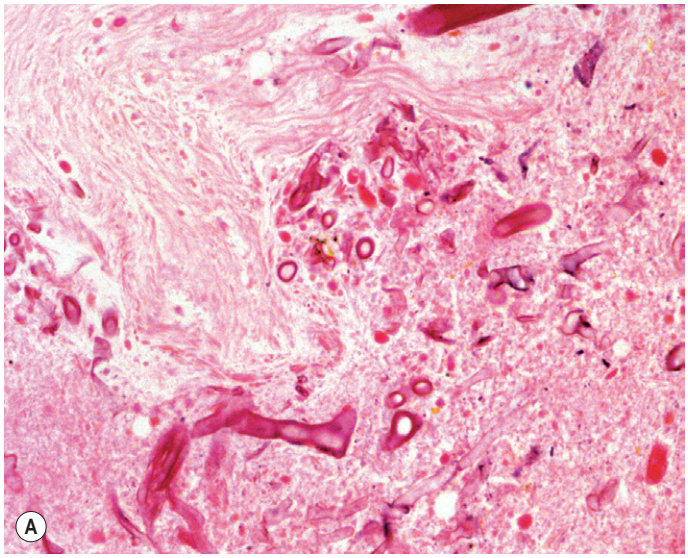
Pseudomembranous *Aspergillus* tracheobronchitis involves only a narrow zone of tissue bordering the major airways; the intervening lung parenchyma is spared.[135–140] In this form of invasive aspergillosis the airways are occluded by a mixture of necrotic debris and fungal hyphae (Fig. 5.4.24). It may be preceded by the obstructive form of saprophytic aspergillosis, described above. A granulomatous response to the fungus may develop, mimicking bronchocentric granulomatosis.[141,142]

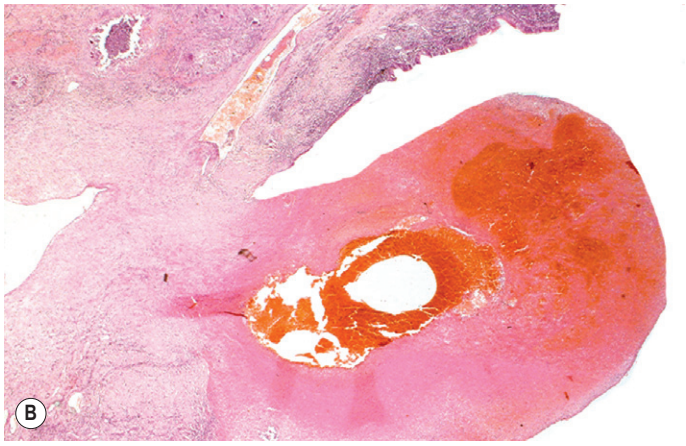
MUCORMYCOSIS

Mycology

Mucormycosis (formerly zygomycosis or phycomycosis) is the name most widely familiar for any infection caused by a fungus that is a member of the class Zygomycetes (formerly Phycomycetes). This class includes the orders Mucorales and Entomophthorales. They are found in soil, dung and dust throughout the world and are common causes of food spoilage. The classic form of mucormycosis is rhinocerebral, where the fungi grow from an infected ulcer in the nasal space to invade the cranial cavity, cerebral blood vessels and the contents of one or both orbits.[143,144] Some of the mucormycoses are primary subcutaneous or orificial mucosal infections, occurring without predisposing disease. Very rarely, dissemination of the fungus from these primary sites results in visceral infection, including pulmonary mucormycosis due to the Entomophthorales *Basidiobolus haptosporus (B. meristosporus)* and *Conidiobolus coronatus (Entomophthora coronata)*. Much more commonly, pulmonary mucormycosis is direct and attributable to lowering of resistance to invasion of the tissues by Mucorales of the species *Absidia, Mucor* and *Rhizopus* which ordinarily are saprophytes on decaying organic matter. It is quite exceptional for one of these moulds to set up progressive infection in a patient who is otherwise in good health.[145]

The Mucorales that cause pulmonary infection are recognisable as such in histological sections by their characteristic morphology (Fig. 5.4.25A) but this does not allow identification of genus or species, which requires immunohistochemistry.[66] The hyphae are characteristically of variable but generally broad diameter, ranging from 3 to 20 µm. They tend to branch perpendicularly, and septation of the hyphae is absent or at most very infrequent. A false impression of septum formation may be given by folds that result from shrinkage. Because of their irregular appearance and the sometimes striking effects of shrinkage during histological processing the hyphae have been likened to lengths of crushed ribbon. Although visible in haematoxylin and eosin preparations, the mucoraceous fungi are best shown by special methods: the methenamine silver stain is often useful, but better results may be obtained by the silver impregnation methods used in the demonstration of reticulin fibres. As in the case of aspergilli, such morphologically specific structures as sporangiophores develop only when the mould is growing in air: they are seldom, if ever, seen in pulmonary lesions in the fresh state, but they may form if a specimen has inadvertently been left exposed before being placed in fixative solution. Culture often fails and





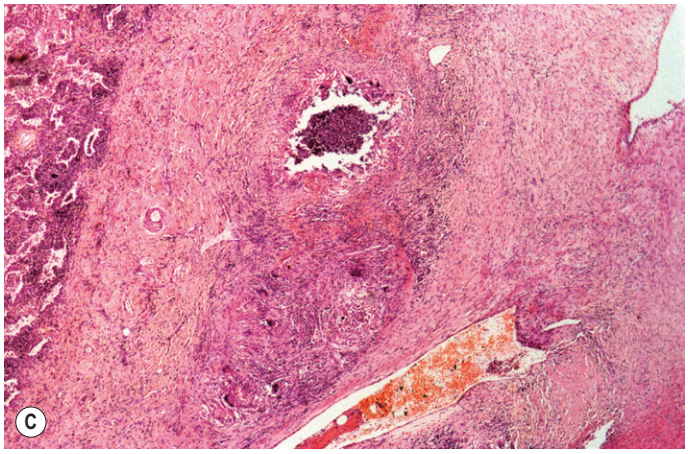


Figure 5.4.25 Mucor. (A) Mucor hyphae have few septa and are irregular in outline. The rounded structures that resemble spores are hyphae cut transversely. (B) Mucormycosis in a lung excised because of massive haemoptysis. Haemorrhage surrounds a partially thrombosed ruptured blood vessel. (C) The wall of the ruptured vessel shows necrotising granulomatous angiitis.

histology may then be the first means of identification, supplemented if required by molecular techniques.[67] The distinction from aspergilli is important because the treatment differs.

Predisposing causes

Conditions predisposing to visceral mucormycosis include AIDS, leukaemia, pancytopenia, myelomatosis, diabetes mellitus and immunosuppression to prevent graft rejection.[142,146,147] Certain therapeutic measures also predispose to these infections, particularly desferrioxamine and the administration of cytotoxic and immunosuppressant drugs, including corticosteroids. Cannulation of blood vessels, when long continued, is a further occasional factor, being a potential portal of infection. Burns, too, have repeatedly become not merely a site of superficial infection but the source of haematogenous dissemination. The predisposing factors to some extent determine the site of predominant infection. For instance, the syndrome of naso-orbitomeningingocerebral mucormycosis occurs usually as a complication of diabetes mellitus or renal failure: these metabolic disorders are comparatively seldom responsible for the development of pulmonary or primarily septicaemic mucormycosis, which in most cases occur as complications of severe blood disease or of the resistance-lowering side-effects of drugs. Similarly, severe malnutrition predisposes to mucormycosis of the stomach or intestine.

Pathological findings

Mucormycotic lesions in the lungs vary greatly in size and number. Multiple lesions are usually the result of haematogenous dissemination, as may occur in cases of naso-orbitocerebral mucormycosis, whereas lesions that are single or few may be the result of direct infection of the lungs by way of the airways. The lesions are firm, hyperaemic or haemorrhagic, and often necrotic. If they extend to the pleura, a fibrinous exudate is found over them and there are often petechial or larger foci of bleeding. Central lesions tend to be spherical and peripheral ones wedge-shaped,[148] the former resembling chronic necrotising pulmonary aspergillosis (see above) and the latter representing infarcts.

Microscopically, the most significant finding is fungal invasion of blood vessels of all sizes, with thrombosis and colonisation of the thrombus by the fungus, and infarction (Fig. 5.4.25B, C). It is clear that many strains of these fungi are thrombogenic, and staining the lesions with phosphotungstic acid haematoxylin or by other appropriate methods clearly demonstrates the formation of fine radiating threads of fibrin on the surface of the hyphae within the blood vessels. Perineural invasion is also commonly seen.[144] The hyphae may be present in great number, not only in the thrombi but throughout the resulting infarcts. The latter soon liquefy, and there may be secondary bacterial infection. Calcium oxalate crystal deposition, as described in aspergillosis (see above), is rarely reported in mucormycosis.[149]

As with other fungal infections occurring as a consequence of predisposing illnesses and drug-induced failure of resistance, mucormycosis is often accompanied by one or more other opportunistic infections, even of the same part. Frequent associations are of mucormycosis with aspergillosis or candidosis but bacterial, viral and protozoal infections may also be present.

CANDIDOSIS (MONILIASIS)

Candida is a yeast-like fungus that forms round or oval budding cells (blastospores), septate hyphae and intermediate structures called pseudohyphae (Fig. 5.4.26). Candidosis generally represents infection

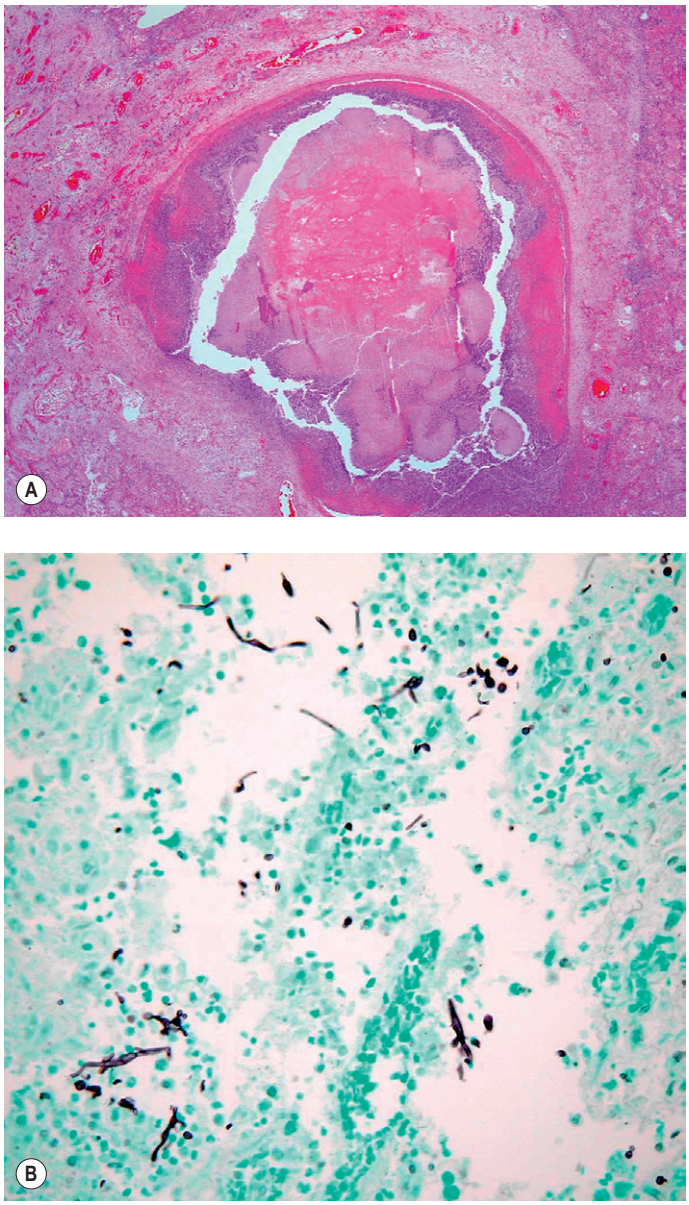


Figure 5.4.26 'Mycotic' candidal aneurysm of a pulmonary artery complicating surgery for complex congenital heart disease. (A) Severe inflammation of the artery has led to mural necrosis (below) and thrombosis. (B) Grocott staining reveals *Candida* spores and hyphae within the thrombosed vessel. Note: the term 'mycotic' is applied to any aneurysm caused by infected emboli regardless of whether the infection is fungal or bacterial.

by *Candida albicans* (formerly known as *Monilia albicans*) but other species may be involved.[150] Speciation requires culture as the species are morphologically identical. *C. (Torulopsis) glabrata* is dealt with separately (see p. 244).

The commonest form of candidosis is oral thrush, but the organism can attack any mucous or moist cutaneous surface. The fungus is often found in the sputum but its presence there generally represents no more than saprophytic growth. The diagnosis of bronchopulmonary candidosis therefore often depends on finding the organism histologically. It is found as a secondary invader of the lower respiratory tract in cases of chronic bronchitis, bronchiectasis and bronchial carcinoma, and in severely ill patients with immunosuppression, including AIDS.[119] In sections, *Candida* may be seen within a pseudomembrane consisting of purulent exudate on the surface of a bronchus, or very rarely in lung tissue as a cause of pneumonia or even lung abscess. In agranulocytic patients there is necrosis with minimal inflammation. *Candida* pneumonia may represent a peripheral extension of *Candida* bronchitis or result from haematogenous dissemination complicating diseases or therapeutic measures that lower resistance. Pulmonary vascular candidosis may complicate endocarditis or infection of central venous catheters inserted for prolonged parenteral feeding (see Fig. 5.4.26).[151,152] Features that distinguish *Candida* from *P. jirovecii* and other yeast-forming fungi such as *Histoplasma* include the mixture of budding yeast cells with pseudohyphae and the pyogenic or necrotising host reaction. The invariable presence of yeasts distinguishes candidosis from aspergillosis and mucormycosis.

CRYPTOCOCCOSIS

Mycology

Cryptococcosis, a disease of worldwide distribution, is caused by the monomorphic yeast-like fungus, *Cryptococcus neoformans*. This organism was formerly known as *Torula histolytica*, and the disease as torulosis. Because it was first recognised in Europe, and is caused by a fungus the cells of which reproduce by budding, cryptococcosis was also sometimes known as European blastomycosis, in contrast to the so-called North and South American blastomycoses (now blastomycosis and paracoccidioidomycosis respectively).

Although perhaps most familiar as a complication of leukaemia or lymphoma, in which the infection typically presents as a progressive meningoencephalitis, cryptococcosis is also known as a primary disease of the lungs without predisposing conditions, particularly when *Cryptococcus neoformans* var. *gattii* is involved.[153,154] The lung is the principal portal of entry and infection of the lungs is probably much commoner than at present recognised. The primary pulmonary lesion of cryptococcosis is comparable to the initial lesion of histoplasmosis and coccidioidomycosis and to the Ghon focus of tuberculosis. Other diseases predisposing to secondary pulmonary cryptococcosis include alveolar lipoproteinosis and AIDS.[119,155,156] Cryptococcal inflammatory pseudotumours are recorded in HIV-positive patients.[157]

C. neoformans is a spheroidal or ovoid organism (Fig. 5.4.27). A characteristic feature is variability in size, the cell body measuring from 3 to 20 µm in diameter, although in many instances it is within the range of 6–9 µm. Another prominent feature is single, narrow-based budding, as opposed to the single, broad-based budding of *Blastomyces dermatitidis* and the multiple narrow-based budding of *Paracoccidioides brasiliensis* (Fig. 5.4.27A). The organism has a mucoid capsule that usually stains with mucicarmine, a reaction that is not given by any other pathogenic yeast-like fungus. Cryptococci can be seen in haematoxylin and eosin preparations because they are refractile and, in polarised light, birefringent. They can also be demonstrated by any of the special methods for staining fungi (Fig. 5.4.27B). The capsule is sometimes deficient, in which case the fungus is not mucicarminophilic.[158] However, in most cases of capsule-deficient cryptococcosis some carminophilic capsular material can be identified around a few yeasts. A Masson–Fontana stain can also help in the recognition of capsule-deficient cryptococci because, unlike other yeasts, cryptococci produce a melanin-like pigment.[159] Alternatively, capsule-deficient strains may be identified by immunohistochemistry.

