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S. Love (Ed.)

Neuropathology

A Guide for Practising Pathologists

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Preface

In commissioning this volume of *Current Topics in Pathology*, the editor of the series, Prof. Sir Colin Berry, asked me to produce something "which is aimed at the general pathologist but from the point of view of the neuropathologist who knows what is not being done well". This was easier said than done. Many aspects of neuropathology are encountered only infrequently in general pathology and are best dealt with by referral of material to a specialist unit. Others need more extensive investigation than is practicable in a general pathology setting. Yet neurological disorders in general are common and are encountered by general histopathologists, paediatric and forensic pathologists on a daily basis, particularly in autopsy practice. In inviting contributions to this volume of *Current Topics in Pathology*, I therefore biased the contents towards disorders in which the conduct of the autopsy and the initial approach to neuropathological investigation are of critical importance in making the diagnosis. The authors all have a wealth of experience and expertise and I believe that this is reflected in their approach, which is both personal and practical. Indeed, the emphasis in this book is very much on the provision of practical advice. All of the chapters contain guidelines on the conduct of autopsies as well as information on the macroscopic and basic histological assessment of the nervous system in the relevant disorders. The book includes an appendix with clear diagrams and advice on the sampling of brain tissue for histology and other investigations. The result is a volume of *Current Topics in Pathology* covering a selection of topics in neuropathology that I hope will be of relevance and interest not only to neuropathologists but to those in other branches of histopathology as well.

Spring 2001

SETH LOVE

Contents

Autopsy Approach to Infections of the CNS

S. Love

1 Introduction

When dealing with infections of the CNS, as with so many other conditions, the key to performing an autopsy that is informative and helpful to clinical colleagues lies in the preparation. This should encompass both a careful review of the clinical notes and investigations, and reflection in advance of the autopsy of the possible pathological processes, their aetiology and pathogenesis. The aim of this chapter is to facilitate the preparation for autopsy investigation of infections of the CNS. Much of the chapter is devoted to considering the likely infective causes of different

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pathological processes in immunocompetent adults and children, immunosuppressed patients and, where appropriate, in neonates (although the chapter does not cover intrauterine infections). In contrast to most reference books on CNS infections, the present text is subdivided according to the pathological features rather than on an aetiological basis. The emphasis is on the typical macroscopic and microscopic manifestations of infections within broad clinical and pathological categories. The detailed histological and microbiological characterisation of different viruses, bacteria, fungi and parasites is well covered in many large reference books and is beyond the scope of the present text. The chapter includes a short section on acute disseminated encephalomyelitis and concludes with advice as to how to obtain appropriate samples for microbiological analysis.

2 Meningitis

2.1 Immunocompetent Adults and Children

2.1.1 Aseptic Meningitis

The commonest form of meningitis is 'aseptic' meningitis, a term used to describe a short-lived illness with headache, photophobia, neck stiffness and a cerebrospinal fluid (CSF) lymphocytosis, the cause of which is not evident on routine microscopy and culture [39, 68, 81]. Because aseptic meningitis is, almost by definition, benign, this type of meningitis is rarely seen at autopsy and then only if patients die from other complications of the (usually viral) infection, such as myocarditis. The brain appears normal apart from the presence of lymphocytes in the leptomeninges and superficial perivascular spaces. Most cases of aseptic meningitis, especially in children, are caused by non-polio enteroviruses [39, 68, 116, 149]. Mumps virus accounts for some further paediatric cases; the meningitis can precede the parotitis and occasionally occurs without the typical systemic manifestations of infection by this virus. Causes of aseptic meningitis in adults include non-polio enteroviruses, herpes simplex virus type 2 (HSV-2), and human immunodeficiency virus (HIV). The main differential diagnosis is partially treated bacterial meningitis, but this syndrome can result from a wide range of other viral, bacterial, fungal and parasitic infections as well as several non-infective processes [39].

2.1.2 Purulent Meningitis

About half of cases of purulent meningitis in immunocompetent adults are due to *Streptococcus pneumoniae* (pneumococcus) [22, 48, 65, 154]. The risk of pneumococcal meningitis is increased in the elderly and debilitated (especially those with a history of alcoholism), in patients who have had a splenectomy and in those with a dural fistula. It may be difficult to find a dural fistula at autopsy, but this should be suspected in patients with meningitis who have a history of head injury

or neurosurgery, particularly if there has been more than one episode of meningitis. *Neisseria meningitidis* (meningococcal) meningitis tends to occur in outbreaks that are facilitated by crowded living conditions, such as army barracks and schools, and is an important cause of purulent meningitis in children. *Haemophilus influenzae* is only very rarely responsible for meningitis in adults but is, like *N. meningitidis*, a relatively frequent cause of purulent meningitis in children, especially in those under 2 years of age. Gram-negative bacilli are often responsible

