

Transmissible diseases

Chapter 72

Biology and neuropathology of dementia in syphilis and Lyme disease

JUDITH MIKLOSSY*

University of British Columbia, Kinsmen Laboratory of Neurological Research, Vancouver, BC, Canada

72.1. Introduction

It has long been known that *Treponema pallidum*, subspecies *pallidum* can in late stages of neurosyphilis cause dementia, cortical atrophy, and amyloid deposition. The occurrence of dementia, including subacute presenile dementia, was also reported in association with Lyme disease caused by another spirochete, *Borrelia burgdorferi*. Both spirochetes are neurotropic and in both diseases the neurological and pathological manifestations occur in three stages. They both can persist in the infected host tissue and play a role in chronic neuropsychiatric disorders, including dementia.

72.2. Spirochetes

Spirochetes are Gram-negative free-living or host-associated helically shaped spiralled bacteria (Fig. 72.1). They are widespread in aquatic environments and are the causative agents of important human diseases like syphilis, Lyme disease, periodontitis, ulcerative gingivitis, and leptospirosis. Their diameter and length vary between $0.1\text{--}3 \times 5\text{--}250 \mu\text{m}$ and the amplitude of their spirals also differs depending on various species and genera. The cytoplasm is surrounded by a trilaminar cytoplasmic membrane, which in turn is covered by a delicate peptidoglycan layer giving to the cell structural rigidity. They possess an outer membrane characteristic of Gram-negative bacteria. Spirochetes possess endoflagellae (periplasmic flagellae) which wind around the cytoplasmic body between the peptidoglycan layer

and the outer membrane (Fig. 72.2). They are fixed via insertion pores at both ends of the spirochete. These endoflagellae confer to the organism the characteristic cork-screw movements, flexions, rotations around their threaded axis which enable movements in viscous medium. The number of endoflagellae varies from 2 to up to 200 depending on genera, and determination of their number can be used for taxonomic characterization. The group includes aerobic, microanaerobic and anaerobic species.

Treponema pallidum and *Borrelia burgdorferi*, the causative agents of syphilis and Lyme disease, are obligate parasites that rely on a host for a multitude of growth factors and nutrients. They belong to the genera *Treponema* and *Borrelia* of the family Spirochaetaceae and order Spirochaetales. They use for a carbon source only sugars and/or amino acids.

T. pallidum, a thin, tightly spiralled organism with 6–14 spirals, measuring 6–20 μm in total length and 0.1–0.2 μm in width, is transmitted by sexual contact. This delicate organism with tapered ends has not yet been grown in synthetic media, although virulent strains of *T. pallidum* have long been propagated in the testes of rabbits and are maintained in cell monolayer systems (Cox, 1994). It contains a single circular chromosome.

B. burgdorferi, which is a larger spirochete, 10–30 μm long and 0.1–0.3 μm wide, with looser spirals, is transmitted by the bite of an infected tick to human. *B. burgdorferi* resembles other spirochetes in the genus *Borrelia*, with 7–11 periplasmic flagella. It is widespread in nature and is maintained in zoonotic

*Correspondence to: Judith Miklossy MD, PhD, University of British Columbia, Kinsmen Laboratory of Neurological Research, 2255 Westbrook Mall, 3N6, Vancouver, BC, V6T 1Z3, Canada. E-mail: Judith_Miklossy@yahoo.com, judit@interchange.ubc.ca, Tel: +1-604-822-7564, Fax: +1-604-822-7086.

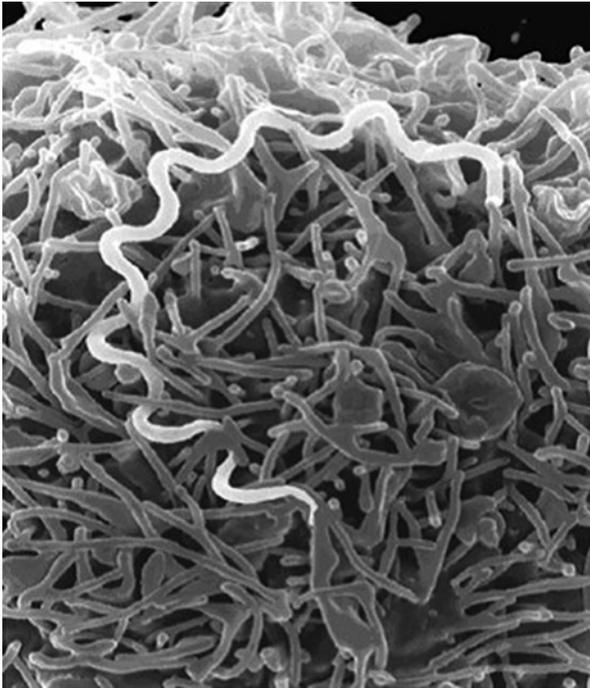


Fig. 72.1. Scanning electron microscopic image of *T. pallidum* on the surface of a human lymphocyte showing the wave-form structure characteristic of spirochetes. Reproduced from Porcella and Schwan, 2001 with permission of the American Society for Clinical Investigation.

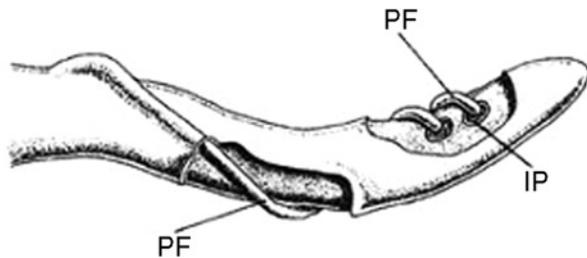


Fig. 72.2. Schematic drawing of a segment of a spirochete showing the characteristic periplasmic flagella (PF) or endoflagella inserted into the cytoplasmic cylinder by way of insertion pores (IP). Illustration by S. Kasas.

cycles involving many species of mammals, birds and ticks. It is routinely grown in liquid cultures in BSK II medium (Barbour, 1984). It grows best at 30–34 °C in a microaerophilic atmosphere, dividing every 8–12 h. *B. burgdorferi* contains a linear chromosome with the co-existence of linear and circular plasmids and an unusual organization of the genes encoding rRNA. Their successful cultivation in synthetic medium contributed a lot to the analysis of the biological characteristics of this organism and to better understanding of the pathogenic mechanisms involved in Lyme disease.

72.3. Neurosyphilis and dementia

Involvement of the CNS may occur years or decades following the primary infection. It is in the tertiary stage of neurosyphilis or late neurosyphilis that dementia develops. General paresis is the most common cause of dementia in neurosyphilis; however, meningovascular syphilis may also contribute to “vascular” dementia by the generation of multiple cerebral infarcts. In mixed forms both participate.

The frequency of syphilis in general parietic patients raised the etiological importance of syphilitic infection in the late neuropsychiatric manifestations of neurosyphilis, such as general paresis. Kraepelin (1904) was among those who thought that syphilitic infection is essential for the later appearance of paresis. Among those who embraced the idea “without syphilis no paresis” there were those who claimed that paresis is nothing more than a particular form of tertiary syphilis. Conversely, there were others who considered that progressive paralysis is not a specific syphilitic disease of the brain and thought that the simultaneous occurrence of syphilitic infection and general paresis was a pure coincidence (Nonne, 1902). Failure to detect *T. pallidum* in the affected nervous tissue contributed to the general concept that in the progressive degenerative process of general paresis, although of syphilitic origin, *T. pallidum* did not play an active role.

It was Noguchi and Moor (1913) who, by detecting *T. pallidum* in the brain of parietic patients, established a direct pathogenic link between spirochetal infection and dementia. Since Noguchi and Moore, multiple authors have described *T. pallidum* spirochetes and their colonies confined to the cerebral cortex in general paresis (e.g., Jahnel, 1917–1922; Pacheco e Silva, 1926–1927, Rizzo, 1931). These reports have given renewed interest to the problem of occurrence, density and distribution of spirochetes in the CNS and added important information to our present knowledge on the pathological processes involved in general paresis.

72.4. Pathological manifestations of neurosyphilis

The clinical and pathological manifestations of neurosyphilis occur in three stages (see Table 72.1).

Following an incubation period of about 3 weeks (stage 1), the typical primary chancre usually begins as a single painless papule which rapidly becomes eroded and indurated with a characteristic cartilaginous consistency on palpation. The histology shows inflammatory infiltrates consisting chiefly of lymphocytes (including CD8 and CD4 cells), plasma cells,

Table 72.1

Pathological manifestations of neurosyphilis occur in three stages

Stages	Pathology
Primary stage	Skin manifestation (chancere)
Secondary stage	Meningeal lues or lues cerebrospinalis
	Meningeal Primary involvement of meninges. Meningitis (sequelae: hydrocephalus)
	Vascular Primary involvement of the leptomeningeal vessels
	Mixed form Meningitis and vasculitis
Tertiary stage	Meningovascular neurosyphilis
	The parenchymal involvement is secondary to the endarteritis obliterans (Heubner's arteritis) cerebral infarcts
	Parenchymatous neurosyphilis
	Chronic meningo-encephalitis caused by the invasion of the nervous tissue by spirochetes
	General paresis
	Encephalitis and/or cortical atrophy
	Tabes dorsalis
	Spinal cord involvement
	Tabo-paralysis
	Tabes dorsalis and general paresis
	Mixed form
	Meningovascular syphilis and general paresis

and histiocytes. Obliterative endarteritis and periarteritis of small vessels are frequently present. *T. pallidum* is demonstrable in the chancre. The primary lesion usually persists for 2–6 weeks, and then heals spontaneously. It is followed by an early latent stage of several months up to 1 year.

