REVIEW ARTICLES

Neuroborreliosis During Relapsing Fever: Review of the Clinical Manifestations, Pathology, and Treatment of Infections in Humans and Experimental Animals

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The spirochetal disease *relapsing fever* is caused by different *Borrelia* species. Relapsing fever is well recognized as an infection of the blood, but little is known about its predilection for the nervous system and the eyes. To investigate neurological and ocular involvement during relapsing fever, we reviewed the clinical manifestations, pathology, and treatment of relapsing fever of humans and experimental animals. The results indicate that *Borrelia turicatae* and *Borrelia duttonii,* the agents of tick-borne relapsing fever in southwestern North America and sub-Saharan Africa, respectively, cause neurological involvement as often as *Borrelia burgdorferi* in Lyme disease. Evidence of this is the frequent occurrence of lymphocytic meningitis and peripheral facial palsy in human disease; the identification of spirochetes in the brain and other nervous tissues of humans, animals, and arthropod vectors; and the persistence of brain infection after treatment with antibiotics that do not readily penetrate the blood-brain barrier.

Relapsing fever was recognized as a distinct disease entity by physicians in ancient Greece, but it was not until the late 19th century that the etiologic agent was identified [1]. It is one of several diseases caused by spirochetes, which are a separate eubacterial phylum [2]. Other spirochetal diseases include Lyme disease, syphilis, leptospirosis, swine dysentery, and some disorders of the gums. Spirochetes are as different genetically from gram-positive bacteria as they are from gram-negative bacteria. Notable features of spirochetes are wavy and helical shapes, length to diameter ratios of as much as 100 to 1, and flagella that lie between the inner and outer membranes of the cell [2].

The spirochetes that cause relapsing fever are in the genus *Borrelia.* Other *Borrelia* species cause Lyme disease, avian spirochetosis, and possibly epidemic bovine abortion [3, 4]. The agents of Lyme disease are three closely related species: *Borrelia burgdorferi, Borrelia afzelii,* and *Borrelia garinii.* All members of this genus are associated with both an arthropod that serves as the vector and a vertebrate that serves as the reservoir host [3]. Natural vertebrate reservoirs of the relapsing fever borrelias include a variety of mammals but most commonly are rodents. Table 1 includes several species, their tick vectors, and an estimate of their geographic ranges. A new presumptive species, *Borrelia lonestari* sp. nov., has been identified in *Amblyomma americanum* ticks in the southern United States, but the relationship between this organism and a Lyme disease–like disorder in this region remains to be determined [5]. Another new species, *Borrelia miyamotoi* sp nov., was isolated from *Ixodes persulcatus,* the vector for Lyme disease in Japan [6]. Other species of relapsing fever agents have been identified [7], but these have been less characterized as those in table 1.

The two major forms of relapsing fever are epidemic and endemic. The epidemic form, caused by *Borrelia recurrentis,* is transmitted by the human body louse *Pediculus humanus.* Humans and perhaps other primates are the principal vertebrate hosts for *B. recurrentis.* During large epidemics of louse-borne relapsing fever (LBRF), millions of people have been infected. The last large epidemic occurred during World War II and its aftermath in the Mediterranean region, North Africa, and the Middle East [8]. LBRF has been reported on most continents and still occurs in East Africa [9, 10].

Endemic relapsing fever is transmitted by soft-bodied ticks of the genus *Ornithodoros.* The several different *Borrelia* species that cause endemic relapsing fever have usually been named for the type of tick that transmits it, as in *Borrelia turicatae* and *Ornithodoros turicata.* Endemic or tick-borne relapsing fever (TBRF) has been reported in the last decade from North America [11], Africa [12, 13], Europe [7], Asia [14], and South America [15]. In the United States TBRF has been reported almost exclusively west of the Mississippi River, in particular the mountainous West (*Borrelia hermsii*) and the Southwest (*B. turicatae*). Common sites of acquisition of the

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Table 1. Relapsing fever–associated *Borrelia* species pathogenic to humans.

Borrelia species	Arthropod vector	Geographical distribution of disease
B. hermsii	*Ornithodoros hermsi*	Western North America
B. turicatae	*Ornithodoros turicata*	Southwestern North America and northern Mexico
B. venezuelensis	*Ornithodoros rudis*	Central America and northern South America
B. hispanica	*Ornithodoros marocanus*	Iberian Peninsula and northwestern Africa
B. crocidurae	*Ornithodoros erraticus*	North and East Africa, Near and Middle East, southeastern Europe
B. duttonii	*Ornithodoros moubata*	Sub-Saharan Africa
B. persica	*Ornithodoros tholozani*	Middle East, Greece, Central Asia
B. uzbekistana	*Ornithodoros papillipes*	Tajikistan, Uzbekistan
B. recurrentis	*Pediculus humanus*	Worldwide

NOTE. Data are from [3].

infection by humans in the United States are recreational cabins, caves, and crawl spaces under buildings [5]. A *Borrelia* species that resembles the agents of relapsing fever has been isolated from dogs in Florida [16], an indication that the risk to humans of relapsing fever agents extends now into the southeastern United States [5].

The clinical hallmark of both forms of relapsing fever is two or more episodes of high fever and constitutional symptoms, such as headache and myalgias. The fevers are spaced by periods of relative well-being. In LBRF the second episode of fever is typically milder than the first; in TBRF there are multiple febrile periods, usually equal in severity [17]. The febrile periods are from 1 to 3 days, and the intervals between fevers are generally from 3 to 10 days. During the febrile periods numerous spirochetes are circulating in the blood. This is called spirochetemia and is sometimes unexpectedly detected during routine blood smear examinations. Between fevers, spirochetemia is not observed. The fever pattern and recurrent spirochetemia are the consequences of antigenic variation of the bacteria, specifically in the outer membrane proteins that confer serotype identity [18].

