Henry VIII of England. Did he have syphilis, and did his consequent lack of fertility lead to divorcing Katherine of Aragon?

Neurosyphilis

Jonathan Carr
Ward A-8-L, Tygerberg Hospital, Tygerberg 7505, South Africa, E-mail: jcarr@sun.ac.za
Practical Neurology, 2003, 3, 328–341

Walking on air
Never a care
When you've met Lues...
Get her on the brain and she'll
drive you insane,
She'll touch your heart with her
own special art,
A light in your eyes,
And we realize,
You've met our Lues.
(Heathfield 1976)

INTRODUCTION

Treponema pallidum is a member of the Spirochaetaceae, a family of bacteria that includes the genera of *Borrelia* and *Leptospira*. The organism has man as its primary host – acute infectious lesions ensure transmission of the organism, while persistence in the host continues for many years (Norris 1988). This comfortable relationship is coupled with great difficulty in growing the organism *in vitro*, forcing investigators to propagate *T. pallidum* in mammals, a significant hindrance to research.

The disease was probably introduced into Europe by Christopher Columbus' crew on their return from Cuba and the present day Dominican Republic, and has been characterised by premature reports of its demise ever since the 16th century. 'The pox as it is at present is much less cruel and easier to cure than at the time it first appeared; it is clearly becoming milder… to such an extent that it looks as if it will disappear in due course' (Quetel 1986). Similarly, in the 20th century, particularly after the introduction of penicillin, articles appeared with such optimistic titles as, 'The decline of neurolues' (Heathfield 1976). However, in the last decade there has been a 50-fold increase in syphilis in Eastern Europe (Tichonova et al. 1997), and in the United States epidemics continue to occur in a 7–10 years cycle. Geographically, the vast majority of new cases arise in the developing world, where as many as 10% of the population are infected (Gerbase et al. 1998).

Nowadays, neurosyphilis is an uncommon disease in developed countries, but the impact of the disease earlier this century must have been remarkable. About 11% of the patients admitted to the National Hospital for Nervous

Diseases in London between 1909 and 1925 had neurosyphilis, a higher proportion than patients with multiple sclerosis (Wilson 1940). The number affected has varied widely in the 20th century, from as much as 26% of the adult male population having primary syphilis in Macon county, Alabama, to as little as 114 cases of neurosyphilis in the whole of England and Wales in 1974 (Lancet 1977) – seven times that number *died* of just tabes dorsalis in the United Kingdom in 1932 (Wilson 1940).

PATHOPHYSIOLOGY

Following primary (Fig. 1) and secondary infection (Fig. 2), partial immunity to syphilis develops, but not enough to eradicate *T. pallidum*, resulting in persistent latent infection in some patients when other organs become involved, predominantly the heart and nervous system. Invasion of the nervous system occurs during the first few weeks or months of infection, with cerebrospinal fluid (CSF) abnormalities in up to 40% of patients at the secondary stage (Lukehart & Holmes 1998). The infection has many similarities to other forms of chronic meningitis – a ventricular component, often with hydrocephalus, and a leptomeningeal component with associated vascular involvement. What is remarkable is the degree of parenchymal infiltration by the organism and the penchant for the disease to affect blood vessels.

Primary syphilis is characterised by chancres (Fig. 1), which are less obvious if they involve the vagina, and so the patient may not be aware she has the disease. The lesions are not necessarily restricted to the genital regions or mucous membranes, hence the South African colloquialism – 'bioscope finger'. Primary syphilis is a self-limiting illness, the chancre heals several weeks after it appears. Secondary syphilis may follow, weeks to months later, and is characterised by a generalised rash (Fig. 2), lesions of moist areas (condyloma lata) and generalised lymphadenopathy. Acute meningitis may be a manifestation of secondary syphilis.

CLASSIFICATION OF NEUROSYPHILIS

Many of the terms associated with the manifestations of syphilitic chronic meningitis and encephalitis are not well defined. For example, in Harrison's textbook of medicine (Lukehart & Holmes 1998), latent syphilis is said to be a condition where the clinical examination is normal but with 'a positive specific treponemal antibody test for syphilis together with a normal CSF examination'. This differs from the 'Medical Progress' section of the *New England Journal of Medicine*, where it is said that the CSF can be abnormal (Hook & Marra 1992). A further problem arises in distinguishing early from late latent syphilis, where periods of 4 years (Lowhagen 1990), 2 years (Young 1992) or just 1 year (Lukehart & Holmes 1998)

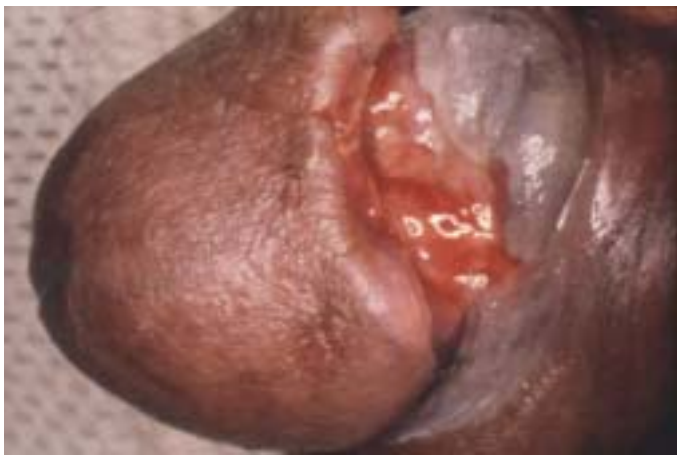

Figure 1 Chancre.

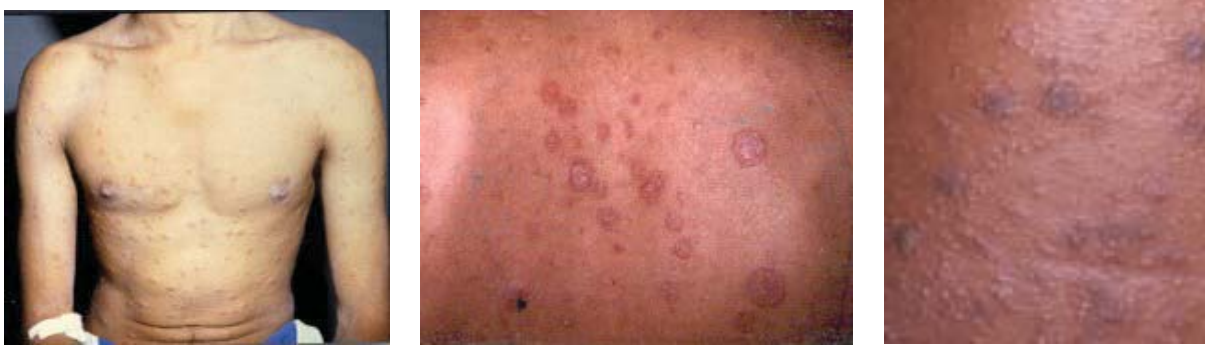

Figure 2 The rash of secondary syphilis.

from initial infection have been suggested as cut-offs between the early and late stages. Other definitions rely on whether a lumbar puncture was performed in order to separate late–latent syphilis (no lumbar puncture) from asymptomatic neurosyphilis (lumbar puncture) (Wiesel *et al*. 1985). The consequences of these difficulties with classification lie in trying to determine which patients should be treated, and with what. Not surprisingly, recommended treatments for early and late latent syphilis, and neurosyphilis, differ significantly from one another.