Shortly following the primary syphilitic infection, *T. pallidum* reaches the CNS via hematogenous dissemination and/or via the lymphatics and leads to the involvement of the meninges and leptomeningeal blood vessels (stage 2, meningeal syphilis). Acute meningitis occurs only in 10% of the patients, but pleocytosis and increased protein have been found in the cerebrospinal fluid (CSF) in about 30% of the patients. The characteristic histological picture is a more or less widespread inflammatory infiltration of the meninges with lymphocytes and sparse plasma cells. *T. pallidum* has been recovered from CSF during primary and secondary syphilis in 30% of patients, which often correlated with other CSF abnormalities, but spirochetes may also be present in patients with otherwise normal CSF. *T. pallidum* has been also observed in the leptomeninges. The secondary manifestations of syphilis subside within 2–6 weeks and are followed by a late latent stage, which may last for many years or even several decades before the clinical and pathological manifestations of tertiary neurosyphilis appear.

Although all types of tertiary neurosyphilis have certain features in common, significant clinical and histological differences distinguish meningovascular

syphilis from parenchymatous neurosyphilis. Mixed forms are frequent. As the name implies, meningovascular syphilis primarily involves the meninges and leptomeningeal vessels. The most common presentation of late meningovascular syphilis is a stroke, associated with a gradually progressive vascular syndrome resulting frequently in multiple cerebral infarcts. These ischemic parenchymal lesions are, as a rule, secondary to the meningovascular pathology and not to the invasion of the nervous tissue by spirochetes.

In contrast, parenchymatous neurosyphilis reflects widespread parenchymal damage due to the direct invasion of brain tissue by *T. pallidum*, and is associated with diverse neuropsychiatric manifestations including general paresis and tabes dorsalis. Taboparalysis describes the simultaneous occurrence of general paresis and tabes dorsalis. Primary optic atrophy is commonly associated with tabes dorsalis, sometimes with meningovascular syphilis and rarely with general paresis. The interval from infection to onset of symptoms is a few months to 12 years (average 7 years) for meningovascular syphilis, 20 years for general paresis, and 25–30 years for tabes dorsalis.

72.4.1. Pathology of meningovascular syphilis

The meningovascular changes generally appear early in the second stage of syphilis. They may persist or commence following a long latent period in the tertiary stage of neurosyphilis. The meninges and meningeal vessels

of the basal areas of the brain are the first and most affected (basal meningitis) and during disease progression the pathological changes progressively reach the convexities of the cerebral hemispheres.

On macroscopical examination, there is a widespread, often diffuse thickening of the pia arachnoid. The white or grayish thickening of the meninges may be more accentuated in the region of the acoustic nerve, and over the front of the pons and basal subarachnoid cisterns. Leptomeningeal thickening around the foramina of Luschka and Magendie of the 4th ventricle may block exit of the CSF, resulting in hydrocephalus (Greenfield and Stern, 1932). Secondary optic atrophy may be present due to papilloedema. The basilar artery might be trapped in a felt-work of thickened meninges. Cerebral infarcts may be present in the territory of large leptomeningeal arteries or of their branches. A number of midline brainstem syndromes are known to be caused by meningovascular syphilis (Merritt et al., 1946).

The meningitis is characterized by a varying degree of lymphoplasmocytic infiltrate, which is usually concentrated around leptomeningeal vessels. They may follow their branches along the Virchow-Robin spaces for a short distance into the brain parenchyma. Miliary gummata with giant cells might be found in the thickened leptomeninges. The floor of the 4th ventricle may be covered by an outgrowth of neuroglial cells and fibers and often by a layer of fibroblastic and collagenous tissue, heavily infiltrated with lymphocytes and plasma cells. Small ependymal granulations and a few perivascular lymphoplasmocytic infiltrates in the subependymal region are frequent. Neuroglial outgrowths through irregular breaks into the thickened pia mater on the ventral and lateral surface of the medulla oblongata are seen. Cranial nerves, especially the oculomotor, abducens and acoustic nerves, may be compressed by thickened leptomeninges and undergo secondary degeneration.

The walls of both leptomeningeal arteries and veins can show lymphoplasmocytic infiltrates. When all layers of the vessel wall are affected it is called panarteritis or panphlebitis luetica. Endarteritis obliterans, described by Heubner (1874), is characterized by lymphoplasmocytic infiltration and intimal proliferation of the arterial wall. Infiltration and degeneration going on to necrosis of the media of some small meningeal vessels, along with swelling and concentric intimal proliferation, frequently occur. Endarteritis obliterans of the vasa vasorum may cause media necrosis and destruction of the elastic lamina. Secondary degenerative changes and fibrosis gradually narrowing the lumen of the affected arteries tend to cause thrombosis (Fig. 72.3) with secondary cerebral infarcts. Numerous spirochetes have been found in the walls of vessels showing Heubner's arteritis.

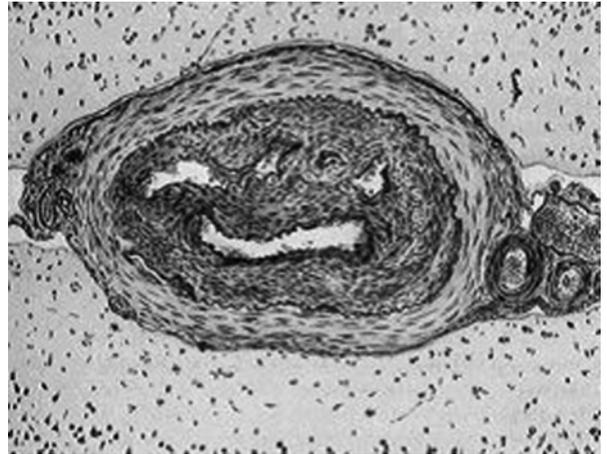


Fig. 72.3. Chronic Heubner's endarteritis obliterans in neurosyphilis illustrated by Straeussler (1958).

The histological changes of Heubner's arteritis were thought to be specific to syphilis, but may also occur in incompletely treated cases of tuberculosis, pneumococcal and other forms of chronic meningitis (Dudley, 1982). The positive serological test for *T. pallidum* and the detection of spirochetes in CSF or meningovascular lesions are necessary to ensure the diagnosis of meningovascular syphilis.

In the interpretation of clinical and pathological findings, it is important to consider that the development of spirochetal diseases may be attenuated by today's antibiotics. The clinical and pathological manifestations may become subtle and therefore difficult to recognize. When the inflammatory reaction in the residual stage of Heubner's arteritis subsides following treatment, only the hyperplastic intima remains.

72.4.2. Pathology of general paresis

General paresis, also known as general paralysis of the insane or paretic dementia, has been a recognized form of insanity for more than 150 years, but its relation to syphilis was not confirmed until the introduction of the Wassermann reaction. Noguchi and Moore (1913), by finding *T. pallidum* in the cortex of patients with general paresis, provided the proof that the disease was a form of syphilitic infection. General paresis is a chronic meningoencephalitis (meningoencephalitis paralytica) caused by the direct invasion of brain parenchyma by spirochetes. Further observations on the distribution of spirochetes in the brain of paretic patients have suggested the occurrence of two different forms (Table 72.2), the infiltrative and atrophic forms (Pacheco e Silva, 1926–1927, 1927; Rizzo, 1931). In the infiltrative form there is a strong cell-mediated immune response consistent with

Table 72.2

The infiltrative and atrophic forms of general paresis

Form of general paresis	Pathology
Infiltrative form	Strong cell-mediated immune response Strong lymphoplasmocytic infiltrates Low number of spirochetes Discrete degenerative changes
Atrophic form	Poor or absent lymphoplasmocytic infiltrates Degenerative changes dominate Cortical atrophy Microgliosis and astrogliosis Amyloid deposition High number of spirochetes
Mixed form	Lymphoplasmocytic infiltrates and cortical atrophy are both present

lymphoplasmocytic infiltrates. It generally progresses over several months to years. In the atrophic form or “stationary paralysis” the cell-mediated immune response is generally poor, and consequently the lymphoplasmocytic infiltrates are minor or absent. The duration of this form may be from several years to several decades. It is characterized by a slowly progressive dementia, and pathologically by a diffuse cortical atrophy. Mixed forms are frequent. An anatomobacteriologic correlation showed that in the infiltrative form the number of spirochetes is low; in contrast, in the atrophic form their number may be very high (Jahnel, 1917–1922; Pacheco e Silva, 1926–1927; Rizzo, 1931). These different types of host reaction—strong versus poor or absent lymphoplasmocytic infiltrates—associated with low versus high number of microorganisms are well known in leprosy caused by *Mycobacterium leprae* (Roy et al., 1997; Alcais et al., 2005).

