Lyme borreliosis, caused by *Borrelia burgdorferi* sensu lato (s.l.), presents with a variety of clinical signs and symptoms and with several variations in the course of the disease. This may frequently result in an uncritical interpretation of manifestations mistakenly attributed to Lyme borreliosis [1]. Most often the diagnosis of Lyme borreliosis is based on erroneous interpretations of serologic or PCR test results and an equation of infection with disease [2, 3]. On the other hand, some patients with typical clinical signs still remain undiagnosed and untreated. In spite of possible variations in the clinical course, certain rules could be useful for identification of patients and confirmation of borrelial infection. Lyme borreliosis should not become a domain in which everyone interprets findings according to their own feelings and intentions. This temptation exists not only with Lyme borreliosis, but also with several other illnesses presenting with numerous clinical features and limited laboratory confirmation. Such behavior regarding Lyme borreliosis is coupled not only with in-
complete information about the disease, but most often with inadequate familiarity with the existing knowledge. This may lead to more restricted recognition of the disease by some (predominantly academic) physicians, and others to the fantasy that substantial numbers of patients with chronic symptoms such as arthralgia, myalgia, headache, fatigue and so on – symptoms quite frequently present in the general population – are suffering from chronic Lyme borreliosis, and thus require long-term treatment with antibiotics. The latter approach appears to be much more frequent than the former, and has been expanding fairly rapidly, not only in the USA but also in several countries in Europe. It is mostly a consequence of the pronounced expectations of patients with nonspecific and/or devastating signs and symptoms and their desire to get a ‘decent’ diagnosis offering efficacious and relatively simple treatment. Therapy in these cases is often coupled with limited proficiency of the care providers and unfortunately in some cases also with malevolent activities of some individuals who are not able to avoid the temptations of financial opportunities in the management of ‘chronic Lyme disease’.

Not knowing what to do is frustrating, not doing what is known is tragic, intentionally doing things that are not efficient and can even be harmful is ethically intolerable.

Diagnosing Lyme Borreliosis

The terms Lyme borreliosis and Lyme disease are generally used synonymously. However, the term Lyme disease was coined to name an enlarging spectrum of symptoms that were obviously linked to each other by an etiology that was unknown until the early 1980s; the first observations of Lyme arthritis and Lyme carditis were made in the USA [4, 5]. After the discovery of the borrelial origin of these disorders, the more specific term Lyme borreliosis was introduced, and now appears to be the more appropriate term to describe a disorder that exists in moderate climates all over the northern hemisphere.

When diagnosing Lyme borreliosis it is important to acknowledge some simple facts that are often neglected or not properly recognized [1–3]. One such fact is that Lyme borreliosis is a disease. Disease is defined as ‘any deviation from or interruption of the normal structure or function of any body part, organ, or system that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown’ [6]. Therefore, there is no disease without signs and/or symptoms, and consequently there is no diagnosis of Lyme borreliosis in the absence of clinical manifestations. The mere proof of an infection with borreliae is not sufficient, because the infection may not always result in illness. It appears that the proportion of symptomatic infections is much higher in the USA, at about 90% [7], than in Europe, where fewer than 50% of infections result in clinical illness [8–10]. In addition, demonstration of antibodies to B. burgdorferi s.l. does not
discriminate between active infection and an immunologic imprint of previous (symptomatic or asymptomatic) infection. Because signs and symptoms form the basis for recognition of the disease, good knowledge of clinical features is important in diagnosing Lyme borreliosis [2]. Case definitions for Lyme borreliosis are beneficial in everyday clinical practice, and especially for comparing the findings of different researchers. Unfortunately, clinically useful definitions are rare. Those of the Centers for Disease Control and Prevention (CDC) in the USA [11] were made primarily for epidemiologic purposes and are, with the exception of the definition of erythema migrans (EM), not applicable in clinical practice, whereas European definitions [12, 13] are somewhat complicated for a busy clinician. Guidelines for diagnosis and treatment (management) are also useful. They are available as the Infectious Diseases Society of America (IDSA) guidelines for the USA [14], were termed clinical case definitions by the European Union Concerted Action on Lyme Borreliosis (EUCALB), and as laboratory guidelines by a working group of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) [12, 13].

Another often neglected fact is that the clinical presentations of Lyme borreliosis in America and Europe differ in some respects, making it inappropriate to uncritically apply the findings from one side of the Atlantic to the other side [15]. Another important aspect is that, because of the much higher publication frequency of USA researchers and physicians in the field of Lyme borreliosis, it is quite possible that the diagnosis of Lyme borreliosis in Europe is predominantly assessed through ‘American eyes’. The opinions offered in the present report are based primarily on European data and experience, and most probably fit better to the situation in Europe.

The only sign that enables a reliable clinical diagnosis of Lyme borreliosis is a typical EM [1–3, 12–14, 16–19]. However, according to current knowledge, even this is valid only for Europe and is less straightforward in the USA where skin lesions of STARI (Southern tick-associated rash illness; Masters’ disease) are very similar to EM [20, 21]. Ear lobe lymphocytoma, meningo-radiculoneuritis (Garin-Bujadoux-Bannwarth syndrome) and acrodermatitis chronica atrophicans (ACA) are also highly supportive of the diagnosis [2, 3, 13]. The large majority of numerous other symptoms and signs, especially when expressed individually, have only minimal or even symbolic diagnostic value. Laboratory confirmation of a borrelial infection is needed for all manifestations of Lyme borreliosis, with the exception of typical skin lesions [1–3, 12–14, 16–19]. An apparently favorable effect of treatment with antibiotics is of small diagnostic value, because the natural course of Lyme borreliosis in an individual patient is difficult to predict (is variable) and, moreover, the majority of clinical manifestations will resolve spontaneously [2, 3]. Individual case reports of unusual clinical manifestations may serve as a trigger for scientific evaluation, but it is incorrect to conclude that these are ‘new’ signs of Lyme borreliosis or new (newly discovered) clinical manifestations of the disease. Moreover, coincidence should be ruled out by controlled prospective clinical studies, since the presence of borrelial antibodies in serum and/or the presence of specific nucleic acid sequences of B. burgdorferi s.l. in a
patient’s specimen, and in some circumstances even the isolation of borreliae from involved tissue or organ, do not alone prove the etiology [1–3].

Little information exists on the frequency of coinfections of tick-borne pathogens and their effects on the clinical manifestations, diagnosis, treatment and outcome of Lyme borreliosis. Dual infection with Babesia microti and B. burgdorferi sensu stricto (s.s.) can result in more serious disease than infection with either agent alone [22]. A combination of Lyme borreliosis with tick-borne encephalitis could cause diagnostic dilemmas, and consequently a delay in antibiotic treatment [23]. Coinfection with the agent of human granulocytic anaplasmosis, Anaplasma phagocytophilum, affects the choice of antibiotic for treatment of early Lyme borreliosis [24].

Only the main clinical manifestations of Lyme borreliosis will be dealt with in this chapter.

Clinical Manifestations

A complete presentation of the disease is an extremely unusual observation, in which a skin lesion follows a tick bite, the lesion is then followed by heart and nervous system involvement, and later on by arthritis; late involvement of eye, nervous system, joints and skin may also occur. Information on the relative frequency of individual clinical manifestations of Lyme borreliosis is limited. The disease has traditionally been divided into stages; however, although this may be valuable for didactic reasons, it is somewhat theoretical and often not in agreement with clinical findings.

Skin Involvement

Skin is the most frequently involved tissue in Lyme borreliosis, and skin manifestations frequently represent clues for the diagnosis. EM, borreial lymphocytoma (formerly lymphadenosis benigna cutis) and ACA are today rated as classic manifestations of Lyme borreliosis. These manifestations were well known as distinct skin disorders long before the discovery of the causative agent [17, 25–27]. In addition, Lyme borreliosis may be associated with several other skin manifestations, such as scleroderma circumscripta, lichen sclerosus et atrophicus and cutaneous B cell lymphoma.

Erythema Migrans

Short Definition

Several definitions of EM have been proposed for different purposes. Best known among these are the definitions of the CDC [11], EUCALB [12] and the ESCMID study group [13]. In Slovenia, a modified CDC definition has been used since 1988. EM is defined as
an erythematous skin lesion that develops days to weeks after infection at the site where borreliae were inoculated into the skin. It typically begins as a red macula or papule and expands over a period of days to weeks to usually an oval or round lesion, with or without central clearing. For a reliable diagnosis, a single primary lesion must reach ≥ 5 cm in size. A lesion < 5 cm qualifies for the diagnosis of EM only if: (1) it develops at the site of a tick bite, (2) a time interval between the bite and the onset of the lesion is reported, and (3) the lesion is enlarging (fulfillment of all 3 requirements is needed). Secondary lesions may also occur. Multiple EM is defined as the presence of 2 or more skin lesions, at least 1 of which must fulfill the size criteria for solitary EM given above.

Frequency
EM is by far the most frequent manifestation of Lyme borreliosis. In the USA, more than 70% of patients registered with Lyme borreliosis had EM [28]. Among 1,471 patients shown to have Lyme borreliosis in an epidemiologic study in southern Sweden, EM was seen in 77% of all cases, and was accompanied by other signs of the disease such as nervous system involvement, arthritis, lymphocytoma and/or carditis in only 6.5% [29]. Mandatory notification in Europe has been instituted in only a limited number of countries. In Slovenia, where notification of Lyme borreliosis has been mandatory for more than 20 years and where during the past 10 years the incidence of the disease has been more than 100 per 100,000 inhabitants, rising to 224 per 100,000 in 2006, EM represents about 90% of registered cases [30, 31]. The relative frequency of individual clinical manifestations in patients registered at the Lyme borreliosis outpatient clinic at the Department of Infectious Diseases, University Medical Center Ljubljana, Slovenia, are shown in table 1.

Etiology
In North America, EM is caused by *B. burgdorferi* s.s., this species apparently being the sole cause of human Lyme borreliosis there. Reports from Europe, based on the

### Table 1. Frequency of the main clinical manifestations of Lyme borreliosis in patients registered at the Lyme borreliosis outpatient clinic in Ljubljana, Slovenia, in 2000

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Adults</th>
<th>Children</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema migrans</td>
<td>621 (83.4)</td>
<td>218 (79.3)</td>
<td>839 (82.3)</td>
</tr>
<tr>
<td>Borrelial lymphocytoma</td>
<td>4 (0.5)</td>
<td>4 (1.5)</td>
<td>8 (0.8)</td>
</tr>
<tr>
<td>Lyme neuroborreliosis</td>
<td>48 (6.4)</td>
<td>40 (14.5)</td>
<td>88 (8.6)</td>
</tr>
<tr>
<td>Lyme carditis</td>
<td>2 (0.3)</td>
<td>0</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Lyme arthritis</td>
<td>21 (2.8)</td>
<td>13 (4.7)</td>
<td>34 (3.3)</td>
</tr>
<tr>
<td>ACA</td>
<td>49 (6.6)</td>
<td>0</td>
<td>49 (4.8)</td>
</tr>
<tr>
<td>Total</td>
<td>745</td>
<td>275</td>
<td>1,020</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages.
characterization of borreliae isolated from skin, revealed that EM is most often caused by *B. afzelii* (up to 96%, most often 70–90%), less frequently by *B. garinii* (up to 33%, most often 10–20%), rarely by *B. burgdorferi* s.s. and only exceptionally by other species such as *B. bissetti*, *B. spielmanii* and as yet unidentifiable species [32–44]. Among 488 skin isolates from Slovenian patients with EM, 433 (89%) were typed as *B. afzelii*, 53 (11%) as *B. garinii* and only 2 as *B. burgdorferi* s.s. [38]. However, in a Finnish series of 82 patients with EM, 21.5% were skin culture positive (a rather low isolation rate), and all the isolates were typed as *B. garinii* [45]. It seems that the predominance of *B. afzelii* is valid for western and central Europe, but may not be for eastern Scandinavia, eastern Europe and Asia. It is of interest that the proportions of the main *Borrelia* species isolated from EM skin lesions do not completely match with the proportions found in ticks. Studies in Slovenia and Germany found that *B. garinii* and *B. burgdorferi* s.s. were relatively more frequently isolated from ticks than *B. afzelii*, and that this differed from the *Borrelia* species isolated from the skin of patients with EM in the same region [39, 46].

Information obtained predominantly from PCR [34, 47, 48] but also from culture results [49, 50] indicates that an individual patient with Lyme borreliosis may simultaneously harbor more than 1 *Borrelia* strain of the same species and even more than 1 *Borrelia* species. Borreliae enter the skin during the blood meal of an infected *Ixodid* tick. Most probably, the bacteria initially accommodate to the new environment and then spread into the skin and other tissue. Results of experimental infection suggest that borreliae may disseminate in the skin over a long period of time without causing disease, unless the host’s defenses are imbalanced [3].

**Tick Bite**

In the USA, only about 1 in 4 patients (14–32%) with EM recall a previous tick bite at the site of the skin lesion [15, 28, 51, 52]. In several European studies, the proportion of patients recalling a tick bite is substantially higher [15, 53–56]. Among 892 adult patients diagnosed with typical EM at the Ljubljana Lyme borreliosis clinic in 1993, 73% reported a tick bite at the site where the EM skin lesion expanded, and in 2000 the corresponding rate was 311 of 535 (58%) [56]. Patients with EM who do not recall a tick bite were most probably bitten, but were not aware of it. The history of an insect bite followed by skin lesion and interpreted as EM is often insecure, and cannot exclude an unnoticed tick bite.