Neurosyphilis has traditionally been divided into four main groups: syphilitic meningitis, meningovascular syphilis, general paresis of the insane (GPI) and tabes dorsalis. Reviews have suggested that these occur in a sequential fashion. But it is not clear where this notion comes from. Adams (1997) reproduces a figure that was initially printed in the monograph he published with Merritt & Solomon in 1946. The figure is unreferenced and does not appear to be based on the work presented in the monograph. Simon, in a review published in 1985, provides a similar figure outlining the stages of neurosyphilis (Table 1). However, the sources are probably not very reliable – his information for vascular disease came from a textbook published by Gowers in 1888; those for GPI from Wilson's textbook published in 1940 (Wilson 1940), and for tabes from Merritt and Adams' monograph (1946). Lukehart's figures (Table 1) are unreferenced, and Hook's figure is referenced to Simon (1985) and to Merritt *et al*. (1946). Foster's figures, in the Oxford Textbook of Medicine (Foster 1996), are unreferenced, as are those in the 8th edition of *Brain* (Walton 1977). Combining the figures from these various sources, the quoted ranges for the time of onset of these various clinical syndromes from primary infection are: meningovascular, months–12 years; GPI, 5–20 years; and tabes, 8–30 years. It is evident there is substantial overlap, and that GPI and tabes need not necessarily present as long as decades after the initial infection.

A study by Wolters comparing pre- and post-antibiotic era neurosyphilis did not show any differences in age between 'early' (meningitis, vasculitis, spinal meningovasculitis) and 'late' neurosyphilis (tabes, dementia and taboparesis) (Wolters 1987). It is likely that age correlates with duration of illness, and it may be that age is a more accurate reflection of disease duration than the estimate of duration derived from just patient recall of their primary or secondary infection.

The bottom line is that the available information is rather limited and so rigid expectations of neurosyphilis behaving in a predictable fashion are likely to be wrong. The practical implication is that patients may present with 'late' syphilitic syndromes relatively early in the course of their illness.

CLINICAL SYNDROMES

As Adams noted, 'Clinical syndromes such as syphilitic meningitis, meningovascular syphilis, general paresis, tabes dorsalis, optic atrophy, and meningomyelitis are abstractions, which at autopsy seldom exist in pure form' (Adams 1997). It is largely the remarkable chronicity of the illness that serves as the substrate for the various manifestations. It is perhaps salient to point out that the late CNS manifestations of Lyme disease, a not dissimilar condition, are classified rather more helpfully into 'meningitis, cranial neuropathies and CNS parenchymal abnormalities' (Reik 1990). These terms are reasonably descriptive, as opposed to the largely pathological terms that are used in neurosyphilis. Pathological samples are not usually obtained in the course of the diagnostic work-up for neurosyphilis, and so clinical-pathological correlation must largely remain a matter of

Table 1 Time from infection to onset of neurosyphilis suggested by various authorities

	MENINGITIS	VASCULAR	GENERAL PARESIS OF THE INSANE	TABES
Simon (1985)	Months	1 year	5–15 years	15–20 years
Lukehart & Holmes (1998)		7 years	20 years	25–30 years
Hook* & Marra (1992)	Months	4–7 years	10–15 years	15–25 years
Foster (1996)		Within 12 years	15–20 years	10–25 years
Walton (1977)		Months-5 years		8–12 years

*Numerical values derived from figures.

conjecture. Caution must be applied to the use of terms whose place should be reserved for the older literature on syphilis, particularly as there is lack of precise definition and consensus as to their meaning and the clinical features that are supposed to accompany them. Neuroradiology, particularly MRI, is making a significant contribution to a better definition of the underlying pathology.

How does neurosyphilis present?

In their 1946 monograph, Merritt *et al*. grouped patients with neurosyphilis into the following categories: 45% tabes, 18% GPI, 4% taboparesis, 15% vascular, 9% meningeal, 1% 8th nerve, 3% optic neuritis, 3% spinal cord and 1% miscellaneous (Merritt *et al.* 1946). Tabes was the most common group, more than twice as common as GPI, but this could partly have been due to ascertainment bias, as patients with largely psychiatric problems were under-represented. It should be noted that combining the groups of meningeal and vascular syphilis amounts to about one-quarter of the total, indicating that meningovascular syphilis was not rare, despite recent suggestions to the contrary (Burke & Schaberg 1985; Musher 1991). Anecdotal evidence suggests that the presentations that were once common and have diminished with time are gummata and tabes dorsalis, most probably related to the introduction of arsenicals and penicillin (Wilson 1940).

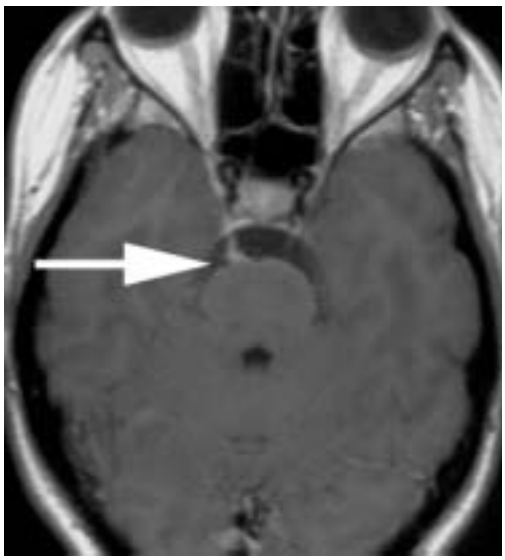

Figure 3 Enhancement of the third cranial nerve (arrowed) shown on T1-MR scanning in a patient with meningovascular neurosyphilis.