Upon macroscopical examination, the brain shows thickening of the leptomeninges, particularly over the frontal lobes, the base of the brain, and the dorsal surface of the spinal cord. The cerebral vessels may be thickened but are not always altered. The lateral ventricles are generally dilated and the ependyma of the frontal horn, and the 3rd and 4th ventricles show a fine granular appearance on their surface. These fine granules are more apparent near the foramen of Monroe and in the floor of the 4th ventricle. The characteristic parenchymal changes of general paresis are localized to the gray matter areas, particularly to the cerebral cortex. In cases which come to necropsy at an earlier stage of the disease, the brain may show little abnormality without apparent brain

atrophy. In contrast, when the patient dies demented following several years of illness the cortical atrophy may be severe and prominent in the frontal and temporal lobes. The primary motor and occipital cortices are frequently spared. In old descriptions, the characteristic macroscopical changes comprised severe thickening of the dura mater (pachymeningitis haemorrhagica) with brownish discoloration due to secondary hemorrhagic lesions. Today, these lesions are less apparent or absent.

Gummas may be multiple or diffuse, but are usually solitary lesions which range from microscopic size to several centimeters in diameter, and histologically consist of a granulomatous inflammation with central necrosis surrounded by mononuclear, epithelial and fibroblastic cells, occasional giant cells and perivascularitis. The lesions resemble many other chronic granulomatous conditions, including tuberculosis, sarcoidosis or leprosy. Although *T. pallidum* was rarely demonstrated microscopically, it has been recovered from the lesions.

In the infiltrative form of general paresis the inflammation consists primarily of lymphocytes together with some plasma cells. Rarely, granulocytes may participate in early inflammatory responses. Lymphoplasmocytic infiltrates in the leptomeninges and in the nervous tissue may be simultaneously present. In some early cases, especially those dying in convulsive attacks, heavier cuffs of lymphocytes and plasma cells are present around smaller cortical arteries and larger cortical venules, and similar infiltrates are also frequent in the leptomeninges. The walls of small cortical vessels may be thickened and surrounded by a single layer of plasma cells. The basal ganglia are less involved, but perivascular infiltrations are sometimes found and in a few cases may be marked. The vegetative nuclei of the diencephalon may be severely involved, explaining the frequent dysregulation of the vegetative functions and marasmus. Inflammatory infiltrates may also occur in the pons and medulla oblongata. Heubner’s arteritis is found in about a quarter of cases, indicating an overlap between meningovascular and parenchymatous changes (Merrit et al., 1946).

In the atrophic form of general paresis the parenchymal changes are prominent. Even in the absence of inflammatory infiltrates the brain parenchyma may be severely involved. The histological changes are concentrated in the gray matter areas, particularly in the cerebral cortex, the vegetative nuclei of the diencephalon and to a lesser extent in the striatum. The diffuse cortical atrophy is more accentuated in the frontotemporal regions and is less evident in the central convolutions and occipital

lobes. All the cellular elements of the cerebral cortex; neurons, astrocytes, microglia, blood vessels and meninges are involved in the process. The most obvious pathology is the neuronal loss. The cytoarchitecture is washed out, making it difficult to distinguish between different cortical layers. Many of the remaining nerve cells show shrinkage of their perikaria with hyperchromatic nuclei and corkscrew-like apical dendrites. In these less affected brains sometimes neuronal loss is not prominent, rendering a diagnosis difficult.

The most characteristic reactive cells in general paresis are hyperplastic microglia, which show a severe, diffuse proliferation all along the cerebral cortex. The bipolar form, normally oriented perpendicularly to the cortical surface, proliferates and becomes hyperplastic and elongated (rod cells of Nissl). The microglial proliferation is accompanied by astrocytic proliferation. Small multifocal myelin loss in the cerebral cortex was proposed to be related to anoxic damage. Diffuse areas of myelin loss and pallor of the periventricular white matter also occur.

Granular ependymitis is frequent in general paresis. The ependymal granules are small glial nodules (0.3×1 mm in diameter) of fibrillary astrocytes. They either elevate the ependymal cell layer or, more frequently, break through the ependymal layer and lie directly on the ventricular surface. Discrete perivascular lymphoplasmocytic infiltrates may be present in or around these granulations. It was suggested that granular ependymitis is formed by the reaction of astrocytes to *Treponema* infection. Hydrocephalus internus and externus, of the communicative type, in cases with severe cortical atrophy are frequent.

Another characteristic lesion of parietic dementia is the accumulation of iron in the infected brain tissue. The Prussian blue method shows iron as fine granules in the cytoplasm of many microglial cells and as larger irregular masses in the walls of many cortical vessels, not only in the cerebral cortex but also in the basal ganglia. As it is more difficult to demonstrate iron in microglia in brains fixed in formaldehyde for several months, Merritt et al. (1946) recommended fixation of brain samples in alcohol. The vascular iron deposits are less soluble and are usually detectable even in brains left in formaldehyde for years. Their fast detection at the time of autopsy on macroscopic brain samples, called "paralytic iron", was used as a diagnostic tool.

T. pallidum has been found in the cerebral cortex in many cases of parietic dementia. The importance of the detection of *T. pallidum* in general paresis was emphasized by several authors (Pacheco e Silva,

1926; Jahnel, 1920, 1921–1927; Dieterle, 1928). Although the microorganism has been identified in most parts of the brain, they are most numerous in the frontal cortex and in the hippocampal gyrus (Jahnel, 1917–1922; Pacheco e Silva, 1926; Steiner, 1940). They may accumulate without accompanying inflammatory infiltrates. Jahnel (1917–1922), Hauptmann (1920), Herschmann (1920), Schob (1925), Pacheco e Silva (1926, 1926–1927), Dieterle (1928) described innumerable spirochetes as black patches forming swarms and perivascular foci scattered through the cerebral cortex (Fig. 72.4). Pacheco e Silva (1926, 1926–1927) who analyzed the brains of more than 50 general parietic patients, noticed that the number of organisms and cortical agglomeration of spirochetes increased with the severity of cortical atrophy. In a number of consecutive reports, Jahnel (1917–1922) described three types of cortical distribution; the diffuse, the perivascular and the vascular type (Table 72.3). In the diffuse type of spirochetosis the microorganisms are scattered evenly through the cerebral cortex (Fig. 72.5), sometimes collected into more or less dense aggregates. In the perivascular type, circumscribed "colonies" of spirochetes are distributed all along the cerebral cortex. Their location is common around small cortical blood vessels (pericapillary form of Dieterle, 1928) where a dense accumulation of spirochetes occurs in a concentric fashion. In the vascular form, thick masses of

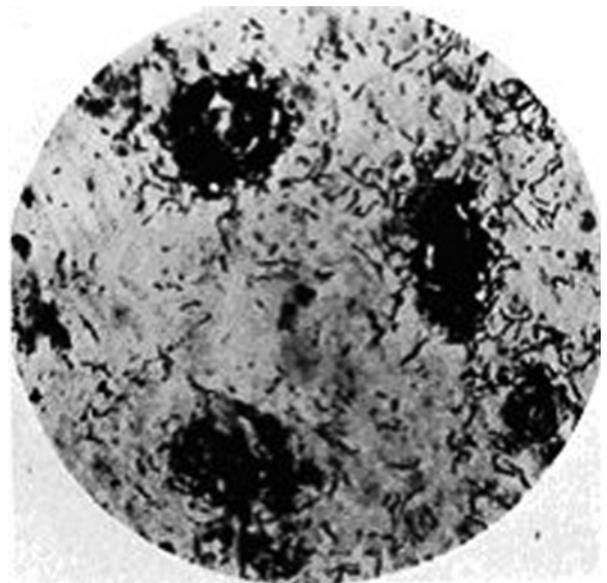


Fig. 72.4. Spirochetes forming perivascular masses in the cerebral cortex in a case of general paresis. Illustration from Jahnel, 1929; Schlossberger and Brandis, 1958. Reproduced with permission from Springer Verlag.

Table 72.3

Types of distribution of spirochetes in the brain in general paresis

Types of distribution	
Diffuse	Disseminated individual spirochetes scattered through the cortex
Perivascular or pericapillary	Aggregates (“colonies” or “balls”) of spirochetes distributed through the cortex frequently around cortical vessels
Vascular	Massive infiltration of vessel walls by spirochetes

microorganisms are collected in cortical vessel walls. Mixed forms are frequent.

