NEUROLOGICAL MANAGEMENT

Meningitis

H P Lambert

Three organisms predominate in causing community-acquired bacterial meningitis, Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae. Meningococcal meningitis is most common in childhood but also affects adolescents and adults. A total of 1302 cases were notified in England and Wales in 1992, 71% of them caused by group B strains against which no vaccine is yet available. Haemophilus influenzae meningitis chiefly affects children less than five years old, although a few older patients are encountered. In 1992, 1089 blood or CSF isolates, or both, were recorded and a seven-year study in the Oxford region has estimated the cumulative risk by the fifth birthday as 1:800. Invasive haemophilus haemophilus meningitis are already showing a gratifying reduction following the introduction of Hib conjugate vaccines in October 1992.

The pattern of pneumococcal meningitis is more complex. It is seen at all ages but affects particularly the extremes of life and is also especially associated with immune defects such as asplenia, as in sickle cell disease, and with fractures of the skull or congenital defects allowing entry of bacteria to the CNS. This infection carries a high mortality, rarely recorded as less than 20%. The overall mortality from meningococcal and haemophilus meningitis is 5–6% in Britain, but the picture is often complicated by inclusion of acute meningococcal septicaemia, with a much higher death rate than that seen in meningitis alone. The overall mortality from childhood meningitis over a 10-year period in Nottingham was 11.6% and at least one in 10 of the survivors suffered permanent sequelae; these consequences of meningitis are discussed later. In developing countries the incidence and mortality from meningitis are often much higher than in wealthier countries.

Meningitis caused by other bacteria is less common but important, as these infections often cause serious difficulties in diagnosis and management. The need to consider other agents has increased with the increasing number of patients with immune defects, especially HIV infection, and the associated resurgence of tuberculosis. To these bacterial causes must be added the problem of cryptococcal meningitis in association with HIV infection. In nosocomial meningitis, Gram-negative organisms such as Escherichia coli, Klebsiella and pseudomonas have to be considered in the differential diagnosis, as also does Listeria monocytogenes. A similar distribution of organisms is seen in neonatal meningitis, a special problem not dealt with in this review.

Clinical diagnosis

In most patients the initial diagnosis of meningitis, or at least its possibility, is obvious from the combination of systemic and neurological features. Malaise, fever, severe headache, photophobia, and neck stiffness are common and sometimes consciousness is disturbed. The discussion will therefore mainly be concerned with difficulties in diagnosis and, as so often, these are greatest at the extremes of life. The problem of diagnosis in infancy is beyond the ambit of this review, but similar difficulties are sometimes encountered in the elderly. Consciousness may become rapidly depressed and soft neurological signs may lead diagnostic thoughts in the direction of a cerebrovascular accident. Fortunately meningism is a sign not easily masked and is usually, but not always, maintained even in comatose patients.

Meningococcal disease may present in several atypical and deceptive ways. At one extreme, fulminating meningococcal septicaemia, the illness may run its short course from onset to death with no element of meningitis. At the other end of the scale of severity patients, especially children, may experience a period of hours, or even days, of febrile illness with no meningeal features before the symptoms and signs of meningitis appear. This sequence has often led to medicolegal problems when a claim of delayed or missed diagnosis may rest on this point. One especially deceptive presentation of meningococcal meningitis, seen in adolescents and young adults, is as acute mania, directing the diagnosis towards acute psychosis, possibly drug-induced. Neck stiffness may not yet have developed or may be impossible to test for.

The rash of meningococcal septicaemia, when present, is a valuable feature, as the combination of petechial-purpuric rash and meningitis is virtually diagnostic for this
organism. The rash may vary from a few inconspicuous petechiae to extensive purpura with skin necrosis. Non-purpuric rashes—and occasionally petechial ones—are seen in some patients with enteroviral rashes, but this aetiology should never be assumed, as the early rash of meningococcal disease may be macular and unimpressive.

Focal neurological signs are relatively uncommon in pyogenic meningitis in previously healthy patients. Ocular palsies usually resolve within days or weeks. In sharp contrast, labyrinthine damage, which often develops early in the illness, is usually permanent. The frequency of convulsions varies greatly between different forms of meningitis, and is much higher in infancy than in older age groups. They are most frequent in pneumococcal meningitis, less common in haemophilus meningitis, and uncommon in meningococcal disease. Fits are also distinctly uncommon in community-acquired meningitis in adult life, in patients with no underlying neurological abnormality. When focal signs, convulsions, or disturbance of consciousness are prominent in the clinical picture, the possibility of an encephalitis as the primary diagnosis should be considered.

In community-acquired meningitis in previously healthy patients there is often no specific aetiological clue such as rash, recent otitis media, or head injury. In such cases the patient's age may be the sole diagnostic pointer, as haemophilus meningitis is rare after the first few years of life, meningococcal meningitis is the most common form at school age and in young adults, whereas in the elderly S pneumoniae becomes more frequent. There are many exceptions to these generalisations, especially now that many reasonably well people in the community may have various forms of immune suppression, notably HIV infection or treatment with immunosuppressive drugs, and may present with uncommon forms of meningitis. Early and accurate laboratory diagnosis therefore remains important and should be achieved as often as possible.