Syphilitic meningitis

In 1917, Wilson described syphilitic meningitis as an acute or subacute onset of headache, nausea and vomiting, with neck stiffness (Wilson & Grey 1917). A series of cases from 1935 (Simon *et al.* 1935), in which the authors noted that the disorder was rare, described two distinct groups of patients. Only one group, termed 'acute syphilitic hydrocephalus', had typical features of meningitis, often with papilloedema. One-quarter of the patients had negative Wasserman tests, and possibly may have only had viral meningitis (Simon 1985). None of these cases had cranial nerve palsies, as opposed to the second group termed 'acute syphilitic meningitis, basilar type' (Merritt & Moore 1935). This group of 34 cases had a period from initial infection to onset of symptoms of 2 months to 20 years: 54% developed symptoms within 1 year of initial infection, much less than in the acute meningitis group, where the corresponding figure was 95%. Representative cases include:

- a 30-year-old female with a primary lesion 2 years previously who developed a IIIrd cranial nerve palsy and subsequently optic atrophy;
- a 34-year-old male with a primary lesion 4 years previously who developed generalised pains and a VIIth cranial nerve palsy, and on examination also had palsies of the IXth and Xth nerves;
- a 56-year-old male with a primary lesion 20 years previously who developed Argyll-Robertson pupils, and Vth and VIIth nerve palsies.

It is apparent that:

- The 'acute meningitis' of neurosyphilis is characterised by headache, neck stiffness, nausea and vomiting, and may be associated with the rash of secondary syphilis.
- 'Basilar type' meningitis is not identical to acute syphilitic meningitis.
- Cranial nerve VII and VIII palsies are most commonly found in 'basilar type' meningitis, which is a more chronic condition likely to be associated with meningovascular syphilis, rather than with acute syphilitic meningitis. The MR scans of typical patients with 'basilar type' syphilitic meningitis are shown in Figs 3–5. The meningeal enhancement, evident midbrain ischaemia and abnormality of the vertebral artery are all compatible with meningovascular syphilis.

Al Capone – the terror of Chicago – died of neurosyphilis at the age of 48 having been in Alcatraz for tax evasion

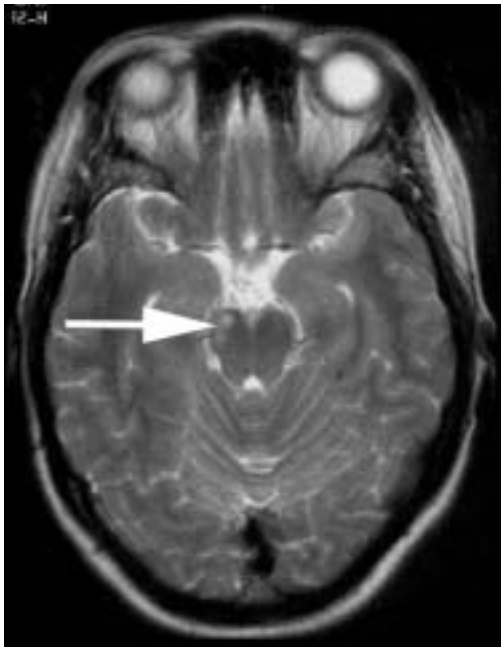

Figure 4 MRI T2 signal alteration in the right cerebral peduncle (arrowed) of a patient with meningovascular neurosyphilis.

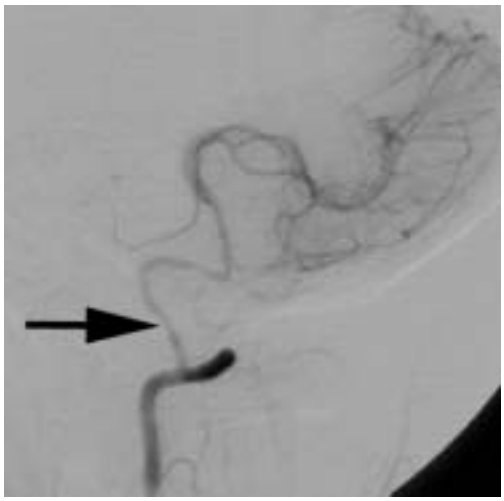

Figure 5 Catheter angiogram showing alteration in the calibre of the vertebral artery (arrow) in a patient with meningovascular neurosyphilis, compatible with obliterative endarteritis (Heubner's arteritis)

Neuropsychiatric presentations

There is a wide range of psychiatric presentations with no particular 'core syndrome'. All these presentations are synonymous with GPI. Clinical features are often an agitated delirium, frequently with psychosis and prominent paranoid ideation and hallucinations, both auditory and verbal, and with extreme motor restlessness. Common symptoms include personality change, memory impairment and hostility (Roberts & Emsley 1992). Wilson (1940) writes of 'an insidious onset with slight defect of memory and of the reasoning and critical faculties, minor peculiarities of conduct, irritability'. With treatment, the delirium and psychosis often improve, exposing a global dementia, with the accent on memory impairment and disrupted frontal lobe function, and with prominent apathy and aggression, referred to as a 'fronto-temporal encephalitis' (Adams 1997). Physical examination typically reveals prominent primitive reflexes with hyperreflexia. Argyll Robertson pupils are by no means an inevitable accompaniment. As Wilson noted, the Argyll Robertson pupil 'is neither constant nor pathognomonic'. Syphilitic encephalitis is typically associated with cerebral atrophy and ventricular dilatation in proportion to the degree of atrophy (Fig. 6).

Stroke

Large vessel ischaemic stroke due to neurosyphilis, most commonly involving the middle cerebral artery, is an occasional cause of stroke in young and middle aged people (Fig. 7). Interpretation of the CSF may be hampered by the usual pleocytosis and raised protein associated with any large infarct. Multiple infarcts are not uncommon, and occasionally patients with neurosyphilis present with vascular dementia, with imaging features compatible with a subacute arteriosclerotic encephalopathy – presumably diagnosed as GPI before the era of neuroimaging. Reports of parkinsonism and progressive supranuclear palsy are likely to be due to blood vessel involvement (Murialdo *et al*. 2000)

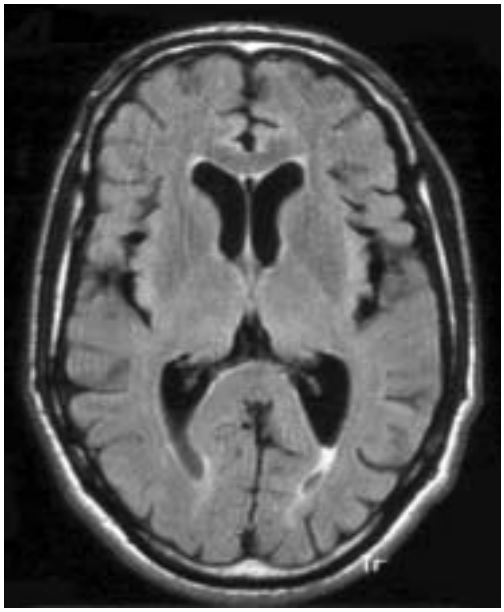

Figure 6 MR scan of patient with general paresis of the insane – the patient presented with stroke-like episode of aphasia, and then developed severe paranoid delusions.

Encephalopathy with seizures.