Vast numbers of spirochetes may accumulate in the cerebral cortex in the atrophic form of general paresis. They frequently show a laminar distribution in the middle cortical layers (III-IV-V) which correspond to the distribution of terminal capillaries of short cortical arteries (Pacheco e Silva, 1926–1927; Dieterle, 1928). Spirochetes may also occur in the basal ganglia. They are rare in the white matter and in the cerebellum. Neurofibrillary tangles have also been described in dementia paralytica (Bonfiglio, 1908; Perusini, 1910; Storm-Mathisen, 1978) and the colloid degeneration was identified by Volland (1938) as local amyloidosis. Amyloid deposition, as illustrated by Volland, is localized in the wall of the cortical arteries.

For confirmation of the diagnosis of general paresis, in addition to the characteristic clinical and pathological findings and serologic testing, the detection of



Fig. 72.5. Illustration of disseminated spirochetes in the cerebral cortex by Rizzo (1931) in a patient with general paresis

T. pallidum antigens or genes in the infected brain or CSF is necessary.

Circumscribed cortical atrophy, restricted to a hemisphere or to the temporal lobe on one side (lobar atrophy), a rare atypical form of general paresis, was distinguished as focal paresis of Lissauer (Lissauer and Storch, 1901). Clinically it is characterized by epileptic or apoplectiform attacks followed by focal neurological signs.

Transmission of *T. pallidum* from the syphilitic woman to her fetus across the placenta may occur at any stage of pregnancy. Congenital syphilis may produce lesions in the CNS similar to those seen in acquired disease. In the late manifestations of congenital syphilis, general paresis may develop. When it occurs, it does not usually show itself until the end of the first or during the second or third decade. The lesions of general paresis due to congenital syphilis are often severe. They differ from the acquired form in being more diffuse and involving not only the cerebral cortex but the cerebellar cortex as well.

It is important to consider that in this era of antibiotics both the clinical and pathological manifestations of neurosyphilis have changed and have become less typical (Hook and Marra, 1992). Neurosyphilis causing psychotic illness is now rare (Dewhurst, 1969) and tends to cause depression, dementia and confusional states rather than the grandiose delusions of classical general paresis of the insane. Many patients with symptomatic neurosyphilis do not present a classic picture, but have mixed, subtle, or incomplete syndromes. In parallel with the clinical pattern, the pathological picture has also changed and certain forms of tertiary neurosyphilis (gummatous form, tabes dorsalis) have almost disappeared.

72.5. Lyme neuroborreliosis and dementia

Lyme disease caused by *B. burgdorferi* sensu lato is transmitted by the bite of an infected tick of the species *Ixodes*. Specific associations exist in some areas between *Borrelia* species and vertebrate hosts (Humair and Gern, 2000). In Europe all the three genospecies, *Borrelia burgdorferi sensu stricto* (*s.s.*), *Borrelia garinii*, and *Borrelia afzelii*, were isolated from humans. However, in the USA only *B. burgdorferi s.s.* has been identified. *B. garinii* and *B. burgdorferi s.s.* frequently cause CNS manifestations, and *B. afzelii* causes arthritis (Shapiro and Gerber, 2000; Weber, 2001). Although the infection was recognized in Scandinavia in the early 1900s, awareness of this disease only began following an “epidemic” of arthritis in a cluster of children in Lyme (Connecticut). This led to

the description of Lyme arthritis and to the discovery of its bacterial etiology (Steere et al., 1977, 1983; Burgdorfer et al., 1982). Neurological complications occur in about 15% of the affected individuals. Accumulating clinical data show a high diversity of chronic neuropsychiatric manifestations in late Lyme disease (Steere, 1989; Fallon and Nields, 1994; Garcia-Monco and Benach, 1995). The first observations of the occurrence of dementia in Lyme disease were reported almost 20 years ago, and the numbers of patients developing cognitive disturbances are increasing. The occurrence of dementia and subacute presenile dementia has been reported in Lyme disease (e.g., MacDonald, 1986; Dupuis, 1988; Fallon and Nields, 1994; Schaeffer et al., 1994; Pennekamp and Jaques, 1997; Miklossy, 2004).

The link between *Borrelia* infection and late clinical manifestations is still the subject of debate, as was the case for general paresis almost 100 years ago. While secondary neuroborreliosis is believed to be an active and ongoing infection (Schmutzhard et al., 1995), several mechanisms are proposed to explain the manifestations of late Lyme neuroborreliosis (Wilske et al., 1996). Increasing evidence indicates that spirochetes may persist in infected tissues, including the brain, and that the major pathological features are linked with the presence of the organism at the site of damage (Barbour and Fish, 1993; Miklossy et al., 2004). The existence of meningovascular and parenchymatous forms of tertiary Lyme neuroborreliosis has been pathologically confirmed (Miklossy et al., 1990; Kuntzer et al., 1991; Liegner et al., 1997; Duray and Chandler, 1997; Kobayashi et al., 1997; Bertrand et al., 1999; Miklossy et al., 2004) and in analogy to tertiary neurophilis may also constitute the morphological basis of progressive dementia.

72.6. Pathological manifestations of Lyme neuroborreliosis

The pathological manifestations of Lyme disease, similarly to syphilis, occur in three stages (see Table 72.4).

The macroscopic appearance of the primary lesion in Lyme disease is the characteristic expanding annular rash—erythema migrans—which usually appears 3–30 days after the infectious tick bite (stage 1). The inflammatory reaction consists of lymphoplasmacytic infiltrates around dermal vessels.

The manifestations of secondary Lyme neuroborreliosis (stage 2) usually appear weeks to months after the initial infection in the form of a meningoradiculoneuritis (Garin-Bujadoux-Bannwarth syndrome) and are accompanied by inflamed CSF.

The CNS manifestations corresponding to meningeal neuroborreliosis are pathologically characterized by meningeal, perivascular and vasculitic

lymphoplasmacytic infiltrates (Duray, 1987–1989; Meurers et al., 1990). Spirochetes are present in most sites in an extracellular location, but are sparse.

The tertiary manifestations of Lyme neuroborreliosis appear months, years, or even decades following the primary infection. Similarly to syphilis a meningovascular form with secondary cerebral infarcts and a parenchymatous form consistent with chronic meningoencephalitis can be distinguished.

72.6.1. Pathology of meningovascular Lyme neuroborreliosis

The clinical manifestation of meningovascular Lyme neuroborreliosis is that of a progressive stroke (Uldry et al., 1987; Olsson and Zbornikova, 1990; Kuntzer et al., 1991). The occurrence of cerebral vasculitis with multiple stenoses of large cerebral arteries and irregularities of the wall of small vessels, associated with frequently multiple cerebral infarcts, has been repeatedly reported (Uldry et al., 1987; Veenendaal-Hilbers et al., 1988; Brogan et al., 1990; May and Jabbari, 1990; Reik, 1993; Keil et al., 1997; Schmitt et al., 1999; Deloizy et al., 2000; Wilke et al., 2000; Zhang et al., 2000; Klingebiel et al., 2002; Romi et al., 2004). It may affect children and adults of ages varying between 5 and 74 years. Cerebral infarcts in the territory of the middle and posterior cerebral arteries, and also of the branches of the basilar and anterior spinal arteries, have been reported. In a neuropathologically confirmed case, the mean histological changes consist of meningovascular alterations.

The histological changes observed in this 50-year-old patient with chronic meningitis, multiple cranial nerve palsies, and progressive occlusive vascular changes were similar to those occurring in meningovascular neurosyphilis (Miklossy et al., 1990; Kuntzer et al., 1991). The leptomeninges were thickened, more prominently at the base of the brain. A fine granular appearance of the floor of the 4th ventricle was seen, and two small cystic infarcts were located in the paramedian and retro-olivary regions of the medulla oblongata (Miklossy et al., 1990; Kuntzer et al., 1991). Histological examination revealed a mild leptomeningeal fibrosis with a few lymphoplasmacytic infiltrates frequently surrounding leptomeningeal vessels. The pia mater was firmly attached to the medullary surface and outgrowth of neuroglia through breaks in the pia mater was present. The elastic lamina was duplicated or fragmented in some arteries; in others, fibrosis with focalized thinning of the media or fibrotic thickening of the adventitia occurred. Lymphocytic infiltrates with a few plasma cells were present in the walls of some leptomeningeal arteries.