**LUMBAR PUNCTURE**

Until recently, suspicion of meningitis was accepted as an almost invariable indication for lumbar puncture, although it was always recognised that it should be avoided or deferred if there was suspicion of an alternative diagnosis that might mimic meningitis, such as brain abscess, cerebral haemorrhage, encephalitis, or posterior fossa tumour. In the last few years, however, concern about the possibility of coning has led to a more cautious approach to lumbar puncture in meningitis. The risk of coning is variously estimated. A recent retrospective survey, from an Australian paediatric referral centre receiving a preponderance of complicated or seriously ill children, noted cerebral herniation in 19 of 445 children (4-3%). There was a strong suggestion that lumbar puncture led to this complication in some patients, although it can certainly occur in patients with meningitis when no lumbar puncture has been done. On the other hand, there are great advantages in making an accurate and early diagnosis, and a Gram-stained smear of the CSF deposit is still the most common way in which this can be achieved. Certainly ‘blind’ treatment is often successful but if the responsible organism is unusual or antibiotic-resistant, or the patient’s progress is unsatisfactory in any way, failure of identification creates an uncertain and unsatisfactory situation.

The dilemma can be resolved by defining genuine risk factors for coning while accepting that lumbar puncture is normally indicated in suspected meningitis. A common injunction is to avoid lumbar puncture if there is suspicion of raised intracranial pressure, a distinctly unhelpful precept as intracranial pressure is raised in nearly every patient with meningitis. More realistic guidelines can be set using known clinical correlates of impending coning, namely coma or rapidly increasing depression of consciousness, focal neurological signs, and tonic or prolonged fits. Fits are common in childhood meningitis in some communities and are not an invariable contraindication to lumbar puncture although, as Mellor points out in a thoughtful review, it is sensible to defer lumbar puncture for 30 minutes after a fit because of the transient cerebral oedema that accompanies it. Papilloedema is a contraindication but is very rare in meningitis and its presence should in any case indicate a wider diagnostic sweep.

Another indication for avoiding or delaying lumbar puncture is unrelated to the question of coning. This is the need for urgent treatment of patients with established or threatened bacterial shock (usually meningococcal septicaemia). The window of opportunity closes rapidly in these patients and treatment should on no account be delayed in order to avoid a lumbar puncture.

CT or MR scans are usually normal or mildly and non-specifically abnormal in meningitis and are not generally helpful in detecting coning.

**TUBERCULOUS MENINGITIS**

In countries with a high prevalence of tuberculosis, tuberculous meningitis acts as one of the markers of the frequency of infection, and the diagnosis is in question in any patient, especially a child, with meningitis. Where tuberculosis has declined the diagnosis is hard to bear in mind, and the problem is compounded by the often deceptive ways in which this disease presents. Its importance is again increasing with the spread of HIV infection and the high prevalence in many countries of the poor social conditions and crowding that are associated with tuberculosis. The relationship of success in treatment to the stage at presentation has rightly been stressed.

There is usually a prodromal illness of days or weeks, with low fever, malaise, and headache before meningeal features develop.
The multiple pathology of tuberculous meningitis, with basal arachnoiditis, vasculitis, infarction, and obstructive hydrocephalus leads to an immense variety of possible focal features; most frequent are cranial nerve palsies and papilloedema. Spinal involvement may take a number of different forms, and rare presentations include a mainly encephalopathic picture. It is important, however, to remember that tuberculous meningitis may present as a meningeval illness with no specific features, so that the diagnosis must be entertained in any patient with non-purulent meningitis. Some persistent myths must be abandoned; the onset may be acute, the CSF glucose is within the normal range in about 20% of cases, and the tuberculin test initially negative in a similar proportion. Because of these protean manifestations, laboratory diagnosis is particularly important (see below), but unfortunately tubercle bacilli are seen in the CSF in only a few cases, depending on the technical skills available, and cultures are not always positive. Indicative features in the clinical presentation include slow onset, contact or family history, ethnic origin, or immigrant status from an area of high prevalence, while a primary lung complex or any evidence of miliary tuberculosis will obviously virtually establish the diagnosis.

**CRYPTOCOCCAL MENINGITIS**

Cryptococcal meningitis also varies widely in its mode of onset. In immunocompromised patients the course tends to be more rapid than in the immunocompetent but in both groups onset may be insidious, with general malaise, low fever, and headache. This subtle form of presentation is common now that HIV infection is the most frequent type of immune abnormality preceding cryptococcal meningitis. Indeed, features indicative of CNS involvement may be entirely absent and the indications for lumbar puncture must be more widely set in these patients than in the immunocompetent. Lumbar puncture in HIV-infected patients should be preceded by CT because of the possibility of a silent mass lesion. A small proportion of patients with cryptococcal meningitis show focal neurological signs, including early visual loss. In some patients the course of the illness is much more protracted, extending over many months before a diagnosis is reached, and sometimes greatly fluctuating in severity.

**LISTERIA MENINGITIS**

This is most frequently seen in the neonate but also has a predilection for the immunocompromised and the elderly. Presentation is usually as an acute purulent meningitis with no particular distinguishing features, but the subtle presentations mentioned in the context of cryptococcal meningitis are seen here also. Neurological signs and disturbance of consciousness are common with a mixed meningitic and encephalitic picture, which is more commonly seen with listeria than with other forms of bacterial meningitis. Listeria also causes a range of other CNS conditions, including single or multiple brain abscess, diffuse encephalitis and, rarely, brain stem encephalitis.