Seizures vary in type, from secondarily generalised tonic-clonic or focal motor seizures with clouded consciousness, to typical complex partial seizures of frontal or temporal lobe origin. There is usually significant impairment of mental status, frequently coupled with recurrent seizures bordering on status epilepticus. Treatment of the seizures may be difficult, particularly in the acute phase.

Cranial nerve involvement

Isolated cranial nerve involvement can occur, or more rarely is associated with brainstem syndromes (see syphilitic meningitis above).

Spinal cord lesions

Acute or subacute myelopathy occurs, sometimes with a picture of spinal shock, but more commonly with the features of a spastic paraparesis of subacute or even chronic onset, perhaps with a partial Brown–Sequard syndrome. The thoraco-lumbar region is the most commonly affected.

Tabes dorsalis is still occasionally seen in its typical form. The classical quartet of features are lightning pains, ataxia, Argyll Robertson pupil and loss of deep tendon reflexes. Optic atrophy and Charcot joints are also found. Sphincter disturbance is characterised most typically by lower motor neuron bladder symptoms, and impotence.

Argyll Robertson pupils are not specific to tabes. The differential includes that of a light–near dissociated pupil – chronic alcoholism and diabetes. Probably, if the pupil is small and irregular, it is more specific for neurosyphilis, but the controversy over whether the pupil size is normal or small is unresolved (Loewenfeld 1999). Similarly, absent reflexes are commonly found in many chronic meningitides, not necessarily due to damage to the posterior columns, but related to arachnoiditis. Severe anterior cereballar vermal syndromes associated with alcohol abuse may sometimes be difficult to distinguish from tabes.

Ocular involvement

Ocular involvement usually results in optic atrophy or uveitis. Uveitis seems to be commonly associated with secondary syphilis and it is unclear whether this has the same implications for treatment and follow-up as neurosyphilis. Argyll Robertson pupils show light–near dissociation, and are classically small and irregular, although they vary in size.

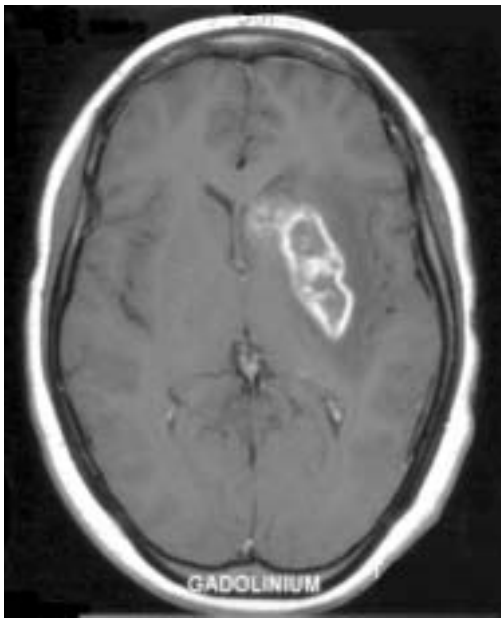

Figure 7 Cerebral infarction in a 22-year old HIV-positive patient with neurosyphilis. T1-weighted image with gadolinium.

Peripheral nervous system

Involvement of the peripheral nervous system is largely limited to spinal root damage secondary to arachnoiditis.

The effect of the antibiotic era on neurosyphilis

In 1968, an article appeared entitled 'Changing clinical picture of neurosyphilis: report of seven unusual cases' (Joffe *et al.* 1968). Of the seven, four had syphilis syndromes that on review seemed rather classical, two probably had cervical spondylosis and one had hemifacial spasm, painless ulcers and a normal CSF. The next series published was of 141 patients, of whom 43% were asymptomatic (Hooshmand *et al.* 1972). The major diagnostic categories were seizures, ophthalmic symptoms and stroke, all compatible with meningovascular syphilis. The small number of patients with GPI apparently occurred because there were no psychiatric services at the institution where the study was done. Nevertheless, the authors commented that 'Neurosyphilis, at the present time, presents itself in a most atypical fashion'. A contemporary study from South Africa reported that 'the

There is no gold standard for the diagnosis of neurosyphilis and so statements concerning the sensitivity and specificity of the tests are likely to be inaccurate

overall picture that emerges is that the majority of patients with neurosyphilis present with subtle clinical signs and with weakly positive or even negative serology' (Joyce & Molteno 1978). This report was strongly biased toward ophthalmological cases and the inclusion criteria were likely to be inaccurate. Subsequently, an editorial in the *BMJ* entitled 'Modified neurosyphilis' suggested that atypical neurosyphilis may be common (British Medical Journal 1978).

In contrast, a study from the United Kingdom reported that 'atypical presentations were not observed', despite 10 out of 17 cases having received antibiotic treatment previously (Luxon 1980). Wolters compared 216 cases from a 15-year period from 1970 with a larger group in the preantibiotic era (Wolters 1987). A decline in tabes dorsalis was noted, but no significant differences were seen in the other syndromes. 23 cases from a 5-year period were reported from Denmark with syndromes typical of GPI and meningovascular syphilis (Nordenbo & Sorensen 1981).

All these reports were rather small, they were retrospective, and came from various populations – general hospital, venereal disease clinic, neurology service, etc. – and used variable diagnostic criteria for the diagnosis of neurosyphilis. Given the lack of a gold standard, and the lack of specificity of the tests (see below), proving that neurosyphilis is causal in possibly mildly affected cases is extremely difficult, and lends itself to a circular argument.

However, there seems little doubt that following the introduction of penicillin, and with the subsequent reduction in primary and secondary syphilis, neurosyphilis syndromes have become rare. But the evidence for neurosyphilis presenting atypically is poor. However, there at least appears to be general agreement that one manifestation of neurosyphilis – tabes dorsalis – has become much less common than it was in the pre-antibiotic era (Nordenbo & Sorensen 1981; Burke & Schaberg 1985; Wolters 1987).

PATHOLOGY

As with tuberculosis of the nervous system, neurosyphilis is characterised by a predominantly chronic inflammatory cell infiltrate of the leptomeninges and superficial parenchyma (meningo-encephalitis). In addition, there is another prominent obliterative vasculitis (Heubner's arteritis), which is not specific to neurosyphilis. Leptomeningeal fibrosis and consequent CSF obstruction is another non-specific sequel, common in any granulomatous inflammatory process. Unlike TB, in neurosyphilis there is typically no evidence of an exudative necrosis within the subarachnoid space and there tends to be a much less obtrusive microvascular proliferative response, the latter being a component of granulation tissue. Although reported in the pre-antibiotic era, it is rare to find extensive or discrete granuloma formation in neurosyphilis (Greenfield & Stern 1932).

Features apparently unique to neurosyphilis include persistence of organisms within the cortical parenchyma with ongoing neurocytopathic effects, and atrophy of the dorsal roots and ganglia with dorsal column degeneration, of unknown pathogenesis.