In a few vessels, all layers of the arterial wall were infiltrated; in others, the infiltrates were partial or localized to the thickened fibrous adventitia. Several medium and small-sized leptomeningeal arteries showed important thickening of their intima. The severe intimal proliferation resulted in the narrowing of their lumen, sometimes with complete obstruction due to an organized thrombus (Fig. 72.6). Histologically, the two small medullary infarcts corresponded to partially cystic infarcts (Fig. 72.7). The fine ependymal granulations appeared as irregular nodular protrusions of subependymal reactive glia. A few spirochetes were detected by silver techniques in the medullary leptomeninges and in the ependymal regions of the fourth ventricle. The typical clinical data and pathological picture, the CSF

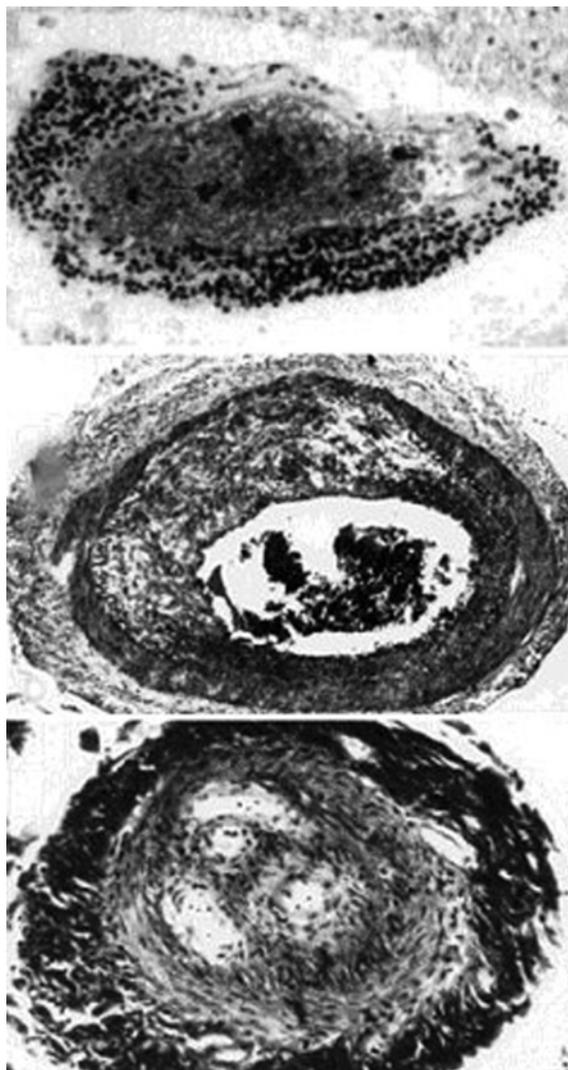


Fig. 72.6. Different stages of vasculitis with resultant occlusion of the vascular lumen (Heubner's arteritis) in meningovascular Lyme neuroborreliosis. Reproduced from Miklossy et al., 1990, with permission from Springer Verlag.

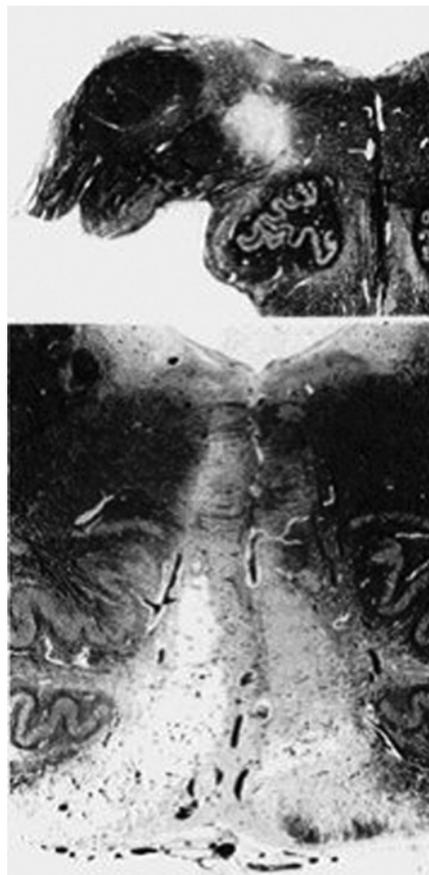


Fig. 72.7. Cerebral infarcts secondary to endarteritis obliterans of leptomeningeal arteries in meningovascular Lyme neuroborreliosis. Reproduced from Miklossy et al., 1990, with permission from Springer Verlag.

pleocytosis, the intrathecal production of anti-*B. burgdorferi* antibodies, and the detection of spirochetes in tissue confirmed the diagnosis of meningovascular Lyme neuroborreliosis.

A progressive stroke syndrome might still go undiagnosed in some patients with Lyme disease. The improvement in symptoms has been repeatedly reported following antibiotic therapy. It is important to recognize that cerebrovascular ischemia can be caused by *Borrelia burgdorferi* infection involving cerebral arteries (Grau et al., 1996), particularly in endemic areas of Lyme disease.

72.6.2. Pathology of parenchymatous Lyme neuroborreliosis

Similarly to neurosyphilis, in tertiary stages of Lyme disease, parenchymatous neuroborreliosis corresponds to chronic meningoencephalitis. It is caused by the direct invasion of brain tissue by *B. burgdorferi*. Pathological observations of cases with strong and

with poor or absent cell-mediated immune responses have been pathologically documented, suggesting that an infiltrative and an atrophic form may also be distinguished in tertiary parenchymatous Lyme neuroborreliosis. In the infiltrative form, the strong inflammatory infiltrates dominate, in the atrophic form where lymphoplasmocytic infiltrates are poor or absent, cortical atrophy is the dominant feature.

Chronic meningoencephalitis associated with a strong cell-mediated immune response occurs in children and adults. Several cases with meningoencephalomyelitis, encephalitis, and transverse myelitis were reported. Lymphocytic infiltrates with perivascular accentuation and vasculitis are the characteristic histological findings (Duray, 1986–1989; Duray and Steere, 1988; Shadick et al., 1994; Nadelman et al., 1996; Iero et al., 2004). In the brain of a 65-year-old patient who developed a progressive meningoencephalomyelitis with secondary hydrocephalus (Fig. 72.8) and granular ependymitis (Fig. 72.9) and who died 8

years following the initial skin rash, the thickened leptomeninges showed severe inflammatory infiltrates (Fig. 72.10). The leptomeninges overlying the floor of the 4th ventricle were particularly involved in the area of the foramina of Luschka. There was a severe granulomatous ependymitis (Fig. 72.11). In addition to the mononuclear infiltration, granulomatous lesions with giant cells were similar to the miliary gummatous lesions occurring in syphilis (Fig. 72.12). The hydrocephalus was apparently the consequence of the occlusion of the foramina of Luschka (Liegner et al., 1997). Leukoencephalopathy with large areas of myelin loss in the periventricular white matter was also described.

If a careful search is done, silver staining can demonstrate the spirochete (Duray and Steere, 1986; Duray, 1989; Shadick et al., 1994).

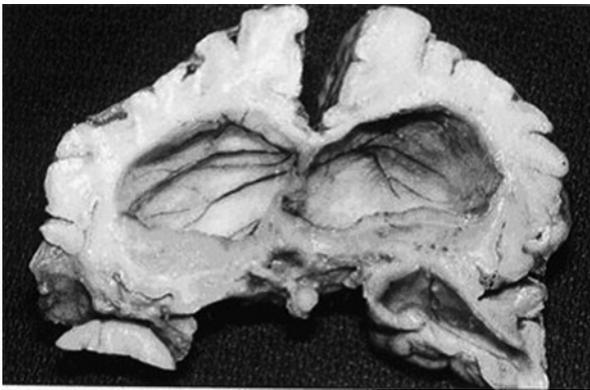


Fig. 72.8. Chronic meningoencephalitis with hydrocephalus in late Lyme neuroborreliosis. Reproduced from Liegner et al. 1997, with the permission of Journal of Spirochetal and Tick-borne Diseases.

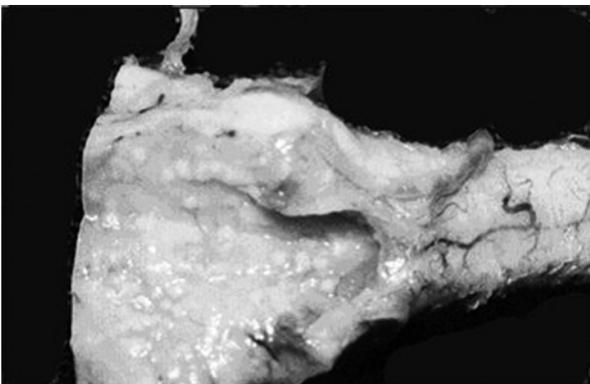


Fig. 72.9. Granular ependymitis on the 4th ventricle. Reproduced from Liegner et al., 1997, with the permission of Journal of Spirochetal and Tick-borne Diseases.

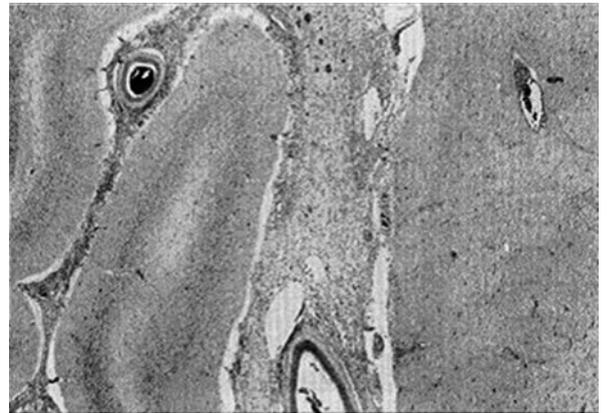


Fig. 72.10. Severe meningitis in a late Lyme neuroborreliosis. Reproduced from Liegner et al., 1997, with the permission of Journal of Spirochetal and Tick-borne Diseases.