**Laboratory diagnosis**

This topic can be discussed only briefly, chiefly to stress its importance and the need for efficient and prompt acquisition of correct specimens by the clinician and for good liaison between ward and laboratory. Gram staining of the centrifuged CSF deposit remains the gold standard for early diagnosis, with occasional help from other specimens such as smears from skin lesions. Later, results of blood and CSF cultures provide the main diagnostic yield. Many methods of early diagnosis have been developed, the most useful of which are antigen detection methods, especially latex particle agglutination, which can be employed using CSF, serum, or urine. These techniques are not generally superior to staining, but have definite value in reducing the diagnostic gap in patients who have been given antibiotics before admission.

Diagnosis of tuberculous meningitis still depends mainly on traditional staining methods on the CSF deposit, but new techniques are being developed, notably the polymerase chain reaction, which may greatly improve the low sensitivity of current diagnostic methods.

Diagnosis of cryptococcal meningitis rests largely on cryptococcal antigen detection in CSF (but not blood), on India ink preparations of CSF to detect capsulated *Cryptococcus neoformans*, and on culture using large volumes of CSF.

**Treatment (see Table 1 for doses)**

Treatment of the three common forms of pyogenic meningitis has been greatly complicated by increasing prevalence of several types of antibiotic drug resistance. Until these changes became widespread, antibiotic treatment of meningitis caused by these organisms could be accomplished using two safe, easily administered and cheap agents, benzylpenicillin (or ampicillin), and chloramphenicol. Benzylpenicillin is still appropriate for meningococcal and pneumococcal disease in most countries, but haemophilus meningitis, and meningitis of uncertain aetiology must now often be treated with extended spectrum cephalosporins, a particular tragedy in developing countries in which meningitis is common and in which the cost of these compounds is beyond the reach of publicly funded health budgets. It is therefore important to remember that penicillin and chloramphenicol remain agents of first choice in many areas, and may indeed be the only agents available. Table 1 gives the dosages of antibiotics commonly used.

Meningococcal meningitis can be treated with equal efficacy by high dose penicillin or ampicillin given intravenously or by chloramphenicol, given by intravenous injection.
Table 1 Dosage of antibiotics commonly used in meningitis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Total dose per 24 hours</th>
<th>Adult (g)</th>
<th>Child (mg per kg)</th>
<th>Dose interval (hours)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td></td>
<td>14-4</td>
<td>180-300</td>
<td>4</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
<td>12</td>
<td>200</td>
<td>4</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Chloramphenicol†</td>
<td></td>
<td>3</td>
<td>50-100</td>
<td>6</td>
<td>Intravenous or oral</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td></td>
<td>8</td>
<td>200</td>
<td>8</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>4</td>
<td>80</td>
<td>24</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Vancomycin†</td>
<td></td>
<td>2</td>
<td>40</td>
<td>6</td>
<td>Intravenous</td>
</tr>
</tbody>
</table>

*Dosage unsuitable for neonates, †Control by blood levels required.

Initially, and by mouth as soon as practicable. The role of cephalosporins was at first controversial, as the earlier compounds were relatively ineffective, but the newer compounds, although most widely used in *H. influenzae* meningitis, are also of established efficacy in meningococcal infections. An important caveat is the emergence of penicillin resistance in meningococci, especially in Spain, but also increasingly recorded elsewhere. The level of risk of encountering a resistant strain that would necessitate a change from penicillin or ampicillin must be kept under review. One important difference between meningococcal and other forms of meningitis is the relative ease with which the organism can be eradicated. Although 10–14 day courses of treatment have traditionally been used in all forms of meningitis, shorter courses are fully adequate in meningococcal disease. Successful trials have included durations of seven, five, and even four days with penicillin. Chloramphenicol is the best choice in patients allergic to penicillin. In field conditions in tropical Africa, several studies have been made of treatment in one or two doses using a long acting preparation of chloramphenicol in oil. For example, in a large, randomised trial involving 528 patients in Mali and Niger, the success of a two-dose scheme of this sort equalled that achieved by intravenous ampicillin given four times daily for five days, and was clearly much more simple to administer. The mortality in all groups in these trials was much higher than that found in the West, again demonstrating the great impact of meningitis in these areas.

Penicillin is also the best agent for the treatment of pneumococcal meningitis, but pneumococci resistant to penicillin have become widespread and are now common enough in several countries, including Spain and Hungary, to preclude the use of penicillin in treatment. The treatment of penicillin-resistant pneumococcal meningitis presents a difficult and partly unsolved problem. The chief alternative, chloramphenicol, may be successful but has failed to eradicate infection in a number of cases. It has been shown, in work from South Africa, that many penicillin-resistant pneumococci, although susceptible to chloramphenicol on disc testing, require high minimum bactericidal concentrations of penicillin, and that this form of partial resistance is associated with poor results of treatment. Vancomycin, although a difficult drug to use, has had some success, but a number of treatment failures have led to the suggestion that it should be used in penicillin/chloramphenicol-resistant pneumococcal meningitis only if high-dose cephalosporins have failed or if the patient has anaphylactic reactions to β-lactam agents.

