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# Modern Neurosyphilis: A Partially Treated Chronic Meningitis

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*Approximately 5,000 new cases of neurosyphilis may occur in the United States each year. General paresis and tabes dorsalis, however, have become relatively rare since the introduction of penicillin. Seizures, neuro-ophthalmologic symptoms, stroke and acute meningoencephalitis are currently the most common manifestations of neurosyphilis.*

*In more than a third of patients with neurosyphilis, nontreponemal tests for syphilis (such as VDRL) are negative and should not be used to exclude the diagnosis. Specific treponemal tests are more sensitive and more specific. Examination of the cerebrospinal fluid may show no abnormalities in neurosyphilis and is not an infallible guide to the activity of the infection.*

*Penicillin is the only proven antibiotic treatment of neurosyphilis. However, low-dose regimens do not produce spirocheticidal concentrations in the brain, and high-dose penicillin therapy is recommended to insure eradication of the spirochetes. Doxycycline, a tetracycline derivation that achieves relatively high concentration in the brain, may also be effective.*

MEDICAL STUDENTS AND PHYSICIANS in training should be challenged by the statement that "Neurosyphilis is not rare, but you will probably fail to recognize your first case of this treatable disorder." Although penicillin has clearly reduced the frequency of the disease, the expectation that it would eradicate neurosyphilis remains unfulfilled. At the same time, formal training in recognizing the variable manifestations of the infection has waned in medical schools, almost to the point of considering neurosyphilis of only historical importance.

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The true incidence of this disease is unknown. However, approximately 50 new cases of neurosyphilis are diagnosed each year in those medical centers where personnel have more experience in recognizing or suspecting this disease.[1,2] In addition, over 50,000 new cases of syphilis are thought to go undetected each year in the United States, and the number of untreated patients with any form of syphilis has been estimated at 510,000.[3-6] This venereal disease is particularly prevalent in large urban areas and within homosexual communities. Assuming that in 10 percent of patients with an untreated form of syphilis, neurosyphilis[7] will develop, then more than 5,000 new cases may occur each year. Clearly, then neurosyphilis still

ABBREVIATIONS USED IN TEXT

AR = Argyll Robertson (pupil)
CSF = cerebrospinal fluid
FTA-ABS = fluorescent treponemal antibody absorption (test)
MHA-TP = microhemagglutination test for *Treponema pallidum*

exists. Its accurate diagnosis, however, requires particular astuteness. The clinical manifestations are extremely variable and may have changed in the postantibiotic era, so that the classic findings of neurosyphilis are often absent.[1,2] Also, routine screening serological tests for syphilis do not detect a third or more of the cases of active neurosyphilis, and specific treponemal tests must be used to exclude the disorder.[8-10] Past penicillin treatment also does not exclude the possibility of active syphilis because some recommended penicillin regimens do not produce spirocheticidal levels in the brain.[11]

To increase the awareness of these and other observations, the present review of modern neurosyphilis was undertaken. The focus of the report is on adults who have *acquired* the treponemal infection. Although many of the comments also pertain to congenital neurosyphilis it is not separately reviewed.

## Historical Background and Classification

The recent history of neurosyphilis began in 1905 when the spirochete *Treponema pallidum* was first described by Schaudinn and Hoffman. A year later Wasserman's complement-fixation test was developed and permitted the serological confirmation of syphilis in patients with neurological disorders. In 1913, Noguchi and Moore found treponemes in the brains of patients with general paresis, providing final proof for the long-proposed postulate that syphilis could infect the brain (see ref. 12 for review).

During this preantibiotic period it was well known that syphillis began with an epithelial lesion that was characterized by a painless, and often ulcerated, papule; this chancre appeared ten days to several weeks after sexual transmission. Serological tests remained negative for one to three weeks but became positive after six to eight weeks—and preceding the variable systemic and mucocutaneous manifestations of disseminated secondary syphilis.[12]

The spirochetes invaded the central nervous system either during the secondary phase of the disease or within two years of the primary infection in 35 percent to 45 percent of untreated cases.[7] The initial mode of infection was a form of meningitis, which varied from an asymptomatic illness to a syndrome with headache, nuchal rigidity and, at times, confusion, cranial nerve palsies, convulsions, increased intracranial pressure and hydrocephalus. Examination of spinal fluid showed a pleocytosis that was predominantly lymphocytic.