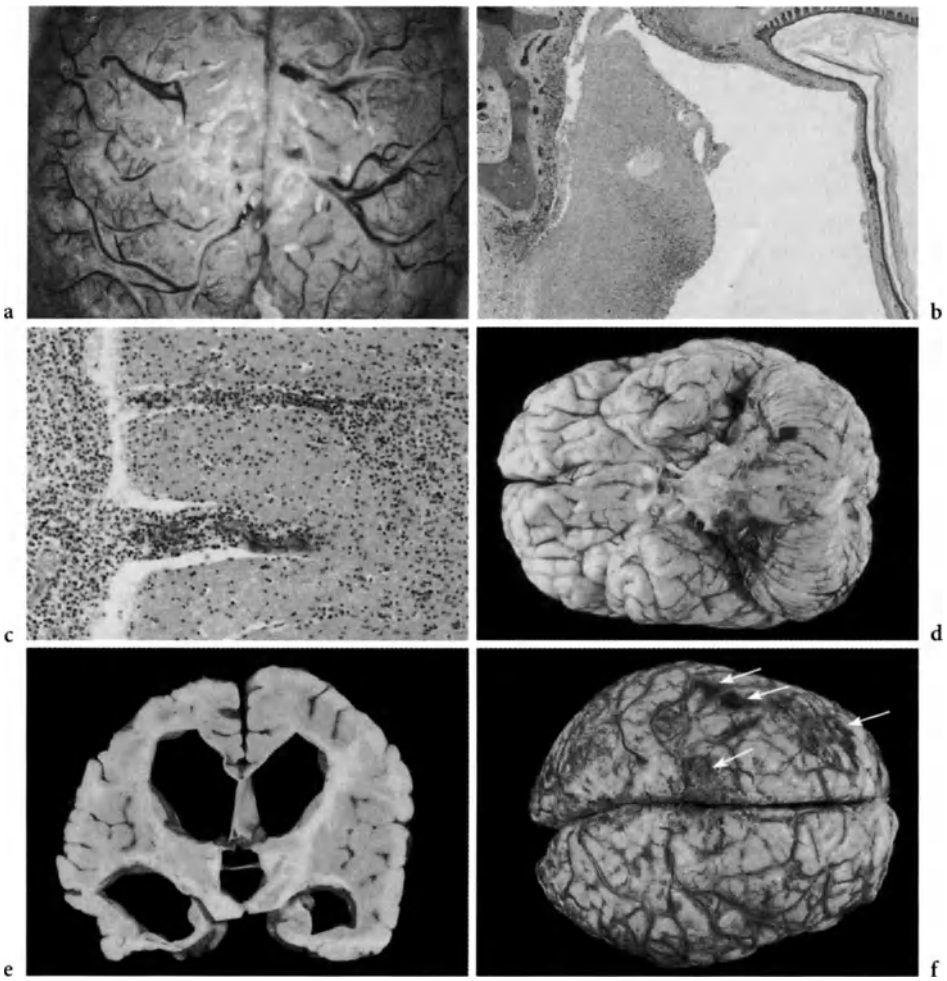


Fig. 1a–f. Purulent meningitis. **a** Purulent exudate over the vertex of the brain of an infant with pneumococcal meningitis. In this case, the infection had spread from the middle ear (**b**), which is filled with purulent material (tympanic membrane to *right* of figure). Case courtesy of Dr. A. Charles. **c** Histology reveals a purulent exudate in the subarachnoid space and extending along perivascular spaces into the superficial cortex. **d** Exudate over the base of the brain in meningitis complicating neurosurgery. **e** Non-communicating (obstructive) hydrocephalus complicating meningitis. **f** Multiple foci of haemorrhagic discolouration due to infarction (*arrows*) are visible in this case of pneumococcal meningitis

for meningitis complicating neurosurgery or head injury. Slime-producing strains of *Staphylococcus epidermidis* are the main cause of meningitis complicating ventricular shunt infection, although *Staphylococcus aureus* or gram-negative bacilli are occasionally responsible.

The clinical presentation of purulent bacterial meningitis is usually with pyrexia, headache, neck stiffness, photophobia, nausea and vomiting, but symptoms and signs of septicaemia and cardiovascular collapse may predominate, particularly in meningococcal infections. About 50% of patients with meningococcal meningitis will have developed a rash, initially maculopapular but later purpuric and often confluent. In children, meningococcal infection is occasionally complicated by Waterhouse-Friderichsen syndrome, comprising septicaemia, shock, acute adrenal haemorrhage and adrenal failure. The presentation of ventriculitis due to shunt infection may be relatively insidious, with malaise, pyrexia, headache and confusion but no neck stiffness or photophobia.

At autopsy, the frontal air sinuses and middle ears should be examined for evidence of local infection (Fig. 1b). The lungs, heart and other tissues should be examined for possible sources of haematogenous infection. Examination of the brain reveals a purulent exudate in the subarachnoid space (Fig. 1c). An exudate may also be present in the ventricles, particularly in patients with meningitis and ventriculitis complicating shunt infection. In *S. pneumoniae* meningitis, the exudate tends to be most prominent over the cerebral convexities, towards the vertex (Fig. 1a). In other types of bacterial meningitis, the exudate is usually, but not always, thickest over the base of the brain (Fig. 1d). The brain is usually swollen, due to oedema and hydrocephalus in variable combination. Mild to moderate hydrocephalus is common (Fig. 1e) and may be either communicating, due to impeded flow of CSF in the subarachnoid space and arachnoid granulations, or non-communicating (obstructive), due to obstruction of the aqueduct or the outflow foramina of the fourth ventricle. Thrombosed cortical blood vessels and foci of infarction may be evident (Fig. 1f).