Relapsing fever is well recognized as an infection of the blood but not as an infection of the nervous system [3, 19–21]. In this organ preference the pathogens are similar to *Treponema pallidum,* the agent of syphilis, and the several varieties of leptospires. A review of relapsing fever in 1969 concluded that neurological complications occurred in 10%–30% of cases of relapsing fever [17]. This frequency of neurological manifestations is similar to that during Lyme disease [22, 23]. Recently, an outbreak of febrile illness in West Texas was first attributed to Lyme disease on the basis of facial palsy in some of the cases and positive serological assays for antibodies to *B. burgdorferi* [11]. The actual agent was identified as *B. turicatae* by identification of the vector, *O. turicata,* at the site of exposure [11]. *B. turicatae* is known to have antigens that are cross-reactive with those of *B. burgdorferi* [3]. Inasmuch as the areas of endemicity of relapsing fever and Lyme disease overlap to some extent, confusion between the two infections can be expected [5]. A comparison between TBRF, LBRF, and Lyme disease is presented in table 2.

Our aim was to review the clinical aspects of neurological complications during relapsing fever, to determine if neurological involvement was more commonly associated with some *Borrelia* species than with others in either humans or experimental animals, and to assess the success of different therapies in curing and preventing neurological complications of relapsing fever among patients and experimental animals. While the term *neuroborreliosis* has hitherto been applied exclusively to the neurological complications of Lyme disease, the review of the literature herein justifies extending use of this term to nervous system dysfunction during a related infection, relapsing fever.

Literature Review

We reviewed the literature on relapsing fever using the MEDLINE database and the abstracts of the *Tropical Diseases Bulletin* back to 1922. Many of the reviewed articles were published before 1950 and in languages other than English. References in English, Spanish, and French were obtained and reviewed in their entirety. English summaries in the *Tropical Diseases Bulletin* were used for articles in German, Italian, and Russian.

A case of relapsing fever was defined as the following: (1) two or more episodes of fever within 2 weeks, (2) the detection of spirochetes by microscopic visualization of the patient's blood or CSF or by animal inoculation, and (3) the absence of clinical or laboratory evidence of syphilis or leptospirosis. In most of the articles reviewed, the louse-borne form could be distinguished from the tick-borne form on the basis of the epidemiology and the country in which the cases occurred. Articles were not included in this review if the type of relapsing fever was not disclosed directly or if the description of the epidemiology was not sufficient for attribution of disease. TBRF *Borrelia* species were classified according to their arthropod vector if this was noted [3]. When the vector was unknown or not stated, the identification of the *Borrelia* species was deduced from the geographic location of the probable exposure (table 1). Articles before 1940 sometimes used spe-

Table 2. Comparison of tick-borne relapsing fever (TBRF), louse-borne relapsing fever (LBRF), and Lyme disease.

Characteristic	TBRF	LBRF	Lyme disease
Agent	Several species	*B. recurrentis*	*B. burgdorferi* sensu lato*
Vector	*Ornithodoros* species (soft ticks)	*Pediculus humanus* (human body louse)	*Ixodes* species (hard ticks)
Usual reservoir	Rodents†	Humans	Rodents
Epidemiology	Endemic	Epidemic	Endemic
Distribution	Tropical and temperate regions	East Africa‡	North America, Eurasia
In vitro cultivation	Yes	No§	Yes
Fever (temperature of ⩾39°C)	Common	Common	Rare
Fever relapses	Multiple	Few	None
Neurological involvement	Common‖	Rare	Common
Local skin rash	No	No	Common (ECM#)
Arthritis	No	No	Common
Spirochetes on blood smear	Yes	Yes	No
Serological assay specificity	Fair to poor	Fair to poor	Good to excellent
Antibiotic therapy	Several doses	Single or few doses	Several doses
Jarisch-Herxheimer reaction	Moderate	Moderate to severe	Mild

* Included are *B. burgdorferi* sensu stricto, *B. afzelii,* and *B. garinii.*
† The reservoir for *B. duttoni* in some locations may be humans.
‡ LBRF has a potential worldwide distribution because of association with the human body louse.
§ In vitro cultivation of *B. recurrentis* has been reported but not confirmed [24].
‖ Common in ⩾10% of patients with disseminated disease.
Erythema chronicum migrans.

cies names no longer in use; in that case the modern equivalent of the species was substituted.

Only articles in which neurological or ocular complications were reported were included in the analysis. Neurological involvement was defined by the presence of one or more of the following: (1) signs and symptoms of inflammation of the meninges, such as meningismus, or of the brain parenchyma [25, 26]; (2) signs and symptoms characteristic of sensory and/or motor dysfunction of the cranial nerves, spinal roots, or peripheral nerves [27]; (3) alterations of the CSF, specifically, >5 leukocytes/mm^3 or >0.45 g of protein/dL; (4) detection of spirochetes in the CSF or brain tissue; (5) evidence of inflammation of the meninges or brain parenchyma on pathological examination; and (6) neuropsychiatric disorders that could not be attributed to fever by itself. Cases that might have been neurosyphilis on the basis of Wassermann or other reagin-based serological assays of the serum or CSF were excluded from the analysis.