The initial meningeal infection, if untreated, either remitted spontaneously or evolved into a chronic, initially asymptomatic, meningitis.[7] This persistent meningitis produced a variable, although largely predictable, sequence of pathological findings that formed the basis of most classifications of neurosyphilis (Table 1).

In the chronic form of syphilitic meningitis pathological findings consisted of diffuse or discrete (for example, gummatous) collections of lymphocytes, plasmacytes and occasional polymorphonuclear leukocytes in the meningeal spaces, with an associated adhesive fibrosing arachnoiditis. However, with time an endarteritis involving large or medium-sized cerebral and meningeal vessels also developed. These vessels became infiltrated by spirochetes and inflammatory cells leading to fibroblastic thickening, cerebrovascular occlusion and stroke (that is, meningovascular syphilis). This endarteritis usually became symptomatic six to ten years after the primary infection but could occur as early as six months or as late as 15 years.

If the chronic fibrosing meningitis bypassed or persisted asymptomatically beyond the meningovascular stage, then parenchymal damage occurred by direct parenchymal invasion of the spirochetes. This parenchymal infection commonly became symptomatic 15 to 20 years after the primary infection. When *T pallidum* maximally infected the cerebral cortex, a meningoencephalitis developed which, if untreated, resulted in irreversible neuronal loss, demyelination and gliosis in the brain. While dementia or behavior change was the initial symptom, the name general paresis was applied to this chronic meningoencephalitis because as the disease progressed, various debilitating complications severely limited activity. Another common area of parenchymal involvement included an admixture of pupillomotor structures and the dorsal roots and columns of the spinal cord that produced a syndrome called tabes dorsalis. Similarly, relatively selective injury of the optic nerves produced loss of vision and optic atrophy; spirochetal

TABLE 1.—*Historical Classification of Neurosyphilis**

| *Clinical* | *Pathological* | *Onset After Primary Infection*† |
|---|---|---|
| Asymptomatic | Chronic meningitis | 2 mo-15 yr |
| Meningeal | Meningitis with or without cranial neuropathy, hydrocephalus | 2 mo-2 yr |
| Meningovascular | Chronic meningitis with: | 6-10 yr |
| Cerebral | Endarteritis and cerebral infarction | |
| Spinal | Infarction of the spinal cord | |
| Parenchymal | Chronic meningitis with: | 10-20 yr |
| General paresis | Chronic encepahlitis | |
| Tabes dorsalis | Spinal root and cord atrophy | |
| Optic atrophy | Optic atrophy | |
| Spinal | Myelitis | |
| Gumma formation | Syphilitic granuloma, usually in proximity to meninges | Variable |
| Congenital syphilis | Includes all of the above | Newborn to adolescence |

*Adapted from Refs. 7 and 12.
†Most frequent time of onset but variable.

invasion of the spinal cord resulted in a meningomyelitis with a spastic paraparesis or quadriparesis.

In a given person one neuroanatomic site often appeared to be selectively involved. However, after progression of the infection, pathological and clinical studies usually showed a great deal of overlap between the different forms of parenchymal neurosyphilis, and even between modes of neural injury. In a single patient parenchymal damage could be due to a combination of spirochetal invasion, a syphilitic endarteritis and a fibrosing arachnoiditis.[7,12]

## Modern Neurosyphilis

The initiation of penicillin therapy in the 1940's radically altered neurosyphilis. While previous forms of treatment such as bismuth, arsenic and malarial therapy were felt to be partially beneficial, penicillin was treponemicidal and effectively treated all forms of syphilis. The result was a substantial decrease in the frequency of new cases of classic neurosyphilis. However, neurosyphilis was not eradicated by the antibiotic era. Instead, its natural history and clinical manifestations were modified, and it became more monosymptomatic and often more subtle.[1,2,13] It is thought that the widespread use of antibiotics given by mouth, such as penicillin, ampicillin and tetracycline, for various infections has inadvertently changed neurosyphilis into a progressive, *partially treated, chronic meningitis*. As a result, partial rather than fully developed manifestations are the rule.