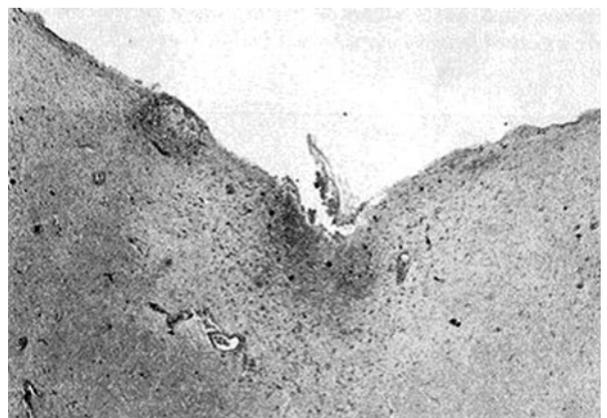


Fig. 72.11. Granulomatous ependymitis in chronic Lyme meningoencephalitis. Reproduced from Liegner et al., 1997, with the permission of Journal of Spirochetal and Tick-borne Diseases.

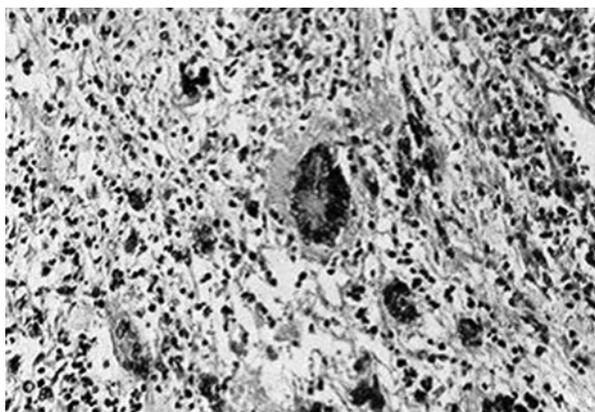


Fig. 72.12. Granulomatous infiltrates with giant cells. Reproduced from [Liegner et al., 1997](#), with the permission of Journal of Spirochetal and Tick-borne Diseases.

Cases with dementia where *Borrelia* spirochetes were detected in the brain or cultivated from the brain ([Fig. 72.13](#)) were repeatedly reported ([MacDonald, 1986](#); [Duray, 1987](#); [MacDonald and Miranda, 1987](#); [Miklossy, 1993](#); [Miklossy et al., 2004](#)). In three patients with slowly progressive dementia, where *B. burgdorferi* s.s. was cultivated from the brain, the most typical macroscopical changes consisted of thickening and opacity of the leptomeninges over the frontal lobes and the base of the brain. There was a diffuse cortical atrophy, more accentuated in the frontotemporal lobes associated with severe neuronal loss. The central convolution, the occipital lobes and the basal ganglia were less affected and the cerebellum was spared. Severe diffuse microglia proliferation was restricted to the affected cortical areas and was accompanied by astrocytic gliosis. Spirochetes were detected in high number in the atrophic cerebral cortex. They were observed in colony-like masses ([Fig. 72.14](#)) together with disseminated spirochetes when stained

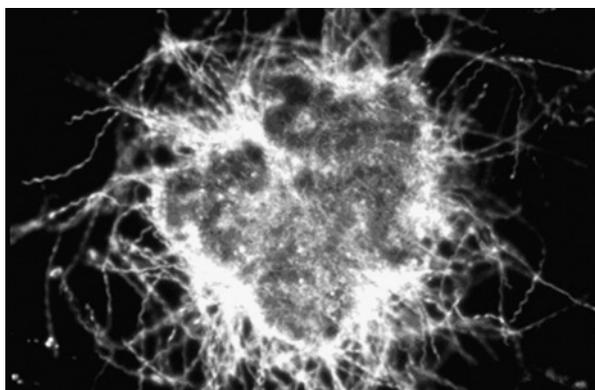


Fig. 72.13. *B. burgdorferi* cultivated from the brain of a patient with dementia maintained in a synthetic medium accumulated here in a large mass.

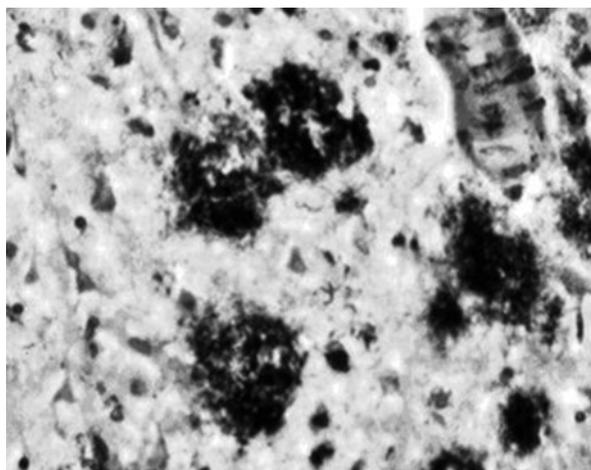


Fig. 72.14. Colony-like masses of spirochetes in the cerebral cortex in the atrophic form of parenchymatous Lyme neuroborreliosis. Reproduced from [Miklossy et al., 2004](#), with permission of the Journal of Alzheimer's Disease.

with silver techniques ([Fig. 72.15](#)) or with anti-*B. burgdorferi* antibodies and ([Fig. 72.16](#)). The high number of spirochetes and their distribution was identical to those of *T. pallidum* in the atrophic form of general paresis. *Borrelia* antigens were also observed in some neurons and in the walls of some cortical and leptomeningeal vessels. The pathological findings observed were consistent with the atrophic form of tertiary parenchymatous Lyme neuroborreliosis. The diagnosis was based on the cultivation of *B. burgdorferi* sensu stricto from the brain, the presence of specific anti-*Borrelia* antibodies in the CSF, the typical pathological findings, and on the identification of *B. burgdorferi* antigens and genes in the brain of these patients ([Miklossy et al., 2004](#)). Positive identification of the cultivated spirochetes as *B. burgdorferi* s.s. was based on phylogenetic analysis of their 16S rRNA.

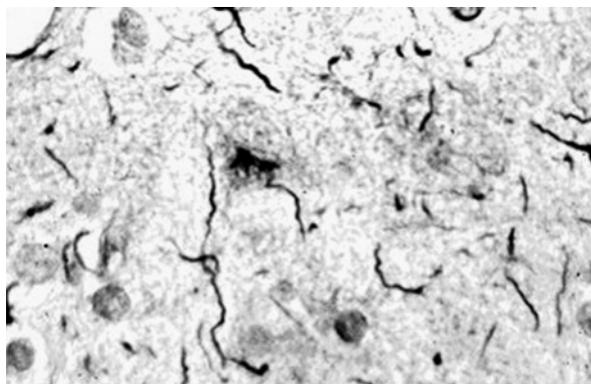


Fig. 72.15. Disseminated spirochetes in the atrophic form of Lyme neuroborreliosis. Bosma-Steiner microwave technique for spirochetes.

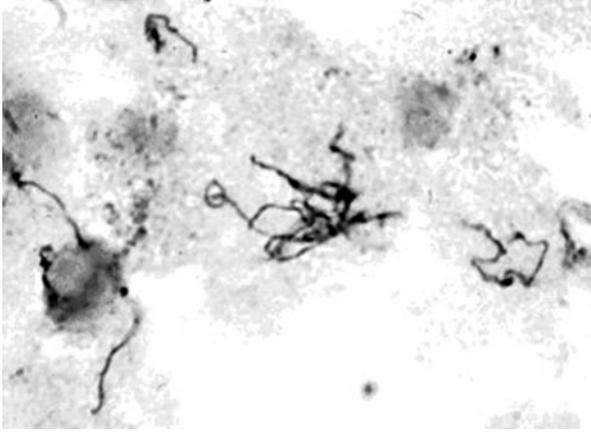


Fig. 72.16. Spirochetes in the cerebral cortex in a case of parenchymatous Lyme neuroborreliosis showing positive immunoreaction with anti-*B. burgdorferi* antibody. Reproduced from Miklossy et al., 2004, with permission of the Journal of Alzheimer's Disease.

As cognitive improvement was reported in patients with Lyme neuroborreliosis following antibiotic treatment, careful consideration of infection as a possible cause of cognitive impairment is important particularly in endemic areas of Lyme disease.