Clinical Features of Neurological Involvement in Humans

In 1918 Leboeuf and Gambier provided the first direct evidence of invasion of the CNS during relapsing fever when they found spirochetes in the CSF of patients in sub-Saharan Africa [28]. Since then, many neurological dysfunctions have been attributed to relapsing fever. The most commonly reported neurological complications of relapsing fever are meningismus and facial palsy. Less common are encephalitis, myelitis, radiculitis, and neuropsychiatric disturbances.

The frequency of all types of neurological manifestations varies by *Borrelia* species, from none to >50%. Commonly associated with neurological complications have been the tick-borne species *Borrelia duttonii* (9%–80%) [29–32] and *B. turicatae* (27%–80%) [33–36] and the louse-borne *B. recurrentis* (39%–43%) [37–39]. Neurological involvement was reported in <5% of cases of infection with *Borrelia persica* [40, 41], *Borrelia hispanica* [42], and *B. hermsii* [43].

Meningismus was described in 27 (48%) of 57 cases of *B. duttonii* infection in West Africa [30], 5 (12%) of 42 cases of *B. duttonii* infection in East Africa [44, 45], 36 (9%) of 399 cases of *B. duttonii* infection in children in sub-Saharan Africa [46], and 9 (56%) of 16 cases of *B. turicatae* infection in Texas [35]. Manifestations suggesting meningeal involvement were noted in 205 (41%) of 492 LBRF cases in East Africa [37, 38, 47]. Meningismus was also noted during epidemics of LBRF in East Africa [48–50], Tunisia [51], China [52], and Korea [53]. The meningismus of LBRF was generally not severe, unless there was an associated subarachnoid hemorrhage [54].

In areas of sub-Saharan Africa in which *B. duttonii* was endemic, CSF abnormalities were found in 50%–100% of cases with meningismus [30, 55, 56]. Mean numbers of CSF leukocytes were 144 in one series [30] and 242 in another [55]. The leukocytes were predominantly mononuclear cells [30, 57], and the mean CSF protein level was 0.331 g/dL in patients with meningismus [30]. Although meningismus or severe head-

ache was commonly reported with LBRF, there were no reports of CSF abnormalities in patients with this form of relapsing fever.

Two methods were used to document the presence of spirochetes in the subarachnoid space. The first was examination of CSF sediment by bright-field microscopy of Giemsa- or gram-stained fixed specimens or by dark-field or phase-contrast microscopy of wet mounts [43]. The second method was inoculation of CSF into susceptible animals, whose blood was later examined for spirochetemia [29, 30]. The latter was preferred because of its superior sensitivity: microscopic examination of CSF sediment failed to reveal infection in several persons with TBRF whose CSF was subsequently found infected by simultaneous animal inoculation [30, 58]. Borrelias were isolated by animal inoculation from the CSF of 14% of 71 persons with TBRF in Africa, even in the absence of neurological manifestations [28, 55, 58]. There is only one report of possible *B. recurrentis* infection of the CSF of patients with LBRF: samples from five of seven patients in China produced infections in splenectomized squirrels [39].

Encephalitis or encephalopathy occurs occasionally in TBRF and LBRF. Generalized and partial seizures were one manifestation [30, 59]. Extreme somnolence was seen during LBRF in East Africa [38] and TBRF in West Africa [30]. Hemiplegia of a few weeks' duration appeared after the second febrile period in 8 cases of TBRF in East Africa; 6 of the 8 cases had CSF with leukocytosis [60]. Hemiplegia was also noted in children with TBRF [61]. Signs of focal involvement of the brain during LBRF were aphasia [62] and ataxia [63]. An extrapyramidal syndrome with akinesia and rigidity appeared after the first relapse in a TBRF case in North Africa. Examination of the CSF in this case revealed 23 mononuclear cells/mm^3, 0.38 g of protein/dL, and spirochetes [64].

Cranial neuritis was a frequent neurological complication of TBRF, but it was not reported in LBRF. The cranial nerve most frequently involved was the seventh, and the most common manifestation was facial palsy. The frequency of facial palsy during infection with a strain of *B. duttonii* in Africa was such that one author suggested that its presence confirmed a diagnosis of TBRF [30]. Facial palsy in relapsing fever typically appears during the second or subsequent episodes of fever but not during the first. It was observed during or after the second, third, or fourth febrile episode with *B. turicatae* [35, 36], 6 weeks after the fifth febrile episode with *B. hispanica* [42], during the fourth or fifth febrile periods with North African strains [65], and during the second or subsequent febrile periods with *B. duttonii* [60].

The frequency of facial nerve palsy varied with the different species; such palsy was present in 8 (38%) of 21 *B. turicatae*–related cases [34–36], in 7 (11%) of 63 cases in North Africa [66], and in 7 (3%) of 230 *B. hispanica*–related cases [42]. Lumbar puncture revealed an elevated protein level in 3 of 3 patients with facial palsy and *B. turicatae* infections [35]. Facial palsy usually resolved with or without antibiotic treatment in 2–9 weeks [30, 34, 35, 42]. Occasionally the facial paralysis persisted [67, 68].

Involvement of other cranial nerves during TBRF was less frequent. Eighth cranial nerve involvement was suggested by vertigo and tinnitus [30] and by deafness [45, 60]. Hearing loss occurred in four (5%) of 94 children infected with *B. duttonii* [61]. Fifth and sixth cranial nerves have also been affected [30, 57].