This proposal is supported by comparing the clinical presentation of neurosyphilis reported to have occurred in Boston from 1932 to 1942[7] with a composite of cases recently reported in the postantibiotic era.[1,2,11,14-26] A total of 610 cases of neurosyphilis reported since 1965 were reviewed, and 324 that met accepted criteria for the diagnosis were selected. The diagnostic criteria for neurosyphilis included the following: (1) Neurological or ophthalmologic symptoms (or both), with positive serological tests for syphilis and abnormal results of a CSF examination (for example, more than five leukocytes per cu mm, elevated protein, elevated gamma globulin, abnormal colloidal gold test, or positive serological tests for syphilis) *or* (2) asymptomatic condition with serological evidence of syphilis and more than five leukocytes per cu mm in the CSF.

Cases of proposed seronegative neurosyphilis with normal CSF findings were excluded. These 324 cases, plus 11 patients personally seen over three to four years, demonstrated a change in the symptomatic presentation of neurosyphilis in the postantibiotic era (Table 2).

General paresis and tabes dorsalis, which were the most common forms of neurosyphilis in the 1930's are now less frequent presenting problems. Instead, seizures and neuro-ophthalmologic symptoms have become prominent manifestations.

### *Syphilitic Seizures*

Following the introduction of serological tests for the verification of syphilis, seizures were considered to be a minor manifestation of neurosyphilis.[7] Convulsions were not part of the tabetic syndrome. Seizures were thought to complicate general paresis only late in the course of illness, and if the paretic patient was treated before their onset, it was unlikely that convulsions would

occur. Seizures were noted, however, in approximately a fifth of the patients with meningovascular syphilis.[7,27] These observations indicate that before the antibiotic era, seizures were an early manifestation in less than 5 percent of patients with symptomatic neurosyphilis. In comparison, seizures are now prominent in more than 25 percent of symptomatic cases (Table 2). Part of the increased frequency may be due to an inclusion of patients in whom the initial manifestation of meningovascular syphilis was seizures. However, a third of the patients with syphilitic seizures were otherwise asymptomatic, indicating that in some, seizures may be the sole manifestation of neurosyphilis.[1]

Syphilitic seizures occur as either partial (such as focal) seizures or partial seizures with secondary generalization. Both a careful history, including observations from a witness of the convulsion, and an electroencephalographic examination may be required to determine the focal initiation of the seizure. More than half of these patients also have abnormal findings on neurological examination, including evidence of a hemiparesis, impaired mentation, pupillary abnormalities, or decreased sensation and muscle stretch reflexes. However, as noted above, a third of the patients have no clinical findings to suggest a cause for their seizures. Therefore a *treponemal* serological test (see below) should be obtained in every adult with the onset of partial seizures of unknown cause.

TABLE 2.—*Comparison of Clinical Presentation of Neurosyphilis in Boston Study With Composite of Cases in Postantibiotic Era*

| Clinical Problem | 1932-1942* No. Patients | 1932-1942* Percent | 1965-1980† No. Patients | 1965-1980† Percent |
|---|---|---|---|---|
| Symptomatic | | | | |
| Seizures | 4 | 1 | 59 | 28 |
| Neuro-ophthalmologic | 20 | 4 | 56 | 26 |
| Meningovascular | 103 | 18 | 42 | 20 |
| Dementia (paresis) | 203 | 35 | 26 | 12 |
| Acute or chronic myelopathy | 19 | 4 | 10 | 5 |
| Tabes dorsalis | 203 | 35 | 9 | 4 |
| Cranial nerve VIII | 9 | 2 | 4 | 2 |
| Miscellaneous | 6 | 1 | 6 | 3 |
| | 563 | 100 | 212 | 100 |
| Asymptomatic | 219 | | 123 | |
| TOTAL | 782 | | 335 | |

*Boston study; the figures for paresis were increased to equal tabes as suggested by Merritt et al.[7]
†Composite of cases, adapted from references 1, 2, 11, 14-26.

### *Neuro-ophthalmologic Findings*

Disorders of the visual fields and acuity, ocular motility and pupillary function are frequent manifestations of neurosyphilis. Syphilitic involvement of the optic nerve produces either a slowly progressive loss of vision due to a parenchymal optic atrophy or a rapid reduction from an acute optic neuritis.[28] The progressive optic atrophy usually occurs over months to years and if untreated will produce blindness in most patients within five years.[28,29] While the nerve degeneration can be segmental, it usually begins peripherally, adjacent to infected meninges, and then proceeds to the center of the nerve. Therefore, a progressive concentric constriction of the peripheral visual fields is a characteristic finding. Although visual acuity is frequently decreased, syphilis can produce a pronounced contraction of the visual field with retention of normal vision. Funduscopic examination shows a retrograde optic nerve axonal degeneration. There is a loss of retinal fibers that produces a sharply demarcated optic disc with reduction of the number of small capillaries at the disc margins but preservation of the central retinal vessels. The symptoms of syphilitic optic atrophy may involve primarily one eye; however, the visual fields and funduscopic findings usually involve both.