The cryptococci may be found in the sputum in cases of pulmonary involvement. They may be seen on microscopical examination of wet films, particularly when the sputum has been mixed with India ink or

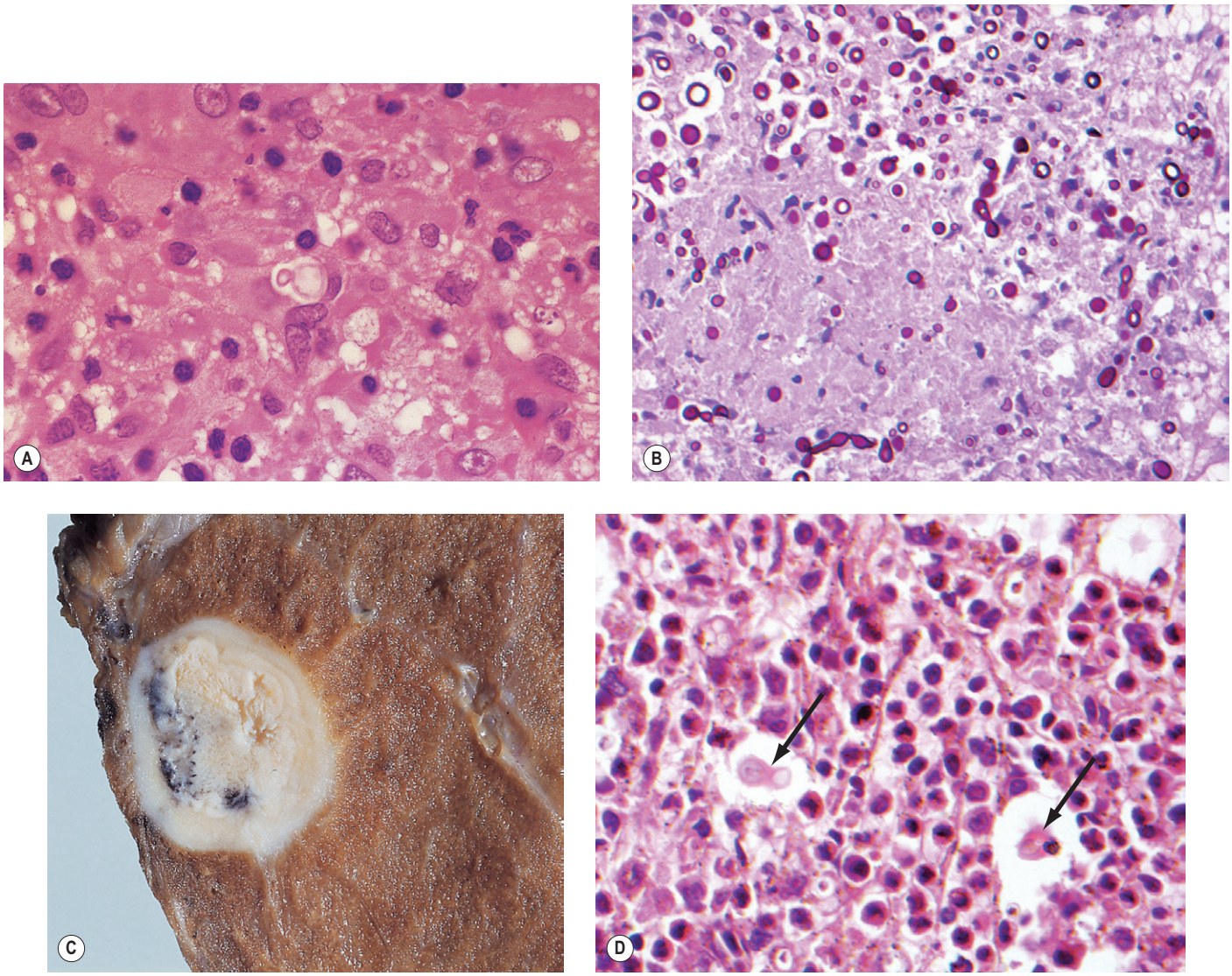


Figure 5.4.27 Cryptococcosis. (A) A single *Cryptococcus* exhibiting single narrow-based budding (haematoxylin and eosin stain). *(Courtesy of Dr A Paiva-Correia, formerly of Oporto, Portugal.)* (B) Cryptococci demonstrated by periodic acid–Schiff staining. (C) A necrotising 4-cm cryptococcoma excised after its chance radiographic discovery. *(Courtesy of Dr M Jagusch, formerly of Auckland, New Zealand).* (D) Fungal spores (arrows) are seen amongst neutrophils in an immunosuppressed patient with disseminated disease. *(B and D courtesy of Dr PM Cury, Rio Preto, Brazil.)*

nigrosin to display the capsule. In dry films the fungal cells disintegrate or become smudged and usually cannot be recognised, although sometimes staining with mucicarmine is conclusive. Cultures are generally the preferred means of confirming the diagnosis, but some strains of the cryptococcus do not grow well and several attempts may have to be made before the organism is isolated. It is notable that the cryptococcus is only exceptionally, if ever, found in sputum in the absence of infection, in spite of its near ubiquity in our environment.

The fungus is often found in the dried droppings of birds, particularly pigeons and starlings; these provide a good culture medium and pathogenic cryptococci can often be isolated from buildings on which these birds roost.[160] Isolation from soil is less frequent, probably because of the avidity with which cryptococci are phagocytosed by soil amoebae. As in the case of histoplasmosis, cryptococcosis has been known to develop in people who have worked in bird-infested buildings, particularly during demolition. The infection in such patients is slow to appear, in contrast to the acute pneumonic form of histoplasmosis. It is clear that exposure to cryptococci must occur very frequently: equally, the great majority of people must have a high immunity, for cryptococcosis is rare in any population.

It is important to remember that any patient with active cryptococcosis is at risk of developing infection of the central nervous system because of the peculiar affinity of the organism for the brain and meninges and the frequency of its dissemination in the blood.

Clinical features

Clinical features range from asymptomatic pulmonary involvement to life-threatening meningitis and overwhelming cryptococcaemia. Imaging shows single or multiple well-circumscribed masses, poorly demarcated opacities or segmental consolidation.

Morbid anatomy

Pulmonary cryptococcosis takes several forms: primary, cryptococcoma, cavitary, pneumonic, miliary and inflammatory pseudotumour.[153,155–157,161–163] Isolated, discrete, encapsulated, subpleural granulomas are occasionally seen at necropsy: these are healed or healing lesions, and the implication of their presence is that they are a manifestation of a primary and non-progressive infection. Less rarely, there are one or more focal lesions in the lungs, up to several centimetres in diameter, that prove to be foci of progressive cryptococcal infection. These are known as cryptococcomas (formerly torulomas) (Fig. 5.4.27C). They are firm, pale tan and rather sharply defined but are encapsulated only when healing. Their cut surface may be dry or gelatinous: the latter is the case when there is less inflammatory reaction to the organisms, which, packed closely in great numbers, account for the mucoid appearance and consistence of such lesions. Cryptococcal inflammatory pseudotumours are solid, firm and grey. Progressive cavitary disease occurs in about 10% of cases. Confluence and continuing enlargement of multiple foci may produce a gelatinous pneumonia involving a segment or the greater part of one or more lobes. In cases of generalised haematogenous dissemination of cryptococcosis both lungs may be studded with miliary or larger foci: close inspection of these discloses their gelatinous nature; they tend to be sharper in outline than miliary tubercles or pyaemic abscesses. The gelatinous collection of cryptococci at the centre of the lesion may be washed out during examination of the tissue, leaving a minute cavity.

Histological appearances

Microscopically, the lesions may be composed largely of the cryptococci themselves, with little cellular reaction: the alveoli and interstitial tissue contain the closely packed organisms, their cell bodies separated by the variable extent of their mucoid capsule. In other cases, particularly those involving capsule-deficient strains, there may be a tuberculoid reaction, the fungal cells being found within the cytoplasm of multinucleate giant cells and of mononuclear macrophages as well as free in the tissue spaces. In lesions of long standing, lymphocytes and plasma cells may be present in large numbers, and fibrosis may be a feature, although not often conspicuous. Occasionally, neutrophils accumulate in considerable numbers (Fig. 5.4.27D), particularly in miliary haematogenous lesions, but in the absence of bacterial infection frank suppuration is not found. Caseation is a rare development, and has to be distinguished from the somewhat similar appearance that may result when large numbers of cryptococci have died and disintegrated into an amorphous, finely granular, eosinophile mass. Cryptococcal inflammatory pseudotumours are composed of plump spindle cells mixed with lymphocytes, plasma cells and the yeast forms of the fungus.

HISTOPLASMOSIS

The first report of *Histoplasma* infection was in 1905 by Samuel Darling, a US Army pathologist stationed in Panama around the time of the building of the canal. Darling observed the organisms in histiocytes (hence the prefix 'histo'), likened them to plasmodia (hence 'plasma') and incorrectly assumed that an artefactual clear space around each organism was a capsule (hence 'capsulatum').

Mycology

Two species of *Histoplasma* are pathogenic in humans, *H. capsulatum* and *H. duboisii*. The latter is found exclusively in tropical Africa and the disease that it causes differs significantly from that caused by *H. capsulatum*, an organism that is geographically far more widespread. In general, when the word histoplasmosis is used without elaboration it refers to disease caused by *H. capsulatum*.

The histoplasmas are dimorphic fungi, growing as ovoid, yeast-like organisms in cultures at 37 °C and in infected tissues (parasitic phase), and in mycelial form, producing characteristic tuberculate macroconidia, in cultures at laboratory temperature (about 18 °C) and in their free-living state in the soil (saprophytic phase). Spores released by the macroconidia are inhaled and at body temperature germinate into yeasts that grow by binary fission.

Histoplasmas can rarely be demonstrated in sputum, even by culture, but complement fixation and precipitin tests may be helpful. However, on occasion, biopsy may be necessary. When this is undertaken, the opportunity to set up cultures must not be lost, although histology is more sensitive than culture.[164] The fungi may be quite focal in their distribution, and therefore difficult to find, but within these foci the spores are usually present in large numbers within the cytoplasm of macrophages or in areas of necrosis. They are readily seen in haematoxylin and eosin preparations, but only if recently viable. They measure 1–3 × 3–5 µm and may contain a distinct nucleus. Histoplasmas that have been dead for some time may escape detection in such preparations, although sometimes birefringence, induced by histological processing, may make a proportion of them visible in polarised light. Fortunately, the methenamine silver stain commonly demonstrates histoplasmas very clearly, even when they have long been dead. Unfortunately, they are difficult to distinguish from other budding yeasts but a granulomatous reaction, their intracellular location and an absence of pseudohyphae help separate them from *Candida* species and *P. jirovecii*.

Epidemiology

H. capsulatum is a soil-inhabiting fungus that requires organic nitrates for growth. These are generally provided by bird droppings. Histoplasmosis results from inhalation of infective spores and the geographical distribution of the disease is determined by environmental conditions. In regions where the fungus cannot survive to complete its saprophytic phase in soil or other organic debris, histoplasmosis does not occur naturally – infection does not ordinarily take place from person to person, the tissue form of the fungus being in general unable to convey the disease. In those parts of the world where the soil or the climate is unsuitable for the saprophytic phase of *H. capsulatum*, the disease is found only among those who have acquired the infection in lands where the fungus is present in the environment, or, much more rarely, as a result of exposure to imported materials contaminated by the infective spores[165] or to laboratory cultures of the saprophytic phase, which develops when the tissue form is grown at laboratory temperature.

Histoplasmosis is endemic in many parts of North, Central and South America, Asia and Africa. In North America, infection is particularly common in the basin of the Ohio and Mississippi river valleys, where as many as 90% of the population give a positive reaction to the histoplasmin skin test. The histoplasmin test has the same significance in relation to histoplasmosis as the tuberculin test in relation to infection by *Mycobacterium tuberculosis*. In Africa, infection by *H. capsulatum* is endemic over an area far greater than that in which infection by the 'African histoplasma', *H. duboisii*, occurs. Histoplasmosis is also endemic in India and South-east Asia but it has not been recognised as an indigenous infection in Australia. Its occurrence in Europe, other than as a result of travel to an endemic area or accidental exposure to the fungus, is exceptionally rare.

Most people who acquire histoplasmosis have no more than a subclinical infection. It has been estimated that clinical manifestations

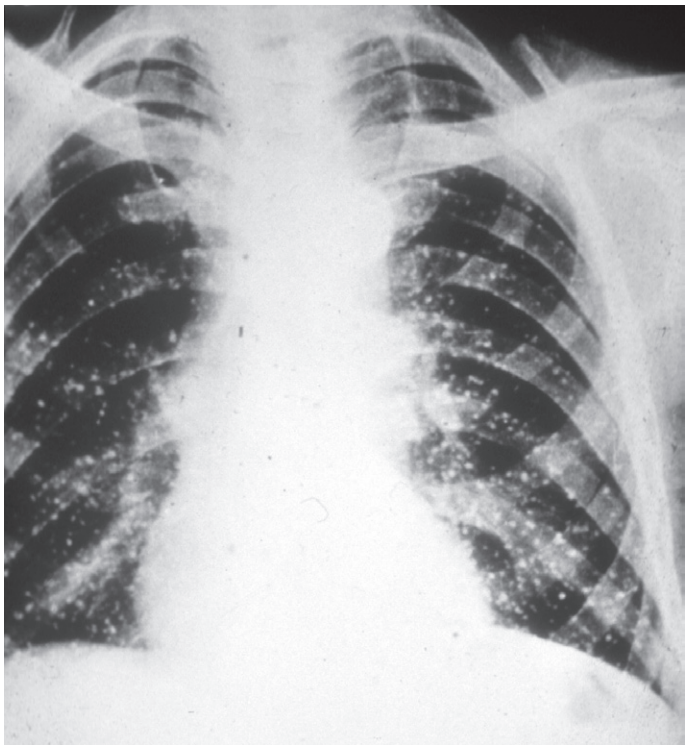


Figure 5.4.28 Histoplasmosis. A chest radiograph shows multiple bilateral calcific nodules in a patient with quiescent histoplasmosis.