In some cases of relapsing fever there has been evidence of radiculomyelitis. Patients with *B. duttonii* TBRF in West Africa developed spastic paraplegia [30] and sciatica [59]. Sciatica was also noted in one case of *B. persica* infection in Palestine [40]. With regard to *B. duttonii* infection in South Africa, Gilger [68] and other investigators reported flaccid paralysis of legs, upper-extremity weakness, and arreflexia that appeared during or after the second febrile period. Other patients have had bladder and bowel incontinence [69]. A patient with TBRF due to *B. turicatae* developed radiculitis of the third, fourth, and fifth lumbar roots during the third febrile period [33]. Transverse myelitis occurred in a patient with LBRF in Iran [70].

Neuropsychiatric abnormalities not solely attributable to high fevers have been reported for both TBRF and LBRF. Delirium, as manifested by the acute onset of mental confusion and excitement, was reported in 59 (11%) of 538 LBRF cases [37, 38, 47, 50, 71]. Hallucinations persisted for several days in TBRF cases in sub-Saharan Africa [72]. Patients with TBRF in Venezuela [73] and West Africa [30] also developed delirium. Signs of mania, such as expansiveness, extreme irritability, garrulousness, flight of ideas, and increased motor activity, were noted in some TBRF cases in Iran [74] and West Africa [30].

Patients with TBRF due to *B. turicatae* infection often required prolonged hospitalization because of persistent fatigue and neurasthenia [35]. During convalescence these patients felt mentally depressed, weak, and unable to return to work. Headaches and backaches were also common. Physical examination findings were normal. Some cases had symptomatic relapses, defined as periods of severe headache, backache, and weakness without fever that occurred at the time of expected relapses and lasted 24–48 hours. The symptoms of mental dysfunction after relapsing fever often persisted for several weeks after the temperature returned to normal [50].

Ocular Complications in Humans

Ocular disorders noted during TBRF include iritis, cyclitis, choroiditis, and optic neuritis. When eye involvement occurred during TBRF, it was bilateral in one-third of the cases and almost always occurred after the third or fourth febrile episode [75]. Once the eye was involved, vision deteriorated rapidly, and most patients had residual visual defects [30, 60]. Ocular disease followed a relapsing course in some cases [67, 75]. Involvement of the eyes during LBRF has not been reported.

The TBRF species most frequently associated with ocular complications in the literature were *B. duttonii* [31, 59, 60, 69, 76], *B. hispanica* [42, 77], and *B. turicatae* [33, 78]. The incidence of optic neuritis or uveitis in *B. duttonii* TBRF in East Africa was 11% [60]. Between 1949 and 1951 about one in five cases of optic neuritis and uveitis diagnosed in an East African hospital was attributed to TBRF [75]. Unilateral uveitis with gross vitreous exudate, iridocyclitis, chronic cyclitis, and persistent headache appeared in 4 (14%) of 28 cases of *B. hispanica* TBRF in North Africa but in none of 63 cases of *B. persica* TBRF in Syria [67].

Neurological Involvement in Animal Models

In 1922 Buschke and Kroo noted the presence of spirochetes in the brains of mice infected with an unknown species of TBRF agent in Russia [79]. Susceptible animals inoculated with brain suspensions subsequently developed spirochetemia. To control for the possibility that the brain specimens were contaminated by infected blood, these investigators tested blood and brain for infectivity over time. They found that brain specimens from the mice were infectious after the blood had ceased to be. This phenomenon was called residual brain infection [80]. More recently, the infection of the brain tissue itself as opposed to the vasculature in mice has been confirmed through the use of serotype-specific IgM monoclonal antibodies to eliminate spirochetes from the blood [81].

Residual brain infection in different experimental animals was the subject of many investigations during the first half of this century [82–92]. Animals in nature also had infected brains [93, 94]. Infection persisted in the brains for up to 3 years after inoculation [95, 96]. Infected tissues in the nervous system included the cerebral hemispheres, cerebellum, optic tract, spinal cord, and cornea [97, 98]. In one study of rats, infection was more commonly found in the medulla than in the cortex [99].

During residual brain infection, animals were protected against reinfection with the same strain [84, 100]. Borrelias causing residual brain infection were susceptible to the serum of the animal from which they were recovered and could not reenter the blood of that animal [87, 101]. These findings suggest that the immune response was not effectively reaching the spirochetes in the brain.

Different *Borrelia* species appear to have different abilities to infect the brain of their mammalian hosts, and mammals differ in their susceptibility to brain infection with these agents. Table 3 lists the animal models of relapsing fever with neurological infection. *B. crocidurae, B. duttonii,* and *B. hispanica* infected the brain of all mammalian hosts examined. *B. recurrentis* infected the brain of primates [50] but not of mice [141]. *B. hispanica* caused residual brain infection in all infected rats, guinea pigs, and rabbits and in 50%–70% of mice, but it caused significant inflammation only in guinea pigs [83].

The frequency of residual brain infection also varied with strains within a species [88, 142, 143]. Residual brain infection occurred in rats infected with the strain of *B. turicatae* studied by Schuhardt and Hemphill [101] but not with a *B. turicatae* strain used by Kemp et al. [144]. Our study of *B. turicatae* in mice indicated that the ability to infect the brain is determined by the same outer-membrane proteins that confer serotype specificity [106].