2.1.3 Granulomatous Meningitis

Much the commonest cause of granulomatous meningitis is *Mycobacterium tuberculosis*. Tuberculosis is increasing in incidence in many parts of the world, particularly in Africa and Eastern Europe, where the increase is probably attributable to the high prevalence of HIV infection [125, 126], and the incidence remains high in parts of South-East Asia and some Western Pacific countries [126]. In immunocompetent individuals, tuberculous meningitis is usually a complication of primary mycobacterial infection. In developing countries, in which primary exposure occurs at an early age, tuberculous meningitis is therefore commonest during childhood. In 'developed' countries, primary exposure to patients with active tuberculosis is much rarer and can occur at any age, as a result of which tuberculous meningitis does not show the same predilection for the young. At any age, tuberculous meningitis can complicate the reactivation of dormant infection in patients whose cell-mediated immunity becomes depressed (see below). The incidence of tuberculosis is increasing in urban communities with large numbers of indigent in-

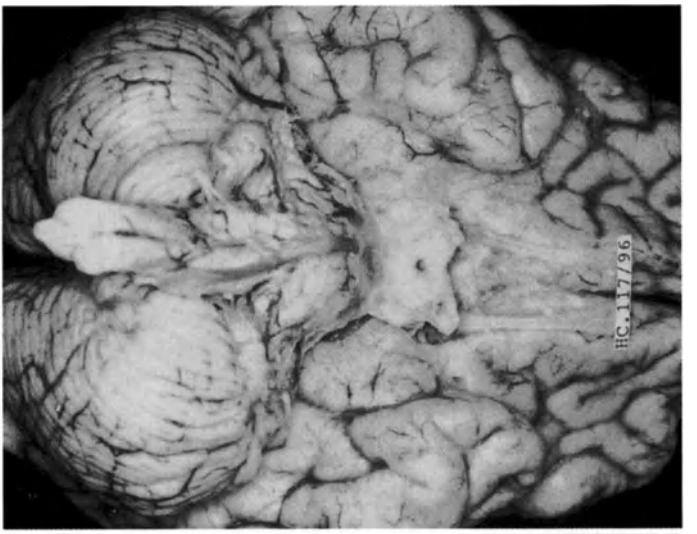
habitants and a high prevalence of HIV infection, and in such conditions there is an increased likelihood of exposure, even of immunocompetent individuals. Tuberculous meningitis tends to have an insidious presentation, with pyrexia, headache, malaise and lethargy and, as the disease progresses, neck stiffness, vomiting and the development of cranial nerve palsies and other focal neurological deficits.

Tuberculous meningitis produces a gelatinous or slightly nodular exudate, most pronounced in the Sylvian fissures and over the base of the brain (Fig. 2a) [48, 65]. The exudate can also involve the choroid plexus and ventricular lining. Small tuberculomas may be visible within the exudate and in the superficial brain parenchyma. Mild to moderate hydrocephalus is frequent. Endarteritis is quite a common complication of tuberculous meningitis and causes infarcts, particularly in the cerebral cortex and basal ganglia.

The main non-infective differential diagnosis of tuberculous meningitis is neurosarcoidosis [29, 61, 69, 169]. The CNS is involved in approximately 5% of patients with sarcoidosis, in whom this may be the only site of disease. The base of the brain around the optic chiasm and over the floor of the hypothalamus usually bears the brunt of the granulomatous inflammation, but this can affect the meninges and superficial brain parenchyma anywhere within the cranial cavity or spinal canal, and can also involve the choroid plexus and ventricular lining. The differential diagnosis of granulomatous meningeal inflammation includes several other rare, non-infective disorders – Wegener's disease, idiopathic hypertrophic pachymeningitis and isolated granulomatous angiitis of the CNS.

Rare infective causes of granulomatous meningitis in immunocompetent adults are infections caused by either of the two dimorphic fungi, *Blastomyces dermatitidis* and *Coccidioides immitis* [18, 30, 91, 174]. The former is responsible for North American blastomycosis, endemic in the south-eastern United States, and the latter for coccidioidomycosis, endemic in parts of the south-western United States and Central and South America. These fungi cause granulomatous inflammation of the meninges and brain parenchyma. The parenchymal disease usually takes the form of multiple small granulomas but purulent inflammation with abscess formation can occur [11]. The portal of entry of both of these fungi is the respiratory tract, and CNS involvement is usually a sequel of pulmonary disease, which should be sought at autopsy. Meningitis due to the yeast, *Cryptococcus neoformans*, can occur in the absence of immunosuppression but is far more often a complication of depressed cell-mediated immunity, malignancy or general inanition and is therefore discussed below (in Sect. 2.2).

Meningovascular syphilis is now rarely seen but in recent years the incidence of early syphilis has risen in certain high-risk groups such as prostitutes and their clients, especially in sub-Saharan Africa, South-East Asia and Eastern Europe [44, 47, 80, 100, 124, 136, 138, 152, 177]. The frequency of meningovascular syphilis and other tertiary manifestations of this disease may also have increased within these groups, particularly in patients with concomitant HIV infection (see Sects. 2.2 and 5.1.2). Meningovascular syphilis comprises a combination of (1) thickened fibrotic leptomeninges that are infiltrated by lymphocytes and plasma cells and may contain miliary gummas, and (2) multifocal intracranial arteritis, in which affected arteries and arterioles are infiltrated by mononuclear inflammatory cells and develop marked collagenous intimal thickening that may completely occlude the lumen [48, 63, 65]. The arteritis may cause ischaemic damage, including frank infarcts.