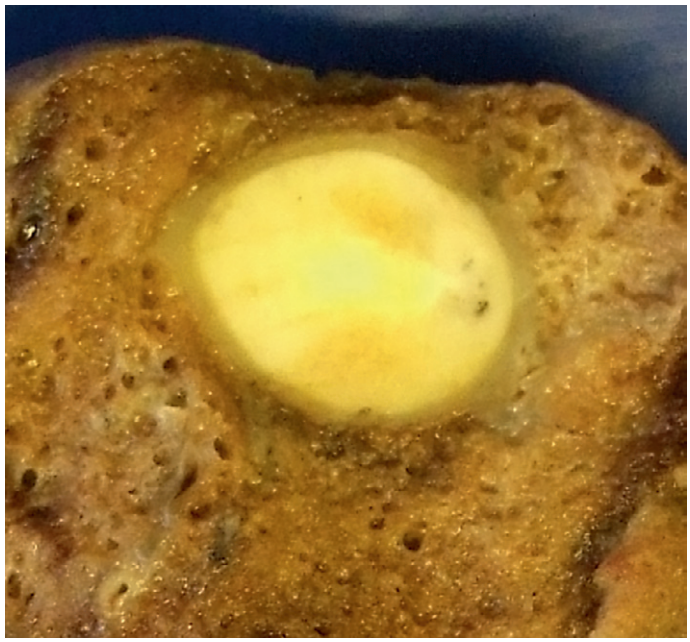


Figure 5.4.29 Histoplasmoma representing quiescent disease.

occur in only about 1% of cases and that few of these patients develop serious illness. Histoplasmosis is seen in rural communities exposed to bird droppings and in urban dwellers exposed to demolition and building sites. Bat guano is rich in organic phosphates and histoplasmas and the likely cause of an acute illness of cave explorers. Several forms of histoplasmosis are desribed, which will now be considered.

Primary pulmonary histoplasmosis

The primary focus of histoplasmosis resembles that of tuberculosis. As with mycobacteria, the main line of host defence is the macrophage. Specific T-cell immunity appears about 10–14 days after infection and macrophages so activated usually terminate the infection. If not, the organisms continue to grow within the macrophage cytoplasm. The disease is spread during its primary stage by infected macrophages migrating to the regional lymph nodes and beyond to disseminate by the blood stream to all organs, but being filtered out particularly well by those rich in reticuloendothelial cells so that the liver and spleen are commonly involved.

The primary lesion may be solitary or there may be two or more, sometimes many, primary lesions in the lungs, the number depending on the heaviness of the exposure to the infecting spores. Primary lesions may occur in any part of the lungs. Generally, and especially when solitary, it is larger than the corresponding lesion of primary tuberculosis but otherwise similar, showing epithelioid and giant cell granulomatous inflammation. Caseation develops within a few weeks of infection and its appearance is believed to coincide with the development of skin reactivity to histoplasmin, an observation comparable to the corresponding events in tuberculosis. Early calcification and the formation of a fibrous capsule are common (Fig. 5.4.28). As in tuberculosis, there is spread of the infection to the hilar lymph nodes, which undergo comparable changes. It is a characteristic of calcified lesions of histoplasmosis that they have a massively chalky appearance and often show a peculiar stippled pattern in radiographs, particularly lesions in lymph nodes. Occasionally, the calcified foci in the lungs have a target-like radiographic shadow because of concentric zones of greater and lesser transradiancy.

Histoplasmoma

The name histoplasmoma is given to any circumscribed, persistent focus of *Histoplasma* infection in a lung. The lesion is an outcome of a primary focus, akin to a tuberculoma rather than an aspergilloma. It occurs typically just under the pleura, and is roughly spherical and from 1 to 4 cm, sometimes more, in diameter (Fig. 5.4.29). Both in radiographs and when examined with the naked eye it has a characteristically concentric pattern of closely set laminae, which may contain appreciable amounts of calcium salts, although by no means invariably. This laminar structure is so characteristic of chronic caseous granulomas of fungal origin that in some centres it is regarded as proof of the non-neoplastic nature of 'coin shadows': this is not necessarily justified, for it has been known for carcinoma to arise in the fibrotic capsular zone round such a long-standing mycotic lesion. In general, histoplasmomas are altogether benign in outlook, and may be left in situ with little chance that the infection will be activated and progress; they may become more heavily calcified as the years pass. If resected, they usually prove to be sterile on culture. The causative organism may then be demonstrated most reliably by the methenamine silver stain, even though it is no longer viable.

Cavitary histoplasmosis

Histoplasmosis may closely reproduce the clinical and radiological picture of cavitating pulmonary tuberculosis. Moreover, if such patients are exposed to a substantial risk of infection by *Mycobacterium tuberculosis*, as may occur if they are nursed in company with

tuberculous patients, tuberculosis may be superimposed on the histoplasmic lesions, with detriment to the chances of successfully treating either infection. In general, cavitary histoplasmosis is seen most frequently in older patients, particularly men with emphysema or other chronic lung disease.[166] It is attributed to a local breakdown in immunity at the site of dormant subapical histoplasmic granulomas. In some cases it is possible that the condition is due to reinfection, thus adding to the similarities between histoplasmosis and tuberculosis. Like the cavities of chronic pulmonary tuberculosis, the lesion of cavitary histoplasmosis may become the site of an aspergilloma. Tuberculoid granulomatous tissue in the lining and vicinity of the cavities contains typical intracellular histoplasmas.

Acute ('epidemic') pulmonary histoplasmosis

The condition that has been described as 'epidemic' pulmonary histoplasmosis is a form of acute histoplasmosis characterised by a severe influenza-like illness that occurs as a result of a particularly heavy inhalational infection in an unprotected individual.[167] The epithet 'epidemic' has been applied because such cases are commonly seen in several patients simultaneously, all of them exposed on the same occasion to a massive contamination of the air by infective spores. It is an unfortunate name, for such cases may occur singly when individuals are so unfortunate as to stir up large numbers of spores when working alone in a contaminated environment. These outbreaks have occurred when infected dust is disturbed in the course of cleaning or demolishing buildings, ranging from hen houses to city halls, that have harboured birds that over years have left the droppings that so perfectly favour the growth of the saprophytic phase of *H. capsulatum*. Similarly, those who enter caves where bat and bird droppings have encouraged the *Histoplasma* to proliferate may suffer comparable group outbreaks of acute histoplasmic pneumonia. The multiple foci of histoplasmosis that form in the lungs of heavily infected patients have the same structure and run the same course as the solitary primary foci described above. However, in some cases the infection is so heavy, and the resulting changes in the lungs are so widespread, that death occurs. Those who have not previously had a histoplasmic infection tend to suffer the severest illness in these outbreaks, but even those already known to have had a primary infection may develop fatal pneumonic lesions under such conditions of massive reinfection. Fatal opportunistic *Histoplasma* pneumonia is recorded[168] but immunosuppression is by no means necessary.

Progressive disseminated histoplasmosis

Mention has been made above of haematogenous dissemination of the infection during its primary stage. In most such cases the widespread lesions heal without ill effects. However, there is another form of disseminated histoplasmosis in which the disease progresses and eventually kills the patient. In some cases of this sort there are no obvious predisposing causes but in most the patient's resistance is lowered by the presence of serious underlying disease leading to defective T-cell function.[169] AIDS is now an important cause of such progressive disease (Fig. 5.4.30).[170,171]

Fatal disseminated histoplasmosis is characterised by heavy parasitisation of the reticuloendothelial cells resulting in hepatosplenomegaly and leukoerythroblastic anaemia. Painful ulcers develop at mucocutaneous junction zones or within the orifices of the body or in the pharynx and larynx. Organising pneumonic exudates and thin-walled cavities may be found in the lungs. Well-formed granulomas are not usually found. Fatal adrenal cortical insufficiency is another important manifestation.

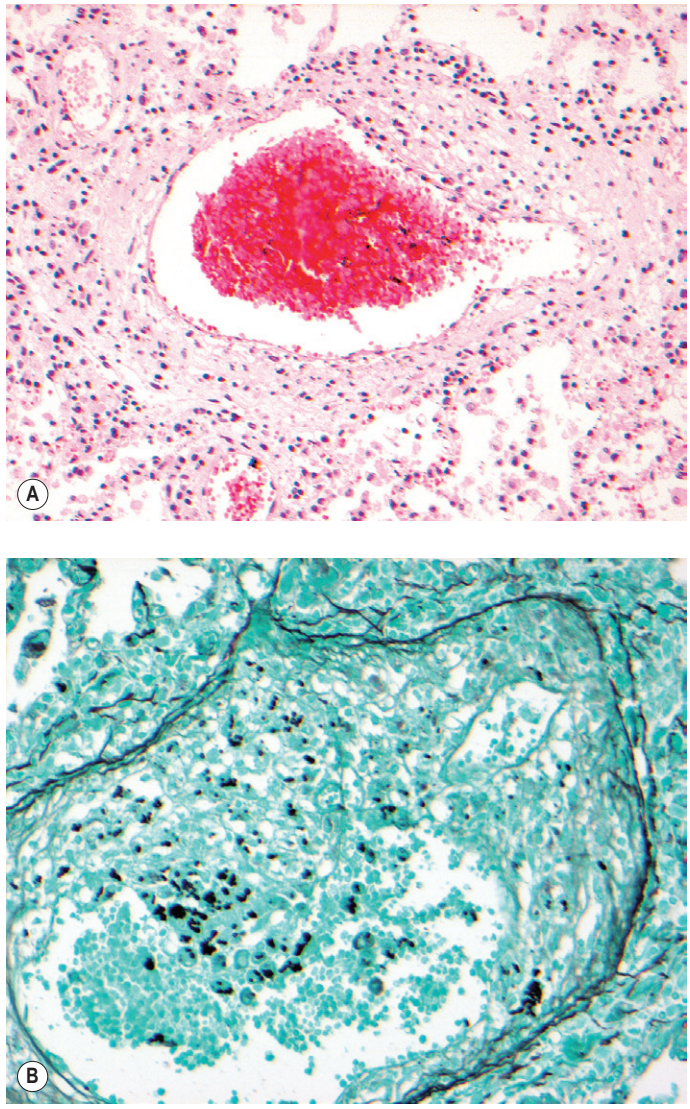


Figure 5.4.30 Progessive disseminated histoplasmosis in a patient dying of acquired immunodeficiency syndrome (AIDS). (A) A pulmonary vessel shows only slight granulomatous inflammation but (B) Grocott staining shows extensive infiltration of the vessel by histoplasmas. *(Courtesy of Dr PM Cury, Rio Preto, Brazil.)*

Fibrosing mediastinitis

In those countries where histoplasmosis is prevalent mediastinal fibrosis with obstruction of some, or all, of the mediastinal contents is recorded as a complication of such infection.[172]

African histoplasmosis

Histoplasma duboisii, an organism larger than *H. capsulatum*, has been recognised as a cause of disease throughout much of Africa between the Sahara and the Zambesi. Its distribution overlaps that of *H. capsulatum*, which, however, is much more widespread on the continent. The source of the infection and the portal of entry of the fungus remain debatable. There is growing evidence that the organism has a saprophytic phase, probably in soil, and that it may enter the body either through the lungs or, in certain cases, by inoculation into the skin. Pulmonary disease as one of its manifestations has attracted less

attention than cutaneous and skeletal involvement, but it is possible that in many cases the lesions in the skin, like those in bones, are the result of dissemination in the blood from inapparent pulmonary foci.

A feature typical of African histoplasmosis is that the fungal cells provoke a foreign-body giant cell reaction, not a simple histiocytosis with or without tuberculoid metamorphosis, as occurs in cases of infection by *H. capsulatum*. The organism is ovoid, has a distinct cell wall and some internal structure, and measures 5–12 µm in its longer dimension. It stains well with all the fungal stains, but is unlikely to be overlooked by the careful microscopist in haematoxylin and eosin preparations.

COCCIDIOIDOMYCOSIS[173–175]

Epidemiology

This disease is endemic in certain parts of North and South America, occurring especially in hot semiarid regions such as Arizona and the San Joaquin valley of California, but also in other such areas of the Americas down to Argentina. It is caused by the fungus *Coccidioides immitis*, the saprophytic, free-living form of which requires special environmental conditions of soil and climate for its survival: these determine its geographical distribution. *C. immitis* grows best in soils free of competing microflora, losing out to competitors when the soil is irrigated. Upsurges of infection may follow dust storms that release the fungus into the air. The fungus may also be transported on inanimate objects such as crops or native artefacts and infect persons outside endemic areas, and of course patients may travel to non-endemic regions while incubating the disease.[176] For example, the 2001 model airplane-flying world championship was held in an endemic region of California and several of those attending from other areas were found to have contracted coccidioidomycosis when they returned home.[177]

Mycology

C. immitis is a dimorphic fungus. Saprophytically, it grows as a mould that produces highly infective arthroconidia: these, inhaled in soil dust, establish the disease. As a parasite, the organism is found almost exclusively in the form of spherules: hyphae develop occasionally in the wall of coccidioidal cavities when air is admitted by them communicating with an airway, but this is exceptional: only spherules and their released spores are usually present, even when air is admitted (Figs 5.4.31 and 5.4.32).

Coccidioides is one of the most dangerous of all organisms in terms of risk of accidental infection of laboratory personnel. It is imperative that clinicians communicate to the laboratory any suspicion that a specimen may contain *C. immitis*. Laboratories dealing with coccidioidal cultures must operate with stringent precautions, including the exclusion of staff not known to have acquired some natural immunity through previous infection. The coccidioidin skin reaction is an invaluable screening test.

Once in the lungs, the arthroconidia develop into endosporulating spherules. These range from 30 to 60 µm or more in diameter and contain from scores to hundreds of endospores (see Fig. 5.4.32). The maturing spherule is usually accompanied by a histiocytic reaction, with the formation of many multinucleate giant cells: the parasite may be enclosed by the latter or lie free in the tissues. The mature spherule attracts neutrophils, which collect to form microabscesses at the centre of the histiocytic granulomatous foci. When the spherule ruptures, the freshly released spores, which range from 5 to 10 µm in diameter, at first lie free in the purulent exudate but soon are engulfed by mononucleate or multinucleate macrophages. They grow, and eventually become transformed into further spherules, thus repeating the cycle and leading to extension of the infection.

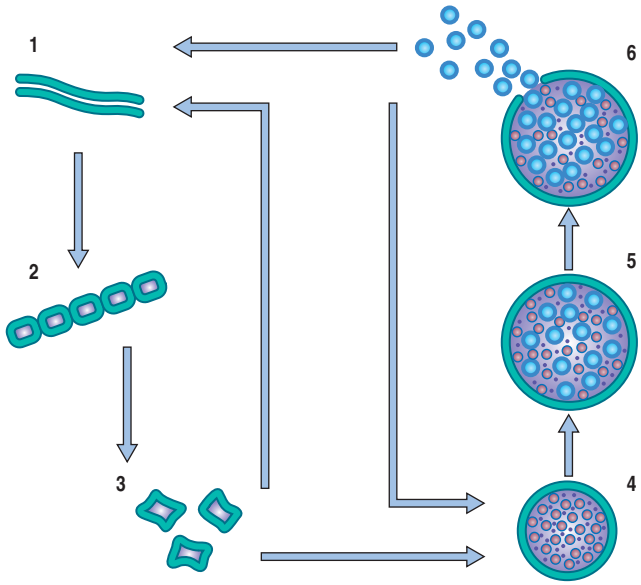


Figure 5.4.31 Life cycle of *Coccidioides immitis*. 1–3: Saprophytic phase in soil; 4–6: parasitic phase in lungs. Mycelial strands (1) growing in soil mature into chains of barrel-shaped arthroconidia (2), which disarticulate (3), become air-borne, and are returned to the soil or are inhaled. The parasitic phase in the lungs begins with the enlargement of the inhaled arthroconidia and their development into thick-walled spherules (4), within which endospores form (5). Released spores (6) can initiate the development of a new spherule in the lungs or if infected material returns to the soil, mycelia (1), so completing the cycle.