*H. influenzae* meningitis has its main impact in children less than four years old, but is seen occasionally in older children and adults. Ampicillin, formerly widely used alone or together with chloramphenicol, has now lost its role because resistance to its action is now present in a large number of isolates, 15–25% in most countries. Chloramphenicol is still the best agent in many areas, but resistance is increasing, and many ampicillin-resistant strains are also resistant to chloramphenicol. For these reasons extended spectrum cephalosporins such as cefotaxime and ceftriaxone have become the chosen agents in haemophilus meningitis or meningitis of uncertain aetiology. Treatment may be modified when laboratory results are available. Although active against the three common pathogens, cephalosporins have limited or no activity against some of the more unusual causes of meningitis, notably listeria and some of the less common Gram-negative organisms. If the patient has an underlying disease that places him or her at risk for these unusual pathogens and treatment has to be started without microbiological information, the initial regimen should include ampicillin together with the cephalosporin.

Antibiotic treatment before admission diminishes the prospects of obtaining a positive finding by CSF microscopy or culture. Occasionally the CSF is altered more profoundly, with a lymphocytic picture. If partly treated pyogenic meningitis is in question (as well as other diagnoses such as brain abscess and tuberculous meningitis), it would be reasonable to begin provisional treatment with a cephalosporin in full dosage while other investigations are in train.

**Tuberculous Meningitis**

Tuberculous meningitis stands apart from other forms of meningitis in many important ways. Diagnosis can be difficult, the course of the disease variable and prognosis uncertain. These and other factors have led to a deficiency of the extensive controlled clinical trials that have established well validated regimens for the treatment of pulmonary and some forms of non-pulmonary tuberculosis. Treatment tends therefore to be based on limited trial data, the empirical opinion of physicians with experience of the disease, and on knowledge of the pharmacokinetics of antituberculous agents. The broad relationship of prognosis to neurological deficit demands that treatment should be started as soon as possible, even when there is still uncertainty about the diagnosis. Fear that diagnosis will then be impossible to establish is largely unfounded, because it can often be made from post-treatment specimens of CSF, or from later results of culture of pre- or
post-treatment specimens. Alternatively, a different diagnosis may later be established—for example, by virological findings that allow the provisional treatment for tuberculosis to be discontinued.

The pharmacokinetics of antituberculous agents in the CSF are well established. Pyrazinamide shows excellent penetration into the CSF. The CSF/serum ratio in Chinese patients is about 75% two hours after the dose is given, and about 110% after five and eight hours. Isoniazid too penetrates well, with concentrations in CSF approaching those in serum. Rifampicin concentrations in CSF are 10–15% those in serum, representing the unbound moiety of the drug. Streptomycin achieves adequate concentration in the CSF after standard intramuscular dosage only when the meninges are inflamed, and this is true also of ethambutol, given orally. Ethionamide and prothionamide, by contrast, penetrate the CSF well, whether or not the meninges are inflamed, although their value is limited by gastrointestinal and other unwanted effects. Initial treatment should employ at least a triple regimen of pyrazinamide, isoniazid, and rifampicin. It is still uncertain whether streptomycin is needed as an addition to this scheme. Workers in Hong Kong with great experience of the disease recommend its inclusion during the first two or three months of treatment, and it should certainly be used if rifampicin cannot be obtained because of its cost. The three principal agents are all given by mouth in once daily dosage, or by gastric tube if the patient cannot swallow. The dose of pyrazinamide is 35 mg/kg for a child, 2 g for an adult, that of rifampicin 10 mg/kg. Isoniazid has customarily been given in higher dosages, 10 mg/kg, than are used in other forms of tuberculosis, but the conventional dose of 300 mg or 4–5 mg/kg is probably adequate. Pyridoxine 10 mg daily is given to prevent isoniazid neuropathy. Streptomycin is administered by intramuscular injection in a dose of 20 mg/kg to a maximum of 1 g daily but careful and continued attention should of course be paid to renal function. Intrathecal treatment can no longer be recommended, although there was evidence of its value in treatment regimens which preceded the use of rifampicin and pyrazinamide.

The optimal duration of treatment is unknown. Because the disease is so serious, it has been customary to use long courses of treatment. This is perhaps illogical because, despite the devastating pathology of the condition, the bacterial population concerned is small compared with that found, say, in cavitated pulmonary tuberculosis. Most authors continue treatment for one year, but shorter courses have been used, for example, a nine-month regimen.

The role of steroids has been debated for decades, but rigorous analysis by controlled trial has never been achieved. A mixture of open studies, anecdotal evidence and possibly shaky inference from the known effects of steroids on inflammatory processes has led to their use in the more neurologically advanced grades of the disease, in infants, in generally very ill patients, and in impending spinal block, which may nevertheless progress even during their administration. The situation with raised intracranial pressure in tuberculous meningitis is more clear cut. CSF block leading to hydrocephalus requires urgent control by shunting. Clinicians working in areas of high prevalence believe that early shunting is an important factor in improving prognosis. Rising intracranial pressure from enlarging tuberculoma can be controlled in most patients by high-dose dexamethasone, and surgical decompression is rarely necessary.

CRYPTOCOCCAL MENINGITIS

Before the advent of HIV infection and AIDS, cryptococcal meningitis was rarely seen in Britain, and then mainly in association with defects of cellular immunity—for example, in patients with lymphoma, those receiving substantial doses of steroids, and in patients with sarcoid whether or not on steroids. In some other countries a substantial number of patients with cryptococcal meningitis had no overt predisposing factors. This picture changed dramatically with the spread of HIV infection and cryptococcal meningitis is now seen as one of the most common CNS infections associated with AIDS. Treatment is difficult and demanding. Failure and relapse are common even in patients without HIV infection; in the presence of HIV, as with other infections, eradication is especially difficult and for this reason much thought has been given to devising practical methods of long-term prevention as well as to improving treatment of established infections.