**Histologic Findings**

Commonly mild superficial perivascular infiltration by lymphocytes and some histiocytes is usually present, and is sometimes accompanied by plasma cells, rarely by neutrophils, in the dermis at the site of the EM lesion and also in the clinically normal-looking skin bordering the lesion [57]. The epidermis is usually unaffected. The presence of T cells and increased numbers of Langerhans cells suggest that cell-medi-
ated immune mechanisms are involved in the initial host response to *B. burgdorferi* s.l. [3]. High levels of mRNA expression of the T cell-active chemokines CXCL9 and CXCL10 and low levels of the B cell-active chemokine CXCL13 have been established in EM. CD3+ T cells and CXCL9 have been visualized using immunohistologic methods [58].

**Clinical Characteristics**

EM affects all ages and both sexes with a slight predominance of females in Europe, but not in the USA. The lesion usually appears on the skin at the site of a tick bite. Days to weeks thereafter, a small red macula or papule appears. In 1 study of adult European patients with *B. afzelii* isolated from skin, the median time from bite to rash onset was 17 days, whereas the median time in *B. burgdorferi* s.s. patients in the USA was 11 days [15]. Because of the close temporal proximity of tick bites and onset of EM, this manifestation of Lyme borreliosis has a pronounced seasonal occurrence. The erythema slowly enlarges and central clearing usually begins— in adult patients in Europe typically by the end of the first week— resulting in a ring-like lesion that spreads outward (EM). Untreated lesions persist and expand over days to several months. EM skin lesions are typically oval or round, but can have an irregular shape. Their diameter may range from a few centimeters to more than a meter. In adult patients EM is most often located on the lower extremities; in children the upper part of the body is relatively more often involved [3, 15–17, 19, 53–56].

About half of adult European patients report local symptoms at the site of EM, usually mild itching, burning or pain; a smaller proportion (20–51%) have systemic symptoms such as fatigue and malaise, headache, myalgia and arthralgia, which are usually intermittent and often vary in intensity and location. In European patients with EM, fever is an exception, being present or recalled in fewer than 5% [17, 19, 54–56, 59], whereas in the USA it is documented in about 16% and recalled by more than one third of patients [28]. Although the frequencies of local symptoms appear similar in the USA and Europe [15], the proportion of patients with systemic symptoms is higher in the USA, where as many as 80% of patients evaluated for EM have simultaneous systemic complaints [28, 60]. In a study on culture-proven EM, 82 of 119 (69%) adult patients in the USA, in whom *B. burgdorferi* s.s. was causing disease, reported systemic symptoms, in contrast to 43 of 85 (51%) Slovenian patients with *B. afzelii* isolated from their skin lesion. The comparison also revealed several other differences, including briefer duration of EM in the USA (median 4 days vs. 14 days in European patients), greater frequency of abnormal findings on physical examination (57 vs. 14%) including lymphadenopathy (39 vs. 9%) and fever (15 vs. 1%), and differences in seroreactivity; central clearing was more likely in European patients (68 vs. 35%). The frequency of multiple EM was greater in the USA than in the Slovenian patients (13 vs. 7%), but the difference was not significant [15]. Several distinctions have also been found in European patients when comparing culture-confirmed EM caused by *B. afzelii* with EM caused by *B. garinii* [33, 61, 62]. According to some
authors, the presence of systemic symptoms associated with a solitary EM skin lesion might indicate dissemination of the etiologic agent; however, this most probably applies more to patients in North America than in Europe. According to the somewhat limited information in Europe, the yield from blood cultures of patients with EM is low and spirochetemia is often clinically silent. The isolation rate from blood was found to be only about 1% in adult patients and 9% in children with solitary EM [59, 63], which is in contrast to reports from the USA where as many as 50% of patients with EM had a positive blood culture [64]. Possible explanations for these distinctions are the much larger volume of blood cultured in the USA than in Europe, and differences in the species causing EM. All blood isolates in the USA belong to *B. burgdorferi* s.s., but only a subset of subtypes of this species is prone to disseminate and to cause spirochetemia. In Europe, *B. afzelii* predominates, not only among skin isolates but also among blood isolates (≥80%) of patients with EM [38, 59, 63]. In 1 study, only 7 of 35 (20%) adult patients with EM and *B. burgdorferi* s.l. isolated from blood reported constitutional symptoms [59]. Comparison of 12 blood culture-positive and 122 blood culture-negative children with solitary EM found no differences in pretreatment characteristics, including the frequency of the associated systemic symptoms [63]. The fact that in Europe only some of the patients with multiple EM report systemic symptoms indicates that the absence of systemic symptoms is not a reliable indication of the lack of dissemination. For example, nearly 50% of adult Slovenian patients and 70% of children with multiple EM do not report any systemic complaints [unpublished data, 65]. Multiple EM is defined as the presence of 2 or more skin lesions in an individual patient and is interpreted as a consequence of hematogeneous dissemination of borreliae from the primary EM skin lesion. The secondary lesions are similar in morphology to the initial solitary lesion, but lack the indurated center usually seen in primary lesions at the site of the tick bite; secondary lesions are also smaller and are only exceptionally associated with local itching or pain. It seems that they are more frequent in children than in adults, and are apparently a more common finding in EM in the USA (up to 50% [60]) than in Europe (3–8% of adult patients) [15, 19, 53–56]. It is of interest that in children with multiple EM, a mild predominantly lymphocytic pleocytosis was seen in 18–26% of patients, although none had clear clinical evidence of central nervous system (CNS) involvement [65, 66], and fewer than half of these patients reported systemic symptoms [66]. European patients with EM are mostly seronegative in convalescent-phase serum samples, whereas the majority of such patients in the USA are seropositive. However, in both groups routine medical laboratory tests do not reveal signs of inflammation or any other abnormalities [4, 15, 51–55, 60].

**Diagnosis**

Diagnosis of a typical EM is clinical [1–3, 14, 16]. For atypical lesions, proof is required by the demonstration of borreliae in skin [2, 3]. However, even ‘typical’ EM may not be considered pathognomonic for Lyme borreliosis, especially in the southern part of
the USA, where skin lesions consistent with EM but with no microbiologic evidence for *Borrelia* infection have been established [20, 21].

**Differential Diagnosis**

EM is sometimes misdiagnosed as fungal infection and vice versa, especially when lesions are present in inguinal or axillary regions. Skin lesions that do not show central clearing may resemble erysipelas, although in patients with erysipelas the onset of the lesion is typically preceded by rigors and high fever and is accompanied by high fever, malaise and laboratory signs of inflammation, which are – at least in Europe – not present in patients with EM. When a skin lesion appears immediately or during the first 24 h after a tick bite, it is usually the result of a hypersensitivity reaction and not a borrelial infection. In Lyme borreliosis there is typically a symptom-free interval of at least some days from the bite to the onset of a skin lesion. Other differential diagnoses may include reaction to an insect bite, urticaria, contact eczema, folliculitis, cellulitis, granuloma annulare, tinea corporis (ring worm), fixed drug eruption or pseudolymphoma [2, 3, 12, 67].

**Borrelial Lymphocytoma**

**Basic Description and Histologic Findings**

Borrelial lymphocytoma is a solitary swelling with a diameter of up to a few centimeters, consisting of a dense lymphocytic infiltration of cutis and subcutis as a result of borrelial infection [17, 68–72]. The infiltration is polyclonal with a predominance of B lymphocytes and may show germinal centers [17, 57, 68, 69, 72, 73]. In contrast to the other 2 main skin manifestations of Lyme borreliosis, EM and ACA, where high levels of the T cell-active chemokines CXCL9 and CXCL10 have been established, in borrelial lymphocytoma high levels of the B cell-active chemokine CXCL13 are found [58]. In children, borrelial lymphocytoma is most frequently located on the ear lobe and in adults in the region of the areola mammae [17, 68–72]. When located on the ear lobe, the involved skin is bluish red; at other locations, the skin color is usually normal. Borrelial lymphocytoma usually appears later, has slower evolution and is of longer duration than EM, but also resolves spontaneously although sometimes only after more than a year [17, 68–70, 72]. Other signs of Lyme borreliosis may develop in the course of (untreated long-lasting) borrelial lymphocytoma [17, 68, 69, 71, 72].

**Frequency**

Borrelial lymphocytoma is a rare manifestation of European Lyme borreliosis. There are no reliable reports on autochthonous borrelial lymphocytoma from North America. Data on the exact frequency of this manifestation in Europe are limited. In a well-designed epidemiologic study in southern Sweden, borrelial lymphocytoma was
found in 16 of 232 (7%) children and in 25 of 1,239 (2%) adults registered with Lyme borreliosis [29]. In Slovenia, only 18 of 1,582 (1.1%) patients registered with Lyme borreliosis in the years 1986–1988 had borrelial lymphocytoma [74]. The proportion of patients with borrelial lymphocytoma diagnosed at the Ljubljana Lyme borreliosis clinic during 1999 is shown in table 1. Similar ratios were also found for the following years [unpublished data].

**Etiology**
Information on the genospecies of borreliae that cause borrelial lymphocytoma is limited. The large majority of isolates from borrelial lymphocytoma tissue have been found to be *B. afzelii*, but in some patients *B. garinii* and *B. burgdorferi* s.s. have been isolated, and in 1 patient the presence of *B. bissetti* was established [38, 70, 71, 75–77].

**Clinical Characteristics**
After the recognition that solitary lymphocytoma (lymphadenosis benigna cutis) is a manifestation of Lyme borreliosis, only 5 studies [68–71, 73] with large numbers of patients, including 1 with a predominantly pathologic orientation [73], and a few reports on a very limited number of patients have been published [78–80]. A review of 36 patients with a solitary borrelial lymphocytoma diagnosed at the Department of Infectious Diseases of the University Medical Center Ljubljana (the department cares for both children and adults) over a 5-year period revealed that in most of these patients the onset of borrelial lymphocytoma was in the second half of the year and that distribution according to sex was well balanced. The lesion was localized on the ear lobe in 47% of patients, on the breast in 42%, and on the nose, arm, shoulder or scrotum in 11%. Patients with ear lobe borrelial lymphocytoma were younger than those with the lesion on the breast (median 12 vs. 42 years); of 17 patients with ear-lobe borrelial lymphocytoma only 3 were adults and all the others were 10 years or younger; in breast borrelial lymphocytoma, all patients but 1 were 18 years or older [69]. This accords with observations of other researchers and with further reports from the same group [68, 70, 71, 73]. The reasons for such distinctive localizations and for differences in location of the lesion according to age are not completely understood. Asbrink and Hovmark [81] hypothesized that borreliae prosper at a temperature below 37°C, which would explain why the ear lobe and the nipple, the cooler parts of the body, are most frequently affected. However, there are some additional explanations. Lymphocytoma on the ear lobe is easy to notice and can be easily recognized from its characteristic appearance, provided the physician is familiar with the disorder. Changes in the nipples and nodules in the breast often scare the patient into seeking medical help, although the physician has to use various diagnostic measures to achieve a possibility of correct diagnosis. Nodules found in other areas of the skin, whether in the dermis or subcutis, are usually no cause for consulting a physician. Even if the patient seeks medical attention in such cases, it is difficult to establish a clinical diagnosis without other manifestations of a borrelial infection. It is also difficult to inter-
pret the differences in localization of borrelial lymphocytoma in children and adults. Possibly, one reason may be the different sites of tick bites. It is known that ticks are usually found on vegetation a few centimeters up to one meter above ground. This explains why children more often have tick bites on the head and neck than adults [29], and consequently why EM is localized much more frequently on the face of children than adults and also why ear lobe borrelial lymphocytoma is found predominantly in children. Yet, the localization of the tick bite does not explain why borrelial lymphocytoma on the breast is an exception in children. It seems that there are local tissue factors which support the development of borrelial lymphocytoma on the breast in adults [69]. In the same study, a tick bite was reported by 29 of 36 (81%) patients, a median of 30 days before borrelial lymphocytoma developed. In 24 (83%) of the patients the tick bite was in close vicinity to the location of the subsequent borrelial lymphocytoma, indicating that in the great majority of patients the spirochetes may spread from the site of the bite to the site where the disorder appears. This is well known in EM, which spreads out from the site of inoculation. In addition, borrelial lymphocytoma was located within the EM in 24 of 25 patients with concomitant EM. The onset of EM, the typical early manifestation of Lyme borreliosis, preceded borrelial lymphocytoma in 19 out of 25 cases. Only 3 of 17 (18%) patients with ear lobe borrelial lymphocytoma had mild systemic symptoms, such as moderate headache, general malaise and fatigue, and 8 (47%) patients reported mild local itching; also in 8 (47%) members of this group, enlarged regional lymph nodes were found on examination. In contrast, 12 out of 15 (80%) patients with breast borrelial lymphocytoma reported constitutional symptoms, and all but 1 reported localized discomfort in the region of the areola mammae – the patients were bothered by clothing and the area was slightly painful to touch. Mild itching, breast tension, burning and pain of the thoracic wall on the affected side were complained of by 9 (60%), 8 (53%), 6 (40%) and 4 (27%) patients, respectively. On inspection, the nipples were found to be asymmetric and, with 1 exception, showed no discoloration; they were edematous, painful to touch, and completely hardened in 8 (53%) patients and partly so in 4 patients. Infiltration was regularly found in the area of areola mammae, within a diameter of up to 3 cm. At presentation, 26 of 36 (72%) patients had borrelial antibodies in serum. Routine laboratory blood tests did not reveal any significant abnormality [69].