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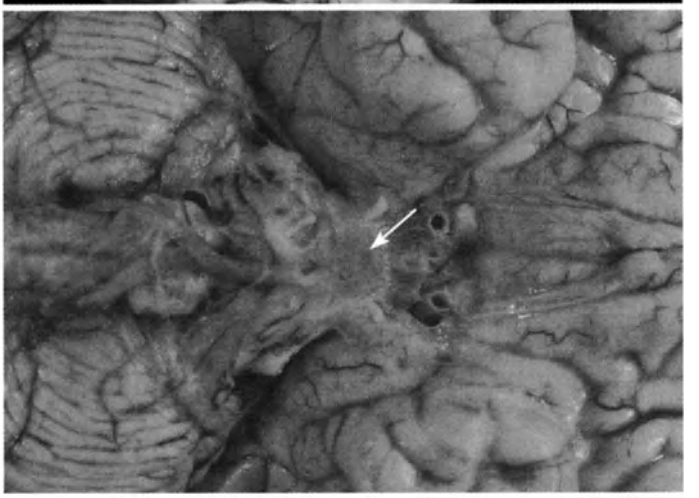

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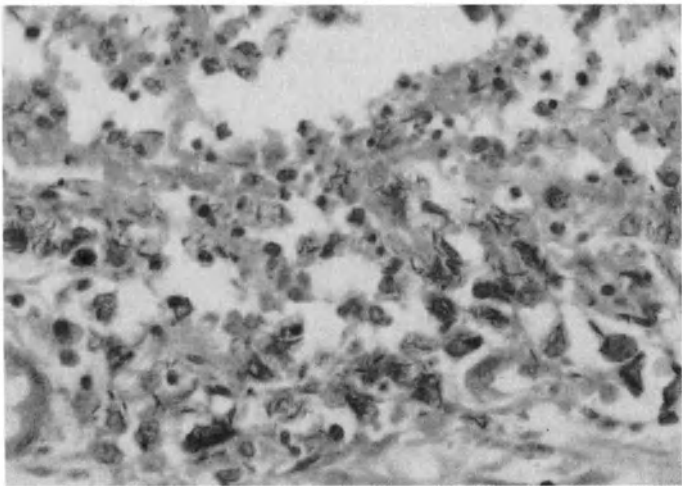

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2.2 Immunosuppressed Patients

As already noted, the risk of pneumococcal meningitis is increased by debilitation and splenectomy. The risk of both pneumococcal and *H. influenzae* infections is also increased in hereditary splenic hypoplasia [87] and a range of other, rare immunodeficiency states. Patients with deficiencies in the 'early' complement proteins, C1, C4 and C2, are at risk of pneumococcal infections, including meningitis [148, 176] and those with C3 deficiency tend to develop recurrent, severe pneumococcal and meningococcal infections [129, 148]. Recurrent meningococcal infections are also associated with 'late' complement protein deficiencies, involving C6–9, but these infections tend to have a low mortality [88, 148, 155, 204]. Inherited deficiency of properdin predisposes to meningococcal infections that have a high mortality [148, 155]. Other inherited immunodeficiency diseases that predispose to purulent bacterial meningitis include X-linked agammaglobulinaemia [82] and glucose-6-phosphate dehydrogenase deficiency [105]. Acquired disorders of humoral immunity, such as granulocytic leukaemia and granulocytopoenia, also predispose to purulent meningitis. This is most often bacterial, due to pneumococcus, gram-negative bacilli (especially *Pseudomonas aeruginosa*) or occasionally *Listeria monocytogenes*. Rarely, *Candida* species are responsible.

Patients with depressed cell-mediated immunity (especially those with AIDS, but also organ transplant recipients, patients with lymphomas and lymphocytic leukaemias and those with rarer immunosuppressive disorders) are at risk of tuberculous meningitis. This is due to reactivation of infection in primary tubercles, either within the brain itself (in so-called Rich's foci) or in other tissues, in which case the CNS is infected during subsequent haematogenous dissemination. In severely immunosuppressed patients, tuberculous meningitis is characterised by the presence of abundant mycobacteria and an absence or paucity of granulomas (Fig. 2c) [48].

There is some evidence of an increased prevalence of meningovascular and other forms of neurosyphilis in HIV-infected patients [14, 17, 54, 72, 160]. HIV infection may accelerate the progression to tertiary syphilis and increase the likelihood of CNS involvement, particularly in the form of meningovascular disease, although this is more contentious [14, 85, 132, 160]. Meningovascular syphilis manifests pathologically with fibrous thickening and chronic lymphocytic and plasmacytic inflammation of the meninges over the brain or spinal cord, and concentric collagenous thickening and inflammation of the intima of arteries and arterioles, leading to foci of ischaemic damage (see Sect. 5.1.2).

Depressed cell-mediated immunity increases the risk of fungal meningitis due to *Cryptococcus neoformans* or *Histoplasma capsulatum* [40, 99, 112, 168, 183, 191,

Fig. 2a–c. Tuberculous meningitis and neurosarcoidosis. **a** Nodular exudate (*arrow*) over the base of the brain in tuberculous meningitis. Original figure courtesy of Prof. L. Chimelli. Reproduced with permission, from [48]. **b** Granulomatous exudate in neurosarcoidosis. The basal meninges are thickened and a yellowish grey exudate (*arrow*) surrounds the optic nerves and pituitary stalk. **c** Numerous acid-fast mycobacteria in an AIDS patient with tuberculous meningitis. Original figure courtesy of Prof. L. Chimelli. Reproduced with permission, from [48]