Whereas the progressive optic atrophy is a form of late parenchymal neurosyphilis, the acute optic neuritis may accompany an early syphilitic meningitis or even occur during the secondary stage of disseminated syphilis. Vision is rapidly reduced, often reaching a maximum density in the first week. Only one eye is usually involved and pain in that eye may precede or accompany the loss of vision. Visual field defects are extremely variable, but, in contrast to syphilitic optic atrophy, the acute neuritis frequently produces a central or paracentral scotoma. Funduscopic examination may show edema of the optic disc or remain normal in cases of retrobulbar syphilitic optic neuritis.[28]

Besides damaging the optic nerve, syphilis can impair vision by infection of the retina and choroid (chorioretinitis), usually in the region of the optic disc or posterior pole of the eye, or by inflammation and opacification of the cornea (keratitis).[28]

Disorders of eye movements are usually due to inflammation and fibrosis of the third, fourth and sixth cranial nerves as they lie within the meningeal spaces. The oculomotor or third cranial nerve

is most commonly involved and may be the only manifestation of neurosyphilis.[21,28] The clinical appearance of a third nerve paresis is so well known that it will not be described beyond stating that an enlarged pupil that is poorly reactive may precede ptosis or eye muscle weakness. This is because the pupillomotor fibers are situated in the periphery of the third nerve, which is also the site of early inflammation and fibrosis in a chronic meningitis.[30]

A more specific pupillary sign of neurosyphilis is a dissociated response to light and convergence in an eye with preserved vision. The pupil reacts poorly to light but well to convergence. Douglas Argyll Robertson in 1869 noted that this light-convergence dissociation was accompanied by miosis and a poor response to mydriatics in tabes dorsalis. While the Argyll Robertson (AR) pupil is usually irregular and bilateral, most neurologists require only the light-convergence dissociation and miosis for its identification. The AR pupil has always been considered and remains *almost* pathognomonic of neurosyphilis (see ref. 31 for the authoritative discussion). However, when a pupil with a light-convergence dissociation is not miotic, a variety of neurological disorders including syphilis may be present.[4,31] Therefore, a clear definition of miosis is needed to identify an AR pupil. In an adult, a pupil 2 to 3 mm or smaller in diameter *in darkness* is miotic. Under the bright light of an examining room, a pupil of 2 to 3 mm may reflect a normal physiological response. However, the same pupil in darkness dilates to 6.0 to 8.5 mm in persons younger than 45 years of age—an AR pupil does not.[31]

The cause of an AR pupil has remained controversial for more than 100 years. Suffice it to say that some neuro-ophthalmologists consider syphilitic involvement of the rostral midbrain most likely, while others think the ciliary ganglion and nerves may be involved.[14,28]

### *Meningovascular Syphilis*

Meningovascular neurosyphilis denotes syphilitic processes of both the meninges and cerebral vasculature. The location and intensity of infection may be quite diverse and produce polymorphic clinical manifestations. In general, a stroke, an acute meningoencephalitis or an admixture of both are the presenting problems. There may be an acute onset of a hemiparesis, homonymous hemianopia or aphasia, indicating a focal area of cerebral ischemia. These signs, however, can be accompanied or overshadowed by a disoriented, confusional state and a cerebrospinal fluid (CSF) pleocytosis. Convulsions may occur and clinical signs of a meningeal inflammation may be prominent or absent. Meningovascular syphilis, therefore, should not be considered only as a treatable cause of stroke, but also entertained in cases of meningitis of an unknown cause and proposed viral meningoencephalitis.

Meningovascular syphilis usually occurs within ten years of the primary infection and, frequently, in patients 30 to 45 years of age. Therefore, in a young patient with a stroke a diagnosis of syphilitic endarteritis is actively pursued. In an older patient with a stroke, syphilis is at times unenthusiastically investigated because in the vast majority of cases the stroke is due to a nonsyphilitic thrombosis or embolus. However, meningovascular syphilis does occur after age 65, and to exclude it as a cause of stroke simply on the basis of age is an error.