Among 85 adult patients with solitary borrelial lymphocytoma diagnosed at the Department of Infectious Diseases, University Medical Center Ljubljana, during a period of 15 years [71], there were 36 (42%) females and 49 (58%) males with a median age of 49 (15–74) years. Borrelial lymphocytoma was located on the breast (nipple/areola mammae region) in 68 (80%) patients, on the ear lobe in 8 (9%) and at other locations in 9 (11%). A concomitant EM enabling clinical diagnosis of Lyme borreliosis was registered or reported in 67 (79%) patients. Fifteen (18%) patients had no accompanying symptoms, 34 (40%) reported local and constitutional symptoms, 23 (27%) recounted local symptoms only and 13 (15%) had solely constitutional symptoms. Clinical findings indicating early disseminated borrelial infection were ob-
At the first visit in 12 (14%) patients: 6 (7%) had multiple EM, 1 had meningitis, 1 meningo- radiculitis and arthritis, 1 radiculoneuritis and arthritis, 1 peripheral facial palsy and concomitant meningitis, and 2 arthritis. In addition, 1 of the patients with borrelial lymphocytoma on the breast had ACA. A seropositive response to borrelial antigens was found in only 30 (35%) patients at the initial examination. In 11 of 46 (24%) patients, infection with *B. burgdorferi* s.l. was confirmed by isolation of the agent from lymphocytoma tissue. Eight of 9 (89%) typed borrelial strains were *B. affzelii*, and 1 (11%) was *B. bissettii* [71].

**Diagnosis**

A reasonably consistent diagnosis of ear lobe lymphocytoma is usually possible on clinical grounds that can often be further supported by the presence or a reliable history of EM (usually in the region of the lymphocytoma), the occurrence of other manifestations of Lyme borreliosis, and/or by the demonstration of borrelial infection – usually by positive serology [17, 69, 70]. The isolation rate of *Borrelia* from lesional skin is difficult to assess because of the limited information; nevertheless, it appears to be considerably lower than from the skin of EM, but similar to that from the skin of patients with ACA. According to 2 reports, borreliae were isolated from skin biopsies of lymphocytoma in 4 of 11 (36%) patients and 11 of 46 (24%) patients [70, 71].

**Differential Diagnosis**

Differential diagnosis in ear lobe borrelial lymphocytoma is much more limited than in patients with breast lymphocytoma or lymphocytoma at other (atypical) locations; thus, the need for histologic examination is much greater in patients with lymphocytoma at locations other than the ear lobe [69]. Diagnostic difficulties in ear lobe borrelial lymphocytoma are usually the result of unawareness, whereas the main differential diagnostic possibility in breast lymphocytoma is a malignancy [17, 69]. It is sometimes difficult to distinguish the difference between borrelial lymphocytoma, B cell lymphoma and other pseudolymphomas [17, 69–71, 82, 83].

**Acrodermatitis Chronica Atrophicans**

**Frequency**

ACA is a chronic skin manifestation of Lyme borreliosis seen almost exclusively in Europe [3, 14, 16]. Reports on this skin condition from the USA are rare, and are predominantly limited to descriptions of the manifestation in immigrants from Europe [84, 85].

ACA is much less frequently observed than EM, but is more common than borrelial lymphocytoma [17]. In an epidemiologic study on Lyme borreliosis in southern Sweden, it was found in only 47 of 1,471 (3%) patients who fulfilled the criteria for Lyme borreliosis [29]. The proportion of patients with ACA diagnosed at the Ljubljana
Lyme borreliosis clinic in 1999 is shown in table 1. Similar ratios were also found for the following years [unpublished data].

Etiology
According to the results of PCR and isolation of borreliae from skin, the large majority of ACA cases are caused by *B. afzelii* [76, 86–90]; however, in some patients *B. garinii* and *B. burgdorferi* s.s. have been isolated from the skin lesion [77, 91]. Analysis of the genetic profiles of 22 strains of *B. burgdorferi* s.l. cultivated from skin biopsies of Slovenian patients with ACA lesions revealed 17 (77%) *B. afzelii* strains, 4 (18%) *B. garinii* and 1 (5%) *B. burgdorferi* s.s., indicating that *B. afzelii* is the predominant, but not the exclusive, etiologic agent of ACA [91]. This was confirmed later in a larger study. According to Ružić-Sabljić et al., among 74 isolates from the skin of patients with ACA, 89% were *B. afzelii*, 7% *B. garinii* and 4% *B. burgdorferi* s.s. [38].

Tick Bite
Because of the long incubation time and the long duration of the skin lesions prior to diagnosis, it is understandable that no reliable data exist on the frequency and location of tick bites. Most patients report being repeatedly bitten every year or being, or having been, outdoor workers in endemic areas, but almost no patient specifically recalls a tick bite at the affected body site [67]. The only exceptions are patients in whom ACA was preceded by an EM lesion in the same location several months to many years before. However, such a history is reported by no more than 10–20% of these patients [67, 92], and only some of them recall a tick bite prior to the onset of their EM skin lesion.

Histologic Findings
Findings depend upon the phase of the illness, which is rather academically divided into an early edematous (infiltrative) and a late atrophic phase. The disease starts with a nonspecific perivascular lymphocytic infiltrate. In early lesions, the epidermis is frequently thinned. The upper and middle portions of the dermis show a band-like and perivascular infiltrate consisting of lymphocytes and plasma cells, often in combination with more or less pronounced edema [57]. Dilated blood vessels can be found in the superficial dermis. Periarticular fibroid nodules seen in some patients with ACA are located in the deeper portions of the reticular cutis extending into the subcutaneous fat. Clinically, they resemble rheumatoid nodules, but have a different histologic structure with a homogeneous eosinophilic center surrounded by irregular fascicles of collagen typically arranged in an onion-like concentric fashion. Perivascular infiltrates of lymphocytes and plasma cells are present predominantly in the peripheral parts of the lesion, and fibrosis is present. In the late stage of ACA, cutaneous atrophy with more or less pronounced inflammation is present. The epidermis often has only a few layers of cells. Dilated blood vessels surrounded by lymphocytes and plasma cells can be found in the superficial cutis [57, 92, 93]. In very long-standing atrophic lesions, the inflammatory infiltrates are sparse or may even be absent.
The collagen fibers are strongly reduced in numbers and degeneration of elastic fibers is present [57]. In general, histologically constant findings in active ACA lesions are telangiectases and a lymphocytic infiltrate with a moderate-to-rich admixture of plasma cells [93]. The histopathologic pattern is not diagnostic in itself, but characteristic enough to alert the experienced pathologist [94].

Clinical Characteristics
ACA is a chronic borrelial skin manifestation that in contrast to EM and borrelial lymphocytoma does not disappear spontaneously [16, 17]. It is most often located on acral parts of the body, usually on the extensor part of hands or feet. Initially, the lesion is usually unilateral, later on it may become more or less symmetrical. The initial changes usually manifest themselves several months or years after the introduction of borreliae into the body. Some patients remember having had other signs of Lyme borreliosis – such as EM, neurologic involvement, heart involvement or arthritis before the onset or diagnosis of ACA – but most patients do not. Asbrink et al. [95] reported that in 9 out of 50 patients (18%) spontaneous healing of EM was followed at the same location by ACA lesions after a latency period of 6 months to 8 years. Thus, ACA can be the first and the only clinical sign of Lyme borreliosis [17, 95, 96].

ACA is more often diagnosed in women than in men, and occurs only very exceptionally in children. Patients are usually over 40 years old; in several reports the median value was over 60 years [17, 95, 96]. The onset is insidious, hardly appreciable: mildly bluish-red discoloration of the skin appears (usually on the foot, knee or dorsal part of one of the hands, mostly pronounced over metacarpophalangeal joints) and enlarges very slowly over periods of months to years. The involved region is usually edematous; swelling may occasionally dominate the clinical picture. Initially, the erythema and swelling may vary in intensity. In some patients, the cutaneous manifestations are confined to a heel that is swollen, sometimes discolored and painful. A common typical sign is that one of the feet (sometimes both) gradually increases in size, and the need for larger shoes arises [96]. After the initial months to years, the edema slowly vanishes and gradually atrophy becomes more and more prominent. The skin becomes increasingly violaceous, thin and wrinkled, with prominently visible underlying vessels. When exposed to a cold environment, the skin becomes pronouncedly bluish. The violaceous color also becomes more visible when involved arms or legs are in a dependent position. Healing of damage to the skin is impaired. In some patients, a concomitant migrating erythema, similar to EM, can be seen at the periphery of ACA lesions [96].

Up to one fifth of patients may have fibrous indurations in the involved regions [67, 95]; they may be band-like (usually in ulnar or tibial regions) or nodular (most often prepatellar or in the vicinity of the olecranon). The indurations are more frequent in the initial years of the evolution of ACA than in the late phase with pronouncedly atrophic skin.

In some patients with ACA, sclerotic lesions develop that are clinically and histologically indistinguishable from localized scleroderma (morphea) or lichen sclerosus
et atrophicus. According to Asbrink and Hovmark [81], about 10% of patients with typical inflammatory ACA have sclerotic lesions. In one of the studies from that group, in addition to ACA lesions, lichen sclerosus et atrophicus-like lesions were found clinically in 5 of 32 (16%) examined patients. Four of these patients displayed a histopathologic picture compatible with lichen sclerosus et atrophicus, suggesting a relationship between these 2 skin conditions [93].

Peripheral nerves and joints are quite often involved in the regions of affected skin [16, 17, 95]. An association between ACA and peripheral neuropathy was established in systematic studies in the 1960s and 1970s. In these reports, nearly half the patients with ACA showed signs of predominately sensory polyneuropathy, often most pronounced in the limbs, with cutaneous involvement [96, 97]. After the recognition that ACA is a manifestation of borrelial infection, it became obvious that the majority of untreated patients with ACA have some kind of mild (mostly) or moderate neuropathy, as indicated by clinical and/or neurophysiologic examination [98, 99]. Peripheral nervous involvement is more frequent in the late phase of ACA. Sensory and motor mononeuropathy or polyneuropathy or patchy dysesthesia may develop at the site of the cutaneous lesions. Patients with ACA quite often complain of hyperesthesia/dysesthesia, muscle cramps, weakness in the muscles and/or sensations of heaviness, mainly in the affected limb(s).

In contrast to peripheral neuropathy, there are far fewer data on CNS involvement in patients with ACA. According to published information, CNS involvement and cerebrospinal fluid (CSF) abnormalities are rare [96].

In an investigation of 50 patients with ACA, radiographic examination revealed subluxation and/or luxations of small joints of the hands or feet in 11 (22%) patients; 4 (8%) patients showed periosteal thickening of bones (similar to dactylitis syphilitica in the late phase of syphilis) [95, 96]. The affected joints and bones were usually located underneath the skin lesions. The patients with skeletal involvement had had their disease for a longer period than the patients with skin lesions alone [81, 95, 96]. In 17 of 86 (20%) patients, episodic attacks of joint effusions of a knee were found to have preceded or have occurred simultaneously with the ACA lesions [81]. Periarticular manifestations – such as knee or olecranon bursitis, epicondylitis, retro- or subcalcaneal bursitis, and Achilles tendinitis on the same extremity as the cutaneous involvement – have been reported; they usually precede, but sometimes also accompany ACA [81, 100].

According to some reports, enlarged regional lymph nodes are a common finding in patients with ACA [101]. Some patients report headaches, myalgia and/or arthralgia [92].

**Diagnosis**

For proper diagnosis, appropriate clinical findings should be corroborated with the establishment of borrelial infection. Patients with ACA usually have high serum concentrations of borrelial IgG antibody; the absence of borrelial antibody in a patient with clinically suspicious ACA should be the reason for rechecking the diagnosis and
searching for an alternative explanation, because ‘seronegative’ ACA patients are almost nonexistent [16, 17, 95, 96]. Histologic examination of the involved skin is also needed in suspected ACA, for exclusion of other possibilities and for consolidating the diagnosis of ACA. The histologic findings depend on the duration and severity of the skin involvement; more or less pronounced lymphocytic and plasma cell infiltration of dermis (and sometimes subcutis) is frequently seen, with or without atrophy [17, 95, 96]. Thus, the diagnosis of ACA is based on clinical, serologic and histologic criteria. Routine laboratory tests may find mild-to-moderately elevated erythrocyte sedimentation rates, and raised γ-globulin and C-reactive protein concentrations, but these are usually in normal range and are not of substantial diagnostic help [17, 96]. Diagnosis of ACA can be further supported by the isolation ofborreliae from the involved skin; isolation is successful in about one third of patients who have not previously received antibiotics [91].

Differential Diagnosis

ACA is a relatively frequent borrelial skin manifestation that usually causes many diagnostic problems [17, 95, 96]. It can be the first and only sign of Lyme borreliosis, although a detailed history may reveal antecedent signs of the disease. Previous EM on the extremity on which months to years later a skin lesion compatible with ACA develops has been reported by about 10–20% of patients. In some patients, the history reveals preceding nervous system or joint involvement [17, 95, 96].

ACA is often overlooked or misinterpreted, not only by patients, but also by their physicians. Frequent visits to the doctor without establishing a proper diagnosis are more often the rule than the exception. Difficulties in recognition are usually the result of limited acquaintance with the disease, but can also be a consequence of atypical clinical features. ACA has many differential diagnoses, which partly depend on the stage of the disease. ACA skin lesions on lower extremities are often falsely interpreted to be a result of vascular insufficiency (chronic venous insufficiency, superficial thrombophlebitis, hypostatic eczema, arterial obliterative disease, acrocyanosis, livedo reticularis, lymphedema, etc.), a consequence of old age (‘old skin’) or chilblains. Fibrous nodules are often misinterpreted as rheumatoid nodules and sometimes as skin involvement in the course of gout (tophi) or even as erythema nodosum. It is not unusual for patients with ACA to visit their doctor because of difficulties with shoes associated with deformations of joints, or because of dysesthesias, hyperesthesias or paresthesias. General physicians and the specialists to whom these patients are quite frequently referred often fail to appreciate ACA skin lesions, do not take them seriously or are not able to associate the skin lesions with the involvement of joints and/or peripheral nervous system [17, 95, 96].