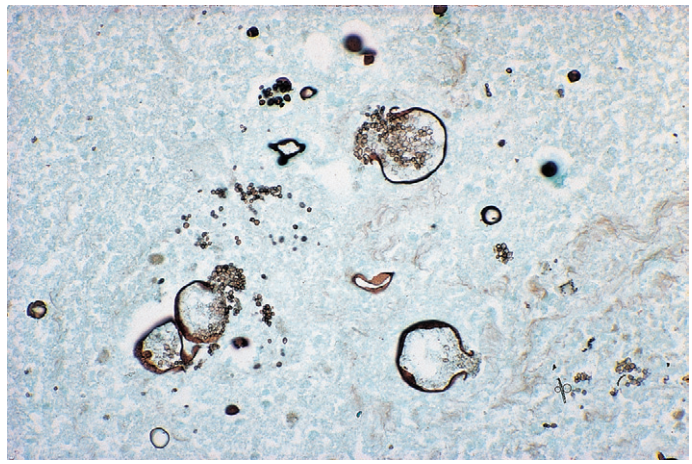


Figure 5.4.32 Coccidioidomycosis. Spherules discharging their spores within lung tissue. Grocott methenamine silver stain. *(Courtesy of Dr JT Gmelich, formerly of Pasadena, USA.)*

The fungal cells are usually well seen in haematoxylin and eosin preparations, except in the early stages when only a few, newly released spores are present, which may be so inconspicuous as to escape detection. The methenamine silver and other stains for fungi demonstrate all forms of the organism very clearly. Whilst the mature or even ruptured spherule is diagnostic, immature spherules or free spores are not: the former may be confused with *Blastomyces* or *Paracoccidioides* and the latter with cryptococci or histoplasmas.

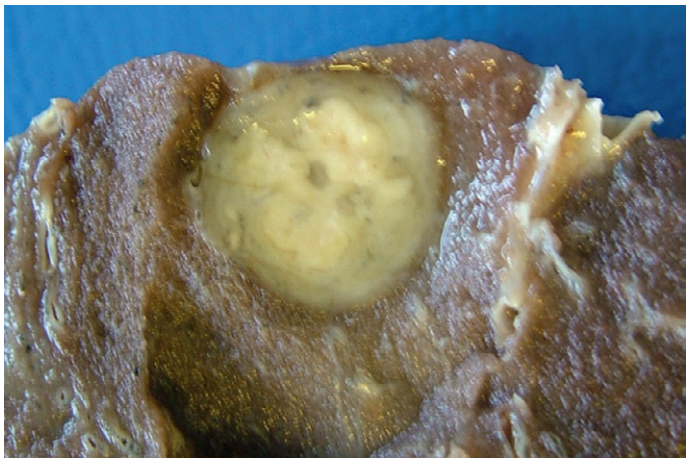


Figure 5.4.33 Coccidioidomycoma representing quiescent disease.

Clinical features

The initial coccidioidal infection is symptomless in about 60% of persons.[178] When disease develops, there is usually an influenza-like fever, which characteristically may be accompanied by erythema nodosum – hence its popular name of 'the bumps' in the San Joaquin valley, where it is also called 'valley fever'. In most cases there is spontaneous recovery from the primary infection. When the disease is more severe, which is likelier to be the case in patients of African or Asian ethnic origin, it may mimic tuberculosis in any of its manifestations. In severe infections generalisation through the blood is a frequent and particularly grave complication. Meningitis is another common complication. Many patients are left with quiescent pulmonary foci.

Pathological findings

At necropsy, the lungs may show focal consolidation, necrotic haemorrhagic areas or extensive necrotic excavating granulomatous nodules. Histologically, there may be a suppurative exudate in the alveoli, or necrotic haemorrhagic and fibrinous lesions, or a tuberculoid granulomatous reaction. Granulomatous inflammation is in general associated with good resistance, and purulent inflammation with poor resistance. However, when a spherule ruptures to release its spores (see Fig. 5.4.32), there may be a transient neutrophil response whatever the underlying pattern of inflammation. Also, the type of reaction is partly determined by the maturity of the developing fungal cells. Patients whose resistance is lowered by other diseases may develop generalised haematogenous coccidioidomycosis as a consequence of activation of a dormant pulmonary focus. The lesion of quiescent pulmonary coccidioidomycosis is typically a fibrocaseous nodule containing a few viable organisms (Fig. 5.4.33).

BLASTOMYCOSIS ('NORTH AMERICAN' BLASTOMYCOSIS)

Epidemiology

It is now recognised that infection with *Blastomyces dermatitidis* occurs very widely throughout Africa and that the geographical designation 'North American', intended to distinguish this disease from 'European blastomycosis' (cryptococcosis) and 'South American blastomycosis' (paracoccidioidomycosis), is inappropriate.

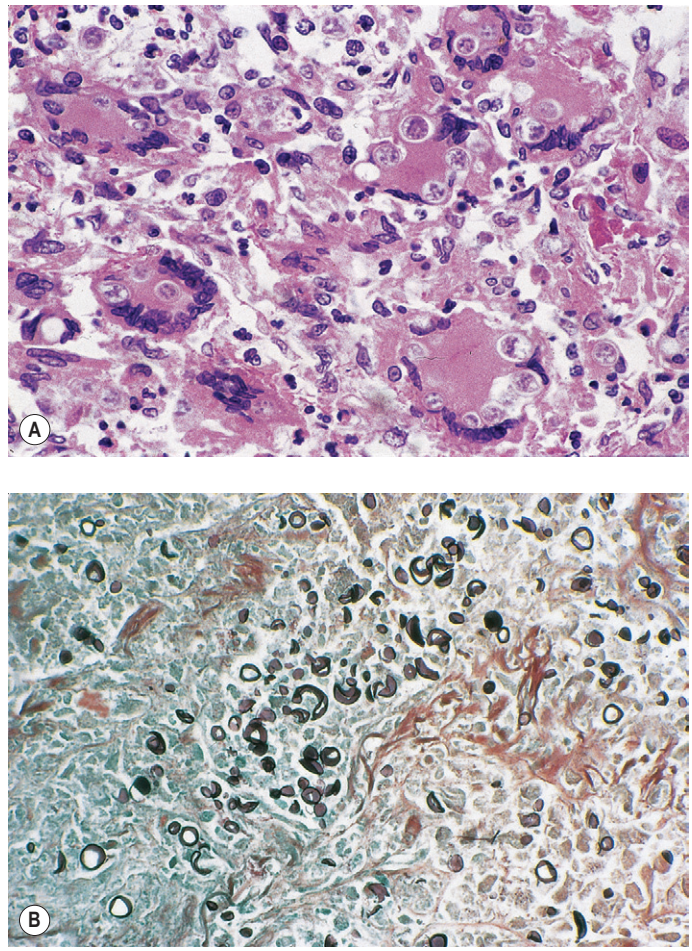


Figure 5.4.34 Blastomycosis. There is a neutrophil and giant cell reaction to *Blastomyces dermatitidis* yeasts, several of which have been ingested by giant cells. (A) Haematoxylin and eosin; (B) Grocott stain.

In North America, the greatest prevalence is in the south-eastern and north central USA, the area drained by the Mississippi, Missouri and Ohio rivers, the Great Lakes region and the eastern provinces of Canada.[179,180] The natural habitat of the fungus is soil, particularly that subjected to flooding. Infection is believed to occur by inhalation.

In Africa, lung disease is not so predominant. Many patients present with bone lesions or skin disease. Also, the antigenic make-up of the fungus differs from that encountered in North America, suggesting that there are at least two variants of blastomycosis, one seen in North America and in scattered foci in other countries (Mexico, Lebanon, Israel, Saudi Arabia and India), the other restricted to Africa.

Mycology

Like the histoplasmas, *B. dermatitidis* is a diphasic fungus.[181] In tissues and in cultures at 37°C it grows as a yeast whereas in cultures at laboratory temperature, and presumably in nature, it grows as a mycelium from which project special slender hyphae known as conidiophores which bear conidia, the infective agents. The yeasts are rounded and usually within the range of 7–15 µm in diameter, although some cells may be as much as 30 µm across (Fig. 5.4.34). They have a thick wall, which may give them a double-contoured appearance, but they differ from the spores of *Cryptococcus neoformans*, which they otherwise resemble, in lacking a capsule and therefore failing to stain with

mucicarmine. It is a special feature of *B. dermatitidis* that it reproduces in tissues by the formation of a single broad-necked bud that protrudes from the surface of the parent cell, enlarging even until it has reached as much as half the diameter of the latter, or more, before the two separate.

Clinical features

As with several other fungi, *Blastomyces* causes a variety of clinical syndromes, including primary, progressive and disseminated disease. Asymptomatic disease is rarely documented, probably because there are no reliable skin or serological tests of infection. The disease is generally first identified on cytology or histology with subsequent positive culture.[181,182] Most patients are immunocompetent.

Primary blastomycosis is characterised by the abrupt onset of chills and cough accompanied by patchy radiographic opacities. Such illness may be self-limiting or followed by progressive disease, which is sometimes first manifest many months or years later, affecting either the lung or extrapulmonary sites. Some patients who have no history of pulmonary involvement develop blastomycosis in tissues such as the skin, the fungus probably having spread there during the course of asymptomatic primary lung infection.

Pathological features

The lungs are the usual portal of entry and within the lungs the upper lobes are predominantly involved.[183] The histological reaction to the fungus is characterised by necrotising granulomas that are typically suppurative, the fungal cells either lying free in the purulent exudate or engulfed by phagocytes. Although neutrophils are generally conspicuous, tuberculoid granulomas also form. A characteristic feature is the so-called 'suppurating pseudotubercle', in which a central microabscess is enclosed within a complex of epithelioid histiocytes and multinucleate giant cells (see Fig. 5.4.34). Alternatively, an overwhelming infection may cause diffuse alveolar damage.[184,185] The infection is usually confined to the lungs and hilar lymph nodes but dissemination by the blood stream may occur, particularly if immunity is impaired.[186] However, blastomycosis is not a common manifestation of AIDS.

PARACOCCIDIOIDOMYCOSIS ('SOUTH AMERICAN BLASTOMYCOSIS')[187,188]

Epidemiology

Infection with *Paracoccidioides brasiliensis* is limited to Latin American countries from Mexico to Argentina but does not occur in all countries in this area. The endemic regions are the tropical and subtropical forests, particularly those of Brazil, Venezuela and Colombia. Paracoccidioidomycosis has not been proved to occur in any other part of the world. Cases reported from North America[189] and England[190] had all lived in South or Central America. The fungus is thought to live in the soil but its exact ecological niche is still unknown. Humans are the only known naturally infected animal host. Person-to-person transmission is of little importance in the epidemiology of the disease, which is thought to be acquired by inhalation.

Mycology

P. brasiliensis is a dimorphic fungus that grows as a mould at ambient temperatures and as a yeast at 37°C. Infection is acquired by inhalation of conidia produced in the mycelial phase. The spores that form its tissue form are round or ovoid and vary in size from 5 to 30 μm.

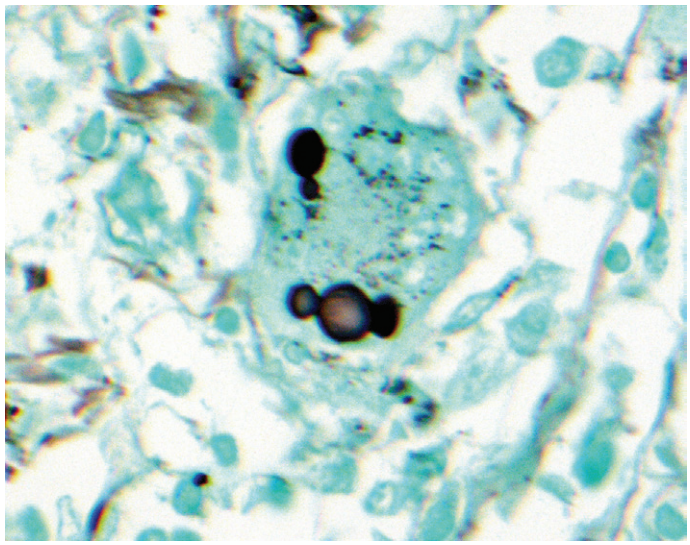


Figure 5.4.35 *Paracoccidioides brasiliensis.* The larger of the organisms illustrated is forming multiple buds. Grocott's methenamine silver stain. *(Courtesy of Dr PM Cury, Rio Preto, Brazil.)*

A characteristic feature is that they reproduce by the development of multiple buds over the surface of the parent cell. The buds have been likened to the handles of a ship's wheel or Mickey Mouse's ears (Fig. 5.4.35). The presence of buds distinguishes *Paracoccidioides* from *Coccidioides* and their multiplicity from *Blastomyces*.

Clinicopathological features

Both pulmonary and disseminated forms of the disease are described.[187] After the establishment of a primary complex in the lung and hilar lymph nodes there may be haematogenous dissemination. Primary infection occurs in childhood and generally heals spontaneously. The sexes are affected equally in childhood but the development of the yeasts is inhibited by oestrogens and in adults the disease is largely limited to male agricultural workers. It is also described in patients with AIDS.[191] Disseminated disease tends to be acute and generalised in children and chronic and localised in adults. Chronic disseminated disease may take the form of lymphadenopathy, painful oropharyngeal ulceration or destruction of tissues such as the adrenal glands. Progressive pulmonary paracoccidioidomycosis is characterised by multiple cavities that mimic tuberculosis, or by progressive fibrosis of the lower lobes with traction bronchiectasis and paracicatricial emphysema in a bilaterally symmetrical distribution.[192] The tissue response is generally granulomatous but may be purulent (Fig. 5.4.36). Calcification is not a prominent feature. The diagnosis is established by recognising the spores in smears or culture of sputum or pus, or in tissue sections, or by serology. Biopsy is an excellent diagnostic procedure. The spores are best recognised with silver stains.

RARE PULMONARY MYCOSES

Fungi responsible for extrinsic allergic alveolitis are listed in Table 6.1.4 (p. 279) and the occurrence of intracavitary colonies of various fungi is mentioned on page 231. Allergic bronchopulmonary candidosis, helminthosporiosis, penicilliosis and curvulariosis, similar to the more familiar allergic aspergillosis, have all been described on rare occasions.[97]

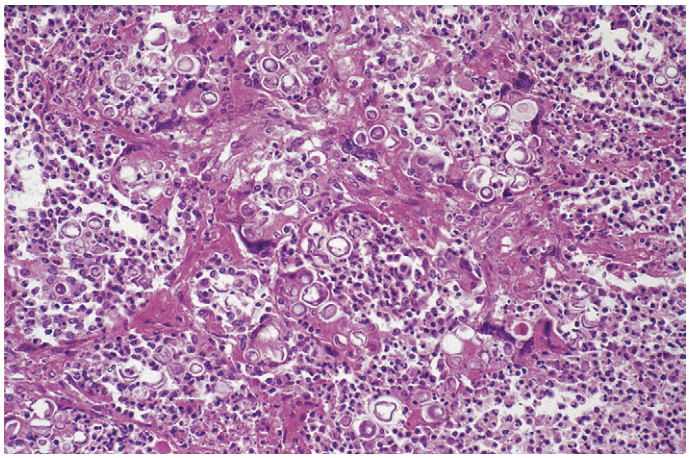


Figure 5.4.36 Paracoccidioidomycosis. There is a giant cell and neutrophil reaction to numerous spores of *Paracoccidioides brasiliensis*.