### *Dementia (General Paresis)*

Although less infrequent, syphilis remains a potentially treatable form of dementia. The presenting symptoms of a chronic syphilitic meningoencephalitis do not differ from less treatable forms of presenile dementia. The first symptoms are insidious in onset and consist of defects in memory, concentration, judgment and calculations. There are often associated behavioral changes such as apathy, deterioration in personal hygiene, emotional lability and, on occasion, delusional ideation and hallucinations. As the disease progresses these initial symptoms intensify. The patient eventually reaches a point of such debilitation (or paresis) that he or she is restricted to bed.

A chronic meningoencephalitis may not be the only pathological cause of a syphilitic dementia. A syphilitic meningitis may impede CSF flow and produce a communicating hydrocephalus that is readily treatable by a CSF shunting procedure.[32] Communicating hydrocephalus should be considered in every case of syphilis-induced dementia that does not respond to optimal antibiotic treatment.

### *Tabes Dorsalis*

The term tabes signifies progressive wasting and emaciation and was initially used to describe patients with chronic spinal paralysis of various causes. However, with time tabes came to indicate a syndrome of spinal syphilis characterized by lightning pains, AR pupils, absence of muscle

stretch reflexes and ataxia.[12] Sensory complaints are early and often predominant symptoms. Lancinating pains occurring in attacks that last minutes to days happen in 90 percent or more of cases. These pains are associated with an inflammatory sensory radiculopathy that results in atrophy and fibrosis of multiple nerve roots.

During the initial evaluation of patients with tabetic sensory symptoms, AR pupils, bilateral ptosis and diminished vibration, proprioception, deep pain sensation and two-point discrimination are often found. Difficulty with urination and sexual impotence are common complaints. Once established, the disease slowly progresses over 10 to 20 years and ataxia becomes increasingly prominent and disabling. This sensory ataxia is due to a loss of proprioception in the legs, and reflects the prominent atrophy of the dorsal roots and columns of the spinal cord.[12]

*Other Manifestations*

Syphilis may also involve the spinal cord by direct parenchymal invasion or indirectly through meningovascular inflammation and vascular occlusion with secondary infarction. Onset of symptoms may be abrupt or gradual and the course may be progressive. Paraparesis or quadriparesis, sensory loss in the extremities, incontinence and hyperreflexia are the usual signs. They may lead to a diagnosis of multiple sclerosis or transverse myelitis, neither of which has a specific treatment. It cannot be stressed strongly enough that *neurosyphilis can mimic every clinical and laboratory manifestation of multiple sclerosis* including disseminated lesions throughout the central nervous system, with remissions and exacerbations. I am personally aware of a 26-year-old woman with a syndrome of progressive myelopathy and optic atrophy, mild pleocytosis and elevated gamma globulin levels in the CSF, and negative serum and CSF *nontreponemal* serological tests. A diagnosis of multiple sclerosis was made and a specific treponemal serological test was never obtained. Postmortem examination demonstrated spinal neurosyphilis.

Other less common manifestations of syphilis include dizziness, hearing loss, psychotic behavior, spinal arachnoiditis, circumscribed gumma formation acting as a mass lesion, atypical neuritic pains, isolated cranial neuropathies and progressive muscular atrophy. These problems will not be considered in detail except to stress that syphilis should be considered in most progressive neurological disorders before a diagnosis of untreated degenerative disease is accepted.

*Asymptomatic Neurosyphilis*

An asymptomatic chronic meningeal infection has accounted for approximately a third of all syphilitic infections involving the nervous system in both the preantibiotic and postantibiotic eras. Patients often have been identified because of serological test findings following a general medical screening examination or because of an incidental pupillary abnormality discovered during a routine ophthalomologic examination. It is particularly important to detect and treat such patients to prevent late disabling symptomatic neurosyphilis. An asymptomatic syphilitic meningitis usually develops within a year of the primary infection.[7] Therefore, it is essential that the CSF is examined in every patient infected with syphilis for a year or more or for an unknown duration. In addition, the British recommend that every patient treated for primary and secondary syphilis should have a CSF examination a year after treatment to verify a cure.[33]