ACA should be considered as a possible diagnosis in a patient with bluish-red discoloration of a limb with or without swelling and/or atrophy [67].
Fig. 1. Adult tick on a human host (kindly supplied by Prof. D. Lipsker).

Fig. 2. Cutaneous biopsy of a tick bite. Mouth piece of the tick (yellow) is within the human dermis (kindly supplied by Prof. D. Lipsker).
Fig. 3. Examples of erythema migrans with or without central clearing. Erythema migrans is a slowly expanding red macule or plaque. Usually, but not always, the periphery of the lesion is more visible and can be slightly raised. Many variants exist, including lesions with more inflammation as well as small lesions. In other patients, the erythema is hardly visible (e) (kindly supplied by Prof. D. Lipsker).
**Fig. 4.** Biopsy specimen of erythema migrans. A perivascular and perisudoral lymphocytic infiltrate is common, and some findings will help lead experienced dermatopathologists to the diagnosis. Clues are interstitial spreading, the presence of plasma cells and perineural involvement (kindly supplied by Prof. D. Lipsker).

**Fig. 5.** A redish-blue nodule on the ear lobe is a typical finding in borrelial lymphocytoma (kindly supplied by Prof. D. Lipsker).

**Fig. 6.** Biopsy specimen of borrelial lymphocytoma. A dense perivascular and perisudoral lymphocytic infiltrate is present and perinervous involvement, as well as the presence of some plasma cells, should raise suspicion of borrelial lymphocytoma (kindly supplied by Prof. D. Lipsker).
Fig. 7. Acrodermatitis chronica atrophicans manifests first as a red violaceous inflammatory patch (a), mainly localized on an extremity. Within months to years it atrophies, and thus the skin becomes wrinkly, and superficial vessels become visible through a transparent epidermis and dermis (b, c) (kindly supplied by Prof. D. Lipsker).
Other Skin Manifestations of Potential Borrelial Etiology

Scleroderma circumscripta and Lichen sclerosus et atrophicus

Soon after the recognition that Lyme disease is a multisystem disorder, several dermatologic entities were proposed as candidate manifestations of the disease. EM was accepted very early as being the essential part of the disease, and has been recognized as a clinical hallmark of Lyme borreliosis; somewhat later, ACA and solitary lymphocytoma (lymphadenosis benigna cutis) were clearly demonstrated to be representations of skin manifestations of Lyme borreliosis. Discussions on the potential borrelial etiology of scleroderma circumscripta and lichen sclerosus et atrophicus (sclerotic skin lesions of unknown etiology) have been continuing.

Borrelial etiology of these 2 entities has been implicated on the basis of humoral and cellular immune responses to B. burgdorferi s.l., immunohistologic findings or silver staining, as well as demonstration of borrelial DNA in and isolation of borreliae from lesional tissue. However, findings reported in the literature are markedly discordant. The highest prevalence of antibodies to B. burgdorferi s.l. was found among scleroderma circumscripta patients in Austria (33–54%) and Switzerland (up to 38%), whereas no differences were found in the frequency or level of borrelial antibodies compared with controls in most other European countries [67], the USA [102] and Japan [103]. Lymphoproliferative responses to B. burgdorferi s.l., reflecting the cellular immune response of patients, were elevated in about one third of 39 Austrian patients with scleroderma circumscripta [104], whereas analyses of 52 Swiss patients gave inconclusive results [105]. Because of pronounced limitations in specificity and sensitivity of lymphocyte proliferation assays, these findings cannot be reliably interpreted; therefore, the use of this diagnostic approach for the diagnosis of borrelial infection has been discouraged [14]. There have been several attempts to demonstrate borreliae in the skin lesions. As reviewed by Mullegger [67] in 2004, spirochetes were found by immunohistology or silver staining of lesional tissue from about 20 patients with scleroderma circumscripta and a similar number with lichen sclerosus et atrophicans. Those methods, however, are susceptible to artifacts and interpretation faults, and the findings could not be reproduced by other investigators. In the same review, Mullegger [67] reported that PCR studies of lesional skin gave positive results in 21 of 140 scleroderma circumscripta patients and 15 of 40 lichen sclerosus et atrophicans patients in Europe (particularly Germany and Italy) and Ja-

**Fig. 8.** Even at late and atrophic stages (a), diagnosis of acrodermatitis chronica atrophicans should be suspected histologically as plasma cells remain abundant (b). There are numerous clinical and pathological variants, mimicking granuloma annulare or interstitial granulomatous dermatitis, but the presence of plasma cells and a perineural involvement are rarely missing (kindly supplied by Prof. D. Lipsker).
pan [106], whereas *B. burgdorferi* s.l.-specific DNA could not be amplified in any of 98 scleroderma circumscripta and 48 lichen sclerosus et atrophicans patients in the USA [106, 107]. With the exception of positive PCR findings in some additional patients, nothing substantially new has happened during the past 4 years (2004–2008). Various types of primer have been used in the PCR studies, for example, primers specific for flagellin, ospA, or rRNA genes of *B. burgdorferi* s.l. The negative studies appear to be more comprehensive in that usually more than 1 primer set was applied to a larger collection of cases [67]. Some of the PCR-positive cases were seronegative; however, a positive PCR in a seronegative patient with a manifestation lasting for several months or even years should be regarded with skepticism [14, 108]. The attempt to isolate *B. burgdorferi* s.l. from lesional skin [67] was successful in 5 scleroderma circumscripta patients from Austria and southern Germany [109–111], but failed in most other studies [112, 113]. For lichen sclerosus et atrophicans, the demonstration of *B. burgdorferi* s.l. by cultivation has succeeded in probably only 1 patient so far [114]. The isolation of the causative agent (borreliae) from the lesion is the most reliable demonstration of the etiology of the process, and indicates that culture-positive scleroderma circumscripta and lichen sclerosus et atrophicus lesions were really caused by *B. burgdorferi* s.l. Although such findings might indicate that a subset of scleroderma circumscripta and lichen sclerosus et atrophicus is of borrelial origin, it may well be that this subset of patients in fact have ACA with sclerotic lesions. Sclerotic lesions, which are clinically and histologically indistinguishable from localized scleroderma (morphea) or lichen sclerosus et atrophicus, develop in about 10% of patients with typical inflammatory ACA [93, 96].

**Cutaneous Lymphoma**

A possible association between primary cutaneous B cell lymphomas and *B. burgdorferi* s.l. infection was first suspected because of raised serum borrelial antibody titers in several small series of patients with primary cutaneous B cell lymphoma. This was later supported by more definite evidence, including demonstration of borrelial DNA by PCR in 18–35% of European patients with various types of primary cutaneous B cell lymphoma [67, 115], and by isolation of *B. burgdorferi* s.l. from skin lesions in 2 further patients [116]. In addition, the results of a recent case-control study in Denmark and Sweden suggest an association between *B. burgdorferi* s.l. infection and risk of mantle cell lymphoma [117]. These European results are in contrast to findings in the USA and Asia, where neither molecular [118] nor epidemiologic [119] studies could demonstrate an etiopathogenetic role for *B. burgdorferi* s.l. in cutaneous B cell lymphoma. This discrepancy was interpreted as possibly due to differences between *B. burgdorferi* s.l. strains on the different continents. As shown in ACA, *B. burgdorferi* s.l. can persist in the skin for many years, despite the presence of an active host immune system, possibly by modulation of surface antigens by the spirochete [17]. In analogy to *Helicobacter pylori*-associated MALT (mucosa-associated lymphoid tissue) lymphomas, it is conceivable that the chronic stimulation of
skin-associated lymphoid tissues in response to *B. burgdorferi* s.l. infection may be operative in the pathogenesis of a subset of primary cutaneous B cell lymphoma [67, 120].

The association of borrelial infection and cutaneous B cell lymphomas might have substantial practical consequences concerning management of these lymphomas. Although from a scientific point of view the magnitude and even the existence of this association are still uncertain, everyday clinical practice has been influenced. The European Organization for Research and Treatment of Cancer and the International Society for Cutaneous Lymphoma recently published consensus recommendations on management of cutaneous B cell lymphomas in which the authors stated that ‘because an association between *B. burgdorferi* infection has been reported in a significant minority of European cases of primary cutaneous marginal zone lymphoma, but not in Asian cases or cases from the United States [115, 118, 120, 121], in European areas with endemic *B. burgdorferi* infection, the presence of *B. burgdorferi* should be investigated by serology and polymerase chain reaction techniques on skin biopsy specimens’ [122]. In the article, treatment with antibiotics is proposed for patients with primary cutaneous marginal zone lymphoma and evidence of *B. burgdorferi* s.l. infection [122]. The proposal is based on analogy with antibiotic treatment of gastric mucosa-associated lymphoid tissue lymphomas to eradicate *Helicobacter pylori* [123–125] and on several recent reviews suggesting that primary cutaneous marginal-zone lymphoma associated with *B. burgdorferi* s.l. infection should first be treated with antibiotics before more aggressive therapies are used [67, 126]. However, the efficacy of antibiotic treatment in borrelia-associated primary cutaneous marginal-zone lymphoma is poorly documented [116, 122, 127–131]. Six of 14 (43%) reported patients achieved clinical response after various antibiotic regimens; data on 8 patients suggest that systemic treatment with cephalosporins is superior to oral treatment with high-dose tetracyclines [122].

We may hope that in the next few years more information will be available on the association of *Borrelia* infection and cutaneous B cell lymphoma, which at the moment seems to be operative in a subset of European patients with this type of lymphoma.

**Nervous System Involvement**

*Lyme Neuroborreliosis*

Lyme neuroborreliosis is the involvement of the central and/or peripheral nervous systems in an infection with *B. burgdorferi* s.l.

**Etiology**

In America, all manifestations of Lyme borreliosis, including Lyme neuroborreliosis, are caused by *B. burgdorferi* s.s.
In Europe, Lyme neuroborreliosis is most often caused by *B. garinii*, less frequently by *B. afzelii*, rarely by *B. burgdorferi* s.s. and only exceptionally by other *Borrelia* species such as *B. valaisiana* [132], *B. bissettii* [39–41] or as yet unidentifiable species [133]. The information is based on results of typing borreliae isolated from CSF of patients with Lyme neuroborreliosis [32, 38, 39, 133–136], demonstration of distinct nucleic acid sequences of *Borrelia* species in the CSF [137, 138] and on species-specific serologic responses [132, 133]. In all the approaches, the principal species found in patients with Lyme neuroborreliosis was *B. garinii*, followed by *B. afzelii* (table 2). However, the design of some of the cited studies does not allow one to draw very precise conclusions on the proportion of the etiologic agents, because of several potential biases in the collection of isolates and in their selection for typing.

A comparison of patients with *B. garinii* or *B. afzelii* isolated from CSF found that patients with *B. garinii* infection have a clinical presentation distinct from that of patients with *B. afzelii* [136]. In contrast to the *B. garinii* group, the large majority of the *B. afzelii* group did not fulfill the European criteria for Lyme neuroborreliosis [12, 13]. The findings of the study might indicate that although *B. afzelii* is able to pass through the blood-brain barrier, it has restricted ability to initiate substantial inflammation.

### Table 2. Genospecies of *B. burgdorferi* s.l. as agents of Lyme neuroborreliosis in European patients [modified from 136]

<table>
<thead>
<tr>
<th>Mode of detection</th>
<th>Reference No.</th>
<th>Genospecies</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><em>B. garinii</em></td>
<td><em>B. afzelii</em></td>
</tr>
<tr>
<td>Isolation from CSF</td>
<td>134</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>133</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>135</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>5</td>
<td>1</td>
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<tr>
<td></td>
<td>38</td>
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</tr>
<tr>
<td></td>
<td>136</td>
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<td>38</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>141</td>
<td>58</td>
<td>27</td>
</tr>
<tr>
<td>PCR (CSF)</td>
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<td>11</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>138</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Serology</td>
<td>133</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>132</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
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</tr>
<tr>
<td>Total</td>
<td>190 (63)</td>
<td>69 (23)</td>
<td>34 (11)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages.

1 *B. garinii and B. afzelii.* 2 *B. bissettii.* 3 Inconclusive. 4 *B. valaisiana.*

In Europe, Lyme neuroborreliosis is most often caused by *B. garinii*, less frequently by *B. afzelii*, rarely by *B. burgdorferi* s.s. and only exceptionally by other *Borrelia* species such as *B. valaisiana* [132], *B. bissettii* [39–41] or as yet unidentifiable species [133]. The information is based on results of typing borreliae isolated from CSF of patients with Lyme neuroborreliosis [32, 38, 39, 133–136], demonstration of distinct nucleic acid sequences of *Borrelia* species in the CSF [137, 138] and on species-specific serologic responses [132, 133]. In all the approaches, the principal species found in patients with Lyme neuroborreliosis was *B. garinii*, followed by *B. afzelii* (table 2). However, the design of some of the cited studies does not allow one to draw very precise conclusions on the proportion of the etiologic agents, because of several potential biases in the collection of isolates and in their selection for typing.

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Frequency
Although in the 1980s early neurologic Lyme disease was reported to occur in approximately 10–15% of untreated patients with Lyme disease in the USA [139, 140], the frequency of this manifestation has become less in more recent reports [14, 16, 141], possibly because of bias of ascertainment in the early studies and/or improved recognition and treatment of patients with EM [14]. In the USA, cranial neuropathy is the most common manifestation of early neurologic Lyme disease [142]. Peripheral facial palsy is the most common of the cranial neuropathies, and bilateral involvement of nerve VII may occur [143, 144]. In areas where Lyme disease is endemic, about 1 in 4 patients who present with nerve VII palsy in nonwinter months can be shown to have Lyme disease [145]. By far the most common borrelial CNS disorder in the USA is lymphocytic meningitis [146]; Lyme encephalitis seems to be extremely rare. Although there are no firm incidence numbers, estimates are that no more than 1 patient per 1 million population at risk will develop this disorder in any year [146].