Relapsing-fever borrelias infect not only nervous tissue of mammalian hosts but also the comparable tissues of arthropod vectors. *B. duttonii* was found in the nerve ganglia, the salivary glands, and the reservoirs of the coxal glands but not the stomach contents of its tick vector *Ornithodoros moubata* for up to 197 days [145]. *B. duttonii* disappeared from the hemolymph of starved *O. moubata* but not from the ganglia, coxal glands, and ovaries [146]. Burgdorfer documented invasion of the central ganglion of *O. moubata* as early as 3 days after infection [147]. Fragments of the central ganglion and coxal organs but not the salivary glands of uninfected ticks provided attractant substances for the migration of *B. duttonii* in capillary tubes [148]. The ganglia and coxal glands of *O. moubata* had the greater density of *B. duttonii* spirochetes among all tissues examined [149]. The frequencies of infection of the central ganglion of *O. moubata* and *O. turicata* were 95% and 60% for *B. duttonii* and *B. turicatae,* respectively [150]. *B. crocidurae* preferably infected the third thoracic and supraesophageal louse ganglia [151].

Neuropathology of Relapsing Fever

Neurological involvement in relapsing fever was studied in several fatal cases of LBRF. The most consistent autopsy findings of macroscopic examination were edema and subarachnoid and parenchymal brain hemorrhages [47, 49, 53, 152, 153]. Anderson and Zimmerman demonstrated by silver stain single and clumped spirochetes within the cerebral microvasculature and the interstitial spaces of the brain of a patient with fatal LBRF [53]. In many of these cases of LBRF, hemorrhage was not limited to the CNS. Many patients had epistaxis, hematuria, gastrointestinal bleeding, and skin petechiae, probably as consequences of disseminated intravascular coagulation [47, 49].

There have been comparatively fewer fatal cases of TBRF and, consequently, less is known of the pathological effects of these infections in humans. The most common finding on microscopic examination was a meningeal and brain parenchymal perivascular mononuclear infiltrate with monocytes, lymphocytes, and plasma cells [57, 153, 154]. The perivascular infiltrate of TBRF had fewer plasma cells and more macrophages than the one of syphilis [155]. Eight TBRF cases examined at autopsy by Belezky and Umanskaja showed a patchy perivascular lymphocytic infiltrate of the pia mater and brain tissue [153]. In this last series the cerebral cortex showed extensive degeneration of ganglion cells. Many neurons were acutely

Table 3. Studies involving animal models of relapsing fever with neurological infection.

Borrelia species	Reference				
	Primates	Rabbits	Guinea pigs	Rats	Mice
B. hermsii	[102]				[81]
B. turicatae	[102]			[8, 88, 103–105]	[106]
B. hispanica		[83, 107, 108]	[83, 84, 95, 96, 100, 109–114]	[83, 93, 115–117]	[83]
B. crocidurae		[83]	[83]	[83]	[83, 118]
B. duttonii	[89, 119]	[82, 89, 107, 119, 120]	[82, 121]	[89, 119, 121–126]	[50, 91, 122, 127–135]
B. persica			[83, 85, 86, 98, 136, 137]	[8, 138, 139]	[140]
B. recurrentis	[50]				

swollen with chromatolysis and vacuolation, and there was only a mild increase in glial cells.

Spirochetes were often detected by silver stains of fixed brain tissue from autopsies in cases of TBRF [153]. Jahnel and Lucksch found borrelias in the brain of patients with fatal TBRF; the bacteria were predominantly within blood vessels but also were found between neurons of the cortex [156]. The distribution of borrelias in the brain was generally perivascular [155]. Spirochetes were observed in the meninges of a newborn with congenital TBRF in the United States [43].

Experimental relapsing fever in animals provided a greater opportunity to study the pathological effects of the infection. Early in the infection with *B. turicatae,* rats had severe congestion of the pia mater vessels and parenchymal capillaries, foci of cortical hemorrhages, and intense microglial reaction in the cerebral and cerebellar cortex and hippocampus [157]. Later in the infection there was only a lymphocytic infiltration of the pia mater. Guinea pigs infected with *B. persica* had perivascular hemorrhage and infiltration with lymphocytes and macrophages in the brain [136]. Selective damage to neurons in the upper part of the spinal cord and posterior columns was found in rats infected with TBRF strains from Russia [158].

To determine the exact localization of spirochetes in infected tissues, most authors relied on silver impregnation techniques. Spirochetes of TBRF species were found in the gray matter between neurons and glias [79] and within cerebral capillaries, pia mater vessels, and choroid plexus [157], but not within cells [119]. They were found not only in the brain parenchyma but also in the meninges [118]. Borrelias were found more commonly in the medulla and deeper parts of the brain than in the cortex of mice and rats infected with strains of TBRF from Africa [97, 99].

Treatment with Heavy Metals

Relapsing fever was one of the first diseases treated with the ''magic bullet'' arsenic compounds of Ehrlich and Hata [159]. Arsphenamine (salvarsan) and its less toxic derivative neoarsphenamine (neosalvarsan) were the most commonly used compounds in animal models of TBRF. Although salvarsan failed to eliminate established infection of the brain [129, 130, 158, 160, 161], it did prevent CNS involvement if administered at or before the onset of the first episode of spirochetemia [162–165]. The persistence of borrelias in the brain through arsenical treatment was not attributable to development of resistance: spirochetes isolated from the brain after neosalvarsan treatment remained susceptible to this compound [165]. The clinical experience with arsenical treatment of human cases also indicated that these compounds were not effective once there was neurological involvement [30, 35, 57, 166, 167].

Antimonials and gold derivatives were other heavy metal compounds assessed for efficacy in animal models of TBRF. Brain infection was prevented by early treatment with several injections of an antimonial compound; treatment was not effective against the infection once the brain was involved [97]. Residual brain infection with *B. duttonii* in rats and mice was cured by the gold derivatives Solganal (aurothioglucose) and A69 but not by arsenic compounds under these experimental conditions [125].