72.7. Detection of spirochetes

T. pallidum and *B. burgdorferi* can persist in the infected tissues, even in the absence of an apparent lymphoplasmacytic infiltration. Therefore their detection is important in infected body fluids and tissues when the clinical and histopathologic features suggest syphilis or Lyme disease. The methods available and their diagnostic values were described and reviewed by several authors (Aberer and Duray, 1991; Shapiro and Gerber, 2000).

T. pallidum cannot be cultivated in synthetic medium. However, *B. burgdorferi* can be cultivated, from erythema migrans, synovial fluid, blood, CSF and also from brains of patients with late Lyme disease. Nevertheless, the cultivation is a long and difficult procedure.

Dark-field and phase-contrast microscopic analyses are useful methods for detection of spirochetes in body fluids and smear preparations. Several histochemical procedures (Gram, Wright, Wright-Giemsa, Giemsa, and polychromes), fluorochromes (thioflavin-T, acridine orange, and rhodamine), silver impregnation techniques (Warthin-Starry, modified Dieterle, modified microwave Dieterle, and Bosma-Steiner) can be used for the demonstration of spirochetes (Aberer and Duray, 1991) and specific antibodies are available to detect *T. pallidum* and *B. burgdorferi* antigens in smears and tissue sections.

Spirochetes undergo important environmental transitions and morphological changes during their complex life-cycles and during their adaptation to different hosts. The granular form of *T. pallidum*, known as "syphilitic granules", maintains infectivity following filtration. Outer membrane-associated cysts, blebs, spherules or atypical helical, ring, globular and granular forms are frequent (Figs. 72.17 and 72.18). They are suggested to correspond, as part of a complex developmental cycle and to resistant or degenerated forms in suboptimal conditions (Brorson and Brorson, 1998). Garon and Dorward (1989) investigated the nature of *B. burgdorferi* membrane-derived vesicles (blebs), and found both linear and circular DNA within them, suggesting that they might play a role in the protection of genetic markers (Garon et al., 1989). Several conditions have been shown to induce the development of atypical forms (Aberer and Duray, 1991; Mursic et al., 1996). *B. burgdorferi* was converted rapidly into a cystic form when incubated in CSF and was then converted back to normal when retransferred to BSK medium (Brorson and Brorson, 1998). Atypical cystic and granular *Treponema* forms occur in the brain in general paresis and are abundant in juvenile general paresis. It is important for the pathological diagnosis to consider the existence of these polymorphic forms.

The polymerase chain reaction (PCR) is a useful and sensitive technique to identify *T. pallidum* and *B. burgdorferi* DNA. Careful interpretation of the results is necessary as bacterial DNA may persist even



Fig. 72.17. Polymorphic forms of *B. burgdorferi* induced in vitro by Thioflavin S and revealed by atomic force microscopy.

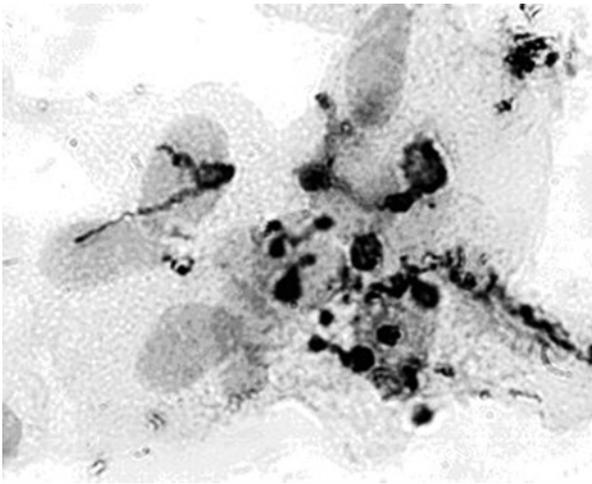


Fig. 72.18. Atypical cystic forms of *B. burgdorferi* following 1 week co-culture with rat astrocytes, immunoreactive with anti-*Borrelia* antibody.

in the absence of a living organism. The presence of brain inhibitory factors may lead to false-negative results (Shapiro and Gerber, 2000).

72.8. Biology of the disease

It seems that *B. burgdorferi*, similarly to *T. pallidum*, is present at the site of inflammation in many organs, including the brain (MacDonald, 1986; Duray, 1987; Oksi et al., 1996; Sigal, 1997; Miklossy, 1990, 2004). Both spirochetes may invade a wide range of tissues. They frequently and preferentially invade conjunctive tissue and extracellular matrix at the first stages of infection (e.g., Duray et al., 2005) but both invade parenchymal cells as well. This intracellular location may confer to the organism protection against host immune reactions and was proposed to be one of the factors contributing to the persistence of these organisms in infected tissues. Infections due to intracellular pathogens are notoriously difficult to treat and cure (Mahmoud, 1992). *T. pallidum* and *B. burgdorferi* are both ingested by phagocytic cells (Norgard et al., 1995). It seems clear that macrophages (microglia) and T cells are intimately associated with the pathogenesis of both diseases. Inflammation maintained by persistent *Borrelia* or *Treponema* antigens is a plausible explanation for persisting disease which, through a complex interaction with the host immune system, may lead to these various clinical and pathological manifestations.

Several differences in the functional genomics, environmental adaptation and pathogenic mechanism of *T. pallidum* and *B. burgdorferi* exist (Porcella and

Schwan, 2001). However, from information that has accumulated over the past several years regarding the molecular and cellular aspects of inflammation, and immunopathologic processes involved in both syphilis and Lyme disease, important common immunopathogenic features emerge.

72.8.1. Chronic inflammation

Bacteria or their synthetic or natural components such as bacterial peptidoglycan, bacterial lipopolysaccharide (LPS), and bacterial lipoproteins have a variety of biological actions in mammals. They are inflammatory cytokine inducers, activate complement, affect vascular permeability, generate nitric oxide, induce proteoglycan synthesis, cause apoptosis and are amyloidogenic (Fox, 1990). Bacterial cell wall components are highly resistant to degradation by mammalian enzymes, which on interaction with the immune system may provide a persisting inflammatory stimulus (Ohanian and Schwab, 1967; Lehman et al., 1983; Fox, 1990; Hauss-Wegrzyniak et al., 2000). During chronic exposure, bacteria or bacterial debris may accumulate and persist in the host tissues, maintaining a chronic inflammation with slowly progressive damage. Identification of putative outer membrane lipoproteins of *T. pallidum* has been controversial; in contrast *B. burgdorferi* is rich in outer surface lipoproteins. However, both organisms synthesize abundant lipid-modified integral membrane proteins. *T. pallidum* and *B. burgdorferi* or their synthetic membrane lipoproteins have similar potent immunostimulatory properties, implicating these lipoproteins as major inflammatory mediators in syphilis and Lyme disease (Radolf et al., 1995; Ramesh et al., 2003). The intradermal response elicited by the synthetic 47-kDa major membrane lipoprotein of *T. pallidum* and the outer surface protein A (OspA) of *B. burgdorferi* was analogous to that observed with whole bacteria (Norgard et al., 1995; Radolf et al., 1995). The induced cellular infiltration is predominantly composed of T lymphocytes and macrophages. During disease progression the cellular immune response is shifted to a predominant T helper cell type 1 (Th1) (Franz et al., 1999).

T. pallidum and *B. burgdorferi* and their lipoproteins evoke cytokine responses in cells of the monocyte/macrophage lineage. In addition to inducing interleukin-1 (IL-1), IL-6, and TNF-alpha, they also induce IL-12, a cytokine recently recognized as critical for driving cellular responses toward the Th1 subset (Radolf et al., 1995; Rasley et al., 2002; Ramesh et al., 2003). This shift toward the Th1 cellular phenotype retards antibody induction by Th2 cells against bacteria, which may contribute to their ability to evade

host immune responses. *B. burgdorferi* also induces NF- κ B, increased expression of Toll-like receptor 2 (TLR-2) and CD14. TLR2 was required for tolerance induction by *Borrelia*, and interleukin-10 was identified as the key mediator involved in this process (Diterich et al., 2003). These studies identified microglia as a previously unappreciated source of inflammatory mediator production following challenge with *B. burgdorferi* (Rasley et al., 2002), which may play an important role in persistent inflammation in tertiary neurospirochetoses.

Borrelia lipoproteins have repeatedly been shown to act as potent cytokine inducers, interacting with TLR-2. *T. pallidum* and *B. burgdorferi* lipoproteins and synthetic lipopeptides also interact with CD14 (Sellati et al., 1998; Schroder et al., 2004). There is some evidence that the acute-phase proteins serum amyloid A (SAA) and C-reactive protein (CRP) are also implicated in *T. pallidum* and *B. burgdorferi* infections (Berlit, 1992; Ray et al., 2004). Tri- or diacylated lipoproteins of *B. burgdorferi* also bind to lipopolysaccharide binding protein (LBP), another acute-phase protein which mediates cytokine induction.