Whereas there are several (minor) differences between American and European Lyme borreliosis, the general trends in the frequency of clinical manifestations in Europe are most probably similar. Among 1,471 patients with Lyme borreliosis in an epidemiologic study in southern Sweden, the most frequent clinical manifestation was EM (77%), followed by Lyme neuroborreliosis (16%) and arthritis (7%) [29]. According to data from the National Institute of Public Health in Slovenia, Lyme neuroborreliosis represented 24% of all cases of Lyme borreliosis in 1988 [30], whereas during the past 10 years about 90% of patients were registered with EM and only 4–7% with Lyme neuroborreliosis [31]. Data from the Ljubljana Lyme borreliosis clinic are shown in table 1. In Slovenia, about 20% of adult patients and 25% of children with peripheral facial palsy are associated with Lyme borreliosis [147, unpublished data].

Tick Bites
In meningopolyneuritis (Garin-Bujadoux-Bannwarth syndrome), the most prominent clinical manifestation of Lyme neuroborreliosis in adult European patients, between one and two thirds of patients remember arthropod bites preceding the onset of the neurologic involvement [148]. According to the study of Kristoferitsch [149], a median of 3 weeks (range 1–18 weeks) elapses from the bite to the onset of neurologic symptoms. However, the causal relationship between an individual tick bite and Lyme neuroborreliosis is rather uncertain; it is most reliable when a bite is followed by an EM. This skin lesion has been reported to precede or sometimes accompany meningopolyneuritis in 34–64% of patients [148–151], and has been found in 18 of 33 (55%) patients with B. garinii or B. afzelii isolated from CSF [136]. Close topical association between the cutaneous region involved by the EM (and thus by the tick bite) and the initial radicular lesion has been established in European patients [148, 151–
156], in contrast to American patients in whom no such association was found [146, 157].

**Histology**
Knowledge of histopathologic findings in the CNS is limited. In patients with meningoradiculoneuritis, lymphocytic involvement of leptomeninges, ganglia, and afferent and efferent rootlets is present. The CNS may show focal microgliosis [57, 158, 159].

In peripheral neuropathy accompanied by ACA, lymphocytes and plasma cells are present around blood vessels in the perineurium, with occasional sparse lymphocytes in the vessel wall. Vessel walls show no signs of necrosis, but may become thickened and obliterated; thrombosis may develop [57]. Fibers within the nerve eventually lose myelin. The most striking finding is axonal degeneration [57, 98].

Neuropathologic and neurophysiologic evidence in patients with peripheral nervous system involvement resulting from borrelial infection [146], and in experimentally infected rhesus macaque monkeys [160], indicates that this infection causes changes in multiple peripheral nerves that are affected individually (mononeuropathia multiplex type of involvement) as a consequence of local damage to vessels (but without evidence of vessel wall necrosis, the usual requirement to be termed vasculitis) [146].

**Clinical Characteristics**
Early Lyme Neuroborreliosis
Lyme neuroborreliosis may appear early, during the first few weeks or months, or late in the course of Lyme borreliosis. The initial clinical report of early Lyme neuroborreliosis was in 1922 [161], although it was not classified as such until more than 65 years later. Early Lyme neuroborreliosis typically comprises lymphocytic meningitis and involvement of cranial and peripheral nerves [3, 156, 157, 162]. Usually the most pronounced clinical symptom is pain as a result of radiculoneuritis. The pain is usually severe and most pronounced during the night; patients may be deprived of sleep for several weeks. When located in the thoracic or abdominal region, the pain is often belt-like. Radicular pain is seen more often in European than in American patients, and is usually more frequent and more pronounced in adults than children [16, 157, 162]. Although painful radiculoneuritis is clinically the most typical and pronounced manifestation of peripheral nervous system involvement in adults with early European Lyme neuroborreliosis, other types of peripheral nerve involvement may be present. Involvement of motoric nerves may lead to paresis, usually asymmetric [162, 163] and, in contrast to general opinion, not always clinically prominent [164].

Patients with borrelial meningitis usually suffer from mild intermittent headache, but in some patients the headache may be excruciating. In adult European patients, there is often no fever, nausea is usually mild or absent, and vomiting is frequently absent. Meningeal signs are usually only mildly expressed or may be absent [162, 163]. Physicians not used to patients with borrelial meningitis are often surprised by ab-
normal CSF findings. These comprise lymphocytic pleocytosis up to several hundred \( \times 10^6 \) cells/l, normal or slight-to-moderately elevated protein concentration, and normal or mildly depleted glucose concentration. Overall, the course of borrelial meningitis resembles relatively mild but unusually protracted viral meningitis with intermittent improvements and deterioration [3].

Any cranial nerve may be affected in early Lyme neuroborreliosis, but facial nerves are by far the most frequently involved (about 80%), resulting in unilateral or bilateral peripheral facial palsy [3, 143, 145–147, 157]. Patients with borrelial peripheral facial palsy often show lymphocytic pleocytosis, even those without any sign or symptom of meningitis [3, 16, 146, 147]. According to general opinion, prognosis of borrelial peripheral facial palsy is good not only in antibiotic-treated patients, but also in those who are not treated [16, 157, 163]. According to data from the USA, more than 90% of patients show improvement leading to, or close to, normal [143, 145, 146]. However, in clinical and neurophysiologic examinations, mild sequelae were found in as many as half of Swedish children who had peripheral facial palsy associated with Lyme neuroborreliosis 3–5 years earlier [165]. Results from another Swedish study revealed that one fifth of children with acute facial palsy have permanent mild-to-moderate dysfunction of the facial nerve, but that other neurologic symptoms or health problems do not accompany the sequelae of the facial palsy, and that treatment of Lyme neuroborreliosis seems to have no correlation with clinical outcome of peripheral facial palsy [166]. Shortly after onset of symptoms, intrathecal antibodies may not be detectable and CSF pleocytosis may be absent in patients (predominantly children) with isolated facial palsy [3]. Patients who present with peripheral facial palsy as the sole neurologic manifestation of Lyme borreliosis only very rarely have (a history of recent) EM. Involvement of most other cranial nerves has been described, but particularly III (oculomotor), VI (abducens) and VIII (vestibulo-auditory). Critical appraisal of the literature suggests that the involvement of some cranial nerves (for example, optic nerve) occurs extremely rarely, if ever [146, 167].

In adult European patients, early Lyme neuroborreliosis usually begins gradually with increasing pain, later on accompanied by palsy and other neurologic signs and symptoms that will, if untreated, not diminish for many weeks [3]. In children, painful radiculoneuritis is rare, but isolated meningitis and peripheral facial palsy are more common than in adults. In Slovenia, about 20% of adult patients and 25% of children with peripheral facial palsy have associated Lyme borreliosis [147, unpublished data]. Pseudotumor cerebri is an unusual manifestation of Lyme neuroborreliosis seen primarily in children [168, 169].

Late Lyme Neuroborreliosis

With the exception of peripheral neuritis in association with ACA, late Lyme neuroborreliosis is most probably very rare. Peripheral neuritis occurs in more than half of patients with long-lasting (advanced) ACA skin lesions [162, 170]. Critical appraisal of the literature suggests that peripheral neuritis without ACA is an extremely rare
condition; that is, among patients with peripheral neuropathy, the proportion of those with Lyme neuroborreliosis is negligible.

Up to 10% of European patients with untreated meningopolyneuritis (Garin-Bujadoux-Bannwarth syndrome) develop features of disseminated encephalomyelitis that may in some respects resemble those seen in multiple sclerosis [162].

Subtle encephalopathy has been reported predominantly by American authors [16, 157, 171].

**Diagnosis**

Lyme neuroborreliosis may appear during the first few weeks or months after infection or not until late in the course of Lyme borreliosis. Early Lyme neuroborreliosis, which is better defined and much more frequent than late Lyme neuroborreliosis [1, 3, 12, 13, 18], typically comprises lymphocytic meningitis and involvement of cranial and peripheral nerves [157]. Clinical diagnosis is straightforward when the triad is complete or when 1 or more manifestations of the triad are associated with the presence of or a reliable history of EM [1, 3, 12, 13, 18, 157].

The diagnosis of early Lyme neuroborreliosis is normally based on clinical characteristics, the presence of lymphocytic pleocytosis and demonstration of CNS borrelial infection, as evidenced by seroconversion, intrathecal borrelial antibody production, isolation of borreliae from CSF samples or demonstration of borrelial DNA in CSF samples [12, 13, 108, 136]. In practice, seroconversion is rarely found to be a useful criterion because by the time that neurologic signs appear, the majority of patients are seropositive. In addition, seroconversion confirms recent borrelial infection, but it does not confirm CNS involvement. The main limitations of PCR for demonstration of borrelial DNA in CSF samples are low sensitivity, the possibility of false-positive findings and the lack of procedure standardization [13, 108]. Isolation of the etiologic agent from patient samples is the most reliable method for diagnosis of borrelial infection, and isolation of the etiologic agent from CSF is the most reliable method for diagnosis of Lyme neuroborreliosis. Isolation also provides live microorganisms that can be further characterized; however, isolation from CSF samples is a markedly low-yield procedure, and results are obtainable only after several weeks [1, 3, 108, 136, 172]. Demonstration of intrathecally synthesized borrelial antibodies has generally been used for establishment of a diagnosis of Lyme neuroborreliosis in everyday European clinical practice. The problem with this diagnostic approach is insensitivity during the first few weeks of CNS involvement and long persistence of the antibodies; intrathecal borrelial antibody production can be detected for several months or years, even after appropriate antibiotic treatment [12, 13, 108, 136].

A diagnosis of Lyme neuroborreliosis involving the peripheral nervous system is even more difficult because of the limited possibilities of demonstrating borrelial infection of peripheral nerves. For a reliable diagnosis, (an objective) proof of the involvement of the nervous system is necessary (clinical, neurophysiologic and neuropathologic approaches are generally available for demonstration of peripheral nervous
system involvement), together with demonstration of (active) borrelial infection (usu-
ally the only available approach in this group of patients is demonstration of borrelial
antibodies in serum; however, serology has many limitations) and proof that the bor-
relial infection really is the cause of the peripheral nervous system involvement. Be-
cause of the many obstacles with all 3 requirements (the second and especially the
third are even harder to fulfil than the first), it is obvious that reliable diagnosis of pe-
ripheral nervous system involvement as a consequence of borrelial infection pro-
foundly depends upon the concomitant presence of CNS Lyme neuroborreliosis (in
which borrelial CNS involvement can be demonstrated by corresponding findings in
CSF examination) and/or the presence of some other manifestations of Lyme borreli-
osis such as EM (for example, in patients with cranial nerve involvement) or ACA.

**Differential Diagnosis**

Differential diagnosis comprises a list of differential diagnoses for each main mani-
festation of Lyme neuroborreliosis [meningitis, radiculo(neuritis), cranial nerve in-
volvement and so on]. However, an exact history and meticulous clinical examination
often substantially narrow the differential possibilities.

**Cardiac Involvement**

**Lyme Carditis**

Lyme carditis is heart involvement related to a *Borrelia* infection that usually presents
with the acute onset of varying degrees of intermittent atrioventricular (A-V) heart
block, sometimes in association with clinical evidence of myopericarditis.

**Frequency**

Information on the relative frequency of Lyme carditis is incomplete. Lyme carditis had
earlier been reported to occur in 0.3–4% of untreated European patients with Lyme bor-
reliosis and in 4–10% of corresponding patients in the USA [14, 173–175]. However, the
frequency of this manifestation is reported to be much lower in more recent series [176,
177]. No evidence of carditis was found among 233 cases with definite Lyme disease in
2 prospective studies on the evaluation of a recombinant OspA vaccine in the USA [178,
179]; in a Swedish epidemiologic study, only 7 of 1,471 (0.5%) patients diagnosed with
Lyme borreliosis had Lyme carditis [29], and at the Ljubljana Lyme borreliosis clinic,
where between 600 and 900 patients with different manifestations of Lyme borreliosis
are diagnosed each year, Lyme carditis represents up to 0.5% of cases [unpublished
data]. This diminution in the frequency of Lyme carditis, like the one observed for acute
neurologic manifestations, could be the result of a bias of ascertainment in early studies
and/or improved recognition and treatment of patients with EM [14].
Etiology
There are no direct data on the Borrelia species causing Lyme carditis. In the USA, Lyme carditis should be caused by B. burgdorferi s.s., the only species causing Lyme borreliosis in humans there; in Europe, the main candidates are B. afzelii, B. garinii and B. burgdorferi s.s. A heart isolate of 1990 [180] was later identified as B. burgdorferi s.s., but this has not been published.

Tick Bites
In a series of 20 patients with Lyme carditis presented by Steere et al. [174], 2 reported a tick bite, and in a series of 66 European patients with Lyme carditis collected by van der Linde [175], tick bite prior to the onset of Lyme carditis was recalled by 31 (47%) patients.