Treatment with β-Lactam Antibiotics

Penicillin replaced arsenical compounds for the treatment of relapsing fever and other spirochetal infections in the 1940s. Studies in animal models indicated that brain infection and relapses of fever could be prevented with low doses of penicillin if treatment was begun during or before the first episode of spirochetemia [104, 168], but not if treatment was delayed for >1 day after the first onset of spirochetemia [169]. If higher doses of penicillin were used and for longer periods of time and with intracranial as well as intraperitoneal injections, residual brain infection of rats was eradicated [103, 170].

Cephaloridine was tested for prevention and treatment of brain infection in *B. duttonii*–infected mice [171]. Brain infec-

tion was eliminated in all mice treated with 120 mg/(kg · d) administered for at least 3 days. A lower dose (30 mg/[kg · d]) failed to prevent brain infection in all mice and did not eliminate spirochetes from the brain when treatment was delayed. In our studies of severely immunodeficient mice infected with *B. turicatae,* ceftriaxone at a dosage of 50 mg/(kg · d) eliminated spirochetes from the brain as well as the blood and bladder [172].

Relapsing fever was one of the first human infectious diseases to be successfully treated with penicillin [35]. The relapse rate in 572 *B. duttonii* cases treated with 8×10^5 units of procaine penicillin intramuscularly daily for 5 days was 5% [46] instead of the expected 70%–90% among untreated historical controls [44, 76]. Failures in treatment of TBRF with penicillin occurred with lower doses or when only one injection was given [35, 44, 60, 76, 173–177]. In contrast to the situation with TBRF, single injections of penicillin, usually intramuscular procaine penicillin, were effective in treatment of LBRF [178–180]. The Jarisch-Herxheimer reaction in LBRF is more common if tetracyclines are used as opposed to penicillin [180].

Treatment with Tetracyclines and Other Antibiotics

Relapses and residual brain infection in mice were prevented by a single subcutaneous dose (25 mg/kg) of oxytetracycline administered 24 hours after inoculation with *B. duttonii* [181]. When a comparable single dose of oxytetracycline was administered 48–72 hours after infection, residual brain infection was not prevented or cured [182].

The tetracyclines are commonly used for treatment of human cases of both LBRF and TBRF. In general, one or two doses of these antibiotics have been less efficacious for TBRF than for LBRF. Four 500-mg doses of oxytetracycline prevented relapses of TBRF in all treated patients, but those given a single dose of 500 mg had a relapse rate of 22%, half of the rate for untreated controls [154]. Tetracycline administered in doses of 250 mg every 3 hours for 3–4 days produced a relapse rate of only 3% in cases due to *B. hispanica,* but after a single dose of 2 g the relapse rate was 40% [183]. Relapses of TBRF have sometimes occurred after multiple doses of tetracyclines administered for up to 10 days [184, 185]. Administration of multiple doses of tetracyclines over several days has been successfully used for treatment of LBRF [38, 186]. There are also reports of prevention of relapses of LBRF with single doses of as little as 250–500 mg of tetracycline [37, 187] and reports of a 42% relapse rate with a single dose of 100 mg of doxycycline [188].

Streptomycin prevented brain involvement by *B. duttonii* in mice if administered early in the infection but did not eliminate residual infection once the brain had been invaded [189]. In the latter case only intracranial streptomycin administered for several days was successful [189]. Among the few reports of treatment of relapsing fever in humans with aminoglycosides was that of a series of 18 TBRF cases in India: 2 g of streptomycin administered at intervals of 3–4 hours for 2 days prevented relapses in all patients [190]. The reported effectiveness of aminoglycosides in these experimental studies and clinical cases is paradoxical; in vitro studies showed that *Borrelia* species are comparatively resistant to aminoglycosides [3, 197].

There is little evidence from animal studies that chloramphenicol is effective for TBRF. Chloramphenicol at a dosage of 500 mg/kg in three divided doses per day for 3 days, started 24–48 hours after onset of the first spirochetemia, did not prevent residual brain infection or subsequent relapses in most white rats and monkeys infected with *B. duttonii* [192]. Chloramphenicol also failed to prevent residual brain infection in mice infected with *B. persica* [140]. In humans with LBRF, though, a single dose of 1–2 g of chloramphenicol was reportedly successful [193].

No studies of erythromycin or other macrolide antibiotics in an animal model of relapsing fever were identified. There were a few case reports on this class of antibiotic for treatment of human cases of relapsing fever. Erythromycin did not prevent neurological complications or further relapse in one case with *B. duttonii* [13]. A patient with TBRF was not cured by a 2 g/d dosage of erythromycin for 10 days [78]. On the other hand, erythromycin in a single dose of 500 mg was an effective treatment for LBRF [187].

Discussion

As the century ends, relapsing fever is less common than it was before 1950 because there are no ongoing, large epidemics of LBRF. Although conditions for wider transmission of epidemic relapsing fever may occur in the future, most cases of relapsing fever in the world at present are endemic TBRF, which occurs as sporadic individual cases or small outbreaks. One such recent outbreak in Texas, in which some of the patients had neurological manifestations similar to those of Lyme disease [11], prompted this review, as did our laboratory studies of the invasion of the CNS by the TBRF agents *B. hermsii* and *B. turicatae* [81, 106].

Most of the literature on the neurological manifestations of relapsing fever, in either humans or experimental animals, was published decades ago. Many studies could not be included in the review because of incomplete information on the clinical manifestations or because of insufficient documentation of neurological involvement in either human or animal infections. Further complicating the review was the ever-changing taxonomy of these infectious agents. Some studies could not be included in the review because the causative agent was not definitely identified or the relapsing fever was not definitely determined to be TBRF or LBRF. Still, as the reference list shows, there were numerous articles on this aspect of relapsing fever that met our criteria for inclusion and provided the subject of the review.