Pulmonary mycoses not dealt with above are rare and ordinarily occur as a result of lowering of the body's resistance by other diseases or their treatment.[193] Some examples are dealt with below. Others include infection by the common saprophytic mould *Geotrichum candidum*, *Trichosporon cutaneum*, the organism of white piedra (tinea alba),[194,195] *Chaetomium globosum*,[65] *Paecilomyces lilacinus*,[196] *Dactylaria gallopava*[197] and *Ochroconis galloparvum*.[198] Chromomycosis (caused by species of *Phialophora* or *Cladosporium*) and rhinosporidiosis (caused by *Rhinosporidium seeberi*) are very occasionally found as infections of the lungs; in most cases such infection has spread, by the airways or in the blood, from a site elsewhere in the body.

Torulopsosis

Torulopsis glabrata, also known as *Candida glabrata*, is a common yeast on the body surface, and is frequently isolated as a contaminant of urine cultures. Human infection is usually opportunistic, taking the form of pneumonia, septicaemia, pyelonephritis or endocarditis in debilitated or immunocompromised patients, particularly those with AIDS or advanced cancer or being treated with wide-spectrum antibiotics.[199,200] Pulmonary infection is often by aspiration. Unlike *Candida albicans* it does not form hyphae. Its cells are nearly invisible in haematoxylin and eosin sections but are easily seen in Grocott preparations. They are difficult to distinguish from those of *Histoplasma capsulatum* but are rounded rather than ovoid.

Sporotrichosis

Sporotrichosis is usually seen as an indurated ulcer of the finger acquired from the prick of a thorn. Pulmonary involvement is rare and when present is generally secondary to disseminated lymphocutaneous sporotrichosis. Primary pulmonary sporotrichosis (involvement of the lung in the absence of cutaneous disease) is distinctly unusual.[201–203] However, because it mimics tuberculosis, its incidence may be greater than is generally recognised. The causative agent, *Sporothrix schenckii*, is a yeast-like fungus that occurs worldwide on decaying vegetation, contaminated soil and living plants, especially roses. Primary pulmonary sporotrichosis is acquired by inhalation of the spores and usually presents as a chronic, cavitary, bilateral, apical disease, most often in a clinical setting of alcoholism and chronic obstructive airway disease: less often it forms a solitary, necrotising, peripheral pulmonary nodule.[202] Fungal stains demonstrate many round or ovoid budding yeast forms, 2–4 µm in size, in the areas of necrosis. Hyphae bearing sessile budding yeasts are found infrequently.

Adiaspiromycosis[204–212]

Adiaspiromycosis is caused by a remarkable fungus, *Emmonsia* (also known as *Chrysosporium)*, which is a dimorphic filamentaous soil saprophyte of worldwide distribution. Its principal species are *E. crescens* and *E. parva*. The term 'adiaspiromycosis' derives from the conidia of this fungus, which are quite small but at 37°C exhibit the unique property of progressive enlargement, perhaps a million-fold in volume, without replication, when they are known as adiaspores.

The disease is ordinarily limited to wild rodents but has been seen exceptionally in humans. It is characterised by the formation of tuberculoid granulomas around the inhaled adiaspores, which are usually solitary. The adiaspores have a prominent yellowish wall, up to about 8 µm in thickness, surrounding a central mass of amorphous cytoplasm in which there is a single nucleus. The adiaspores are remarkable for the great size that they may reach – as much as 600 µm in diameter. They are too large to be effectively mobilised by the host cells and the granulomatous response usually maintains a bronchiolocentric distribution indicative of inhalational infection. Dissemination is unusual but is recorded in AIDS.[210] Diagnosis relies on recognition of the fungus in tissue sections, as serology and culture are unreliable.

Light infection may result in a solitary adiaspiromycotic granuloma which would only be found incidentally in an asymptomatic individual. Widespread adiaspiromycotic granulomas are indicative of heavy infection and patients so affected may complain of fever, cough and dyspnoea and show a diffuse, micronodular pattern on chest radiographs.[207] Death is very unusual.[208] Healing is by progressive fibrosis and calcification.

Malasseziosis

Malassezia furfur, the causative organism of tinea versicolor (pityriasis versicolor), is dependent for its growth on high concentrations of fatty acids and is normally limited to the skin. Systemic infection has however complicated prolonged lipid infusions through central venous catheters, in which circumstances the small yeast-like organisms have been noted infiltrating the walls of pulmonary arteries and in small pulmonary thromboemboli.[213,214] As is so often the case with fungi, identification of the species depends upon cultural characteristics.

Pseudallescheriosis (monosporiosis)

Pseudallerscheria boydii (syn. *Petriellidium boydii, Allescheria boydii*) is a fungus of worldwide distribution in soils, and is of low pathogenicity. It is the commonest cause of mycetoma in Europe and North America, gaining access to the subcutaneous tissues through cuts and abrasions in the skin. Pulmonary involvement may occur through the inhalation of airborne spores, taking the form of an intracavitary fungal ball, comparable to an aspergilloma, or in conditions such as leukaemia it may be invasive and disseminate widely.[104,215–218] Allergic bronchopulmonary pseudallescheriosis is also described.[96]

Pseudallerscheria boydii usually grows in hyphal form within the body but within air-filled cavities conidia may develop. The conidial state is known as *Monosporium* (syn. *Scedosporium*) *apiospermum* and infection showing such growth may be termed monosporiosis. The hyphae are slender, thin-walled and of fairly constant diameter with numerous septa and branching points. The hyphae are slightly indented at the septa. They are more slender and their branches less

clearly dichotomous than those of aspergilli but the differences are insufficient to discriminate between them with confidence morphologically. This requires immunohistochemistry.[66] The distinction of these two fungi is important because their drug sensitivities differ.[217]

Penicillium marneffei infection

Penicillium marneffei is a dimorphic fungus endemic in South-east Asia.[219] At room temperature it grows as a mould with red to black conidia whereas in tissue it forms a 3–5-µm yeast-like cell that divides by binary fission. The yeasts therefore display clear central septation, unlike *H. capsulatum* and other fungi that divide by budding. Infection, which is highest after the rainy season, is by inhalation but the pulmonary changes are usually overshadowed by systemic features such as hepatosplenomegaly, skin lesions and bone marrow involvement. However, there may be diffuse infiltration, mass lesions or cavities in the lungs. While it can affect the immunocompetent, infection is mainly associated with AIDS, for which it is a clinical marker in the endemic areas.[220]

Microsporidiosis

Microsporidia, once thought to be protozoa, are now regarded as extremely reduced fungi. They are obligate intracellular parasites that infect many animals and have emerged as important opportunistic pathogens in AIDS.[221,222] They are also being increasingly recognised in HIV-negative individuals.[223] Four microsporidian genera, *Enterocytozoon*, *Encephalitozoon*, *Pleistophora* and *Nosema*, have been reported to infect humans. Infection generally involves the gastrointestinal tract but may become generalised.[223,224] Pulmonary involvement is unusual but heavy infestation of the tracheobronchial mucosa is recorded.[225–229] The infected respiratory epithelium may show focal proliferation with little inflammation or there may be a lymphocytic infiltrate of the airway epithelium similar to that seen in the bowel; heavy infestations cause sloughing and ulceration of the tracheobronchial mucosa and severe subacute inflammation. In haematoxylin and eosin-stained sections the parasite appears as a supranuclear 'blue body' but the staining is weak and it is easily overlooked, even when infestation is heavy. It is ovoid or spherical, and measures approximately 2 µm in length, and is Gram-positive. Microsporidia differ from cryptosporidia, which attach to the outer surface of infected epithelial cells, in being obligate intracellular parasites. Immunocytochemistry, electron microscopy and in situ hybridisation are useful for confirming the diagnosis.[230] Antiretroviral therapy has been shown to improve gastrointestinal symptoms, presumably through restoring immunity,[231] and albendazole has also been effective in some patients.

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Chapter 5

5.5 *Parasitic infestations*

CHAPTER CONTENTS

This chapter describes infestation of the lungs by certain parasitic protozoa, helminths and arthropods, of which man may be either the natural or the accidental host.

Protozoal diseases of the lungs include toxoplasmosis, leishmaniasis and amoebic abscess while severe malaria may be complicated by acute respiratory failure. Also, parasites usually confined to other organs may be identified in the lungs, for example cryptosporidia in AIDS and trichomonas in aspiration lesions.

Helminths of all three major classes may infest the lung. Trematodes include the blood flukes (genus *Schistosoma*), the lung flukes (genus *Paragonimus*) and certain liver flukes (genus *Opisthorchis*). The cestodes are represented by the larval forms of *Echinococcus* and *Taenia*, which are responsible for hydatid disease and cysticercosis respectively, whilst nematodes found in the lung include immature forms of *Ascaris, Strongyloides, Ancylostoma, Necator, Wuchereria* and *Brugia* and the adult forms of heartworm (*Dirofilaria*) and gapeworm (*Syngamus*).

Arthropods include the ticks and mites (arachnids), adult forms of which may cause pulmonary acariasis. Pulmonary pentastomiasis is a manifestation of infestation by larvae of *Linguatula* or of *Armillifer*.

The mode of transmission is variable. Some of these parasites are transmitted by an insect bite e.g. those causing tropical pulmonary eosinophilia, dirofilariasis and malaria, while some penetrate the skin directly e.g. *Strongyloides*, hookworms and schistosomes, and others are ingested e.g. *Paragonimus*, *Entamoeba* and *Echinococcus*.

The human lungs may be involved in the life-cycle of these parasites in various ways:

1. The lungs may be the natural location of the parasite, for example *Paragonimus* and *Syngamus.*
2. The larval form of the parasite may encyst in the lungs, for example *Echinococcus*.
3. The lung may be a migratory route for the larvae of the parasite: this includes most of the nematodes listed above and the larvae responsible for pentastomiasis.
4. The parasite may reach the lungs as an embolus: most schistosomal ova and the dead adult canine heartworm, *Dirofilaria*, are examples of this.
5. The parasite may invade the lung through the diaphragm from the liver, for example *Entamoeba histolytica* and the liver fluke *Opisthorchis*.
6. The lungs may be involved in disseminated parasitosis, for example microsporidiosis in the acquired immune deficiency syndrome.

Although immunodeficient patients are particularly prone to parasitic infestation, most of these pulmonary parasites are capable of infecting and causing disease in the immunocompetent; only a few are opportunists (e.g. Cryptosporidium spp.). Many of them have a characteristic distribution, often in tropical or subtropical countries. In the developed world parasitic diseases of the lung mainly affect immigrants and tourists.

PROTOZOA

Protozoa are unicellular eukaryotic microbes that reproduce vegetatively (as trophozoites) but encyst when conditions are unfavourable. Some are parasitic to man. A comprehensive review of those that affect the human lungs, including their taxonomy and treatment, has recently been provided.[1]

Toxoplasmosis

Toxoplasmosis represents infection with the coccidian parasite *Toxoplasma gondii*, this name deriving from the crescentic bow shape of the parasite's tachyzoites and its discovery in the gondi, a North African rodent used as a laboratory animal. The domestic cat is the usual definitive host from which man is infected but the disease occurs in many species of wild and domestic birds and mammals, all of which provide a ready source of human infection. Ingestion of infected animal material is the usual route of infection of adults but neonatal disease generally reflects placental transmission. Toxoplasmosis is one of the most prevalent protozoal infections of man but the parasite rarely harms its host and the vast majority of human infections remain occult throughout life, causing damage only when cellular immunity is impaired. Gametogenesis and oocyst formation take place in the intestine of animals such as cats; outside the body, sporozoites are liberated which can infect other species, including man. Only asexual cysts containing dormant bradyzoites are formed in normal accidental hosts but if immunity fails the cysts liberate motile tachyzoites and it is these that swarm through the host tissues causing cell damage and inflammation.

Pulmonary toxoplasmosis is rare and most cases have been in patients suffering from generalised disease attributable to immunodeficiency from diseases such as lymphoma and AIDS. Transplant recipients are also liable to develop toxoplasmosis. Because many of these patients undergo toxoplasma sero-conversion after they receive new organs, it is likely that the parasite is introduced in the donor tissues in which it presumably lay dormant. In lung transplant patients, recognition of the parasites in transbronchial biopsies is important in distinguishing infection from the changes of graft rejection. Because of the size of the parasite relative to the thickness of tissue sections, many laboratories involved in transplantation work cut serial sections through these small biopsies.

Pulmonary infection is initially non-specific. There is an interstitial infiltrate of lymphocytes, and alveolar macrophages are increased. Hyaline membranes may develop, indicating necrosis of the alveolar epithelium, and the changes are then those of diffuse alveolar damage. Alveoli adjacent to those lined by hyaline membranes show type II pneumocyte hyperplasia. Up to this stage the parasites are scanty but if immunity is sufficiently impaired, enormous numbers of tachyzoites develop. These cause necrosis on a major scale. Air spaces may be filled with necrotic debris or broad tracts of the lung undergo coagulative necrosis.[2–7] In one case macrophages filled with toxoplasma trophozoites formed a mass lesion.[8]

Individual tachyzoites are very difficult to recognise in histological sections but their identification is facilitated by immunocytochemistry,[6,7] which is superior to the Giemsa stain formerly used. The tachyzoites are crescentic in shape and measure within the range 4–7 × 2–3 µm with a prominent central nucleus.[9] The intracystic bradyzoites tend to be shorter and more rounded. The cysts, which represent the latent form of the parasite, lie free in the intercellular tissues and provoke no inflammatory response (Fig. 5.5.1). They vary considerably in size but are commonly of the order of 60 µm in diameter. Single tachyzoites are difficult to identify but they invade

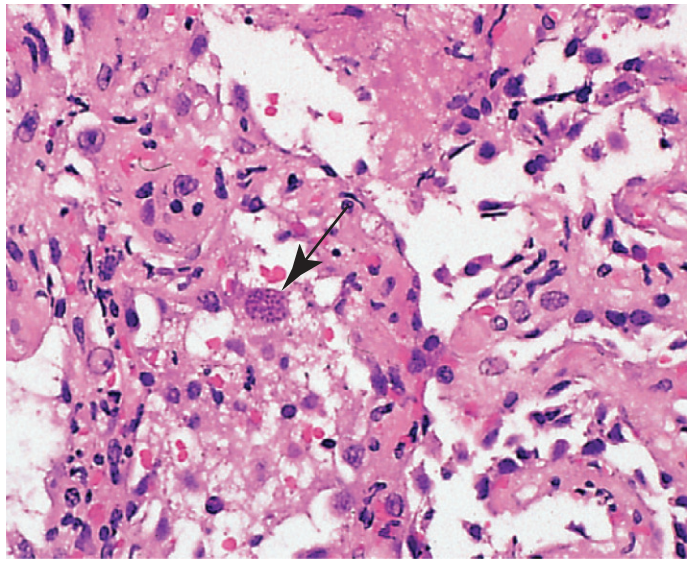

Figure 5.5.1 A *Toxoplasma* cyst exciting little inflammatory reaction in the surrounding lung.

and proliferate within host cells to form distinctive collections known as pseudocysts. These resemble true cysts in size and appearance but are intracellular and lack an outer membrane. Cysts and pseudocysts are easier to recognise than individual tachyzoites but both are generally very rare.