## Serological and CSF Test Findings

Serological tests used to identify a treponemal infection are either nontreponemal or treponemal. Nontreponemal tests consist of complement-fixation or flocculation procedures aimed at detecting a nonspecific globulin complex called reagin. Reagin serological tests for syphilis, such as the Venereal Disease Research Laboratory (VDRL) flocculation test, lack sensitivity and *should not be used to exclude the diagnosis of neurosyphilis.* More than a third to a half of the patients with neurosyphilis have a negative VDRL test in serum and more than a third have a negative VDRL test in CSF.[1,8-10,34] False-positive reactions occur in collagen vascular diseases, after vaccinations and various viral infections and during pregnancy.[35] Therefore, a nontreponemal serological test is neither sensitive nor specific for neurosyphilis.

Treponemal serological tests are based on a specific immune response to *T pallidum.* The serum fluorescent treponemal antibody absorption (FTA-ABS) test, developed by Hunter, Deacon and Meyer in 1964,[36] is the test of choice to confirm the diagnosis of neurosyphilis. The test consists of incubating a patient's serum with a slide coated with dead *T pallidium* organisms. After this incubation, fluorescein-tagged antibody to human gamma globulin is added. Fluorescence of the

treponemes indicates that antitreponemal antibodies are in the patient's serum.

The FTA-ABS test is reactive in the serum of 95 percent to 100 percent of cases of neurosyphilis.[8-10] A negative FTA-ABS test essentially excludes the diagnosis of neurosyphilis and makes examination of the CSF unnecessary. Its false-positive rate is less than 1 percent in celibate nuns and normal controls, though the incidence of biological false-positive tests may be increased by the presence of collagen vascular disorders.[37] Therefore, the FTA-ABS test is both sensitive and relatively specific for detecting a past syphilitic infection.

A second treponemal test, the microhemagglutination test for *T pallidum* (MHA-TP), can complement and may replace the FTA-ABS test in the near future because it is easier to carry out.[38] This test is based on the ability of serum with antitreponeme antibodies to agglutinate erythrocytes previously coated with antigen from *T pallidum*. It has not yet been determined if the selectivity of the MHA-TP test is equal to that of the FTA-ABS test in patients with neurosyphilis.

A reactive serum treponemal test indicates past infection with syphilis, but it does not by itself indicate active neurosyphilis. A patient successfully treated for syphilis may have a reactive FTA-ABS response indefinitely. Therefore, classically, the spinal fluid has been used as a guide to the activity of neurosyphilis.[39] The VDRL currently remains the test indicated for detecting a syphilitic immune response in the CSF; when positive in CSF it is strong evidence for neurosyphilis.[34,40] False-positive tests rarely occur. The CSF may have a reactive VDRL response in the absence of neurosyphilis either by contamination with seropositive blood (due to a traumatic spinal tap or subarachnoid hemorrhage) or due to entry of serum reagin into the CSF in association with meningitis. As noted above, the VDRL test may be nonreactive in a third of patients with a chronic syphilitic meningitis. Though still under investigation, the FTA-ABS test in CSF currently has no place in the practical management of neurosyphilis. It has a false-positive rate as high as 4 percent to 6 percent and may represent only antibodies that have passively entered the CSF from the serum.[41]

Other abnormalities of the CSF that commonly accompany neurosyphilis include elevated protein (50 to 400 mg per dl) level, lymphocytic pleocytosis (up to 200 to 300 cells per cu mm), and an elevated gamma globulin level. The sugar content is usually normal. The colloidal gold test has been largely replaced by an electrophoretic analysis of gamma globulin.

If the CSF is totally normal in a patient with clinical signs of neurosyphilis then some physicians feel the process has "burned out" and there is no need for further treatment. However, this clinical approach is being seriously challenged in patients in the postantibiotic era who may have partially treated neurosyphilis.

## Cerebrospinal Fluid Controversy

J. Lawton Smith, professor of neuro-ophthalmology at the University of Miami, states that "the definite majority of patients with parenchymatous neurosyphilis seen in practice today have cerebrospinal fluids that are essentially normal to all customary clinical parameters, and that such patients also more often have non-reactive serum reagin tests (i.e., VDRL) than not."[14]

Recently, the opposite view has also been stated,

> The CSF is an almost infallible guide, probably even more than the clinical symptomatology, in the diagnosis and treatment and prognosis of the disease. If the CSF is negative in a case in which there are symptoms of neurosyphilis, it may be safely concluded that the syphilitic inflammation in the nervous system is burned out and that further progression of the disease probably will not occur. In cases with progressive neurologic symptoms and a completely negative CSF, a postmortem examination usually discloses a nonsyphilitic neurologic disease.[42]

Thus, a controversy exists on whether totally normal CSF findings exclude active neurosyphilis in need of penicillin treatment. While present evidence cannot resolve this controversy for an individual patient, it does indicate, particularly in the postantibiotic era, that the CSF findings are not infallible.