From this review and from our own experimental studies, we made the following conclusions. (1) Some *Borrelia* species

that cause relapsing fever are neurotropic in humans and experimental animals. (2) The risk of neurological involvement during relapsing fever is greater with species that cause TBRF than with *B. recurrentis,* the cause of the louse-borne form of the disease. We discuss these major conclusions as well as the following considerations: similarities and dissimilarities between relapsing fever and Lyme disease with respect to neurological involvement, the diagnostic approach to relapsing fever, and recommendations for treatment.

The term *neurotropic* is commonly used in biomedical literature, but its usage is often imprecise. We take the meaning of the term to be the following: the localization of a particular microorganism or other parasite into the central or peripheral nervous system under conditions in which a similar or related microorganism does not invade the nervous system. Using this definition, one can legitimately speak of rabies virus and certain herpesviruses as being neurotropic. As reviewed above, our and others' studies of relapsing fever in experimental animals, including the tick vectors themselves, indicate that some *Borrelia* species that cause TBRF are neurotropic.

Clinical findings supporting this conclusion are the frequent occurrence of neurological manifestations during relapsing fever, the isolation or other direct detection of spirochetes in the CNS, and the failure of many antibiotic treatments that do not readily penetrate the blood-brain barrier. The histopathologic studies demonstrated the presence of spirochetes primarily in the tissues surrounding small vessels. As was found in experimental animals, some *Borrelia* species that cause TBRF were more commonly associated with neurological involvement than were other species.

There is less evidence of nervous system involvement by the louse-borne agent *B. recurrentis.* Indeed, neurological disorders attributable to actual invasion of the brain by *B. recurrentis* appear to be uncommon. Although signs and symptoms consistent with meningitis have been described as occurring in LBRF, there is little if any documentation of inflammation or invasion of the meningeal space or brain itself. The pathological studies cited above indicate that neurological complications of LBRF may more frequently be the result of hemorrhage in the CNS than that of direct involvement of the spirochetes. In the one study in which spirochetes were demonstrated in the CSF, the authors used splenectomized squirrels for animal inoculations [39]. Inasmuch as most investigators have not found *B. recurrentis* to be infective for animals other than primates [8], the accuracy of the species designation in this study must be questioned.

In the majority of cases with LBRF in which the CSF was examined, the fluid had either normal or only slightly elevated levels of cells and protein. While cranial neuritis and ocular disorders were frequent complications of TBRF, in particular among those cases caused by *B. duttonii* in sub-Saharan Africa, *B. hispanica* in the Mediterranean region including North Africa, and *B. turicatae* in North America, these were uncommon complications of LBRF. The usual success of single or two doses of an antibiotic in the treatment of LBRF, in contrast to the usual failure of such regimens for TBRF, is another indication that infection of the subarachnoid space or brain itself is uncommon during LBRF.

The frequency of involvement of the nervous system during many types of TBRF (10%–40%) is similar to that observed in Lyme disease in North America and Europe [20, 22]. Most striking is the frequent occurrence of cranial neuritis, especially involving the seventh cranial nerve, in both relapsing fever and Lyme disease [20, 194–196]. In both infections the facial palsy appears later in the infection and seldom if ever during the episode of fever. In an animal model of cranial neuritis during relapsing fever, namely, *B. turicatae* infection of mice, the cranial neuritis appeared to be peripheral and not central [106]. In many cases of seventh nerve palsy during Lyme disease in humans, the CSF is normal [197].

In other cases of Lyme disease there is the same clear evidence of spirochete invasion and inflammation of the brain, as has been found with relapsing fever. There are symptoms and signs of focal or generalized encephalitis and elevations of both cells and proteins in the CSF [194, 196]. *B. burgdorferi* has been isolated from the CSF of patients with ''neuroborreliosis,'' the suggested equivalent of neurosyphilis for relapsing fever and Lyme disease [198, 199]. Other patients with Lyme disease have had ocular disorders, such as iritis, that are similar to those noted during relapsing fever [200, 201]. *B. burgdorferi* has been isolated from the iris of such a case [202].

Although they share some of the same neurological manifestations, TBRF and Lyme disease can be differentiated in other respects. A localized skin rash, such as the hallmark erythema migrans of Lyme disease, does not occur during relapsing fever. Temperatures above 38°C are frequent during relapsing fever but uncommon during Lyme disease [203]. Patients with relapsing fever may complain of diffuse myalgias and arthralgias, but frank arthritis does not occur. In Lyme disease, some of the manifestations such as chronic encephalitis or arthritis do not appear for weeks to months after the start of the infection. There does not seem to be an equivalent ''late'' or ''chronic'' form of relapsing fever. In general, relapsing fever is a more quickly evolving infection than Lyme disease. The time course of TBRF or LBRF is measured in days to weeks instead of weeks to months or even years.

A likely explanation for the differences between relapsing fever and Lyme disease in the time period for disease evolution is the higher burden of microorganisms in the blood during the former infection than during the latter. During relapsing fever, there are numerous spirochetes in the blood, often outnumbering WBCs. Spirochetes circulate in the blood during the early stage of infection with *B. burgdorferi,* but these have not been observed directly in the microscope [191]. Their demonstration requires culture or PCR. Animal studies indicate that there are a thousandfold fewer spirochetes in the blood during early Lyme disease than during relapsing fever [204]. When

spirochete burdens are low, as they are in the blood during Lyme disease, pathogen-specific antibodies appear weeks after the start of the infection [191]. In relapsing fever, serotype-specific neutralizing antibodies are detectable in the blood within a few days of the infection's start [18, 102].