Agents available for chemotherapy include amphotericin in various forms, flucytosine and some of the more recently developed triazole compounds, of which fluconazole has been most extensively studied. Trials completed before the onset of HIV established the value of amphotericin, despite its formidable toxicity, and showed how the unwanted effects could be partly mitigated by using the synergy, demonstrable in vitro and in vivo, between this agent and flucytosine. A major multicentre study showed that a combination of amphotericin in a dose of 0·3 mg/kg daily together with flucytosine in a dose of 150 mg/kg daily given for six weeks gave results at least as good as with amphotericin alone at 0·4 mg/kg per day for 10 weeks. The patients given combination therapy showed superior results at a non-significant level by a number of criteria; eight of 34 patients in the combination group died compared with 15 of 32 given amphotericin alone. Since this trial the methods of using amphotericin have been to some extent refined, with a trend to give larger doses, 0·5–0·7 mg/kg daily, or 1·0–1·2 mg/kg on alternate days. Duration of treatment may also be varied. Four weeks may prove adequate for patients with no adverse prognostic factors. These factors include underlying
immune defects (and therefore all those with cryptococcal meningitis superimposed on HIV infection), neurological deficit, a high cryptococcal antigen titre (>1:32) in the CSF and a low (<20 mm³) CSF leucocyte count. Treatment may, however, fail even in patients with no identifiable adverse features.

The onerous nature and limited success of these methods of treatment is even more notable in AIDS-associated cryptococcal meningitis, in whicharrow suppression by disease or by other drugs used in therapy maylimit or prevent the use of flucytosine. The potential of triazole compounds, with lower toxicity and the advantage of oral administration, is therefore especially interesting in this group of patients. After favourable early results, a formal comparison of fluconazole and amphotericin was made in a randomised, multicentre trial.18 Fluconazole was given in a dose of 200 mg daily, amphotericin at 0.4–0.5 mg/kg daily. The gravity of this infection is clearly revealed, with successful treatment in only 40% of 63 patients in the amphotericin group and in 34% of 131 patients given fluconazole. There was no significant difference in overall mortality, but deaths were more frequent in the fluconazole group during the first two weeks of treatment and CSF culture reverted to negative more slowly than in the amphotericin group. Comments on this trial emphasised that dosage of both drugs might now be thought too low. Other schemes being evaluated use a higher dose of amphotericin with or without flucytosine at 100 mg/kg, either as definitive treatment or for the first two weeks followed by fluconazole. Other studies involve higher doses: 400 mg or 800 mg of fluconazole. Favourable results are also being reported with itraconazole,19 although this compound does not reach the CSF in detectable concentrations.

The prospects for preventing recurrence of cryptococcal meningitis after initial successful treatment are more promising. A comparison of fluconazole 200 mg daily, with amphotericin 100 mg weekly showed clearly superior results for fluconazole, with relapse in 2% compared with 18% in the amphotericin group.20 The high relapse rate in patients with AIDS and other forms of immune suppression make it essential to use long-term prophylaxis following initial treatment. What is still uncertain is whether, at least in areas where cryptococcal meningitis is a common feature of AIDS, primary prophylaxis should be attempted. A retrospective study reported only one patient with cryptococcal meningitis of 329 given daily fluconazole as against 16 in 329 historical “controls”. This type of primary prevention may come to be vitiated by the development of fluconazole resistance, already emerging in Candida albicans infections.

ROLE OF STEROIDS

There is now abundant evidence that endogenously released factors play an important role in causing the inflammatory changes of meningitis, and increasing interest in the possibility that measures aimed at inhibiting this response might be beneficial.

Although much detail remains to be filled in, the relevant processes can be summarised briefly. In the case of meningoencephalitis and H influenzae, the initiating factor is endotoxin, a lipopolysaccharide component of cell wall released in the form of vesicles from the bacteria. Similar processes are induced in pneumococcal infection by the release of other cell wall components, mainly teichoic acid and peptidoglycan. After a time lag of a few hours, pro-inflammatory cytokines are induced, including tumour necrosis factor (TNF), and interleukins (IL) 1, 6, and 8. These and other factors produced from macrophages and from platelets have been shown in experimental systems to induce the changes of acute inflammation in the CNS. An additional complicating factor is that neutrophils, although an important component of the defence systems against pyogenic infection, themselves contribute to the inflammatory process when, after adhesion and migration, they degranulate and produce pro-inflammatory factors including reactive oxygen species.21

The link between inflammatory mediators and the timing and intensity of CSF changes is well established in experimental work, and there is increasing evidence of their relevance to human meningitis. For example, the outcome of meningitis can be correlated with the level of TNF and pro-inflammatory cytokines in the CSF.2223 These relationships are also clearly established in septicaemic meningococcal infection, in which there is a close relationship between plasma endotoxin levels and prognosis, and between endotoxin levels and levels of TNF-α, IL-1, and IL-6.24

An especially taxing question is whether lytic antibiotics, given to cure the infection, might themselves have an adverse effect by causing rapid release of bacterial products and thus provoking an increased inflammatory burst. In an experimental model of meningitis it is clear that an increase of several mediators, and a consequent inflammatory burst, follows the administration of lytic antibiotics such as β-lactams.25 This increased inflammatory response can be significantly mitigated by dexamethasone if given at the same time as, but not one hour later than, the antibiotic.26 Again, the evidence from human meningitis is necessarily more fragmentary. In one study, eight children with H influenzae meningitis had repeat lumbar puncture two to six hours after their initial dose of antibiotic, ceftriaxone. The second specimens showed increased concentration of endotoxin correlated with the decrease in viable bacteria, together with increase in lactate and decrease in glucose concentration in the CSF. In some cases TNF concentration in the CSF rose about four hours after starting treatment.27 It is therefore possible that diminishing the endogenously mediated inflammatory processes might be beneficial and that some or all of this benefit might...
accrue from diminishing a possible adverse consequence of essential treatment, the sudden lysis of large numbers of bacteria.