Treatment with pyrimethamine and sulfonamides is effective if initiated promptly.[10] The mortality for toxoplasma pneumonia is 55%, although survival is much better in the immunocompetent.[11]

Amoebiasis

Entamoeba histolytica, the causative organism of amoebic dysentery, is a protozoon with a trophozoite and a cystic stage that is endemic in much of sub-Saharan Africa, South America and southern Asia. Infection is acquired by the ingestion of food or water contaminated by amoebic cysts. Trophozoites develop in the small intestine and are carried to the large bowel, which they ulcerate. From there they may spread in the blood, giving rise to metastatic foci of infection. These are found most frequently in the liver, lungs and brain, in that order. Although the lesions in these organs are conventionally described as abscesses, they are not accompanied by suppuration unless there is secondary bacterial infection.

If there is amoebic ulceration of the lower part of the rectum, amoebae may reach the rectal venous plexus and, bypassing the liver, make their way directly in the systemic circulation to the lungs. More often, amoebic pulmonary abscesses are secondary to those in the liver: the amoebae pass though the diaphragm to infect the lungs and are therefore commoner in the right lung. Whether the pleural cavity becomes infected in the course of this extension of the disease from liver to lung depends on whether adhesions have formed that bind the apposed pleural surfaces sufficiently to protect the cavity from invasion. Pleuropulmonary complications develop in less than 5% of patients with intestinal amoebiasis but in 50% of those with liver abscesses. They may include bronchohepatic fistulas.[12]

An amoebic abscess in the lung, like one in the liver, is essentially a focus of localised destruction in which part of the lung is converted into a cavity filled with reddish-brown, viscous fluid. There is little inflammatory reaction in the surrounding tissues but amoebae with their characteristic ingested erythrocytes may be seen in the zone

bordering the cavity or on aspiration cytology.[13] Often the area of destruction extends to involve one of the bronchi, and much of the contents, often blood-stained, may then be expectorated. Should this happen, there may be secondary bacterial infection of the cavity. Metronidazole is the treatment of choice.[12]

In addition to *E.histolytica*, certain free-living amoebae have occasionally caused disease in man, of which two, Acanthamoeba spp. and *Balamuthia mandrillaris* have been responsible for pulmonary disease.[14]

Malaria

Severe *Plasmodium falciparum* malaria may be complicated by acute respiratory failure.[15–17] This is usually due to non-cardiogenic oedema, reflecting increased permeability of the alveolar capillaries.[18] Alternatively, patients may display the acute respiratory distress syndrome, which as usual has diffuse alveolar damage as its pathological basis.

It is suggested that the various cytokines that have been identified in the general circulation in complicated forms of malaria[19–21] may be more important than the ischaemia occasioned by heavy erythrocyte parasite burdens rendering the red blood cells less deformable and so inclined to occlude capillaries. However, blood sludging undoubtedly takes place in the lungs as well as the brain and elsewhere. The pulmonary capillaries are engorged with parasitised erythrocytes, pigment-laden macrophages and neutrophils. This is contributed to by endothelial activation and increased expression of intercellular adhesion molecule-1[22] as well as the non-deformability of the parasitised cells. The alveoli are filled with protein-rich or haemorrhagic oedema fluid, often containing pigment-laden macrophages, or show the hyaline membranes of diffuse alveolar damage.

The parasites in the lung are largely early trophozoites or ring forms rather than the later schizonts that predominate in cerebral vessels, possibly because the higher oxygen levels in the lung inhibit plasmodium maturation.[23] Therapeutic measures resulting in fluid overload and oxygen toxicity may aggravate the respiratory distress. Even after treatment, altered pulmonary function in malaria is common, with airflow obstruction, impaired ventilation, impaired gas transfer, and increased pulmonary phagocytic activity. This occurs in both vivax and falciparum malaria suggesting common underlying inflammatory mechanisms.[24]

Leishmaniasis

Visceral leishmaniasis, which is contracted by the bite of an infected sandfly, is characterised by fever, weight loss, splenomegaly and hepatomegaly. Most patients also complain of cough but there are few reports of pulmonary involvement. As in the spleen and liver, the leishmania are contained within macrophages (Fig. 5.5.2) but are difficult to find. One study identified chronic interstitial pneumonitis in 10 of 13 cases of visceral leishmaniasis, accompanied in 7 by focal interstitial fibrosis.[25] *Leishmania donovani* were identified in only 3 cases but leishmanial antigenic material was recognised immunocytochemically in all cases showing pneumonitis and in none of the others.

Cryptosporidiosis

Cryptosporidia species cause diarrhoea in many species.[26] In man, enteric cryptosporidiosis was first recognised in an immunodeficient patient and the disease has now become a serious problem in AIDS.[27] It also affects the immunocompetent and is a common cause of short-term diarrhoea in day nurseries and in travellers. Infection is by faecal–oral transmission of an encysted form and generally involves drinking contaminated water. A small number of immunocompromised patients show respiratory as well as enteric infection, complaining of cough and chest pain (Fig. 5.5.3).[28–31]

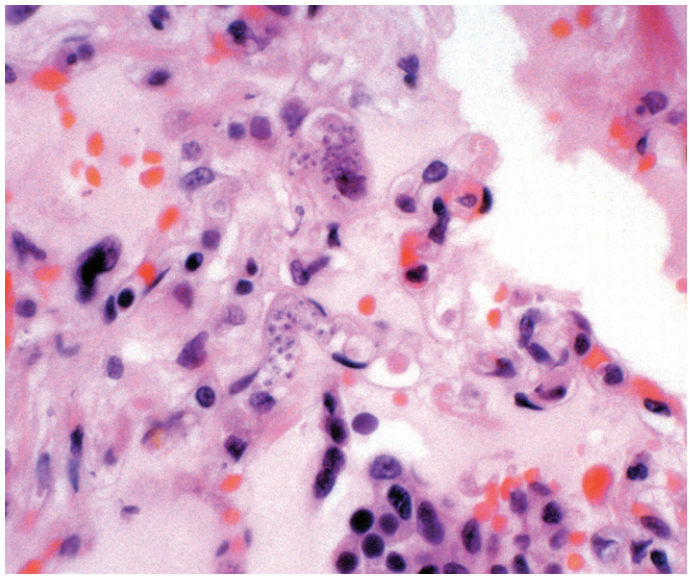

Figure 5.5.2 Pulmonary involvement in disseminated leishmaniasis. The protozoa are seen within macrophages in alveoli and capillaries. *(Courtesy of Dr J DeGaetano, Malta.)*

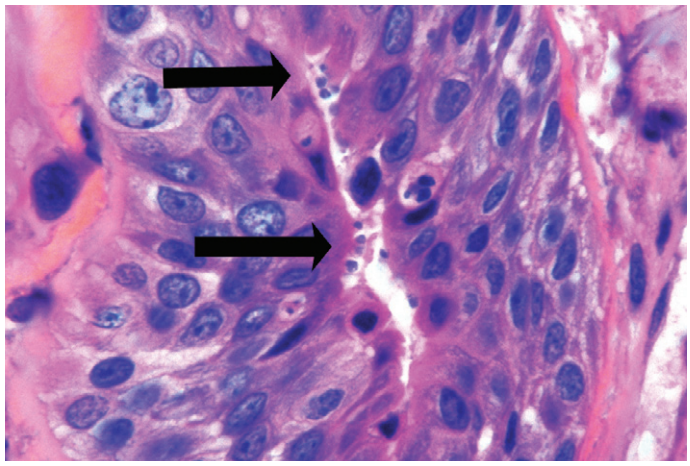

Figure 5.5.3 Cryptosporidia (arrows) are seen in the bronchial lumen of a patient suffering from acquired immunodeficiency syndrome (AIDS). *(Courtesy of Dr M Antoine, Paris, France.)*

Cryptosporidia are extracellular protozoan parasites which adhere to the surface of lining epithelia. They are seen as faintly haematoxyphil dots measuring up to 5 µm arrayed along the mucosal surface. In the respiratory tract they have been identified on the surface and glandular epithelium of the trachea and bronchi and in the lung parenchyma, associated with extensive squamous metaplasia of the conductive airways.[29] The superficial location of cryptosporidia helps distinguish them from microsporidia, which are found within the cytoplasm of epithelial cells. Electron microscopy shows that cryptosporidia occupy a vacuole that communicates with the cell surface: they lie just beneath the level of cell membrane but are nevertheless extracellular.

Treatment may require immune reconstitution as well as the administration of drugs such as paromomycin, azithromycin and nitazoxanide, for which varying success is reported.[26,32,33]

Trichomoniasis

The finding of trichomonads in human lungs is rare. *Trichomonas hominis*, the intestinal trichomonas, has spread to the pleura via an enteropleural fistula, and *T.vaginalis* has been isolated from the respiratory tracts of newborn babies, but pulmonary trichomoniasis is usually caused by aspirated *T.tenax*.[34–36] Trichomonads cannot persist without associated bacterial infection and *T.tenax* is generally found as a harmless commensal in patients with poor oral hygiene, surviving in carious teeth where it feeds on the bacteria responsible for the dental decay. Pulmonary trichomoniasis is usually found as part of a mixed infection in adult men with chronic purulent or necrotic lung disease such as lung abscess or bronchiectasis. The flagellated protozoan may be identified by microscopic examination of wet-smear, Gram-stained or Papanicolaou-stained preparations but cultural identification is reputed to be superior to these methods.[34] Aspirated pulmonary trichomoniasis is an opportunistic infection of dubious pathogenicity, but it seems advisable that it be treated appropriately (with metronidazole).

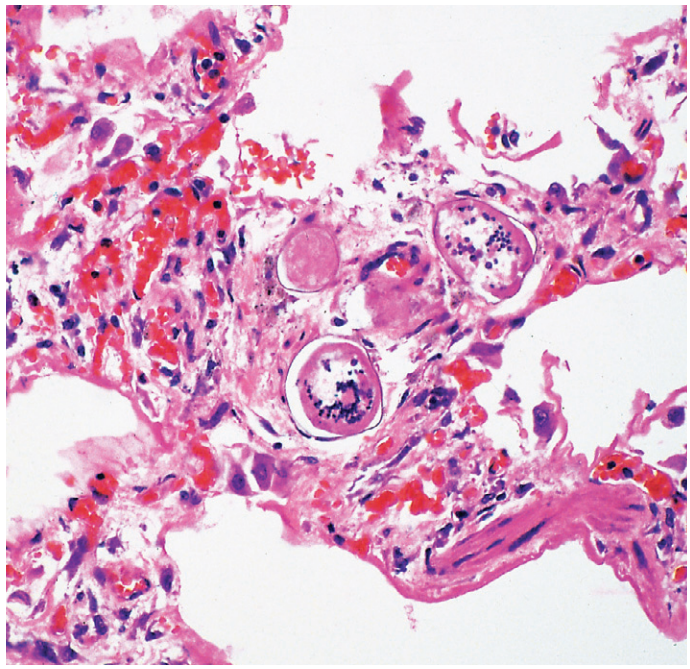

Figure 5.5.4 Schistosomiasis. Schistosomal ova are evident (centre) within the alveolar interstitium, which also shows a lymphocytic infiltrate.

HELMINTHS

Trematodes

Schistosomiasis

Pulmonary schistosomiasis (bilharziasis) may be due to any of the three most important species of human blood fluke, *Schistosoma haematobium*, *S.mansoni* and *S.japonicum*. Although involvement of the lung is relatively infrequent as a cause of clinical disease in comparison with the major locations of schistosomal infestation, it is recognised wherever schistosomiasis is endemic. However, with increased international travel, it seems that the non-endemic population has a higher incidence of pulmonary involvement once infected.[37,38] Specific changes are found in the lungs in a third of cases of clinically evident schistosomiasis in Egypt but contribute to death in only about 2% of these patients.[39,40] The frequency of pulmonary involvement is least in the Far East where schistosomiasis is due to *S.japonicum*.

The schistosomal cercariae thrive in fresh water and penetrate the skin to to transform into immature adults, which are transported in the blood to mature in venous plexuses around the bladder or rectum, where they reproduce. Pulmonary infestation generally comes from ova being carried to the lungs in the blood, either bypassing the portal venous circulation or having been produced by flukes inhabiting plexuses that drain directly into the inferior vena cava. Alternatively, if adult parasites are present within the pulmonary vasculature itself, ova are produced locally.

The ova, which measure from 70 to 170 µm in length by 50 to 70 µm in breadth, according to the species, are bound by their dimensions to lodge in blood vessels of corresponding calibre; local thrombosis and organisation result, with the formation of a characteristic tuberculoid granuloma round the egg itself (Figs 5.5.4 and 5.5.5).[39] Medial hypertrophy, intimal fibrosis, thrombosis, necrotising angiitis and angiomatoid lesions (see p. 422) develop in the obstructed arteries.[39,41] Eosinophils may be conspicuously numerous in the vicinity of the ova. It is uncertain whether the necrotising arteritis and

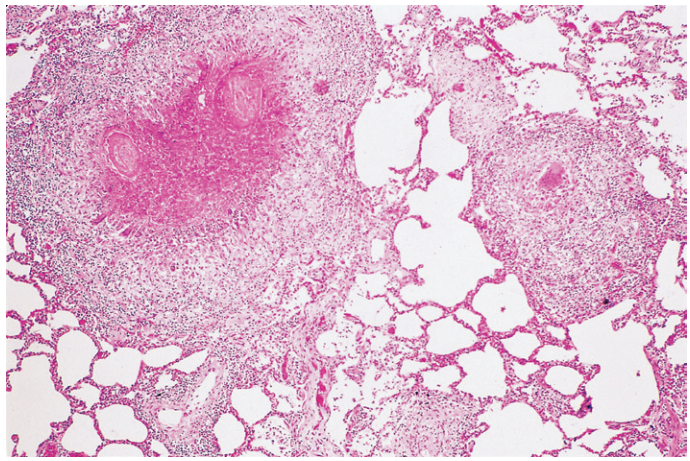

Figure 5.5.5 Schistosomiasis. Lodgement of the schistosomal eggs in the pulmonary microcirculation has provoked a vigorous granulomatous response.

consequent angiomatoid lesions are attributable to vascular obstruction by the ova, to an allergic response to the parasite, or to the 'pipestem' hepatic fibrosis that is commonly found in schistosomiasis permitting vasoconstrictive substances that normally are metabolised in the liver to reach the pulmonary arteries.[41] Cor pulmonale may complicate pulmonary schistosomiasis and aneurysmal dilatation of the pulmonary trunk has been observed in long standing cases.

The ova also pass through the walls of the pulmonary vessels and initiate parenchymal lesions characterised by a similar granulomatous reaction and more widespread lymphocytic infiltrate and interstitial fibrosis. Although the ova may be much distorted during tissue processing, they are readily seen and recognised, particularly if they were viable at the time when the specimen was obtained (see Fig.

5.5.4). Dead ova often become heavily calcified but may long retain identifiable traces of the contained embryo. Eosinophilic infiltration and necrotising angiitis are only seen in the presence of viable ova. The presence of eggs, viable or dead, is generally the clue to the diagnosis, but in some cases pulmonary arterial lesions, including thrombosis and arteritis, develop where no ova are demonstrable.