On imaging, the microvascular proliferation intrinsic to granulomatous inflammation is assumed to be the basis of the meningeal enhancement and is non-specific – it can be seen in other granulomatous inflammatory meningitides. Discrete granuloma formation with ring-form or peripheral enhancement and T2 hypointense (non-enhancing) contents is the hallmark of gummatous necrosis (Fig. 8). This is distinct from caseous or liquefactive necrosis, where lesions have T2 iso- or hyperintense contents (Fig. 9). However, gummatous necrosis is common to both TB and neurosyphilis, currently being much more prevalent in the former, and neither size nor location can provide any useful distinction between the two conditions.

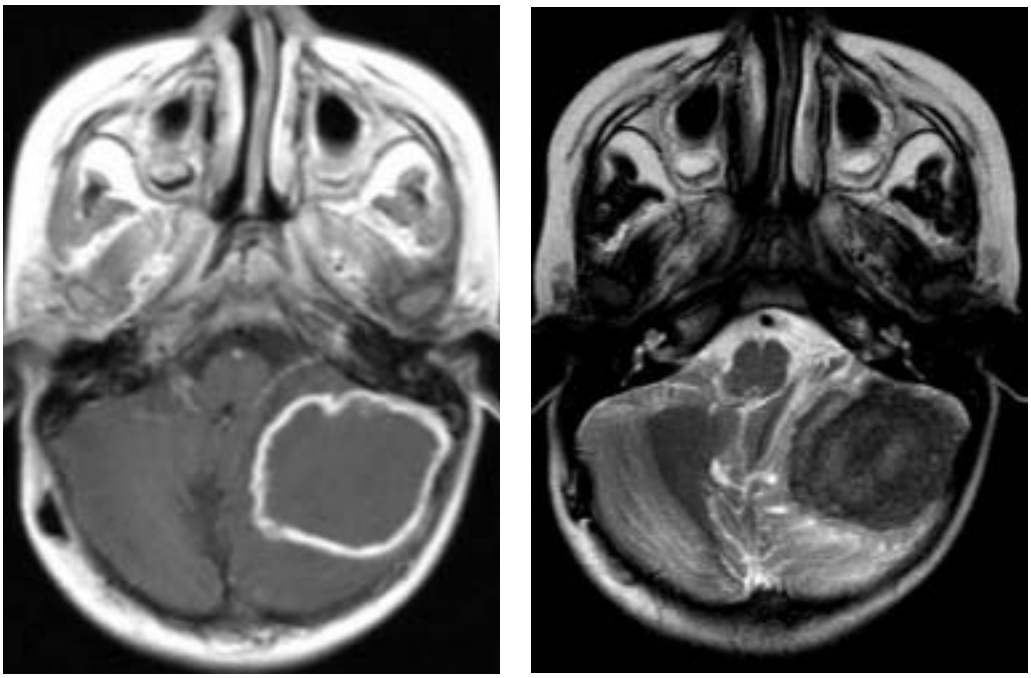

Figure 8 Cerebellar mass, isointense on T1-weighted imaging (marked rim enhancement with gadolinium) and hypointense on the T2-weighted image, typical of a gumma.

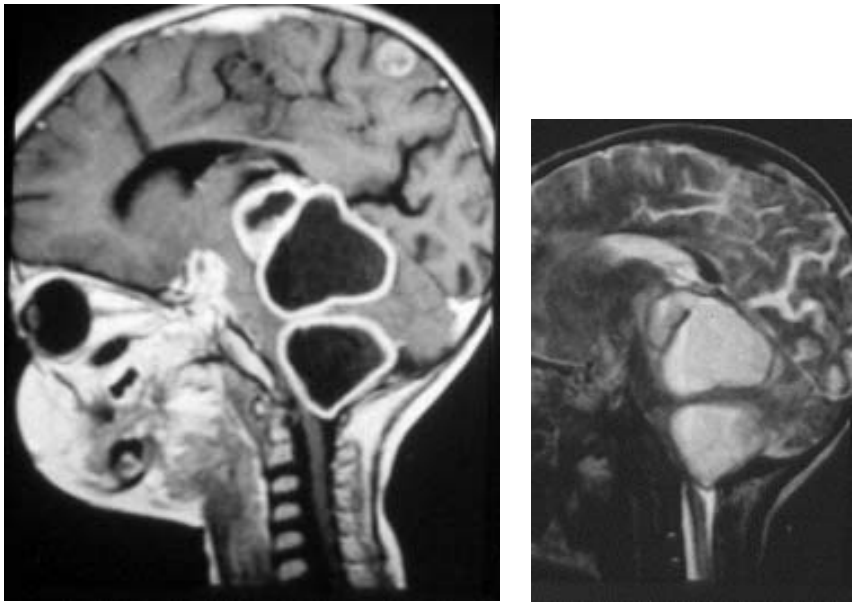

Figure 9 Multiple tuberculomas, hypointense on T1-weighted imaging (with marked rim enhancement with gadolinium). On the T2-weighted image, there is obvious hyperintensity, compatible with caseous/liquefactive necrosis.

SPECIAL INVESTIGATIONS

There is no gold standard for the diagnosis of neurosyphilis and so statements concerning the sensitivity and specificity of the tests are likely to be inaccurate, with most references using the circular argument of assigning affectedness on the basis of clinical status and then determining sensitivity and specificity of the tests. It is unlikely that performing multiple serological tests will help. Also, if tests are used indiscriminately in 'neurology' patients as 'a screening test' for neurosyphilis, the false positive rate will be high, as is always the case when tests of less than 100% specificity are applied to a population where the prevalence of the disease of interest is low. The decision to use screening tests, whether it be for primary syphilis, or for neurosyphilis, depends on the likely prevalence of the condition, available resources and the likelihood of epidemics developing. Thus, if the prevalence is very low, statements such as 'the continued use of screening tests for syphilis on CSF from unselected patients in whom there is no clinical suspicion of syphilis seems hard to justify' (Lancet 1977) are likely to be correct. However, in a region of high prevalence, the opposite may hold true. In a series of 21 cases of neurosyphilis detected by screening tests in South Africa, no referring doctor had considered the diagnosis, and it was only twice considered by specialist psychiatrists (Roberts & Emsley 1992).

Syphilitic infection produces two types of antibodies: non-specific reaginic antibody and specific antitreponemal antibody, measured by non-treponemal and treponemal tests, respectively. The VDRL (Venereal Disease Research Laboratory) and RPR (Rapid Plasma Reagin) tests are non-specific, while the FTA-ABS (fluorescent treponemal antibody absorption) and TPHA (*T. Pallidum* haemagglutination) tests are both specific for treponemal antibody.