J. H. Stokes, in 1940—before the era of penicillin treatment—felt that 12 percent of patients with "undoubted neurosyphilis" had normal spinal fluid findings.[43] This conclusion was supported by the observation of patients with signs, symptoms and serological findings of neurosyphilis in whom arsenic treatment provoked an increase in CSF protein and pleocytosis in spinal fluid previously thought to be normal.

More recently, an infectivity test has been used to demonstrate the presence of *T pallidum* in CSF having normal laboratory measurements. Because treponemes cannot be cultured in vitro, an in vivo infectivity test using rabbits or primates has been used. Although interpretation of these infectivity tests differs among investigators,[44] an infective *T*

*pallidum* can be isolated from presumed normal spinal fluid.[20] This evidence suggests that normal CSF findings do not rule out active neurosyphilis, particularly in the present era when patients may have been partially treated inadvertently with antibiotics. Because of this conclusion, it is recommended that an untreated patient with both signs of progressive neurosyphilis and a reactive treponemal serological test be treated with antibiotics irrespective of the CSF findings. In these patients the CSF should be reexamined approximately a week after initiation of treatment to determine if a reactive pleocytosis had been provoked.[43] This finding would help confirm the diagnosis of neurosyphilis, which can be particularly important if a question of retreatment later develops.

## Treatment

Penicillin is the only proved antibiotic treatment for neurosyphilis. However, the optimal preparation, dose and duration of treatment remain unknown. Neurologists in general use larger doses of penicillin than venereologists because of an unsatisfactory cure rate with lower doses. Overall, approximately 25 percent of symptomatic patients and 10 percent of asymptomatic patients treated with various low-dose penicillin regimens fail to have a satisfactory response.[45] Manifestations of parenchymal neurosyphilis, such as general paresis, optic atrophy and tabes dorsalis, are particularly notorious for not responding to low-dose penicillin therapy. Because of these problems, recommended penicillin regimes are based on three principles.[46]

1. The accepted spirocheticidal concentration of penicillin in infected tissue is 0.03 units per ml (0.02 $\mu$g/ml). Penicillin, however, penetrates the blood brain barrier poorly and CSF levels may only be 2 percent of serum levels. Brain parenchymal levels of penicillin may be even less than CSF levels, a factor of particular importance when treating parenchymal neurosyphilis.

2. Penicillin's bacteriocidal actions occur during the stage of active spirochete multiplication. Therefore, intervals of subspirocheticidal penicillin concentrations should be shorter than the treponeme replication rate (about 30 to 33 hours in early syphilis and probably longer in neurosyphilis).

3. Response to therapy is related to both the total dose and duration of penicillinemia, as well as the extent and duration of parenchymal brain damage. Injury to the brain, either by neuronal loss, demyelination, gliosis or infarction may be permanent. Noncurative doses of penicillin may not halt or prevent parenchymal injury and, thus, permit progressive irreversible brain damage.

Only two penicillin regimens have been shown to comply with the above guidelines. The first consists of 12 million units of aqueous crystalline penicillin G given intravenously each day (2 million units every 4 hours) for 10 to 15 days.[11] Though it requires that the patient be in hospital, this is the best regimen for a symptomatic condition and is clearly indicated in any patient whose neurological examination suggests a major infection of nervous tissue. Patients who have minor findings (such as an isolated AR pupil) or who refuse hospitalization may be treated as outpatients with 1.2 to 2.4 million units per day of procaine penicillin G given intramuscularly in combination with 500 mg every six hours of probenecid given orally.[47] Probenecid increases penicillin levels in both serum and CSF by decreasing renal and CSF excretion.