192]. The abnormalities on external examination of the brain in cryptococcal meningitis tend to be mild. The surface of the brain may appear slimy and the leptomeninges thickened. Sectioning of the brain shows perivascular spaces in the cortex and basal ganglia to be expanded by numerous thickly encapsulated yeasts to form multiple small cystic spaces, likened to soap bubbles (Fig. 3a). The cryptococcal yeasts may be mistaken for corpora amylacea on casual microscopic examination (Fig. 3b). Involvement of the CNS by histoplasmosis is usually a

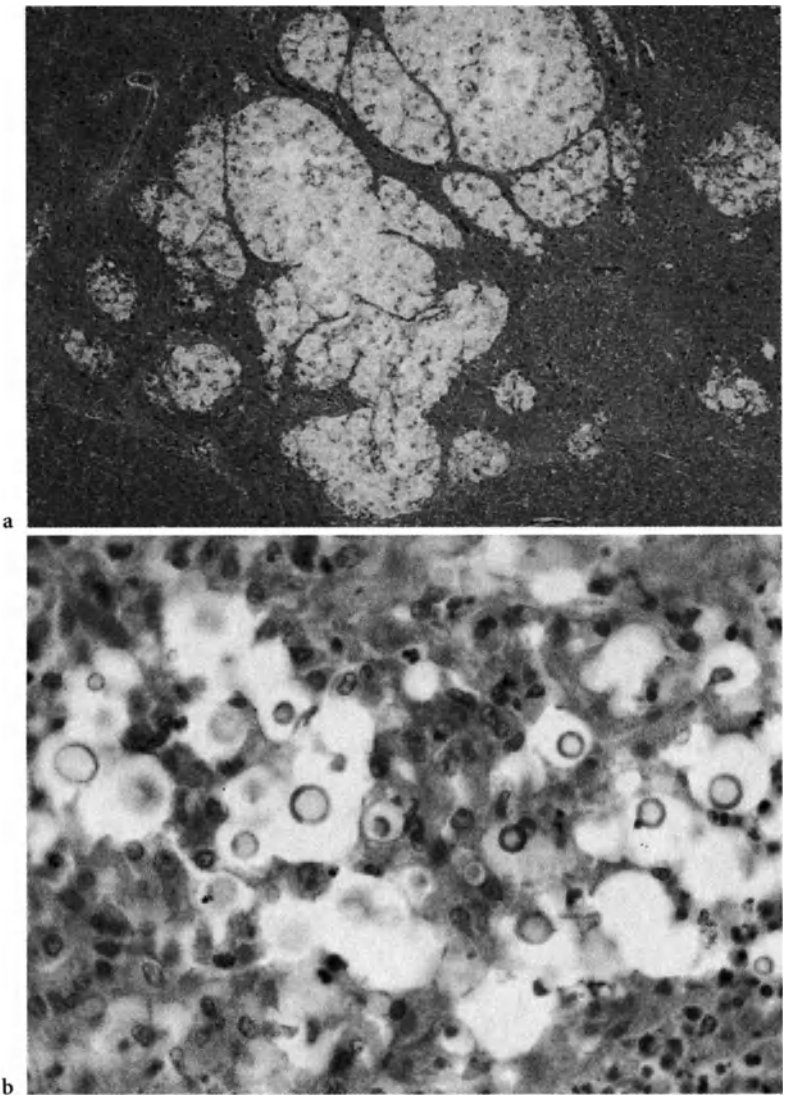

Fig. 3a, b. Cryptococcal meningitis. **a** Expanded perivascular spaces in the basal ganglia contain numerous yeasts. **b** Meningeal inflammatory exudate within which are scattered, spherical yeasts resembling corpora amylacea

manifestation of disseminated fungal infection. *Histoplasma* causes a granulomatous meningitis resembling that of tuberculous infection. A gelatinous or nodular, yellowish grey exudate is usually visible over the base of the brain and small granulomas or abscesses are often present in the brain parenchyma. The yeasts measure only 2–5 μm in diameter and are difficult to see in haematoxylin- and eosin-stained sections but, like other fungi, are readily demonstrated by PAS staining or methenamine silver impregnation. Both acquired defects in cell-mediated immunity and certain rare inherited immunodeficiency disorders predispose to systemic candidal infections, including meningitis [60, 98]. However, in *Candida* infections of the CNS, parenchymal brain lesions usually predominate (see below).

Free-living amoebae of the genera *Acanthamoeba* and *Balamuthia* are an occasional cause of granulomatous meningoencephalitis in patients who are immunosuppressed or severely debilitated [48, 109, 153]. The meningeal inflammation is patchy, the distribution of meningeal exudate being related to necrotic lesions in the underlying brain parenchyma. Granulomatous meningoencephalitis is described in more detail in Sect. 3.2.

2.3 Neonates

The commonest causes of meningitis in neonates are bacterial: group B streptococci and *Escherichia coli* [56, 73, 119, 143, 171, 186]. Low birth weight, prolonged rupture of amniotic membranes and puerperal sepsis are the major risk factors. Group B streptococci are readily spread by contact within hospital wards, leading to local outbreaks of this type of neonatal meningitis. Other bacteria that are, less often, responsible for meningitis in neonates include *Listeria monocytogenes*, *S. aureus*, *Citrobacter*, *Klebsiella* and *Enterobacter* species, *Pseudomonas aeruginosa* and other gram-negative bacilli.