Investigation of serum

Given its high sensitivity (Deacon *et al.* 1966), it is likely that a negative FTA test rules out neurosyphilis (Simon 1985). The FTA test is sensitive in the detection of primary syphilis, but also remains positive for many years in late or treated syphilis (Sparling 1971), with a sensitivity close to 100% (Deacon *et al.* 1966). Non-treponemal tests have a tendency to become negative with advancing age (Rockwell *et al*. 1964) and the sensitivity of the VDRL in serum for late syphilis is only about 70% (Larsen *et al*. 1981).

Investigation of CSF

The following tenets are probably true, although they have not been subjected to rigorous testing:

- A positive VDRL is very specific, but not very sensitive, in that it is negative in about a quarter of cases of patients with neurosyphilis (Hart 1986). Borderline VDRLs are common in areas of low disease prevalence and where the test is ordered as a routine (Dans *et al*. 1986).
- A positive FTA is highly sensitive, but not specific (Dans *et al.* 1986). The FTA is useful in that a negative result is highly likely to exclude neurosyphilis (CDC 2002). Similar comments can be applied to the TPHA (Simon 1985; Lowhagen 1990) There has previously been concern about the diagnostic utility of the FTA, particularly in the United States (Jaffe *et al*. 1978). The CSF-FTA is useful in that, because the CSF-VDRL has only moderate sensitivity, the CSF-FTA may be the only serological marker of neurosyphilis. However, utility is related to prevalence of the condition in the population examined.
- The prozone effect occurs with the VDRL test, which can be falsely negative in either undiluted serum or CSF. This is because aggutination is inhibited by excess antibody, but the phenomenon does not occur if the sample is diluted (Spangler *et al*. 1964).

DIAGNOSIS

Diagnosis rests on three pillars: the clinical syndrome; positive serology, usually in both serum and CSF; and markers of activity in spinal fluid. Thus, one definition would be:

A combination of a compatible clinical syndrome with:

- positive CSF VDRL or
- positive CSF FTA with:
  - abnormal CSF cell count (polymorphonuclear leucocytes and/or lymphocytes > 5/mL), or
  - CSF protein > 0.45 g/L, or
  - CSF IgG index > 0.6. (Roberts & Emsley 1992; Russouw *et al*. 1994)

Markers of activity are frequently held to be CSF protein and cell count, but it should be noted that neither need be particularly elevated, presumably reflecting the extremely indolent nature of the condition. Occasionally cell counts are normal (Dewhurst 1969). The IgG index is frequently remarkably elevated, and is a useful and easy test to perform (Dewhurst 1969). In particular, the dissociation between a relatively low cell count and a very raised IgG index may contribute to greater diagnostic certainty in neurosyphilis.

Given the inevitable diagnostic difficulties, complete diagnostic certainty in neurosyphilis is often unattainable, and the decision of which patient to treat, and how to treat, inevitably varies from one physician to another. This reflects the inherent problems of the special investigations used for identifying neurosyphilis, coupled with reasonable concern about a potentially treatable condition that will progress without appropriate therapy.

FOLLOW-UP – WHEN IS THE DISEASE CURED?

Another great uncertainty is to do with follow-up and, in particular, when and how often lumbar punctures should be repeated. Recommendations have been made for rechecking the CSF at 6 weeks, 3 and 6 months (Hart 1986). The dictum of Dattner (1951) that the cell count should revert to normal within 6 months after treatment is often repeated. Given that CSF markers of activity are often not significantly raised when the diagnosis is first made, the determination of whether they have fallen appropriately is difficult. CSF protein takes longer to normalize than the cell count. In addition, serological markers such as the FTA and TPHA may remain positive for a prolonged

period after treatment (Felman & Nikitas 1980; Luger *et al*. 1981). A reasonably good study from 1991 of 1090 patients, reported that in primary and secondary syphilis, the higher the titre, the lower the likelihood of reversion of RPR titres to normal (Romanowski *et al.* 1983). The rate of decline was also influenced by the stage of the disease, being slower in latent syphilis, where after 2.4 MU of benzathine penicillin, only 13% of early latent syphilis had seroreverted at one year (Romanowski *et al.* 1983). Another study using the VDRL, reported that 42% of secondary syphilis seroreversed at 1 year (Schroeter *et al*. 1972).

In practice, the clinical response may be the best method of determining response to treatment. Clearly, if the VDRL is not a sensitive marker, it will not be a useful way to follow progression in many cases. Of note, two-fold changes in titre are commonly due to technical factors (Sparling 1971) and, in general, the VDRL titre in CSF tends to be low (Graman *et al.* 1987).

Current Centre for Disease Control (CDC) guidelines are that if the cell count has not *decreased* after 6 months, or if the CSF is not normal after 2 years, re-treatment should be considered (CDC 2002).

TREATMENT

No adequate comparative trials have been conducted to help the clinician in deciding what the amount or duration of treatment should be. Treatment guidelines as outlined by the CDC are available at http://www.cdc.gov/std/treatment/2TG.htm#Syphilis (see Box). Treatment may also depend on the patient – those who are psychotic and very agitated may not be able to be given intravenous medication.

Current CDC recommendations (CDC 2002)

Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 h or continuous infusion, for 10–14 days or
Procaine penicillin 2.4 million units IM once daily
PLUS
Probenecid 500 mg orally four times a day, both for 10–14 days.

PROGNOSIS

In general, there is reasonable expectation that the stroke–like syndromes of neurosyphilis carry the same prognosis as any other stroke, noting that in neurosyphilis typical strokes often involve relatively large territories in patients in their third to fifth decades. The underlying cause of stroke can be treated, and cure of the neurosyphilis is to be expected. In contrast, the encephalitis associated with dementia may show significant and permanent neurological sequelae. Acute features such as delirium and florid hallucinations should improve, but cognitive impairment will frequently persist, despite cure of the illness as judged by microbiological and serological testing.

THE INTERACTION BETWEEN HUMAN IMMUNODEFICIENCY VIRUS AND NEUROSYPHILIS

Patients acquiring syphilis are also at risk of becoming HIV-positive, as are those who have a history of intravenous drug abuse (Hutchinson *et al*. 1991).

An editorial in the *New England Journal of Medicine* in 1987 ended with the statement that 'in patients with HIV infection, syphilis … follows a malignant and protracted course' (Tramont 1987). The author referred to treatment failure of syphilis in HIV-infected patients and called for higher doses, 'maintenance therapy', and also raised concerns about the possibility that antibody testing for syphilis in AIDS was inaccurate (Tramont 1987). A further editorial in 1994 (Musher & Baughn 1994) referred to atypical forms of neurosyphilis associated with HIV infection 'unlike typical tertiary neurosyphilis' and characterised by acute meningitis, cranial nerve palsies or stroke . It also pointed out that treatment may be ineffective for this form, which may also develop more rapidly.