It is against this background that the current renewed interest in a role for steroids in pyogenic meningitis has arisen, after a 20-year lapse since their first trial.28,29 The first favourable evidence of a beneficial effect on outcome was gained from two trials involving 200 children, predominantly with haemophilus meningitis.30 In one trial the antibiotic used was cefuroxime (not now considered entirely satisfactory as the cephalosporin of choice in meningitis), in the other ceftriaxone. In both, patients were randomly allocated to receive placebo or dexamethasone in a dose of 0.15 mg/kg six hourly for four days. The dexamethasone group showed a significant increase in the speed with which abnormal CSF findings resolved, and, at follow up, substantial hearing loss was found in 10 placebo and three dexamethasone recipients; hearing aids were needed in 12 and one respectively. A smaller trial of 60 patients gave similar, although non-significant results.31 Notable reductions in the IL-1 β concentration were also demonstrated, together with improved prognosis, in dexamethasone-treated children. An open study in Egypt involved adults and children with meningitis, alternate patients being given dexamethasone. Seven of 52 patients with pneumococcal meningitis given dexamethasone died, compared with 22 of 44 controls. Sequelae were also less common in the dexamethasone group.32

Two more substantial controlled trials in childhood meningitis have taken account, in their design, of the importance of timing in experimental models. Children in Costa Rica33 were given placebo or dexamethasone in the same dose as in the previous studies (0.15 mg/kg six hourly for four days) but beginning 15–20 minutes before the first dose of the antibiotic, cefotaxime. At 12 hours the dexamethasone-treated group showed improvement compared with the controls in CSF pressure and in inflammatory indices and cytokine concentrations in the CSF. At follow up seven of 51 dexamethasone-treated children (14%), and 18 of 48 controls (38%) had neurological or audiological sequelae (relative risk 3.8, 95% CI 1.3 to 11.5). A Swiss trial34 differed in the dose and duration of dexamethasone administration, 0.4 mg/kg 12 hourly for two days, starting 10 minutes before the first dose of antibiotic, ceftriaxone. Follow up at 3, 9, and 15 months showed sequelae in three of 60 dexamethasone recipients (5%) and nine of 55 placebo recipients (16%) relative risk 3.27, 95% CI 0.93 to 11.47. Table 2 summarises the results of these important studies.

The trials also showed few adverse effects in the dexamethasone groups, mainly a higher incidence of gastrointestinal bleeding, usually detected only by investigation rather than by a significant clinical event. Moreover, cases of viral meningitis inadvertently treated with dexamethasone showed no adverse effects. It is reasonable to conclude that steroids, given in high dosage for a short time, and initiated early and preferably shortly before starting antibiotics, have a beneficial effect on outcome in childhood haemophilus meningitis, with lesser but suggestive evidence of benefit in other forms and at other ages.

Several other modes of damping the inflammatory response and its adverse pathophysiological consequences have been successful in experimental systems. They include non-steroidal anti-inflammatory agents, monoclonal antibodies against some of the cytokines involved, and antibody inhibiting leucocyte adhesion to endothelium. No method of modulating the inflammatory process, however, other than administration of steroids, is yet available for use in human meningitis.

**Table 2 Neurological and audiological sequelae of meningitis. Trials of dexamethasone**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. in study</th>
<th>Dexamethasone (no. (%)</th>
<th>Placebo (no. (%))</th>
<th>Moderate or severe deafness (no. (%))</th>
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<tr>
<td>30,31</td>
<td>260</td>
<td>3(4)</td>
<td>9(12)</td>
<td>3(4)</td>
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<td>115</td>
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<td>5(9)</td>
<td>7(13)</td>
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</table>

**Other aspects of management**

Might any aspects of therapy other than antibiotics and steroids help to mitigate the continued high mortality and residual morbidity associated with bacterial meningitis? Fits must, of course, be brought under control as promptly as possible, and mannitol infusions are of established value if signs of increasing intracranial pressure appear. Changes in the cerebral circulation in meningitis may be important, and certainly in experimental models, the inflammatory process leads to a complex interaction of brain oedema and raised intracranial pressure with changes in cerebral blood flow and perfusion. Especially notable is loss of autoregulation so that the cerebral blood flow becomes passively responsive to the systemic blood pressure.35 Few measurements of the cerebral circulation have been made in human meningitis, and these largely in infants and children. Two important studies by non-invasive techniques are notable. Goh and Minns36 made serial measurements of cerebral blood flow velocity using transcranial Doppler ultrasound. They found an increase in flow velocity as meningitis resolved with a decrease in the final resistance index, suggesting a decrease in cerebral perfusion during the acute phase of the illness. Mannitol infusion, by reducing intracranial pressure, increased cerebral perfusion pressure with a resultant decreased resistance index and increase in blood flow velocity. Another study, involving seriously ill children, employed stable xenon CT.37 This showed diminished blood flow in only a few patients (five as against 18 with normal cerebral blood flow) but did reveal marked
regional variations in flow changes. Determinations in artificially ventilated patients at different pCO₂ tensions showed that hyperventilation to low pCO₂ tension could reduce regional blood flow below ischaemic thresholds. In these and other studies cerebral autoregulation appeared to be generally preserved and pressure passivity was only seen in some very ill children with grossly abnormal neurological signs.