The initial clinical signs of neonatal meningitis are usually non-specific and include poor feeding, diarrhoea and vomiting, irritability or lethargy. The development of neck stiffness, bulging of the fontanelle and signs of shock are late manifestations. At autopsy, the brain appears swollen and the leptomeninges markedly congested. A purulent subarachnoid exudate is usually visible, particularly over the base of the brain (Fig. 4a). A particularly frequent finding in this age group is the presence of haemorrhagic infarcts, associated with thrombosis of superficial veins and arteries (Fig. 4b) [48]. Another occasional finding is the presence of coexistent cerebral abscesses, especially in gram-negative bacterial infections.

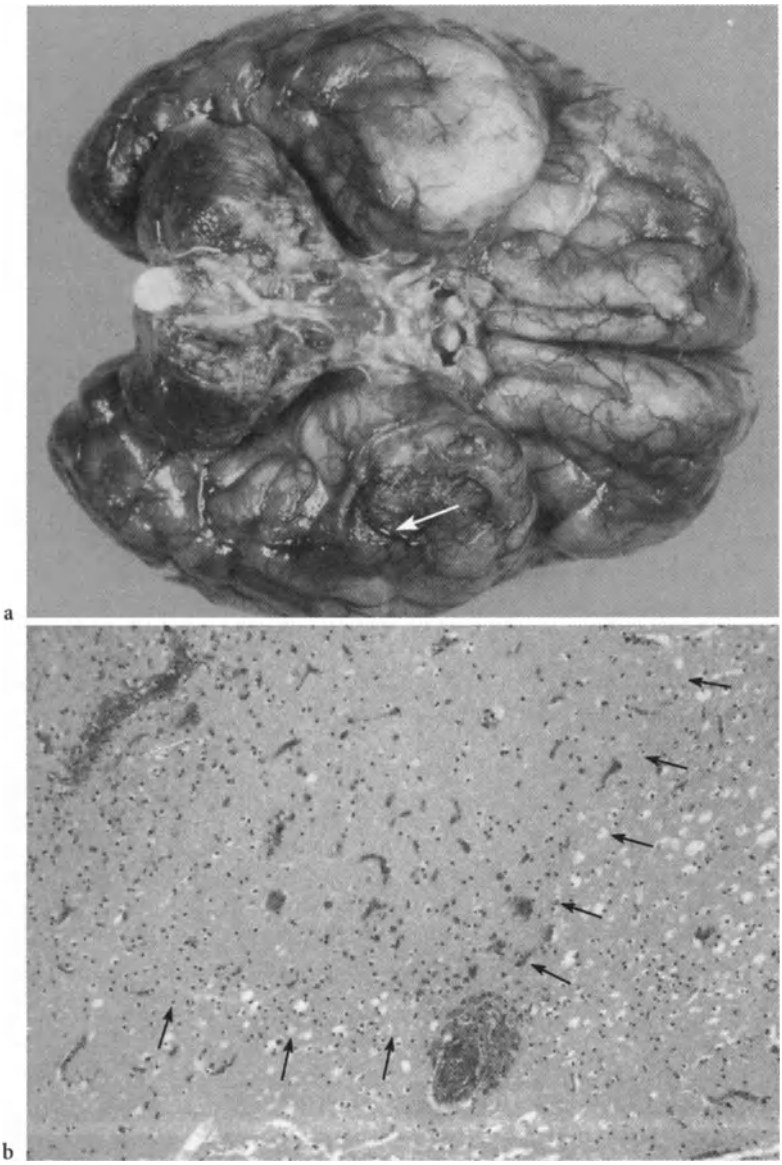

Fig. 4a, b. Neonatal meningitis. **a** External examination of the brain in this case of group B streptococcal meningitis reveals a scanty basal purulent exudate, marked leptomeningeal congestion and focal venous thrombosis (*arrow*) with infarction of the underlying temporal cortex. Original figure courtesy of Dr. H. Porter. Reproduced with permission, from [48]. **b** Thrombosis of superficial cortical blood vessels with acute infarction of the adjacent cortex (*arrows*)

3 Abscesses, Empyemas and Parenchymal Granulomas

3.1 Immunocompetent Adults and Children

3.1.1 Brain Abscess

Approximately half are due to local spread of infection from a paranasal sinus, middle ear or dental root [19, 46, 147, 162, 199]. The pathogen most often isolated from these brain abscesses is *Streptococcus milleri*. Bacteria less frequently isolated include a wide range of aerobic and anaerobic streptococci, staphylococci and gram-negative bacilli. The resulting abscess is usually solitary, the location varying according to the source of infection. When the source is an infection of a paranasal sinus, the abscess involves the adjacent part of the frontal lobe. Abscesses associated with middle ear infections tend to involve the temporal lobe or anterior part of the parietal lobe but may occasionally occur in the cerebellum. Cerebral abscesses complicating dental root infections usually involve the frontal lobes; occasionally responsible in such cases is *Actinomyces israelii*, a filamentous gram-positive bacterium that tends to cause multiloculated cerebral abscesses.

Haematogenous sources of infection in adults include bronchiectasis, lung abscess and endocarditis. In children, congenital heart disease or pulmonary arteriovenous malformation with right-to-left shunting carries a substantial risk of development of brain abscesses (Fig. 5a), presumably because of the combination of relative hypoxaemia, bypass of the pulmonary capillary bed, and increased blood viscosity due to polycythaemia. Patients with haematogenously derived infection may develop multiple brain abscesses. Although typically these occur at the junction of cerebral cortex and white matter (Fig. 5b), in some cases microabscesses are widely scattered throughout the brain. The most frequent pathogens are *Streptococcus viridans* and microaerophilic or anaerobic streptococci. Rare, non-bacterial causes of brain abscesses in immunocompetent patients include *Entamoeba histolytica*, *C. neoformans* (cryptococcomas), *C. immitis* and *B. dermatitidis* (for further information about these last two pathogens see also Sect. 2.1.3). Amoebic brain abscesses occur only in patients who already have intestinal and liver or pulmonary amoebiasis. Cryptococcomas are described in Sect. 3.1.4.