Occasionally, ova reach the respiratory bronchioles and cause a local tuberculoid bronchiolitis. Sometimes a tumour-like mass forms in the lungs, abutting and obstructing a bronchus: this proves to be a confluent growth of granulomatous tissue and scarring around great numbers of schistosome ova.

When adult flukes reach the lungs they appear to cause no reaction while alive, any associated lesions being caused by the presence of their ova. However, when the flukes die, thrombosis and arteritis result, and there is commonly an accompanying focal consolidation of the adjacent parenchyma. This gives rise to nodules up to 1 cm and more in diameter that show as small 'coin' shadows in chest radiographs.

Katayama fever

As well as the classic chronic form of schistosomiasis described above, pulmonary symptoms such as cough feature in the severe form of acute schistosomiasis known as Katayama disease.[15] This systemic illness signifies seroconversion and develops about 3–6 weeks after penetration of the skin by water-borne cercariae. It is almost exclusively a disease of non-immune visitors to endemic areas and has been reported in several groups of tourists returning from such areas, especially those participating in water sports. The disease is self-limiting but recognition and treatment are important to avoid the sequelae of chronic infection.

Paragonimiasis

Infestation by lung flukes is endemic in the Far East, and to a lesser extent in central Africa and parts of the Americas.[42–44] In its early stages the disease is characterised by chest pain or discomfort. Later, when it has become chronic, there is persistent cough and recurrent haemoptysis. Characteristic operculate eggs can then be found in the sputum; they are golden-brown and measure about 90 µm in length. In some cases the presence of the parasite is borne well; in others it leads to anorexia and debility. As long as the flukes remain in the lungs the disease is rarely fatal, but should they reach the brain, as happens in a minority of cases, the prognosis is grave. Occasionally the disease mimics lung cancer.[45] Rapid and reliable immunodiagnostic methods are now available, and there are PCR techniques that distinguish individual species.[46,47]

The species most frequently responsible are *Paragonimus westermani* in the Far East and *P.kellicotti* in the Americas.[44] Morphologically these differ from each other only slightly. The adults infest the lungs of many predatory animals: *P westermani* in the dog, cat and pig, and *P.kellicotti* in the mink. Small groups of them become sexually mature within the lung tissue, where necrosis and the formation of a fibrous capsule produce characteristic 'worm cysts' (abscess cavities) that eventually enlarge and break into the bronchial lumen (Fig. 5.5.6). The ova that thus escape pass up the respiratory tract and are either expectorated or swallowed, to be eventually excreted in the stools. The life cycle of the fluke is a complex one: after several weeks in water or moist earth, the ovum hatches into a miracidium, a free-swimming form that eventually enters and parasitises water snails of the genus *Melania*. After its larval life in the snail, the fluke emerges as a cercaria, which in turn parasitises small fresh-water crabs and crayfish. It is through the consumption of these crustaceans, raw or insufficiently cooked, that man becomes infested. Pickling the crabs does not destroy the parasite. The disease may also be acquired by eating the flesh of another host, such as a pig, that has eaten infected crabs or crayfish. On reaching the duodenum of the human host, the parasite penetrates the gut wall and thence passes by way of the peritoneal cavity and diaphragm to the pleura and the lungs. It grows to a length of 12 mm and attains maturity about five weeks after reaching the lungs and so completing its life cycle.

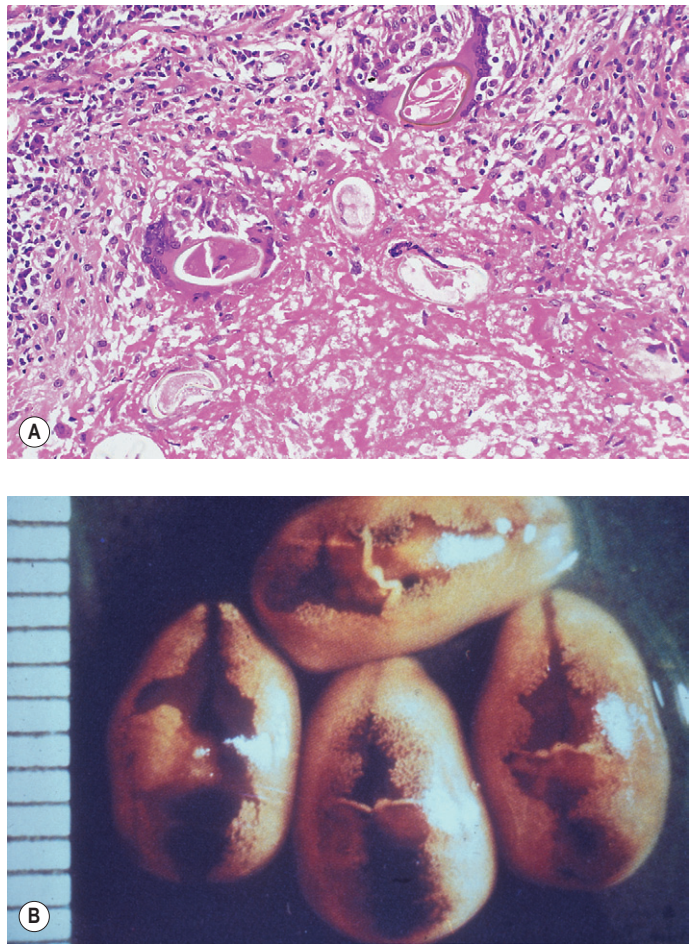

Figure 5.5.6 Paragonimiasis. (A) A 'worm cyst' including several *Paragonimus* eggs in the chronic inflammatory granulation tissue that borders the central necrosis. (B) *Paragonimus* eggs removed from the lung (scale divisions = 10 µm).

In man the flukes often lie singly in the connective tissue 'worm cysts', the number of which rarely exceeds ten, each about 1 to 2 cm across. They may excite an eosinophilic pneumonia, give rise to a pleural effusion or cause pneumothorax.[48] Sometimes the young worms go astray and reach the liver, spleen, kidneys or brain. Occasionally dead worms in the lungs are associated with distant tissue reactions that probably have a hypersensitivity basis. The diagnosis is based on the demonstration of the eggs in bronchial secretions, pleural fluid or faeces.

Opisthorchiasis

Liver flukes generally remain within the hepatic bile ducts but in Thailand *Opisthorchis viverrini* has on rare occasions made its way from the liver through the diaphragm to the right lung.[49]

Figure 5.5.7 Hydatid cyst, the encysted larval form of the *Echinococcus granulosus* tapeworm, filled with numerous 'daughter' cysts.

Figure 5.5.8 Hydatid cyst. The encysted larva of the *Echinococcus granulosus* tapeworm has died and the parasite's capsule has collapsed away from the fibrous capsule formed by its human host.

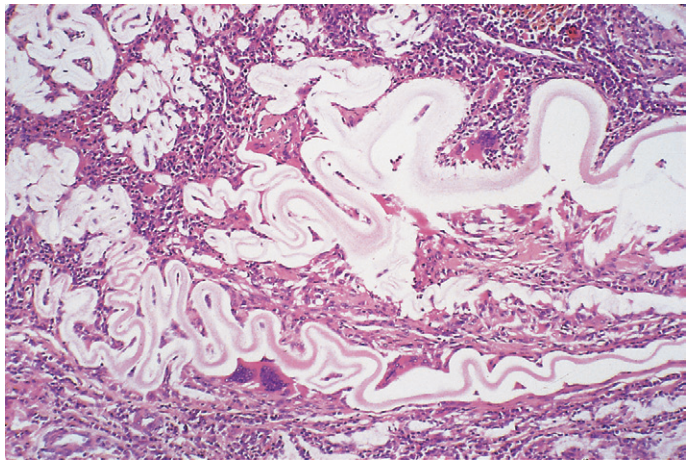

Figure 5.5.9 Hydatid cyst. The convoluted chitinous layer of a collapsed dead hydatid cyst.

Cestodes

Hydatid disease (larval echinococcosis)

This disease has long been endemic in sheep-raising countries, notably Australia, New Zealand, Wales, parts of South Africa and South America, and the Middle East.[50] Control measures are steadily lessening its incidence. The dog is the usual host of the mature tapeworm, *Echinococcus granulosus*, and sheep the commonest host of its larval stage. The ova in the faeces of the dog reach sheep or man in contaminated food or water and, after hatching in the small intestine, larvae penetrate the gut wall and enter the portal circulation. Most are retained in the liver, but some negotiate the hepatic barrier to reach the systemic venous circulation and the lungs. The larval forms of this helminth thus tend to occur most frequently in the liver and the lungs. They take the form of hydatid cysts (Fig. 5.5.7). If a hydatid cyst is demonstrated in the lung, others are almost always present in the liver. Pulmonary hydatid cysts are usually solitary but bilateral instances are recorded.[50–52]

The wall of a hydatid cyst is formed of a semipermeable laminated capsule, which is composed of chitin, and an inner germinal layer. Outside these is the pericyst, formed of a layer of chronic inflammatory granulation tissue or a fibrous capsule, these representing the host reaction to the parasite (Figs 5.5.8 and 5.5.9). The germinal layer gives rise to brood capsules and from the germinal layer of these arise scolices. Free brood capsules and scolices form the hydatid 'sand' that can be seen as minute white grains in the otherwise clear cyst fluid (Fig. 5.5.10). When sheep tissues containing hydatid cysts are eaten by a dog, the scolices attach to the intestinal mucosa and develop into the adult worms, thus completing the life cycle. Scolices also have the potential to develop into secondary cysts if released by cyst rupture. They also form daughter cysts within the mother cyst, each daughter cyst being an exact true replica of the mother cyst. The daughter cysts may be packed together in the mother cyst or float freely in the mother cyst cavity. In older cysts, the contents degenerate into gelatinous material known as the matrix, which may be mistaken for pus. The cysts are usually bacteriologically sterile but they may become infected, resulting in true suppuration. Calcification commonly develops in the pericyst without affecting the viability of the parasite but calcification of the endocyst indicates that it is dead.

Because the parasite has evolved mechanisms to avoid host immunity, the infection is often asymptomatic until a mechanical complication occurs.[53] Thus, most cases of pulmonary hydatid disease are discovered on routine chest radiography. Symptoms stem from compression, infection or rupture into a bronchus. The sudden escape of a large amount of its fluid contents may give rise to a grave, even fatal,

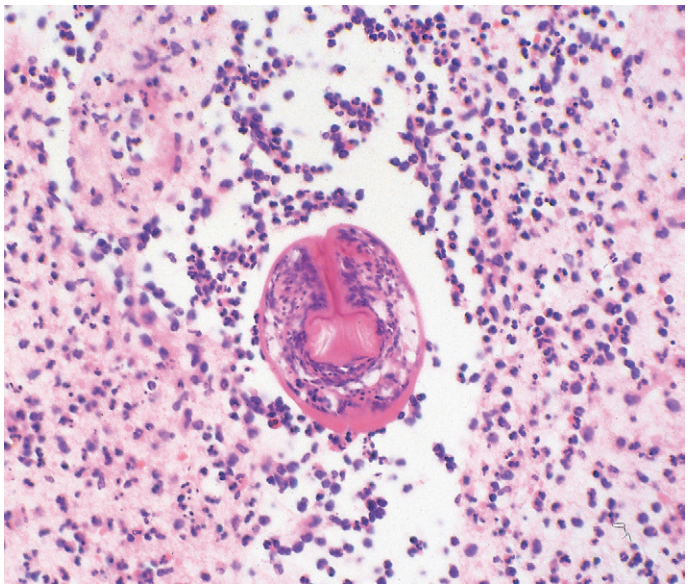

Figure 5.5.10 Hydatid cyst. An echinococcal scolex from a ruptured hydatid cyst is surrounded by pus.

anaphylactic reaction. Rupture of a hydatid cyst into a bronchus may also cause bronchocentric granulomatosis[54] or lymphoid hyperplasia. Aspiration of the cyst contents should not be undertaken because of the risk of spillage and a consequent hypersensitivity reaction. The treatment of choice for compressive cysts is surgical resection, with particular care being exercised to avoid rupture of the cyst, and post-operative drug therapy using albendazole.[55–57]

Cysticercosis (larval taeniasis)

Cysticercosis occurs when man becomes the intermediate host of the porcine tapeworm, *Taenium solium*, through the ingestion of the worm's eggs present in faecally contaminated water or food or on soiled hands, or by the eggs hatching within the intestine of those harbouring the adult worm.[58,59] The disease is common in Africa, China, south east Asia and South America. Once hatched, the embryo penetrates the intestinal wall and is disseminated by the blood stream, giving rise to an encysted larva. Such cysticerci may form anywhere but the brain is particularly vulnerable. The lungs are seldom affected but may be the seat of either solitary or multiple lesions, the latter generally as part of disseminated disease, which probably reflects immune impairment. The larva has an inverted scolex and lies within clear fluid bounded by a thin fibrous capsule. Little inflammation is induced while the larvae are alive but after their death a variable response is seen, often culminating in calcification.

Nematodes

Ascariasis and toxocariasis ('visceral larva migrans')

Although essentially an intestinal parasite, the large roundworm *Ascaris lumbricoides* passes through the lungs during one phase of its complex life cycle. Infection is endemic in much of Africa, Asia and South America. The infestation is acquired by ingesting food or water contaminated with ova passed in the faeces of an earlier host. The ova hatch in the small intestine, where the larvae quickly penetrate the mucosa and are carried either to the liver in the portal bloodstream or in lymph to the systemic veins, reaching the lungs about five or six days after ingestion of the eggs. In the lungs, the larvae pierce the alveolar wall to reach the air space, whence they are cleared to the pharynx to be swallowed. Maturation, copulation and ovulation occur in the small intestine.

Toxocara canii and *cati* are respectively the corresponding roundworms of dogs and cats, human infection by which is acquired through close contact with these animals or with soil contaminated by their faeces. Toxocarae do not complete their life-cycle in man but dissemination of their larvae simulates visceral ascariasis, resulting in what is known as visceral larva migrans.

Migration of these worms through the lungs may cause self-limiting pulmonary eosinophilia (Löffler's syndrome, see p. 460) during which eosinophils and Charcot–Leyden crystals are often conspicuous in the sputum, although the larvae themselves are rarely seen. The illness is usually over within three weeks but in exceptional cases respiratory distress becomes so severe that the patient may die.[60]

Microscopical studies of the pulmonary lesions have been infrequent except in the rare fatal cases, or when the parasites are present by chance in lungs examined as a result of other disease. The larvae may be found in capillaries, the interstitial tissues, or air spaces, accompanied by eosinophils and neutrophils. When a larva dies, an intense reaction may develop, with dense local accumulation of eosinophils, lesser numbers of macrophages and neutrophils, and fibrin. Identifiable remnants of larvae may be seen, sometimes in multinucleate giant cells. There may be local haemorrhage.

The larvae of *A.lumbricoides*, the ascarid parasite of man, are difficult to distinguish from those of other ascarids, such as species of *Toxocara*, that may also be found in human lung tissue or pleural fluid.[61] Morphological differentiation of these larvae in histological preparations is commonly beyond the ability even of professional parasitologists but investigation by means of specific immunocytochemical staining may be decisive. The larvae of the toxocarae have a greater tendency than those of *A.lumbricoides* to die in the lungs when they infest man: they then cause pulmonary eosinophilia and tuberculoid granulomas that eventually lead to fibrous encapsulation of the remains of the parasites.