There are a number of issues here:

- Is HIV-associated neurosyphilis atypical in its clinical presentation? Most reports of patients with both HIV and syphilis have referred to patients with acute meningeal syphilis, stroke, GPI or ophthalmic syphilis (Johns *et al.* 1987; Katz *et al.* 1993). But these are all typical syndromes of syphilis, as described in the pre-antibiotic era (Merritt & Moore 1935; Merritt *et al*. 1946).
- Does HIV-associated neurosyphilis develop at a more rapid rate (Berry *et al*. 1987; Johns *et al.* 1987; Katz & Berger 1989; Musher 1990)? There is currently no evidence to answer this

question. The supposition may be based on faulty understanding of the natural history of neurosyphilis in the pre-antibiotic era, with one editorial stating that 'a 4-year course of illness was essentially unknown' in the pre-HIV era, which is incorrect (Musher & Baughn 1994). There is no difference in the frequency of CNS invasion in patients with and without HIV infection as determined by rabbit inoculation, although numbers were small and confidence intervals wide (Lukehart *et al*. 1988).

- Are there treatment failures specifically associated with HIV in neurosyphilis (Lukehart *et al.* 1988; Gordon *et al.* 1994; Berry *et al.* 1987)? Treatment failure is not uncommon in 'ordinary' neurosyphilis (Schroeter *et al.* 1972; Whiteside 1989). In particular, the later the stage and the higher the titre, the lower the likelihood of a rapid response to therapy. In one study on treatment failure in patients with HIV and neurosyphilis, PCR failed to detect *T. pallidum* after treatment (Gordon *et al.* 1994). There are few studies with only a small numbers of patients and most show a typical response to treatment, despite claims to the contrary (Johns *et al.* 1987; Lukehart *et al.* 1988; Dowell *et al*. 1992; Gordon *et al.* 1994). For example, in a study published in 1994, a conclusion was drawn that the standard neurosyphilis regimen was not consistently effective in HIV. There were only 11 patients, and in the seven cases with 6-month follow-up, mean CSF cell count fell from 21 (range 4–70) to 7 (range 0–20) and there was neurological improvement in 91% of patients (Gordon *et al.* 1994).
- Is the sensitivity and specificity of the serological tests different in HIV-associated neurosyphilis? Comparing serology in different groups, HIV-positive patients were found to have higher titres in secondary syphilis in one study (Hutchinson *et al.* 1991), and in primary syphilis in another (Gourevitch *et al*. 1993).

All the studies typically involved small numbers of patients, and frequently included in their cohort patients who had secondary syphilis with rash complicated by uveitis or acute meningitis (Musher 1991; Katz *et al.* 1993; Gordon *et al.* 1994). VDRL titres were typically very high (median of 512 in one study; Gordon *et al.* 1994), which probably reflected the acute nature of the illness associated with secondary syphilis (Katz *et al.* 1993).

CONCLUSIONS

- The earliest potential neurological manifestation of syphilis is the meningitis associated with secondary syphilis.
- The most common presentation of neurosyphilis is dementia.
- Tabes dorsalis is now rare
- Neurosyphilis may cause ischaemic stroke in either brain or spinal cord.
- Imaging typically shows generalised cerebral atrophy or stroke lesions, sometimes with meningeal involvement.
- Normal serum FTA rules out neurosyphilis.
- CSF VDRL is highly specific but not very sensitive
- CSF FTA is very sensitive but has a high false positive rate
- Neurosyphilis causes a very chronic meningitis and the CSF cell count may be normal.
- Screening for syphilis in populations with low prevalence is likely to yield many false positive cases.

ACKNOWLEDGEMENTS

The help rendered by Professor Richard Hewlett to the Neuropathology section and the MRI images is gratefully acknowledged. This article was refereed by David-Hilton Jones, Oxford

REFERENCES

Adams RD (1997) *Principles of Neurology*, 6th edn. McGraw-Hill, New York.

Berry CD, Hooton TM, Collier AC & Lukehart SA (1987) Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. *New England Journal of Medicine*, **316**, 1587–9.

Burke JM & Schaberg DR (1985) Neurosyphilis in the antibiotic era. *Neurology*, **35**, 1368–71.

CDC Morbidity and Mortality weekly report. http://www.cdc.gov/std/treatment/2–2002TG.htm#Syphilis 51, May 10, 2002.

Dans PE, Cafferty L, Otter SE & Johnson RJ (1986) Inappropriate use of the cerebrospinal fluid Venereal Disease Research Laboratory (VDRL) test to exclude neurosyphilis. *Annals of Internal Medicine*, **104**, 86–9.

Deacon WE, Lucas JB & Price EV (1966) Fluorescent treponemal antibody-absorption (FTA-ABS) test for syphilis. *JAMA*, **198**, 624–8.

Dewhurst K (1969) The composition of the cerebrospinal fluid in the neurosyphilitic psychoses. *Acta Neurologica Scandinavica*, **45**, 119–23.

Dowell ME, Ross PG, Musher DM, Cate TR & Baughn RE (1992) Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus [see comments]. *American Journal of Medicine*, **93**, 481–8.

Editorial (1977) Routine tests for syphilis on cerebrospinal fluid. *Lancet*, **2**, 595.