Irrespective of the underlying aetiology, virtually all patients will develop headache and pyrexia and, depending on the size and site of the abscess or abscesses, evidence of raised intracranial pressure and focal neurological deficits. Other clinical manifestations will vary according to the predisposing conditions, the source of sepsis and the presence of associated pathology, such as embolic infarcts in patients with endocarditis.

The macroscopic and microscopic appearances of abscesses vary according to their age [48, 65, 199]. During the first week or so, when the histology is that of focal suppurative encephalitis and the abnormalities are often poorly circumscribed, the macroscopic changes may be limited to focal brain swelling and congestion. The early microabscesses associated with haematogenous infection are often centred on small blood vessels showing fibrinoid necrosis; macroscopically, these appear as small haemorrhages or foci of haemorrhagic softening [131]. Older abscesses will

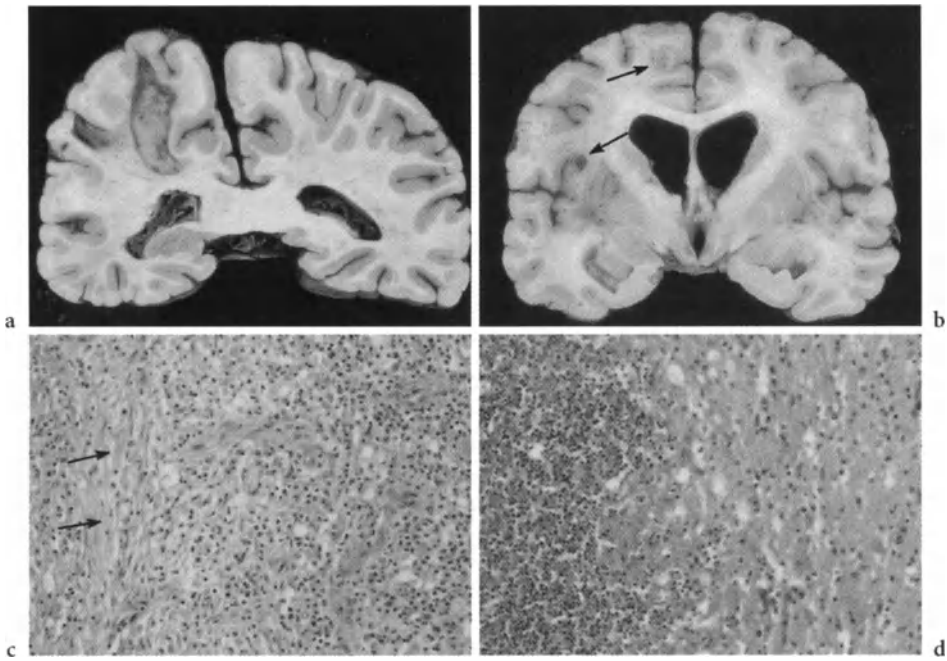

Fig. 5a–d. Brain abscess. **a** Large abscess in parietal lobe of a patient with a complex cardiac malformation and right-to-left shunting. **b** Multiple small abscess (*arrows*) at the junction of cortex and white matter in a patient with septicaemia due to *S. aureus*. **c, d** Sections through the superficial (**c**) and deep (**d**) parts of a cerebral abscess. Note the proliferation of fibroblasts and deposition of collagen (*arrows*) in **c** and their absence from the deep margin of the abscess

have collagenous capsules of variable thickness and a well-defined core of purulent material. The capsule tends to be thicker on the superficial aspect of the abscess (Fig. 5c) than on its deep aspect (Fig. 5d). If cutting into an abscess releases a foul odour (usually detectable even after fixation of the brain), anaerobic infection is likely. Amoebic brain abscesses have irregular necrotic cores that are surrounded by reactive brain tissue without collagenous encapsulation [48, 109]. The trophozoites, which are often mistaken for macrophages, have a round vesicular nucleus with a central karyosome and can usually be found in the 'wall' of the abscess.

3.1.2 Subdural Empyema

The antecedents of subdural empyemas are similar to those of brain abscesses (local infections, trauma, neurosurgery and systemic foci of purulent infection) and likewise the range of pathogens [45, 93, 199]. In children, the development of a subdural empyema may complicate purulent meningitis. The macroscopic and microscopic features are simply of pus in the subdural space, usually but not always in the supratentorial compartment. The pus may be encapsulated by granulation tissue of variable thickness.

3.1.3 Extradural Empyema

This usually occurs within the spinal canal. The source of infection is often local – adjacent vertebral osteomyelitis or a retropharyngeal abscess – but haematogenous spread may occur from distant foci of purulent infection [58]. *S. aureus* is the bacterium usually isolated, gram-negative bacilli much less frequently.

3.1.4 Parenchymal Granulomas

The differential diagnosis of parenchymal brain granulomas includes tuberculosis, syphilis, Whipple's disease, fungal infections and parasitic diseases.