Strongyloidiasis

Strongyloides stercoralis is another intestinal parasite that at one stage in its development passes through the lungs. Infection is endemic in much of the tropics and subtropical regions. The filariform larvae of strongyloides, like those of hookworms and schistosomal cercariae, have the ability to penetrate intact human skin, following which they are carried to the lungs where they penetrate the alveoli and migrate via the airways and upper gastrointestinal tract to the small intestine. Here they mature into parthenogenetic adult females, the eggs of which release rhabditiform larvae within the intestine, unlike the eggs of other intestinal helminths which are passed intact in the faeces to embryonate in the soil. The rhabditiform larvae of *Strongyloides* may pass with the faeces to complete a free-living sexual cycle in the soil or differentiate within the intestine into filariform larvae, which are capable of penetrating the bowel wall or the perianal skin to repeat their parasitic asexual cycle, an endogenous process known as auto-infection. This difference between *Strongyloides* and other intestinal helminths is important in maintaining the infection and, in immunocompromised hosts, leading to potentially fatal hyperinfestation.

Chronic strongyloidiasis has been well described among individuals who were prisoners of the Japanese during the second world war: decades later, it affected a fifth of the survivors of those who worked on the notorious Burma railway.[62,63] Most infestations cause at most a creeping skin eruption (larva migrans) or chronic diarrhoea but there is a real danger of fatal hyperinfestation if the individual becomes immunosuppressed. This may happen when corticosteroid drugs are

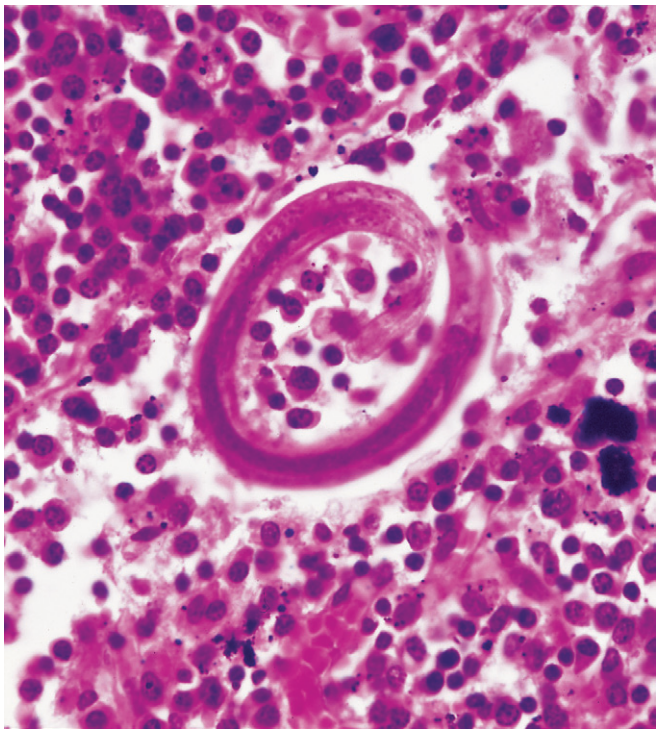

Figure 5.5.11 *Strongyloides stercoralis* filaria in the lung in a case of strongyloides superinfection. *(Courtesy of the late Professor BE Heard, Brompton, UK.)*

administered, particularly in the treatment of unrelated conditions but also because of resistant asthma caused by unrecognised strongyloidiasis. In cases of such asthma the dose of corticosteroids may be progressively increased when the patient would have been better treated with anti-helminthic drugs.[64] Worsening asthma as the steroid dosage is increased should alert the clinician to the possibility of hyperinfestation. Heavy infestation is often associated with blood eosinophilia and fleeting pulmonary opacities that represent eosinophilic pneumonia but these features may be absent in those who are immunosuppressed. Other risk factors include advanced age, chronic lung disease and altered cellular immunity, particularly that found in adult T-cell leukaemia complicating human T-lymphotropic retrovirus (HTLV-1) infection.[65–68]

The respiratory features in hyperinfestation may be those of the acute respiratory distress syndrome. At necropsy in such cases, the larvae are seen in huge numbers within the lumen and walls of airways of all sizes down to the alveoli and within interlobular septa (Fig. 5.5.11). They excite an inflammatory response, chiefly of plasma cells with smaller numbers of lymphocytes and eosinophils. Diffuse alveolar haemorrhage may be seen.[69] More chronic infestation may result in restrictive lung disease due to interlobular septal fibrosis[70] or a mass lesion.[71]

Hookworm infestation

The larval forms of the hookworms *Ancylostoma duodenale* and *Necator americanus*, like those of *Ascaris lumbricoides* and *Strongyloides stercoralis*, migrate through the heart, lungs and trachea to reach the intestine where they mature. On their way through the lungs, they may similarly cause fleeting eosinophilic pneumonia.

Filariasis: tropical eosinophilia

Filariasis is endemic in the tropics. The adult nematodes, *Wuchereria bancrofti*, *Brugia malayi*, *Brugia pahangi* and *Onchocerca volvulus* inhabit lymphatics where they produce eggs from which are released embryos known as microfilariae. These circulate in the blood and disseminate widely in the tissues, to be transmitted to others by mosquitoes.

Some of those infected present with 'tropical eosinophilia', a name that was given to a condition that was initially described from the coast of southern India but is now known to have a far wider distribution in the tropics.[72] The clinical signs are fever, loss of weight, dyspnoea and asthmatic attacks; there is marked blood eosinophilia and radiographs show nodular shadows in the lungs. The condition is benign and little is known of the changes in the lungs. Such reports as have been published describe whitish nodules 3 to 5 mm in diameter, scattered irregularly throughout the lungs. Histologically, the nodules are composed of groups of alveoli consolidated by eosinophils enmeshed in fibrin. In the centre of some of the nodules, the alveolar walls are destroyed and the area becomes an 'eosinophil abscess'. In others, a central collection of epithelioid cells becomes arranged in a palisade manner round deeply eosinophilic hyaline material that probably represents inspissated granules of eosinophil leukocytes. Giant cells and fibrosis are seen in some lesions and microfilariae are sometimes observed.[73,74] The condition is thought to represent an immunopathological response to the parasite rather than direct damage by the microfilariae because it is confined to those individuals who are highly sensitised to filarial antigens.

Tropical eosinophilia is readily distinguished from other forms of eosinophilia (which are described in Chapter 9) by the patient's history of residence in the tropics, by the presence of extraordinarily high levels of both serum IgE and antifilarial antibodies, and by a dramatic therapeutic response to the filaricide diethylcarbamazine.

Dirofilariasis (heartworm infestation)

Pulmonary dirofilariasis occurs when man becomes an alternative host of the canine heartworm, *Dirofilaria immitis*, after being bitten by a mosquito or sandfly infested with the microfilariae. Early development occurs in a subcutaneous nodule, whence after a few weeks' development the young adult worm migrates to the right side of the heart and the pulmonary arteries. In man, the adult worm typically dies while it is immature and is carried from the heart to the lungs as a parasitic embolus to occlude a small pulmonary artery. This generally causes no symptoms. A necrotising granuloma forms about the dead worm and this is seen as an incidental 'coin' lesion in chest radiographs,[75] often prompting a needless thoracotomy as carcinoma is the principal differential diagnosis. The diagnosis is almost always made only when resected tissue is submitted to microscopy. The granuloma is rounded rather than wedge-shaped and is not haemorrhagic, appearances favouring an immune reaction to the worm rather than infarction. The young adult worm in the centre of the granuloma is about 3cm in length but the mature female measures up to 30cm x 2mm with the male about 20cm x 2mm. Very rarely an embolic tangle of worms results in major pulmonary infarction (Fig. 5.5.12A).

Heartworm is enzootic in the Gulf states of America but since the first report of human infestation in 1961 it has become recognised in dogs throughout the United States and in southern parts of Canada. Human cases have now been reported also from Japan, Australia, Brazil and various other countries.[76–81] The smaller *D.repens*, which is common in Italy, may result in a similar pulmonary nodule but the lung is a relatively rare locus for this species.[82–84]

The lesions in man are usually solitary, peripheral and lower lobar in distribution (Fig. 5.5.12B), but multiple bilateral nodules have been reported. They range in size from 1 to 4 cm. Most patients are

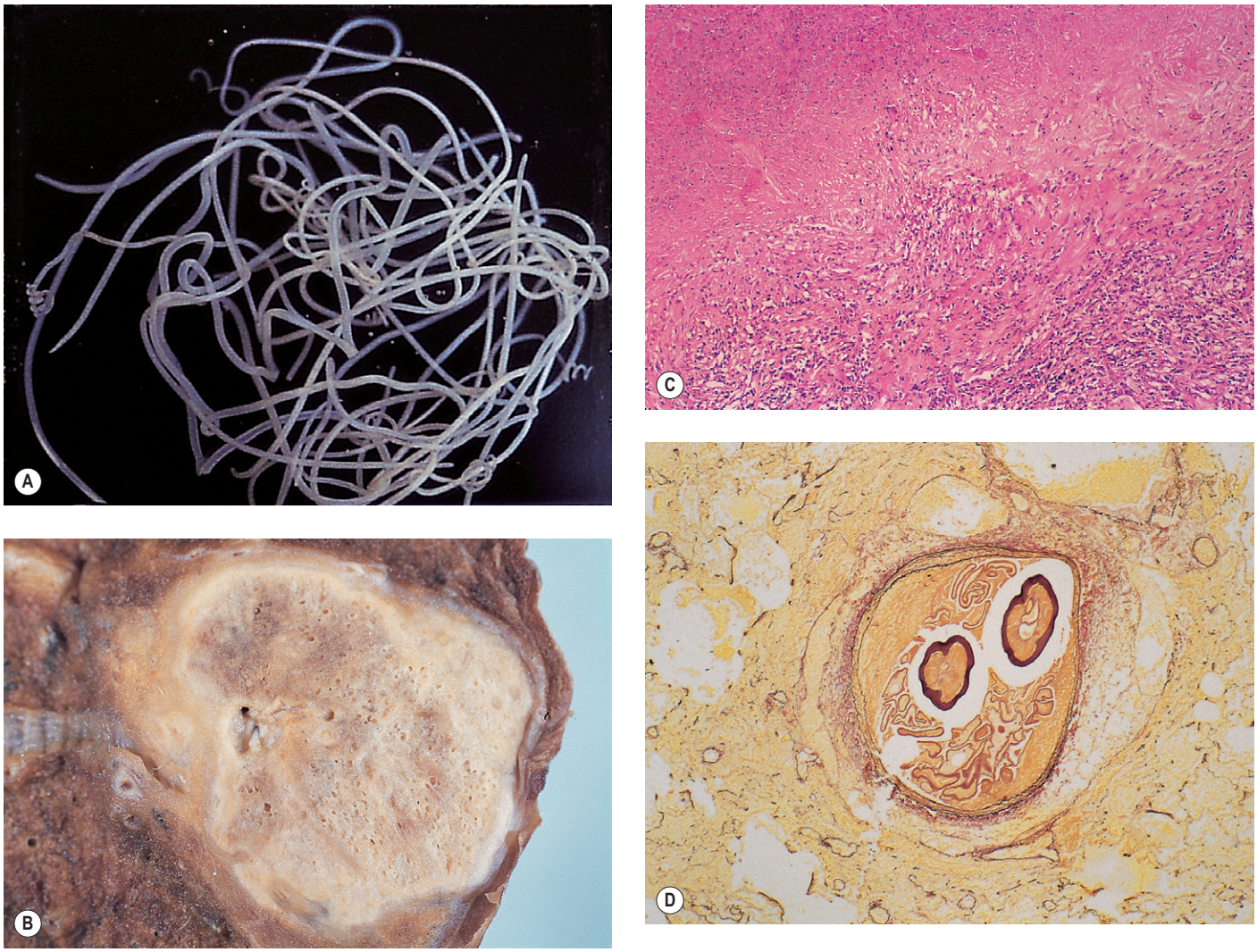

Figure 5.5.12 *Dirofilaria immitis*, the dog heart worm. (A) A tangle of *Dirofilaria* worms that was removed surgically from the pulmonary artery of a merchant seaman. Magnification ×1.8. *(Courtesy of Professor F Ho, Hong Kong.)* (B–D) *Dirofilaria immitis* causing a 3-cm, rounded, necrotising nodule in the lung of a man who had lived rough in tropical countries. (B) Gross appearances; (C) microscopy; (D) elastin stain showing the worm situated within a pulmonary artery. *(B–D courtesy of Dr M Jagusch, Auckland, New Zealand.)*

asymptomatic but some complain of cough, chest pain, haemoptysis and fever, with up to 20% showing eosinophilia. Microscopically, a large central area of coagulative necrosis is surrounded by a thin band of chronic inflammatory granulomatous tissue containing occasional giant cells (Fig. 5.5.12C).[80,85,86] Eosinophils may be numerous but are often absent. The diagnosis is made by identifying the dead worm within a thrombosed artery in the central area of necrosis (Fig. 5.5.12D). This may require step sections, which are therefore advisable when examining any necrobiotic nodule of obscure aetiology. Methenamine silver and elastin stains aid the identification and localisation of the parasite (Fig. 5.5.12D), which has a thick cuticle and in man seldom measures more than 300 µm in diameter.

Syngamiasis (gapeworm infestation)

Gapeworms of the Syngamidae family infest domestic mammals, rodents and birds, producing in domestic fowl a disease known as 'the gapes', which is characterised by dyspnoea and an asphyxial death due to the worms obstructing the bird's trachea and bronchi. Human infection is rare but isolated cases have been reported from the West Indies, Brazil, the Philippines and Korea.[87–90] Affected patients complain of dyspnoea, cough, wheeze and pain or a feeling of tightness in the chest. Ova and adult worms may be found in the sputum or on bronchoscopy. The adults live off the host's blood and are therefore bright red. The female measures up to 2 cm and the male a quarter of this. They live in permanent copulation and since the vulva opens in the mid region of the female's body, each pair forms a characteristic Y shape. It must be disconcerting to see the paired worms wriggling away from the bronchoscopy forceps.[87]

ARTHROPODS

Pulmonary acariasis

Adult ticks and mites are occasionally found in the sputum of those exposed to organic dust in tropical climates, probably representing bronchial saprophytes. This is known as pulmonary acariasis. Mites were found in the sputum of 5% of Chinese grain workers.[91]

Pentastomiasis

The upper or lower respiratory passages of some dogs, birds and snakes are inhabited by certain arthropods of debatable taxonomic standing, the so-called 'tongueworms' or pentastomes, which include *Linguatula* and *Armillifer*. [92,93] The eggs of *Armillifer* may be transmitted to snake handlers in Africa and the Far East and those of *Linguatula* are transmitted to dog handlers worldwide. Larvae develop in the human intestine and penetrate the wall to reach many viscera, including the lungs, where in their natural host they mature to adults but where in man they die. A recognisable larva is occasionally encountered in human lungs but more often, barely recognisable parasitic remnants are observed within encapsulated, partly calcified, necrotic debris. Their identification from other metazoal remnants may be impossible, even for professional parasitologists.

Myiasis

Myiasis is caused by parasitic dipterous fly larvae feeding on the host's necrotic or living tissue. The disease is a serious problem in the livestock industry and is fairly common in rural human populations in tropical and subtropical regions. The insect that attacks man is *Dermatobia hominis*, the human bot-fly. The infestation is usually cutaneous but many other parts of the body may be affected, including the respiratory tract on rare occasions. Respiratory involvement is usually identified when a patient complaining of cough or haemoptysis coughs up a recognisable maggot.

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