Some tentative conclusions relevant to clinical management may be drawn from these studies. It would seem sensible, in patients seriously ill with meningitis, to aim at avoiding fluctuations of blood pressure in either direction which might lead to changes in cerebral blood flow. In particular, hyperventilation with the aim of reducing intracranial pressure may sometimes prove disadvantageous and it may be preferable to maintain the pCO₂ within the normal range.

A common error in management is to limit fluid intake unduly with the aim of controlling inappropriate secretion of antidiuretic hormone and, it is supposed, thus reducing the likelihood of cerebral oedema. It has been shown in childhood meningitis, however, that the observed high levels of arginine vasopressin are an appropriate response to hypovolaemia and that levels return to normal when fluid replacement is achieved. Fluid deficits in meningitis should be corrected with the appropriate replacement fluids and normal maintenance requirements provided.

Communication
The diagnosis of meningitis brings with it enormous fear and anxiety for many reasons. Will the patient die? Will the patient be brain damaged? Will other members of the family or other people "catch" meningitis? All these questions must be discussed as often as necessary. Especially difficult is the oft-expressed question, why did this particular person develop meningitis? A simple account of how these bacteria spread is often helpful to the family and needs including with discussion of the patient's progress. To this must be added the common anxiety of health service staff about the possibility of infection when treating patients with meningococcal meningitis or septicaemia. The consultant in communicable disease control must be informed as soon as possible so that preventive measures (see below) can be rapidly brought into operation. Close liaison with the laboratory is of course essential, to ensure the best possible quality of specimens and thus the best chance of identifying the causal organism and its antibiotic sensitivity.

Sequela
Most previously healthy survivors of community-acquired meningitis recover completely but an important minority is left with residua ranging from mild neurological or audiological defects to profound and lifelong disability. Bacterial meningitis is the most common cause of acquired sensorineural deafness. Its frequency has been analysed in a thoughtful review by Fortnum accepting only published series with well-defined criteria avoiding the many possible confounding factors in such studies (table 3). Deafness complicates meningitis in about 10% of patients, and will be bilaterally profound or total in 1–4%.

Pneumococcal meningitis is generally reported to carry a much higher risk of deafness than the other two common forms, although the difference may not be as great as has been supposed. Certainly the risk of deafness exists in all forms of meningitis and at all ages, and no reliable predictors of this complication are available. Whether the trend towards steroid treatment will make an impact on the frequency of deafness remains to be seen.

The likelihood of other serious long-term sequelae is hard to estimate but may occur at about the same frequency as severe deafness—for example, four of 48 children who survived haemophilus meningitis in Wales suffered long-term neurological sequelae (8%).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Permanent hearing loss after bacterial meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of meningitis</td>
<td>No. in study</td>
</tr>
<tr>
<td>Unselected</td>
<td>1175</td>
</tr>
<tr>
<td>Hemophilus influenzae</td>
<td>876</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>398</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>66</td>
</tr>
<tr>
<td>After Fortnum.</td>
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</tr>
</tbody>
</table>

RELATION BETWEEN DURATION OF ILLNESS AND OUTCOME
The relationship between clinical features and the known pathophysiology of meningitis is important to our understanding of the disease. The question is also important in the medicolegal context as actions about neurological damage following meningitis often centre on a claim of missed or delayed diagnosis. Inflammatory changes in the CNS are related to bacterial load, which suggests a connection between prognosis and delayed diagnosis, but attempts to analyse the point reveal a more complex picture. One prospective analysis showed that children with a history of less than 48 hours illness did significantly worse than those with longer histories. A recent exhaustive examination of 22 studies involving 4707 patients with meningitis attempted to analyse the question in more detail. Many of the studies were unsuitable for formal meta-analysis, but the previous finding that children with a slow and insidious presentation had a better outlook than those with acute illness was confirmed. At the other extreme, in a small subgroup with fulminant meningitis, the influence of antibiotics seemed minimal. Between these lies the group with clinically overt meningitis but without septicaemic shock; data were
Meningitis vaccines of these strains b. The infection. are infections haemophilus meningitis, gitis ryngeal carrier by followed of used Great Britain.44 potency render them complex by with old years successfully body is is oneous deficiency morbidity from persistently The Prevention meningitis makes developments often event adverse come is septicaemia. severe than in meningococcal the mortality from meningitis, some sponds with the meningitis make this of the entire illness is subsequently designated as meningitis, presumably the early phase corresponds with the bacteremic illness preceding localisation to the meninges, or perhaps in some cases a preceding viral infection. In either case the host–parasite relationship is more evenly balanced, and the illness less severe than in fulminant meningococcal septicemia.

A further point bearing on the complex relation between duration of illness and outcome is that deafness, the most common adverse event leading to longterm disability, often develops very early in the course of meningitis.