Tuberculomas are still relatively common in parts of the world with a high prevalence of tuberculosis, particularly in much of Africa, South-East Asia and some Western Pacific countries [125, 126]. They most often occur in children, in whom the tuberculomas tend to be infratentorial: in the cerebellum or pons. In adults, tuberculomas usually occur above the tentorium [63]. Their appearances are similar to those of tuberculomas elsewhere in the body, with central caseous necrosis surrounded by a granulomatous inflammatory reaction that includes Langhans-type giant cells, and a surrounding zone of collagenous fibrosis Fig. 6).

Syphilitic gummas are now rare, although as noted in Sect. 2.1.3, this situation may change, as the incidence of syphilis increases in some Eastern European,

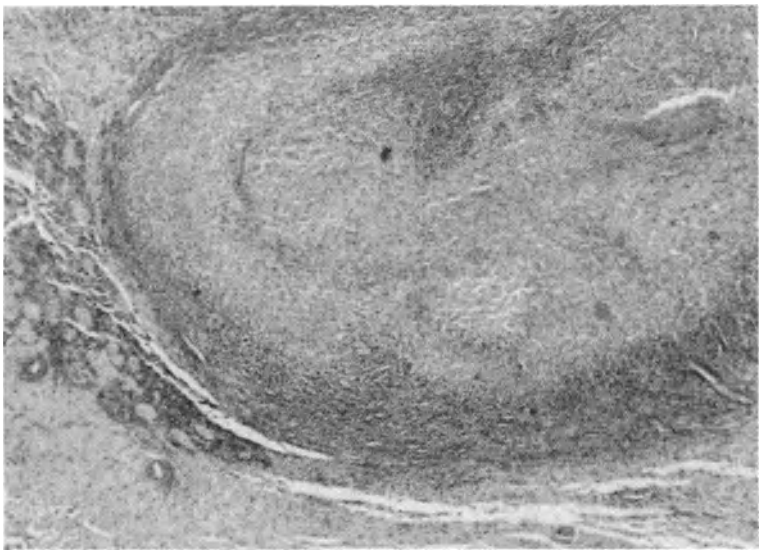

Fig. 6. Cerebral tuberculoma. The section includes part of a tuberculoma and the adjacent brain tissue. There is a central caseous necrosis surrounded by a rim of epithelioid macrophages and Langhans-type giant cells, and an outer zone of lymphocytes, fibroblasts and collagen. The collagen fibres appear dark in this haematoxylin/van Gieson preparation

South-East Asian and sub-Saharan African countries, especially in high-risk groups such as prostitutes and their partners [44, 47, 59, 80, 95, 100, 124, 136, 138, 152, 165, 177].

Whipple's disease is caused by a gram-positive bacillus, *Tropheryma whippelii*, that accumulates in large numbers within macrophages in affected tissues. The small intestine is the main site of disease in most patients, but other tissues may be involved, including the CNS [137, 139, 159, 198]. The manifestations of CNS disease are variable and can include ophthalmoplegia, oculomasticatory myorhythmia, facial or ocular myoclonus, sleep and eating disturbances, confusion and dementia [3, 43, 111, 141, 187, 203]. Macroscopic examination of the brain may reveal foci of granular yellow discolouration, especially in the thalamus, hypothalamus and around the aqueduct. Microscopy shows these foci to contain clusters of macrophages within which is intensely PAS-positive, diastase-resistant material. The bacilli may be difficult to demonstrate with a Gram stain but can be impregnated with methenamine silver.

Isolated parenchymal or meningeal fungal granulomas are a very infrequent finding in immunocompetent patients although multiple small granulomas or abscesses are a feature of *Blastomyces dermatitidis* and *Coccidioides immitis* meningitis. Cryptococcomas are an unusual manifestation of *C. neoformans* infection but, when they do develop, tend to affect patients with preserved immune function. The appearance of cryptococcomas is variable: some are densely fibrotic lesions with granulomatous inflammation, others are large gelatinous lesions full of yeasts, or they may resemble bacterial abscesses [30, 48, 153].

Symptomatic CNS involvement in schistosomiasis is relatively rare and occurs in patients in whom large, discrete deposits of ova within the brain or spinal canal elicit a focal granulomatous reaction. These deposits of large numbers of ova are thought to result from anomalous migration of adult worms to sites within or close to the CNS [134]. Patients develop clinical features of an intracranial space-occupying lesion or of a painful radiculopathy and myelopathy that may progress within days to paraplegia. More common is the presence of sparsely scattered and usually asymptomatic granulomas that result from retrograde embolisation of ova through the pelvic veins and valveless vertebral venous plexus in patients with hepatointestinal schistosomiasis and portal hypertension or with severe urinary schistosomiasis. In such cases *S. haematobium* and *S. mansoni* ova are most likely to lodge within the meninges surrounding the lumbosacral spinal cord but *S. japonicum* ova may lodge within the brain. The sparsely scattered granulomas that develop in relation to the ova are usually an incidental finding at autopsy but may be associated with seizures or, rarely, focal haemorrhage [134]. The occurrence of granulomatous inflammation in relation to parasitic cysts is considered in Sect. 4.

3.2 Immunosuppressed Patients

In addition to those already discussed, a wide range of bacteria, fungi and protozoa can cause brain abscesses or, at least, focal necrotic lesions, in patients who are immunosuppressed. The potential bacterial pathogens include *Nocardia asteroides*, *Listeria monocytogenes,* a range of gram-negative bacilli and *M. tuberculosis*. The principal parasite to consider in this context is *Toxoplasma gondii*. The range of