Histology
Information on histologic findings is limited, and is based on rare cases of heart tissue examination obtained at autopsy and on material acquired by endomyocardial biopsy. Histopathologic findings include an interstitial infiltrate of lymphocytes and plasma cells involving the myocardium, pericardium and endocardium. Aggregates of lymphocytes may be seen in the myocardium. Muscle fibers are usually intact, but individual myocardial fibers show sporadic infiltration with lymphocytes. The endocardium shows band-like infiltrates of lymphocytes and plasma cells [174, 175, 181, 182]. Examination of the heart conducting system in 1 patient revealed localized edema and slight lymphocytic infiltration of sinoatrial and A-V nodes, fibers with contraction band necrosis in an edematous area of the sinoatrial node, focal edema in the bundle of Hiss, and a fibrotic lesion in the left bundle branch [57]. Vasculitis involving the small and large intramyocardial vessels can be present [173]. The small vessels frequently show endothelial cell edema, whereas large vessels show adventitial infiltrates with loose reticulin and increased collagen deposition [158, 183]. Spirochetal forms located inside and near cellular infiltrates, between muscle fibers, and in the myocardium [158, 184, 185] have been found in endomyocardial biopsy [184] and autopsy specimens [181]. They have also been cultured from biopsy specimens [180]. Whether the presence of live borreliae is required for continued disease or whether the disease results (predominantly) from immune-mediated mechanisms remains to be determined [173].

Clinical Characteristics
Lyme carditis typically occurs between June and December, usually within 2 months (range 4 days–7 months) after the onset of infection, and more often affects men than women [14, 174, 176, 186]. The cardiac manifestations are often coincident or in close temporal proximity with other features of Lyme borreliosis such as EM [174, 186, 187], Lyme neuroborreliosis [174, 187] or arthritis [174, 185]. In a large European series of patients who had Lyme carditis, EM was found in 67%, joint complaints in 51% and Lyme neuroborreliosis in 27% [185]. However, there are patients who present with
Lyme carditis (usually with complete heart block) as the sole manifestation of Lyme borreliosis.

Cardiac involvement may be asymptomatic. When symptomatic, the most common complaints include light-headedness, syncope, dyspnea, palpitations and/or chest pain [173]. Patients with symptomatic cardiac involvement associated with Lyme borreliosis usually present with the acute onset of varying degrees of intermittent A-V heart block, sometimes in association with clinical evidence of myopericarditis [174, 176, 183, 185–187]. Electrophysiologic studies have usually demonstrated block occurring above the bundle of Hiss, often involving the A-V node, but heart block may occur at multiple levels [174, 176, 185]. Cases of pericarditis, endocarditis, myocardial infarction, coronary artery aneurism, QT-interval prolongation and congestive heart failure have also been associated with Lyme borreliosis [173], but for some of these the causal association remains uncertain.

Lyme carditis is characterized by changing A-V blocks as a result of conduction disturbances [18, 174, 176, 185]. The course is usually favorable. In both antibiotically treated and untreated patients, complete heart block usually disappears within a week, whereas symptoms of heart involvement and ECG abnormalities usually vanish within 3–6 weeks [14, 174, 176, 185]. Hospitalization and permanent ECG surveillance are needed in patients who have first-degree A-V block with P-Q interval longer than 0.30 s, second- or third-degree A-V blocks, quickly changing A-V blocks or hemodynamically important arrhythmias [3, 176, 185]. In a case of complete heart block, insertion of temporary heart pacemaker may be life-saving. Complications are rare and include partial improvement of conduction disturbances with a consequent persistent (first-degree A-V) block, and possible induction of chronic cardiomyopathy [180]. Complete heart block would be the only reason for a lethal outcome in patients with Lyme borreliosis, and fortunately it is an extremely rare event [3, 16, 188].

Diffuse ST segment and T wave changes on surface electrocardiograms were noted in 65% of patients in the series of patients with Lyme carditis of Steere [174]; although nonspecific, these findings may indicate diffuse myocardial involvement [173]. Myocardial involvement may lead to cardiomegaly, left-ventricular dysfunction or clinical congestive heart failure and is thought to be present in 10–15% of patients with Lyme carditis [185, 186]. In most cases, myocardial dysfunction is mild and self-limited [174, 189].

It has been suggested that borreliae may play a causative role in chronic heart failure. This hypothesis originated from a 1990 Austrian case report on a 54-year-old man with a 4-year history of dilated cardiomyopathy, high levels of B. burgdorferi s.l. IgG antibodies in serum, and isolation of B. burgdorferi s.l. from an endomyocardial biopsy specimen [180]. The hypothesis was supported in some later reports on a limited number of patients [190, 191], whereas in other reports, apparently more convincing ones, it was not backed up [192]. Further studies are warranted to clarify the potential role of B. burgdorferi s.l. in acute and chronic congestive heart failure [173]. According to the recent IDSA guidelines [14], severe or fulminant congestive heart
failure or development of valvular heart disease are not associated with Lyme disease [176] and, at least in the USA, there is no convincing evidence that Lyme disease is a cause of chronic cardiomyopathy [192, 193].

**Diagnosis**

Lyme carditis usually presents with the acute onset of varying degrees of intermittent A-V heart block, sometimes in association with clinical evidence of myopericarditis [174, 176, 183, 185–187].

Diagnosis of Lyme carditis should be based on demonstration of heart involvement manifested by either conduction disturbances (established by electrocardiographic and/or electrophysiologic findings) and/or myo(peri)carditis (demonstrated pathohistologically in endomyocardial biopsy specimens, or suggested by electrocardiographic, echocardiographic and/or MRI findings), and corroborated with the demonstration of borrelial infection by 1 or more of the following: (1) isolation of borreliae from an endomyocardial biopsy specimen and/or demonstration of borrelial DNA in the specimen; (2) by seroconversion to borrelial antigens; (3) by the presence of *Borrelia* antibodies in serum; (4) by the presence of EM and/or Lyme neuroborreliosis together with or in close temporal proximity to Lyme carditis. In practice, there are several obstacles to the proposed diagnostic approaches. Endomyocardial biopsy is not a routine diagnostic procedure in patients with suspected Lyme carditis because the potential yield is suboptimal, due to the focality of myocarditis, and the procedure carries an inherent risk [173]. In addition, seroconversion is rarely found to be a useful criterion, because at the time of the appearance of Lyme carditis the majority of patients are seropositive [175, 176]. Moreover, seroconversion confirms recent borrelial infection, but does not confirm heart involvement and, in addition, seropositivity cannot distinguish between recent and delayed infection or between active and past infection. In practice, therefore, the most reliable method of demonstrating borrelial infection to enable the interpretation of heart involvement to be Lyme carditis is the presence of another typical manifestation(s) of Lyme borreliosis. Because Lyme carditis usually occurs within 2 months after onset of infection, EM [174, 186, 187] or Lyme neuroborreliosis [174, 187] quite often occur concomitantly or in close proximity to the carditis. In fact, concurrent EM, which enables a reliable diagnosis of early Lyme borreliosis, is present in up to 85% of cases [186].

The diagnosis of Lyme carditis should be further substantiated by the absence or exclusion of other (obvious) explanations for cardiac abnormalities.

**Differential Diagnosis**

The differential diagnosis of Lyme carditis is extremely broad and includes diseases that can cause conduction disturbances, endomyocarditis and pericarditis that may be due to infectious agents (viral, bacterial, mycotic and parasitic), as well as noninfectious causes. Because of a large number of potential other causes, the attribution of rhythm disturbances to the infection is highly problematic [175], and is usually sup-
ported with only indirect demonstration of infection (often limited to demonstration of specific antibodies in serum). The clinical manifestations of other diseases, specific laboratory tests, epidemiologic data and general information, such as age and state of health at the onset of the illness, can help in differentiating from Lyme carditis [175].

### Joint Involvement

**Lyme Arthritis**

Lyme arthritis, the main joint manifestation in the course of Lyme borreliosis, is an inflammatory arthritis associated with *B. burgdorferi* s.l. infection. It is predominantly a monoarticular or oligoarticular form of arthritis, and typically involves the knee.

**Frequency**

Although Lyme arthritis was reported to occur in 60% of untreated patients with Lyme disease in the USA about 20 years ago [194], the frequency of this manifestation has been ≤10% in recent series [141, 178, 179, 195], probably because of improved recognition and earlier treatment of patients with early Lyme disease [14]. However, this is in contrast to the much higher frequency of arthritis among Lyme disease cases reported to the CDC [142]. For example, during 2003–2005, the CDC received reports of 64,382 Lyme disease cases. Records for 32,095 (50%) of these patients met the criteria for evaluation of symptoms. A history of EM was reported for 70%, arthritis for 30%, facial palsy for 8%, radiculopathy for 3%, meningitis or encephalitis for 2%, and heart block for <1% [142]. Possible explanations for the higher proportion of arthritis cases in national reporting include reporting bias favoring the tabulation of seropositive Lyme disease cases, confusion between arthritis and arthralgia by the treating healthcare provider, and inaccuracy of Lyme disease diagnosis. In addition, surveillance report forms differ by state, and reported seropositivity in support of a diagnosis of Lyme arthritis is not necessarily based on recommended two-tier testing [14, 142].

The existence of Lyme arthritis in Europe was recognized only after the reports from the USA. Although joint abnormalities in patients with ACA had been repeatedly described in the European dermatologic literature since 1922 [100], and even the term ‘akrodermatitis atrophicans arthropathica’ had been proposed [196], a causal relation of joint and bone abnormalities with ACA had been questioned [101]. Joint symptoms had been mentioned in case reports of patients in Europe with erythema chronicum migrans [100, 197] and lymphocytic meningitis [100, 198, 199], yet the association of arthritis with EM and neurologic disease was not recognized until Lyme arthritis was described in the USA [5].

From the very beginning of understanding that arthritis is a manifestation of Lyme borreliosis, there has been a firm conviction that this is less common in Europe than in the USA [100]. However, information on the (relative) frequency of Lyme ar-
arthritis in Europe is limited. In an epidemiologic study in southern Sweden, 98 of 1,491 (7%) patients diagnosed with Lyme borreliosis had Lyme arthritis [29], and among Lyme borreliosis cases at the Ljubljana Lyme borreliosis clinic arthritis is present in 2–5% of adult patients [unpublished data]. However, in a nationwide survey in Germany where 3,935 patients were reported to be diagnosed with Lyme borreliosis in a 1-year period (March 1998 to February 1999), the most frequent clinical manifestation was EM in 50.9% of the patients, 24.5% had Lyme arthritis (14.7% mono- or oligoarthritis, 9.8% polyarthritis) and 18.4% had neuroborreliosis [200]. Possible explanations for the relatively high proportion of Lyme arthritis in that survey, especially in comparison with the frequency of neuroborreliosis, could be at least partly similar to those for the national reporting system in the USA.

**Etiology**

Since the isolation rate of borreliae from joint fluid and synovia is notoriously low [108], data on the etiology of Lyme arthritis are based predominantly on detection and typing of borrelial DNA in synovial fluid or synovial tissue by PCR. Information on the etiology in Europe is limited. Because of the apparently (much) higher prevalence of Lyme arthritis in the USA than in Europe, there was a conviction that in Europe the arthritis was due to infection with *B. burgdorferi* s.s., the strain causing Lyme borreliosis in North America. However, the association of European Lyme arthritis and *B. burgdorferi* s.s. does not appear to be firm. PCR-based analyses of samples from European patients with Lyme arthritis gave inconsistent results, indicating that *B. burgdorferi* s.s. appears to be either the sole, the major or just one of the pathogens involved. In the Netherlands, borrelial DNA was detected in synovial tissue and synovial fluid in 3 of 4 patients with Lyme arthritis; in all 3, *B. burgdorferi* s.s. was identified by reverse line blot [201]. However, among 10 consecutive PCR-positive patients with Lyme arthritis from northeastern France, 2 species were identified in synovial samples: *B. burgdorferi* s.s. in 9 cases and *B. garinii* in 1 case [202]. The conclusion that *B. burgdorferi* s.s. is the principal but not the only *Borrelia* species involved in Lyme arthritis was further substantiated by another report of 2 cases of treatment-resistant Lyme arthritis, in which DNA amplification of the flagellin gene followed by dot-blot hybridization in the synovial fluid identified *B. garinii* as the causative agent [203]. A study from Munich, using ospA type-specific PCRs, found *B. burgdorferi* s.l. DNA in synovial fluid in 13 of 20 patients with the diagnosis of Lyme arthritis (positive serologic findings and fulfilled clinical criteria): *B. burgdorferi* s.s. was established in 27%, *B. afzelii* in 33% and *B. garinii* in 40%. The conclusion of the authors was that in Europe *B. burgdorferi* s.l. strains causing Lyme arthritis are considerably heterogeneous, and that there is no prevalence of particular genospecies or OspA types among these strains [204]. Similar results have been reported by Eiffert et al. [205], where PCR was used to identify a part of the ospA gene in 7 of 11 synovial fluid samples of patients with Lyme arthritis: sequencing the amplified DNA found *B. burgdorferi* s.s. in 3 patients, *B. garinii* in 3 patients and *B. afzelii* in 1 patient.
**Pathogenesis**

In spite of abundant research, several issues in the pathogenesis of Lyme arthritis remain obscure. As in other manifestations of Lyme borreliosis, the presence of the causative agent (most information on Lyme arthritis is for *B. burgdorferi s.s.*) and immune mechanisms are involved; in Lyme arthritis, the immune mechanisms are probably even more important than in most other manifestations of Lyme borreliosis. After transmission in the bite of an infected tick, the borreliae change expression of several immunostimulatory outer-surface lipoproteins thought to play a role in dissemination to synovial tissue and in the pathogenesis of inflammation in the joint itself [206]. *B. burgdorferi* s.l. does not produce proteases, and therefore does not cause the rapid joint destruction seen in classic septic arthritis [207]. The acute arthritis results from borrelia-induced infiltration of mononuclear cells into the synovial tissue and the accumulation of neutrophils, immune complexes, complement and cytokines in the synovial fluid. In untreated Lyme arthritis, host factors involved may include TLR2 and MyD88 [208]. Other arthritogenic factors may comprise adhesion molecules such as P66 that bind the extracellular matrix, decorin-binding proteins A and B, Bgp and BKK [209]. Matrix metalloproteinases may be involved in the pathogenesis of erosive features in the joint in long-standing infection, and possibly also in antibiotic-refractory arthritis [210, 211].