The comparatively large number of spirochetes in the blood during relapsing fever provides the opportunity for the simplest method for laboratory diagnosis of the infection: by Wright stain of a thin blood smear or by dark-field or phase-contrast microscopy of a wet mount of plasma. The blood should be obtained during or just before the peaks of body temperature. Between fever peaks, spirochetes often can be demonstrated by inoculations of blood or CSF into special culture medium or experimental animals. Enrichment for spirochetes is achieved with use of the platelet-rich fraction of plasma or the buffy coat of sedimented blood. In the United States the most common causes of relapsing fever are *B. hermsii* and *B. turicatae;* both will grow in Kelly's culture medium or its modifications [205, 206] and in young mice or rats [3]. *B. recurrentis* until recently has not consistently grown in artificial medium or in nonprimate laboratory animals [3, 8, 24].

Whereas direct visual detection of organisms in the blood or CSF is the most common method for laboratory confirmation of relapsing fever, immunoassays for antibodies are the most common means of laboratory confirmation of *B. burgdorferi* infection [191, 203]. Although serological assays have been developed for the agents of relapsing fever, these are not widely available and are of dubious utility. The antigenic variation displayed by the relapsing fever species means that there may be hundreds of different serotypes. If a different serotype or species is used for preparing the antigen, only antibodies to conserved antigens may be detected.

For this reason, a standardized ELISA with *B. burgdorferi* as antigen may be the best available serological assay for relapsing fever. The ELISA for antibodies to *B. burgdorferi* is routinely done across the United States and Europe. If a positive result for IgM or IgG antibodies is obtained, the western blot for antibodies to *B. burgdorferi* antigens would be expected to discriminate current or past Lyme disease from relapsing fever, as well as from syphilis, another cause of a positive Lyme disease ELISA [207, 208].

Until recently, it was thought that Lyme disease and relapsing fever could also be distinguished on purely epidemiological grounds. The areas of endemicity for each disorder in North America and Europe did not appear to coincide. Lyme disease has been most commonly reported in the northeastern and north-central United States, while relapsing fever is more common in the Far West, the Rocky Mountain region, and the Southwest. Whereas Lyme disease is most common in northern Europe, relapsing fever is more often encountered in countries around the Mediterranean [7]. Lyme disease occurs across the northern breadth of Russia, but relapsing fever is more common in those states of the former Soviet Union that comprise Central Asia. Lyme disease is not known to occur in South America or Africa, two continents in which TBRF is endemic.

At least in the United States, though, the geographic distinctions between the two infections are now less clear-cut. *B. burgdorferi* has been found in California, where *B. hermsii* is endemic [3, 8]. In the southeastern and south-central United States, a Lyme disease–like disorder may be caused by a new *Borrelia* species that is more closely related to relapsing fever species than it is to *B. burgdorferi* [5]. Relapsing fever and Lyme disease may also overlap in Spain and possibly other regions near the Mediterranean [209]. In cases in which the distinction is not possible on clinical or epidemiological grounds, PCR analysis of the flagellin gene can be used to differentiate between relapsing fever and Lyme disease borrelias [210].

If there are symptoms and signs of meningitis or encephalitis without clinical and/or radiological signs of increased intracranial pressure, a lumbar puncture is indicated in both Lyme disease and TBRF. The finding of elevated levels of cells and protein would usually call for the use of parenteral antibiotics, such as penicillin G, cefotaxime, or ceftriaxone, for 14 days or more. The CSF, injected into mice or rats or inoculated in culture medium, may also provide documentation of a relapsing fever or a Lyme disease agent after spirochetes have disappeared from the blood.

Less obvious is whether to examine the CSF in cases of Lyme disease or TBRF with isolated facial palsy. The cranial nerve involvement in such cases may be peripheral and may not be indicative of CNS disease. Moreover, if the treatment would be expected to eliminate spirochetes in the brain or CSF in any case, then there may be little to be gained from a lumbar puncture in cases with cranial neuritis but with no signs of meningoencephalitis. However, if oral therapy with a tetracycline, macrolide, or β-lactam antibiotic is being considered, especially in the case of suspected or documented TBRF with neurological or ocular manifestations, then assessment of the presence of meningeal inflammation may be prudent.

In the absence of neurological or ocular manifestations at the time of presentation or diagnosis of relapsing fever, the principal aim of antibiotic therapy is to prevent further fever and the neurological complications. As reviewed above, the latter tend to appear during or after the second or third fever episode. The comparatively less frequent occurrence of neurological involvement during LBRF suggests that administration of a single dose or a few doses of an oral antibiotic is usually sufficient for prevention of relapses of this infection.

The situation with TBRF is different. The clinical studies and laboratory experiments reviewed above indicate that some tick-borne species of relapsing fever agents, notably *B. turicatae* in the southwestern United States and *B. duttonii* in Africa at present, commonly invade the CNS early in the infection. Oral antibiotics for one to a few days may eliminate spirochetes from the blood in these cases, but it is likely

that the infected brain provides a reservoir for spirochetes to repopulate the blood once antibiotics have been withdrawn. For this reason, further relapses and involvement of the nervous system during TBRF are more successfully prevented by early treatment with at least 1 week of oral or parenteral antimicrobial therapy, preferably with a β-lactam antibiotic or a tetracycline.

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