72.8.2. Complement

The complement system is well known for its role in antimicrobial immunity. It provides the first-line defense against all kinds of infectious agents, including bacteria (Szebeni, 2004). The importance of the complement system in *T. pallidum* and *B. burgdorferi* infection has been repeatedly reported (e.g., Fitzgerald, 1987; Blanco et al., 1999; Kraiczy et al., 2001; Lawrenz et al., 2003). Both spirochetes are capable of activating the classic and the alternative pathway. Bacteria, including *T. pallidum* and *B. Burgdorferi*, employ a broad range of strategies to survive and to persist in the host. There is evidence of evasion by acquisition of host-derived complement-regulatory proteins. Bacterial surface proteins can fix functionally active human complement regulators, which allows the pathogen to regulate complement activation directly on their surface (Szebeni, 2004). They inhibit binding of the opsonizing components C4b and C3b and lysis by the membrane attack complex by interacting with C8 and C9. Up to five distinct surface proteins have been identified in *B. burgdorferi* which bind host immune regulators (Kraiczy et al., 2001). *B. burgdorferi* evades complement-mediated killing by expressing a CD59-like complement inhibitory molecule with a preferential binding to C9 (Pausa et al., 2003). *B. burgdorferi* also binds specifically to the alternative pathway regulators Factor H and

FHL-1 (Kraiczy et al., 2001). Impaired opsonization and lysis was also observed in *T. pallidum* infection (Blanco et al., 1999). With such an evasion strategy these spirochetes can subvert the host immune response. Blockade of the complement cascade enhances microbial survival and allows progressive growth of the spirochetes in an immune competent host.

72.8.3. Amyloid formation

Chronic bacterial infections (e.g., rheumatoid arthritis, leprosy, tuberculosis, osteomyelitis) including chronic syphilitic infections are frequently associated with amyloid deposition in the infected tissues. Experimental amyloidosis can also be induced by injecting living, attenuated or killed bacteria to experimental animals (Picken, 2001).

Recently it has been shown that bacteria contain amyloidogenic proteins (Jarrett and Lansbury, 1992; Chapman et al., 2002; Gebbink et al., 2005). Previous observations suggested that *T. pallidum* and *B. burgdorferi* also contain amyloidogenic proteins (Miklossy, 1993; Ohnishi et al., 2000). The outer surface protein (OspA) of *B. burgdorferi* forms amyloid fibrils in vitro (Ohnishi et al., 2000) and amyloid deposits were induced following exposure of primary mammalian CNS cells to *B. burgdorferi* (Miklossy et al., 2005). The processes which drive amyloid formation in the infected tissues are unknown. Increased proteoglycan synthesis plays a significant role in amyloidogenesis. An important role for proteoglycans in major histocompatibility complex (MHC)-mediated infections (e.g., bacterial) is well documented. Induction of proteoglycans by host cells in response to *T. pallidum* and *B. burgdorferi* infections has been also documented.

72.8.4. Genetic regulation

There is accumulating evidence that host responses and susceptibility to bacterial infections are genetically controlled. Patients with genetic risk factors, or promoter polymorphisms in pro-inflammatory cytokines, have been shown to be associated with susceptibility to infections (Knight et al., 1999). Tumor necrosis factor (TNF) is a critical mediator of host defense against infection but may cause severe pathology when produced in excess. TNF gene polymorphism may determine a strong cell-mediated immune response or a weak or absent cellular response, which may reflect genetic variability in cytokine production (Sigal, 1997; Shaw et al., 2001). In the absence of cell-mediated immune response, the microorganism can spread freely and accumulate in the infected host

tissues (Roy et al., 1997). This leads to the occurrence of two different phenotypes in leprosy. In lepromatous leprosy the number of *Mycobacterium leprae* is very high (bacillary form) despite the absence of inflammatory infiltrates. In contrast, in tuberculoid leprosy (paucibacillary form) there is a strong inflammatory infiltration and only a few microorganisms. The influence of TNF in *T. pallidum* and *B. burgdorferi* infection was repeatedly reported (e.g., Rasley et al., 2002; Marangoni et al., 2004). It seems that a polarity in host reactions (infiltrative form with a few microorganisms versus atrophic forms with numerous spirochetes) in response to chronic *T. pallidum* and *B. burgdorferi* also exists. The potential role of TNF polymorphisms has not yet been investigated.

Class II major histocompatibility genes also influence the host immune response to *B. burgdorferi* infection. Almost 90% of patients with HLA-DR2 and/or HLA-DR4 alleles develop chronic arthritis resistant to therapy. This compares with 27% having arthritis of short duration (Steere et al., 1990). These HLA specificities appeared to act as independent, dominant markers of susceptibility.

72.8.5. Iron and oxidative stress

Iron, which is essential for bacterial growth, is now recognized as playing a vital role in infection. There are several mechanisms by which iron may contribute directly to cellular injury. Iron has been shown to increase the formation of reactive oxygen intermediates, leading to lipid peroxidation and subsequent oxidative damage to proteins and nucleic acids. Iron also affects the antigen-specific cellular responses by affecting T cell generation, T cell functions and proinflammatory cytokine production by macrophages (Griffiths et al., 2000). Free (non-transferrin-bound) iron abolishes the bactericidal and bacteriostatic effects of serum and leads to greatly enhanced virulence that can overwhelm natural defense mechanisms (Griffiths, 1991; Weinberg, 1978, 1992).

B. burgdorferi contains a transferrin-binding protein (Carroll et al., 1996). To overcome oxidative stress *B. burgdorferi* uses a single iron-containing superoxide dismutase (SOD) and *T. pallidum* a non-heme, single iron protein superoxide reductase (SOR) (Whitehouse et al., 1997; Niviere et al., 2001; Berthomieu, 2002; Auchere et al., 2003). It was suggested that host SOD and host catalase may function for the benefit of *T. pallidum*. It was proposed that a surface coat produced by host proteins may protect the spirochete by masking immunogens or promoting membrane integrity (Austin et al., 1981). It was also shown that *B. burgdorferi* induces matrix metalloproteinases

(MMPs) (Perides et al., 1999), suggesting that MMPs may also play a direct role in the pathogenesis of Lyme neuroborreliosis.

72.8.6. Other neuropsychiatric disorders

Various neuropsychiatric disorders were found to be associated with neurosyphilis and Lyme neuroborreliosis, which include multiple sclerosis (Beaman et al., 1994; Ackermann et al., 1985; Kohler et al., 1988; Fallon et al., 1998; Hartmann and Pfadenhauer, 2003; Brorson et al., 2001; Wolfson and Talbot, 2002), progressive supranuclear palsy (Murialdo et al., 2000; Brusa and Peloso, 1993; Garcia-Moreno et al., 1997), parkinsonism (Neil, 1953; Buge and Lauras, 1956; Beaman et al., 1994; Cassarino et al., 2003), amyotrophic lateral sclerosis (Lubarsch et al., 1958; Waisbren et al., 1987; Hansel et al., 1995; Halperin et al., 1990; Harvey et al., 2007), psychosis and mood disorders (Lubarsch et al., 1958; Favre et al., 1987; Fallon et al., 1994) and Alzheimer's disease (Perusini, 1910; Bonfiglio 1908; Lubarsch et al., 1958; Beaman et al., 1994; Barrett, 2005; MacDonald and Miranda, 1987; Miklossy, 1993; Miklossy et al., 2004, 2006; Meer-Scherrer et al., 2006). The relation between these neurodegenerative disorders and spirochetal infection is not fully understood.

The exploding number of observations related to the mechanisms involved in *Borrelia burgdorferi* infections indicates that the exposure of host to these spirochetes or to their toxic products, through a complex interaction with the host immune responses, induces persistent chronic inflammation. This persistent inflammation can lead to a slowly progressive tissue destruction and neuronal damage.

The important role of persistent chronic inflammation in the pathogenesis of the majority of these neuropsychiatric disorders, which may be associated with syphilis and Lyme neuroborreliosis, was established

Table 72.4

Pathological changes in Lyme neuroborreliosis

Primary stage (Stage 1)	erythema chronicum migrans
Early latent stage	
Secondary stage (Stage 2)	early Lyme neuroborreliosis, meningeal involvement
Late latent stage	
Tertiary stage (Stage 3)	late Lyme neuroborreliosis meningovascular Lyme neuroborreliosis parenchymatous Lyme neuroborreliosis

following the pioneer work of McGeer (McGeer et al., 1987; McGeer and McGeer, 2001, 2002), Rogers (Rogers et al., 1988, 2002) and Griffin (Griffin, 1989; Griffin et al., 2006).

Increased cytokine production, complement activation, formation of free radicals, apoptosis, increased proteoglycan synthesis and amyloid formation are also key players in the pathogenesis of several of these disorders, including Alzheimer's disease, which is the most frequent cause of dementia. The possibility of an association between chronic infection and these various neuropsychiatric disorders, including Alzheimer's disease, was repeatedly suggested. Further studies will be necessary to elucidate a putative infectious origin of these disorders.

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