A small subset of patients who have already received standard antibiotic treatment may have persistent Lyme arthritis. In general, 3 main models for the immunopathogenesis of antibiotic-refractory Lyme arthritis have been proposed [207]: persistent infection, T cell epitope mimicry and bystander activation. None of them has enabled a reliable and complete explanation for all patients: the etiology is most probably multifactorial and may vary from patient to patient [207].

**Histologic Findings**

The pathologic alternatives in Lyme arthritis correspond to a nonspecific synovitis.

The inflammatory infiltrate shows predominately lymphocytes, often in follicular structures with incomplete germinal centers, and plasma cells. Mast cells can easily be found in the areas of increased vascularization [57, 158, 212].

Chronically inflamed hypertrophic synovial villi with deposition of fibrinaceous eosinophilic material in the synovia are seen in specimens of synovectomized patients. Unlike other nonspecific inflammation of joints, in Lyme arthritis the synovium is rarely scarred. Obstruction of small blood vessels with synovial fibrin deposition is quite often seen [57, 100, 212, 213].

**Clinical Characteristics**

The spectrum of articular manifestations in Lyme arthritis can be, rather academically, classified into 3 categories: (1) arthralgias (musculoskeletal pain) without objective findings; (2) arthritis (intermittent or chronic) with objective clinical findings; (3) chronic joint and bone involvement under the affected skin in ACA [100]. The main
and the most important rheumatic manifestation of Lyme borreliosis is arthritis, and
the most elusive presentation is arthralgia that may precede, accompany or follow ar-
thritis, but may sometimes be the only rheumatic manifestation of Lyme borreliosis.

The most complete description of the clinical evolution of Lyme arthritis is in the
report by Steere et al. [194] on 55 untreated patients who had EM during the years 1976–
1979, that is, before antibiotic treatment of Lyme disease was established in the USA. Of
these 55 patients, 11 (20%) had no musculoskeletal symptoms after the resolution of
EM, arthritis developed in 34 (62%; in about half, the arthritis was preceded by arthral-
gias), and arthralgias alone were seen in 10 (18%) patients. Those with arthralgias had
brief episodes of pain in joints, tendons, enthesis, bones or muscles without objective
signs of inflammation. The symptoms tended to be migratory, with onset from 1 day
to 8 weeks (mean, 2 weeks) after the onset of EM. Symptoms lasting from 1 month to
as long as 6 years (mean, 3.1 years) had a relapsing/remitting pattern, and were often
accompanied by fatigue [194]; however, patients with arthralgias associated with Lyme
borreliosis (who may or may not have Lyme arthritis) generally did not experience
widespread chronic pain [207]. No corresponding European report on the natural his-
tory of a large number of untreated EM patients exists, most probably as a consequence
of antibiotic treatment of EM which has been widely practiced in Europe since 1951
[214], long before the complete clinical picture of Lyme borreliosis (including arthritis)
and the etiology of the disease were established. It has been reported that only 1 of 16
Swedish patients developed arthritis after spontaneous healing of EM [215].

The succession or coexistence of intermittent attacks of musculoskeletal pain and
arthritis have also been reported in Europe, and have been interpreted as particular-
ly indicative of Lyme arthritis [100]. In 25 of 65 patients with Lyme arthritis in
Germany [216], episodes of severe pain in joint and periarticular sites had either pre-
ceded arthritis for several weeks or months (8 patients), had preceded and continued
after arthritis (5 patients), or had developed as late as arthritis (12 patients). Particular
episodes lasted from some hours to several days, and were separated by days to months
of remission. Episodes of arthralgias sometimes alternated with attacks of arthritis.
Predominantly large but also small joints were affected in an often migratory pattern,
but commonly only 1 or 2 sites were affected at any one time [100].

Arthralgias are a relatively frequent complaint early in the course of Lyme bor-
reliosis, in patients with EM before therapy and in some patients even after antibi-
otic treatment, and more commonly accompany EM in the USA than in Europe. In
the early studies, arthralgias were reported in as many as 48% of patients with EM in
North America [60], but in only 22% at the most in European patients [53]. In a group
of culture-positive adult patients in New York state with EM caused by B. burgdorferi
s.s., arthralgias were reported in 48 of 119 (40%) prior to treatment, whereas in Slo-
venian patients with B. afzelii isolated from the skin lesion, the frequency was only 23
of 85 (27%) [15]. In a study in 1994 on 231 European patients with culture-confirmed
EM at the Ljubljana Lyme borreliosis clinic, 27 (12%) patients reported arthralgias
that as a rule were mild-to-moderately severe [55]. Arthralgias may be present in some
patients after standard antibiotic treatment of EM, usually during the first few weeks after treatment, but normally vanish within 6 months after treatment. Whether they had arthralgias or not, patients treated for solitary EM with standard courses of antibiotics only very exceptionally develop later objective manifestations of Lyme borreliosis, including arthritis [14].

Lyme arthritis affects both children and adults. Several patients remember tick bite(s); however, temporal association between an individual tick bite and the onset of Lyme arthritis is often difficult to assess and is most reliable in patients who develop EM at the site of the bite. In patients from North America who had EM but did not receive antibiotic treatment and were followed up for a mean duration of 6 years (range 3–8 years), arthritis occurred from 4 days to 2 years after disease onset (mean 6 months) [194]. In a European series of patients [216], the period from tick bites or EM to the onset of arthritis ranged from 10 days to 16 months (median, 3 months). However, there are case reports of patients in whom tick bite and EM had preceded arthritis for much longer periods of time [100]. Since the latent period between infection and onset of Lyme arthritis is highly variable and mostly runs for several months, there is no seasonal peak in the occurrence of Lyme arthritis [100].

Lyme arthritis can be preceded or accompanied by other manifestations of Lyme borreliosis. In the initial description of Lyme disease in the USA, 13 of 51 (25%) patients reported having had EM before they developed arthritis [5]. Of 65 German patients with Lyme arthritis, 40 were without history of well-defined Lyme borreliosis or concurrent extra-articular disease manifestations, whereas 25 (38%) had at least 1 additional manifestation including EM (21 patients, 32%), Lyme neuroborreliosis (14 patients, 22%), ACA (5 patients, 8%) and carditis (1 patient) [100]. In a 1-year nationwide survey in Germany, 32% of patients with Lyme arthritis remembered having had an EM [200]. An epidemiologic study of Lyme borreliosis in southern Sweden found that among 98 patients diagnosed with Lyme arthritis, the arthritis was the sole main manifestation in 65 (66%) patients, whereas in the others it was associated with additional manifestation(s) such as EM (10 patients), Lyme neuroborreliosis (8 patients), ACA (8 patients) and borrelial lymphocytoma (1 patient); 6 patients with arthritis had at least 2 additional main manifestations of the disease [29].

Several European authors have emphasized that Lyme arthritis often begins in the extremity that was affected by a tick bite or EM [216–218]; for example, this correlation was observed in 15 of 18 patients in whom EM had preceded arthritis [216]. Such an observation has not been reported from the USA.

Lyme arthritis usually consists of intermittent attacks of inflammation of one or a few joints and is often preceded by intermittent migratory joint pain. Joint involvement is usually asymmetric, onset of arthritis is acute and with effusion, and skin over the affected joint is warm but of normal color [16]. The arthritis is frequently mono- or oligoarticular, only rarely polyarticular. In a European series of 65 patients with Lyme arthritis [100], the course was intermittent in 55 (85%), initially intermittent and later chronic in 4 (6%) and unremitting (chronic) in 6 (9%); the pattern of
Joint involvement was monoarticular in 39 (60%; onset of arthritis was monoarticular in as many as 55 patients), oligoarticular in 21 (32%) and polyarticular in 4 (6%) patients. One patient had isolated heel swelling [100].

Large joints are predominantly involved, most often the knee. In 28 patients with a relapsing/remitting course of Lyme arthritis presented in a classic series by Steere et al. [194], the knee was involved in all but 1 patient; shoulder, ankle, elbow, temporomandibular joint, wrist and hip were affected in the range of 28–43%, and metacarpophalangeal, proximal interphalangeal, distal interphalangeal and metatarsophalangeal joints were involved in 3 (11%) patients. One patient had sternoclavicular involvement. Similarly, in the European series of 65 patients with Lyme arthritis reported by Herzer [100, 216], involvement of the knee was by far the most common (outnumbering the frequency of any other joint involvement by ≥2.5 times), followed by ankle, wrist, finger, toe and elbow (seen in 10–30% of patients); involvement of midtarsal joints, sternoclavicular joint and hip occurred only exceptionally. Heel swelling was found in 6 (9%) patients (1 had heel swelling only) and sausage digits (dactylitis) in as many as 15 (23%). In a subgroup of 24 patients with knee involvement investigated by ultrasound, Baker cysts were found in as many as 12 (50%).

Joints are painful; however, some patients with pronounced joint (knee) effusions may have disproportionately mild pains [194]. Joint inflammation usually lasts a few days to weeks, sometimes several months [194]. The course of Lyme arthritis is very variable, usually recurring and may continue for several years. In the beginning, the attacks of arthritis are more frequent and short, later they may be more prolonged. Every year about 10–20% of patients have complete resolution of the attacks. About 10% of patients develop chronic arthritis with duration of a year or longer; in some of them erosions may develop [194, 219].

Although constitutional symptoms mostly occur early in Lyme borreliosis [60], they occasionally outlast the initial period and may accompany arthritis [194]. In the study by Herzer [100, 216], 9 of 65 patients with Lyme arthritis also had fatigue, malaise, low fever or night sweats.

Clinical characteristics of joint involvement in association with ACA are outlined in the section ‘Skin Involvement’.

Lyme arthritis is one of the rare inflammatory joint diseases in which routine laboratory parameters are often completely normal. Only about half the patients with Lyme arthritis have moderately elevated erythrocyte sedimentation rate (>20 mm/h) with median values of approximately 20–30 mm/h [194, 216]. Concentration of C-reactive protein is usually in the normal range or slightly elevated. Findings of an erythrocyte sedimentation rate >80 mm/h or demonstration of pronounced elevation of other laboratory indicators of inflammation in a patient with arthritis points strongly against Lyme arthritis. Some patients have white cell blood counts slightly above 10 × 10^9 cells/l, some have elevated serum IgM. Cryoglobulins and circulating immune complexes may be present. Rheumatoid factors and antinuclear antibodies are usually negative, but in some patients may be positive in low titer [4, 16, 194, 216, 220].
Elevated white cell counts in synovial fluid, usually $10^7 - 35 \times 10^9$ cells/l (range 0.5–110 $\times 10^9$ cells/l) with predominance of polymorphonuclear leukocytes (average 70–80%), are found [5, 100, 194, 216, 219]. Total protein concentration commonly ranges from 3.5 to 5.6 g/l [5, 100, 194, 216]. Cryoglobulins and abnormal C1q binding consistent with antigen-antibody complexes are commonly present in synovial fluid [220, 221].

There are no specific radiographic findings for Lyme arthritis. Soft tissue changes, particularly effusions, are commonly present. Erosions are rare and generally seen only in some long-lasting (persistent) cases. Osseous changes, including subarticular cysts and osteophytes are uncommon [100, 222].

In patients with Lyme arthritis, borreial IgG antibodies in serum are almost always strongly positive; negative IgG serology essentially rules out Lyme arthritis [108, 207]. Investigation of paired sera with the aim of identifying seroconversion to *Borrelia* antigens is usually unsuccessful because almost all patients with Lyme arthritis are seropositive at presentation. Serologic investigation of paired samples of serum and synovial fluid for determination of intra-articular antibody production (parallel to determination of intrathecal antibody synthesis in Lyme neuroborreliosis) is of no value because of the lack of a blood/synovial barrier that would efficiently prevent diffusion of immunoglobulins from blood into synovial fluid and vice versa. In patients with arthritis and borreial IgG antibodies in serum, the diagnosis of Lyme arthritis is substantially supported by demonstration of borreial DNA in synovial fluid or in synovial tissue.

**Diagnosis**

Diagnosis of Lyme arthritis is based on the medical history and clinical features, laboratory findings, exclusion of other causes of arthritis and demonstration of serum IgG antibodies to *Borrelia* [1–3, 16, 18]. Unfortunately, serology has many methodologic limitations and several pitfalls in interpretation of the results. Demonstration of borreial (IgG) antibodies in serum does not enable distinction between symptomatic and asymptomatic infection, between active and past infection, or between acute and chronic (short- and long-lasting) infection; it also does not enable location of the disease process. Thus, demonstration of borreial antibodies in the serum of a patient with arthritis does not guarantee that the infection is active or that it is located in the joints – it does not indicate Lyme arthritis. Isolation of *Borrelia* from synovial fluid is rarely successful. Detection of borreial DNA in synovial tissue or synovial fluid by PCR is much more sensitive (up to 85%) [14, 108, 201, 202, 204, 205, 223, 224]. However, a positive PCR finding in a seronegative patient is most probably of low diagnostic value, and should be regarded with skepticism [14, 108]. Cultures of synovial fluid and synovial tissue for the presence of *Borrelia* have been generally unsuccessful [108, 207].

The presence or a reliable history of other manifestations of Lyme borreliosis such as EM, Lyme neuroborreliosis or ACA is of substantial help for relatively straightforward diagnosis.
Differential Diagnosis
The differential diagnosis of Lyme arthritis is broad and generally includes inflammatory rheumatic diseases, bacterial (septic) arthritis, viral arthritis and crystal-induced arthritis [3, 18, 100, 219].