Prevention VACCINATION

The persistently high mortality and residual morbidity from meningitis make it likely that substantial further progress can be made only by improvements in prevention. Recent years have seen encouraging advances in vaccination, with the promise of more to come.

Capsular antigen plays an important role in pathogenesis for all the common causes of bacterial meningitis, and anticapsular antibody is correspondingly important in protection. Unfortunately children less than two years old show poor and transient responses to these polysaccharide antigens.43 This serious deficiency in the value of these antigens in immunisation programmes has been successfully addressed in the case of H influenza by formulating conjugates of the capsular antigen with various protein moieties that render them fully immunogenic in infancy as well as in older age groups. The problem is complex as different conjugates so far devised vary in their immunological properties and in their potency as antigens in infancy. There are also variations in host response dependent on ethnic, nutritional, and demographic factors. Despite these intricacies, several conjugate vaccines have been developed and widely used in many countries including Great Britain.44 Their introduction has been followed by rapid reduction in the incidence of haemophilus meningitis and an additional, unexpected benefit, reduction of the nasopharyngeal carrier rate. In Finland, which has been in the forefront of immunisation against haemophilus meningitis, this form of meningitis has been almost eliminated.45

The great majority of invasive haemophilus infections are caused by one serotype, group b. The situation is more complex in meningococcal infection. Capsular polysaccharide vaccines have been developed against groups A and C strains, and are available for use in contacts and for outbreak control when one of these strains is responsible, for travellers to areas of high prevalence, and for individuals at special risk of meningococcal disease.46

The development of vaccine against meningococci of group b, the predominant group in Britain, has proved difficult, but several approaches to this problem are now being pursued. One involves developing conjugate vaccines, another using outer membrane proteins (OMPs) rather than the polysaccharide capsular material as antigen. As these OMPs are strain specific, this approach necessitates the development of multivalent vaccines. Trials of OMP vaccines have been achieved in several countries, including Norway, Brazil, and Cuba, with overall efficacy rates varying between 50% and 90%, but with less efficacy in children.47 48

Pneumococcal vaccines49 are relevant mainly in the prevention of respiratory disease and otitis media, but here too the successful development of conjugate vaccine against a high proportion of important serotypes might in future contribute to a general vaccine against the main types of bacterial meningitis. Alternatively, other anti-meningitis components may come to be added to combinations, already being developed, of diphtheria, pertussis, tetanus with Hib vaccine.

CHEMOPROPHYLAXIS

The risk of meningococcal and of haemophilus meningitis is significantly higher in certain contact groups than in control populations. For this reason chemoprophylaxis is used in these contacts to eradicate nasopharyngeal carriage of the causal organism and thus diminish the likelihood of disease.50

Although the alarm which is engendered by the diagnosis of meningitis leads naturally to great emphasis on treatment of contacts, it has to be emphasised that chemoprophylaxis is a control measure of very limited value, compared with preventive vaccination, or early diagnosis and treatment of cases. There are several reasons for this, chiefly that in most patients with meningitis the source is unknown, and the patient could therefore not have received chemoprophylaxis. In addition, spread of both H influenzae and the meningococcus between carriers may be quite slow, and the risk to contacts extends long beyond any practicable period of chemoprophylaxis.52

Moreover, sometimes the carrier state is not eradicated, and resistance may develop to the agent used.

Rifampicin is used for contacts of both these forms of meningitis, although there are important differences in dose and duration (10 mg/kg 12 hourly for two days for meningococcal contacts, 20 mg/kg daily for four days for haemophilus contacts, maximum 600 mg per dose). Two other authenticated forms of chemoprophylaxis are available, ciprofloxacin in a single oral dose, or ceftriaxone as a single injection. In general, close family, household, and nursery contacts are given chemoprophylaxis, and also the index case before leaving hospital, as, paradoxically, successful chemotherapy for
meningitis does not eradicate the carrier state. It is most important that contact between health professionals and families of patients with meningitis should include careful discussion of possible early features of meningitis, and the limitations of chemoprophylaxis.

Resource implications
Hospital management of meningitis requires well trained and well staffed medical and paediatric units with easy access to the relevant supporting services. Most essential is liaison with the laboratory on a 24-hour basis, and with the relevant clinical specialists, including especially neurological and infectious disease services. Access to a fully staffed intensive care unit may become essential for some very ill patients, with facilities for safe transfer if this is not available on site. Outside the hospital, communication with the relevant specialist in public health medicine should extend beyond the legal requirements of notification and should include detailed discussion of possible contacts and control measures. Audit of services for meningitis might measure, in addition to mortality and morbidity, such factors as completeness of notification, duration of illness before admission, whether antibiotics were given before admission, time between admission and definitive treatment and appropriateness of treatment regimens employed.

At a later stage, rehabilitation facilities will be needed for patients with residual disability. The needs of children with hearing problems have been well studied. Early skilled assessment is required because, although some hearing loss in the acute illness and during recovery is conductive and may be transient, early identification of sensorineural loss is essential so that rehabilitation can begin promptly. It has been strongly argued that all children who have had meningitis should have auditory assessment, initially 4–6 weeks after discharge from hospital. This would involve 30–40 appointments annually for a health district with a population of 250,000. This requirement will move with successful vaccination programmes, although there is evidence that at present not all patients who need assessment are referred.