Editorial (1978) Modified neurosyphilis. *British Medical Journal*, **2**, 647–8.
Felman YM & Nikitas JA (1980) Syphilis serology today. *Arch Dermatol*, **116**, 84–9.
Foster JB (1996) *Oxford Textbook of Medicine*, 3rd edn. Oxford University Press, Oxford.
Gerbase AC, Rowley JT & Mertens TE (1998) Global epidemiology of sexually transmitted diseases. *Lancet*, **351** (Suppl. 3), 2–4.
Gordon SM, Eaton ME, George R *et al*. (1994) The response of symptomatic neurosyphilis to high-dose intravenous penicillin G in patients with human immunodeficiency virus infection [see comments]. *New England Journal of Medicine*, **331**, 1469–73.
Gourevitch MN, Selwyn PA, Davenny K *et al*. (1993) Effects of HIV infection on the serologic manifestations and response to treatment of syphilis in intravenous drug users [see comments]. *Annals of Internal Medicine*, **118**, 350–5.
Graman PS, Trupei MA & Reichman RC (1987) Evaluation of cerebrospinal fluid in asymptomatic late syphilis. *Sexually Transmitted Diseases*, **14**, 205–8.
Greenfield JG & Stern RO (1932) Syphilitic Hydrocephalus in the Adult. *Brain*, **55**, 367–90.
Hart G (1986) Syphilis tests in diagnostic and therapeutic decision making. *Annals of Internal Medicine*, **104**, 368–76.
Heathfield KW (1976) The decline of neurolues. *Practitioner*, **217**, 753–62.
Hook EW & Marra CM (1992) Acquired syphilis in adults. *New England Journal of Medicine*, **326**, 1060–9.
Hooshmand H, Escobar MR & Kopf SW (1972) Neurosyphilis. A study of 241 patients. *JAMA*, **219**, 726–9.
Hutchinson CM, Rompalo AM, Reichart CA & Hook EW (1991) Characteristics of patients with syphilis attending Baltimore STD clinics. *Archives of Internal Medicine*, **151**, 511–6.
Jaffe HW, Larsen SA, Peters M, Jove DF, Lopez B & Schroeter AL (1978) Tests for treponemal antibody in CSF. *Archives of Internal Medicine*, **138**, 252–5.
Joffe R, Black MM & Floyd M (1968) Changing Clinical Picture of Neurosyphilis. report of seven unusual cases. *British Medical Journal*, **1**, 211–2.
Johns DR, Tierney M & Felsenstein D (1987) Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. *New England Journal of Medicine*, **316**, 1569–72.
Joyce CN & Molteno AC (1978) Modified neurosyphilis in the Cape Peninsula. *South African Medical Journal*, **53**, 10–4.
Katz DA & Berger JR (1989) Neurosyphilis in acquired immunodeficiency syndrome [see comments]. *Archives of Neurology*, **46**, 895–8.
Katz DA, Berger JR & Duncan RC (1993) Neurosyphilis. A comparative study of the effects of infection with human immunodeficiency virus. *Archives of Neurology*, **50**, 243–9.
Larsen SA, Hambie EA, Pettit DE, Perryman MW & Kraus SJ (1981) Specifity, sensitivity, and reproducibility among the fluorescent treponemal antibody-absorption test, the microhemagglutination assay for Treponema pallidum antibodies, adn the hemagglutination treponemal test for syphilis. *Journal of Clinical Microbiology*, **14**, 441–5.
Loewenfeld IE (1999) Midbrain Syndromes: Argyll Robertson pupils. In: *The Pupil*, Vol. 1 (ed. Loewenfeld I E). Butterworth-Heinemann, Boston.
Lowhagen GB (1990) Syphilis: test procedures and therapeutic strategies. *Seminars in Dermatology*, **9**, 152–9.
Luger A, Schmidt BL, Steyrer K & Schonwald E (1981) Diagnosis of neurosyphilis by examination of the cerebrospinal fluid. *British Journal of Venereal Disease*, **57**, 232–7.
Lukehart SA & Holmes KK (1998) *Harrison's Principles of Internal Medicine*, 14th edn, McGraw-Hill, New York.
Lukehart SA, Hook EW, Baker ZS, Collier AC, Critchlow CW & Handsfield HH (1988) Invasion of the central nervous system by Treponema pallidum: implications for diagnosis and treatment. *Annals of Internal Medicine*, **109**, 855–62.
Luxon LM (1980) Neurosyphilis. *International Journal of Dermatology*, **19**, 310–7.
Merritt HH, Adams RD & Solomon HC (1946) *Neurosyphilis*. Oxford University Press, New York.
Merritt HH & Moore M (1935) Acute syphilitic meningitis. *Medicine*, **14**, 119–83.
Murialdo A, Marchese R, Abbruzzese G, Tabaton M, Michelozzi G & Schiavoni S (2000) Neurosyphilis presenting as progressive supranuclear palsy. *Movement Disorders*, **15**, 730–1.
Musher D (1990) Syphilis. *Pediatric Infectectious Disease Journal*, **9**, 768–9.
Musher DM (1991) Syphilis, neurosyphilis, penicillin, and AIDS. *Journal of Infectoius Disease*, **163**, 1201–6.
Musher DM & Baughn RE (1994) Neurosyphilis in HIV-infected persons [editorial; comment]. *New England Journal of Medicine*, **331**, 1516–7.
Nordenbo AM & Sorensen PS (1981) The incidence and clinical presentation of neurosyphilis in Greater Copenhagen 1974 through 1978. *Acta Neurologica Scandinavica*, **63**, 237–46.
Norris SJ (1988) Syphilis. In: *The Immunology of Sexually Transmitted Diseases* (ed. Wright DJM), pp. 1–31. Kluwer Academic Publishers, Boston.
Quetel C (1986) *History of Syphilis*. Polity, Paris.
Reik L (1991) Lyme Disease. In: *Infections of the CNS*, 1st edn. (eds Scheld WM, Whitley RJ & Durach DT), pp. 657–89. Raven Press, New York.
Roberts MC & Emsley RA (1992) Psychiatric manifestations of neurosyphilis. *South African Medical Journal*, **82**, 335–7.
Rockwell DH, Yobs AR & Moore MB (1964) The Tuskegee study of untreated syphilis: the 30th year of observation. *Archives of Internal Medicine*, **114**, 792–8.
Romanowski B, Starreveld E & Jarema AJ (1983) Treatment of neurosyphilis with chloramphenicol. A case report. *British Journal of Venereal Disease*, **59**, 225–7.
Russouw HG, Roberts MC, Emsley RA & Joubert JJ (1994) The usefulness of cerebrospinal fluid tests for neurosyphilis. *South African Medical Journal*, **84**, 682–4.
Schroeter AL, Lucas JB, Price EV & Falcone VH (1972) Treatment of early syphilis and reactivity of serologic tests. *JAMA*, **221**, 471–6.
Simon RP (1985) Neurosyphilis. *Archives of Neurology*, **42**, 606–13.
Spangler AS, Jackson JH, Fiumara NJ & Warthin TA (1964) Syphilis with a negative blood reaction. *JAMA*, **189**, 87–90.
Sparling PF (1971) Diagnosis and treatment of syphilis. *New England Journal of Medicine*, **284**, 642–53.
Tichonova L, Borisenko K, Ward H, Meheus A, Gromyko A & Renton A (1997) Epidemics of syphilis in the Russian Federation: trends, origins, and priorities for control. *Lancet*, **350**, 210–3.
Tramont EC (1987) Syphilis in the AIDS era [editorial]. *New England Journal of Medicine*, **316**, 1600–1.
Walton JN (1977) *Brain's Diseases of the Nervous System*, 8th edn. Oxford University Press, Oxford.
Whiteside CM (1989) Persistence of neurosyphilis despite multiple treatment regimens. *American Journal of Medicine*, **87**, 225–7.
Wiesel J, Rose DN, Silver AL, Sacks HS & Bernstein RH (1985) Lumbar puncture in asymptomatic late syphilis. An analysis of the benefits and risks. *Archives of Internal Medicine*, **145**, 465–8.
Wilson SAK (1940) *Neurology*. Butterworth, London
Wilson SAK & Grey ACE (1917) Acute Syphilitic Meningitis. *British Medical Journal*, 419–21.
Wolters EC (1987) Neurosyphilis: a changing diagnostic problem?. *European Journal of Neurology*, **26**, 23–8.
Young H (1992) Syphilis: new diagnostic directions [editorial]. *International J STD AIDS*, **3**, 391–413.