In patients with predominantly meningovascular syphilis or no symptoms, it may be acceptable to use an outpatient regimen consisting of 20 million units of procaine penicillin G given intramuscularly in divided doses (2.4 million units every other day) over three weeks.[1] Almost all of these nonparenchymal infections appear to be cured by this amount of penicillin even though the reliability of obtaining therapeutic penicillin levels has not been determined.

The above recommendations differ considerably from the 1976 treatment schedules published by the Venereal Disease Control Advisory Committee for the Center for Disease Control. Their recommendation was as follows:

1. Benzathine penicillin G—7.2 million units total: 2.4 million units by intramuscular injection weekly for three successive weeks;

*or*

2. Aqueous procaine penicillin G—9.0 million units total: 600,000 units by intramuscular injection daily for 15 days.

However, neither of these regimens produces spirocheticidal levels of penicillin in the CSF.[11] In particular, benzathine penicillin G, while convenient for both the patient and physician, should be avoided in neurosyphilis.

Adverse reactions to penicillin occur either in the form of an allergic (urticaria, rash, anaphylaxis) or a Jarisch-Herxheimer reaction. None of these reactions are dose related. Anaphylaxis,

the most serious allergic response, occurs in 0.04 percent of patients with syphilis.[46] Jarisch (1895) and Herxheimer (1902) described a reaction occurring within 24 hours of the first dose of mercury treatment for syphilis that was characterized by both fever and aggravation of syphilitic symptoms and lesions.[48] It has since been found that the Jarisch-Herxheimer reaction can follow any form of treatment. It occurs most commonly in early syphilis and is thought to be caused by the release of products from dead spirochetes. The Jarisch-Herxheimer reaction occurs infrequently with neurosyphilis, being noted in approximately 2 percent of patients with general paresis, and it rarely affects the long-term outcome. However, this reaction is feared in parenchymal infection of the optic or auditory nerves in which acute blindness or deafness may occur. Therefore, some authors recommend a concomitant course of prednisone in patients with these disorders even though it is not of proved benefit.[46]

There is little published evidence, beyond case reports, that antibiotics other than penicillin are effective in the treatment of neurosyphilis. Tetracycline is known to cure early syphilis and doxycycline, a derivative of oxytetracycline, is particularly lipophilic and achieves five times the concentration of tetracycline in the brain.[49,50] Therefore, 300 mg of doxycycline a day given orally in divided doses for 30 days is an acceptable alternative drug for patients with confirmed penicillin allergies.

Erythromycin has also been tried for neurosyphilis because it is effective systemically. However, its penetration into the CSF is poor and its use cannot be recommended here.[51] It is clear that any patient treated with antibiotics other than penicillin needs particularly close follow-up.

## Response to Treatment

As noted above, the clinical response to treatment is dependent on both the penicillin regimen selected and the extent and duration of nervous tissue damage. In general, high-dose penicillin therapy should cure a syphilitic infection limited to the meninges and stop the progression, usually with some clinical improvement, of a parenchymal disorder.[1] Patients must be followed closely to verify that the above goals are obtained. Quantitative reagin serological tests (such as the VDRL) are obtained every three months the first year and should show a drop in titer unless already low. CSF cell count, protein levels, VDRL response and gamma globulin levels are examined at 6 and 12 months and, if not totally normal, again at two years. If after three years the patient remains clinically improved and the CSF and serological tests have reverted to normal, then further observation is not needed.[42,52] However, if during that period there is evidence of clinical progression or failure in improvement of laboratory results, retreatment must be considered. It is recommended to retreat with high-dose, intravenously given penicillin G if any of the following exists:

- There is clinical progression and reevaluation does not indicate an alternative neurological explanation. Retreatment in these patients is especially indicated when there is an initial improvement after penicillin treatment, a persistent CSF pleocytosis, or when the initial treatment is suboptimal.
- There is a failure of the CSF cell count to decline to normal at six months.
- Failure of VDRL titers for serum or CSF to decline or a fourfold rise in titer.
- The initial treatment involved a suboptimal penicillin regimen such as benzathine penicillin.

Some authors also consider a rise in CSF levels of gamma globulin an indication of continued infection. Otherwise, an isolated elevation of CSF protein is not an indication for retreatment.

Tabetic sensory symptoms may not respond to penicillin and in themselves are not an indication for retreatment; presumably, they result from the fibrosis and atrophy of dorsal roots and posterior columns rather than the presence of treponemes. The lightning pains can be reduced by the anticonvulsant carbamazepine.[23]

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