The acute presentation of (monoarticular) Lyme arthritis can be mistaken for bacterial (septic) or crystal-induced arthritis (gout, pseudogout) and sometimes also for sarcoid arthritis in *Borrelia*-seropositive persons. In Europe, adult patients with Lyme arthritis only very exceptionally have fever (>38°C), do not have signs of sepsis, and usually have normal or slightly elevated laboratory indicators of inflammation, which – in addition to synovial fluid smears for the presence of bacteria and synovial fluid culture – permits a fairly reliable distinction of Lyme arthritis from septic arthritis. The presence of hyperuricemia and *Borrelia* IgG antibodies in serum may be conflicting diagnostic criteria in a patient with acute monoarticular arthritis unless crystals are demonstrated in synovial fluid. Acute sarcoid arthritis, which commonly affects the ankles, may be wrongly diagnosed as Lyme arthritis, especially in cases of sarcoidosis without erythema nodosum.

Migratory arthritis in Lyme borreliosis is similar to that of rheumatic fever, disseminated gonococcal infection and viral infections. Diffuse hand swelling, which may occur in some patients with early Lyme arthritis, may also occur in viral infections such as those with parvovirus B19 [100].

With regard to the intermittent course, Lyme arthritis may be mistakenly diagnosed as intermittent hydarthrosis or palindromic rheumatism in persons with borrelial antibodies in serum. Recurrent episodes of arthritis may precede (more) indicative signs of Whipple’s disease [100].

In general, Lyme arthritis is most like pauciarticular juvenile arthritis in children and reactive arthritis in adults [3]. Thus, there may be difficulties in differentiation between Lyme arthritis and reactive arthritis, as well as between Lyme arthritis (in children) and HLA B27-positive juvenile oligoarthritis or antinuclear antibody-positive pauciarticular juvenile arthritis. The pattern of joint involvement in Lyme arthritis resembles that in seronegative spondyloarthopathies; in addition, heel involvement and sausage digits are not limited to seronegative spondyloarthopathies, but are also seen in some patients with Lyme arthritis [100]. Other differential diagnoses include psoriatic arthritis, early rheumatoid arthritis and systemic lupus erythematosus in patients who have borrelial antibodies in serum.

Musculoskeletal pain in Lyme borreliosis may be mistaken for psychogenic rheumatism or fibromyalgia. However, more often fibromyalgia in *Borrelia*-seropositive persons is wrongly diagnosed as Lyme borreliosis. In contrast to the rather distinctive intermittent and migratory pattern of musculoskeletal pain in Lyme borreliosis, fibromyalgia is characterized by more generalized chronic pain and by symmetric tender points [100].
Eye Involvement

Information on eye involvement in the course of Lyme borreliosis is limited. It appears to occur very rarely, and is often associated with other signs of Lyme borreliosis [16, 225, 226] such as EM, Lyme neuroborreliosis or Lyme arthritis, but can also be the sole manifestation of the disease. Ocular Lyme borreliosis may be underdiagnosed because of difficulties in the (serologic) diagnosis and because the clinical ocular features are often not recognized [227–229]. Some ophthalmologists are not acquainted with the possibility of ocular manifestations of this disease, nor are most other specialists and general practitioners. Intraocular material is usually not available from humans, therefore serology is the main aid in diagnosis. False seropositivity and asymptomatic seropositivity can lead to substantial overdiagnosis, particularly in highly endemic regions. Frequent association of eye involvement with other manifestations of Lyme borreliosis may be the consequence of diagnostic bias.

The interval from EM to the onset of eye involvement is variable and may be from a few days to years, conjunctivitis being representative of an early ocular lesion, whereas keratitis appears late in the course of Lyme borreliosis [16, 230].

Eyes can be affected primarily as the result of inflammation, such as conjunctivitis, keratitis, iridocyclitis, retinal vasculitis, chorioiditis, optic neuropathy, episcleritis, panuveitis, panophthalmitis (some of these manifestations appear to be extremely rare and not all are reliably proven to be the consequence of borrelial infection), or secondarily as a result of extra-ocular manifestations of Lyme borreliosis, including pareses of cranial nerves (VII, III, IV or VI cranial nerve), pseudotumor cerebri and orbital myositis [227, 229, 231, 232]. Inflammation, particularly when long-lasting, may lead to severe impairment or even complete loss of vision [16, 226, 228–230].

According to the reports on EM that were published soon after Lyme borreliosis was recognized, conjunctivitis was found in as many as 35 of 314 (11%) patients in the USA [230], whereas in Europe the proportion of patients with EM and conjunctivitis was lower: of 104 patients with EM in southern Germany only 1 had conjunctivitis [53], and it was found in 23 of 425 (5%) Slovenian patients diagnosed with EM before 1990 [230] and in 10 of 231 (4%) skin culture-confirmed patients diagnosed in 1994 [136]. In the majority of later series on EM, conjunctivitis was reported only rarely or not mentioned at all. Among 19 European patients with intraocular involvement interpreted as due to borrelial infection, 12 had chorioiditis (bilateral 8, unilateral 4; diffuse or disseminated 8, focal 4), 3 had neuroretinitis, 2 bilateral retinal vasculitis, 1 bilateral iridocyclitis and 1 keratitis [230]. Borrelial infection was demonstrated in all the patients by the presence of borrelial antibodies in serum, and in 9 it was also indicated by the presence of other objective manifestation(s) of Lyme borreliosis (3 patients had lymphocytic meningitis, 1 had meningoradiculitis with second-degree A-V block, 2 had peripheral facial palsy – 1 also had lymphocytic pleocytosis,
and 3 had oligoarthritis). None of these 9 patients had EM, but 3 of the 10 remaining patients had a reliable history of EM. Patients were treated with antibiotics, and were followed for a median of 12 months (range 3–49 months). Visual acuity, which was initially found impaired in 18 patients (1 patient was not assessed), improved or normalized in the large majority of patients [230]. Huppertz et al. [233] reported that 3 of 84 (4%) children and adolescents with Lyme arthritis had ocular inflammation, including keratitis, anterior uveitis and uveitis intermedia. All 3 had symptoms of decreased visual acuity. Whereas anterior uveitis disappeared without sequelae, corneal scarring and permanent loss of visual acuity remained in the patients with keratitis and intermediate uveitis. The authors stressed that loss of vision appears to be symptomatic, making regular ocular screening of such patients unnecessary.

Several case reports and some series of patients with (presumed) ocular Lyme borreliosis have been published [226–229], indicating that uveitis (which may be associated with photophobia, macular edema, retinal vasculitis and decreased vision), neuroretinitis and choroiditis with retinal detachment may develop, and that interstitial keratitis, episcleritis and follicular conjunctivitis are possible anterior-segment manifestations. Transient worsening of symptoms as a result of a Jarisch-Herxheimer reaction after the intravenous administration of ceftriaxone has also been described [226].

Diagnosis of borrelial ocular involvement is difficult. It should be based on medical history (epidemiologic data and information on other antecedent or concurrent manifestations of Lyme borreliosis are of particular importance, but often fail to be noticed), complete physical not only ophthalmologic examination and demonstration of borrelial infection. In clinical practice, demonstration of serum antibodies is the most often used test. In addition to several problems of borrelial serology that are discussed elsewhere, concerns have been expressed that in some patients with isolated borrelial eye involvement the antibody response to this localized *Borrelia* infection might be inadequate [226–228]. Antibodies in ocular fluid could also be determined, and demonstration of intraocular production of borrelial antibodies could be of substantial diagnostic help [234]. However, eye puncture is not a procedure included in routine clinical practice, and the volume of obtainable ocular fluid is small. In the literature, there are many reports of eye involvement attributed to Lyme borreliosis, in which borrelial infection was indicated only by the presence of serum antibodies. It is very difficult if not impossible to prove that an individual ocular clinical sign (particularly without the presence of or a reliable history of other manifestations of Lyme borreliosis) is really a result of infection with *B. burgdorferi* s.l. without direct demonstration of the causative agent in the involved eye [225, 226, 228, 230]. Isolation of *Borrelia* from eye tissue has been reported only once [235], but there are several publications on the demonstration of borrelial DNA in eye structures and ocular fluid [226, 228, 236]. However, several patients with positive PCR findings were reported to be seronegative to borrelial antigens, a finding that needs critical interpretation [14, 108].
The ocular manifestations described resemble those seen in ocular syphilis in some ways, and are not pathognomonic for Lyme borreliosis. Differential diagnosis is rather broad [226, 230]. Granulomatous iridocyclitis or choroiditis are seen in several diseases caused by bacteria (such as syphilis, tuberculosis and leprosy) and protozoa (Toxoplasma gondii), and can be associated with fungal infections and immunologic processes of unclear etiology such as sarcoidosis and Vogt-Koyanagi-Harada syndrome, as well as with rheumatic disorders [230], particularly in children and adolescents with pauciarticular juvenile rheumatoid arthritis (typical ocular manifestation is chronic anterior uveitis) and juvenile spondyloarthropathy (acute anterior uveitis) [233]. Generally, the association of arthritis and uveitis is suggestive of HLA B27-positive spondyloarthropathies, and uveitis is a typical feature of antinuclear antibody-positive pauciarticular juvenile arthritis [100].

**Other Rare (Potential) Manifestations of Lyme Borreliosis**

Some case reports have implicated *B. burgdorferi* s.l. infection as a possible cause of 2 subtypes of scleroderma circumscripta, progressive facial hemiatrophia (suggested by silver staining) and eosinophilic fasciitis (Shulman syndrome, indicated by silver staining, immunohistology, PCR) [67, 237–239]. There are case reports on patients with myositis [240–242], the existence of which has also been demonstrated in an animal model in nonhuman primates [243], dermatomyositis [244, 245], nodular fasciitis [246], panniculitis [247–249] and osteomyelitis [250]. Most authors are of the opinion that borrelial infection is not causally associated with the syndrome of fibromyalgia [3, 16]. There are also reports on the effect on individual organs or organ systems, such as the liver, lymphatic system, respiratory tract, urinary tract and genitalia [16], but proof of the existence of such involvement in humans is weak.

**Short Comment on Chronic Lyme Borreliosis and ‘Chronic Lyme Borreliosis’**

The designation chronic Lyme borreliosis should be reserved for patients with objective manifestations of late Lyme borreliosis (in Europe typically represented by ACA, chronic arthritis and rare cases of chronic Lyme neuroborreliosis without ACA) and not misused for: (1) symptoms of unknown cause with no (objective or valid) evidence of *B. burgdorferi* s.l. infection, (2) well-defined illness unrelated to borrelial infection (even with the presence of borrelial antibodies in serum), (3) symptoms of unknown cause, with antibodies against *B. burgdorferi* s.l. but no history of objective clinical findings that are consistent with Lyme borreliosis, or (4) post-Lyme borreliosis (post-Lyme disease) syndrome [251, 252]. A definition of post-Lyme disease syndrome was proposed in the recent IDSA clinical practice guidelines [14]. The problems associ-
ated with diagnosis and management of patients with ‘chronic Lyme disease’ (patients in categories 1, 2, 3 and especially 4) have been discussed in several articles, including a critical appraisal in the *New England Journal of Medicine* [251] and a recent review in *Infectious Disease Clinics of North America* [252]. The information in these reports is valid not only for North America, but also for Europe.

**Lyme Borreliosis in Special Groups of Patients**

Although Lyme borreliosis has been recognized for more than 30 years, knowledge of the course and outcome of the illness is limited in certain groups, including pregnant women and immunocompromised patients. Lyme borreliosis during pregnancy is discussed elsewhere in this book; here, we present some basic data on Lyme borreliosis in immunocompromised patients.

**Lyme Borreliosis in an Immunocompromised Host**

In general, it is well known that bacteria can induce infections of varying severity, and that the preinfection immune status is often crucial for the clinical course of a disease. Information on the course and outcome of *B. burgdorferi* s.l. infection in immunocompromised patients is very limited; as a consequence, neither the natural course nor the efficacy of treatment of Lyme borreliosis has been accurately assessed in this diverse group comprising several distinct types and severities of immunosuppression. Data in the literature are scant and predominantly restricted to individual case reports, such as a report on a *B. burgdorferi* infection in a patient with dermatomyositis [253], a description of a morphea-like skin condition apparently caused by *B. burgdorferi* in an immunocompromised patient [254], a case of Lyme borreliosis in a transplant recipient [255] and several cases of Lyme borreliosis in conjunction with human immune deficiency virus infection [256–258]. We were able to find only 3 reports on a series of cases of Lyme borreliosis in immunocompromised patients.

In the first report, several distinctions were revealed in a comparison of the course and outcome of borrelial infection in 67 adult patients with typical EM and an underlying immunocompromised condition with 67 previously healthy age- and sex-matched individuals with EM, who were examined and diagnosed in the period 1990–1996 at a single center. The duration of EM after starting antibiotic treatment was similar in the 2 groups, but the occurrence of early disseminated borrelial infection before treatment and the frequency of treatment failure were found more often in immunocompromised patients than in the control group (16/67 vs. 6/67, respectively). Treatment failure was defined as the occurrence of severe minor or major manifestations of Lyme borreliosis, persistence of *B. burgdorferi* s.l. in the skin and/or
persistence of EM after treatment; the mode and duration of antibiotic treatment was the same in both groups of patients. Re-treatment was required in 13 (19%) immunocompromised patients, but in only 5 (7%) patients in the control group. However, in spite of the more severe course and the more frequent need for retreatment among patients whose immune system was impaired, both groups had a favorable outcome of borrelial infection after 1 year [259]. Persistence of B. burgdorferi s.l. in normal-looking skin at the site of previous EM 2 months after treatment was found in 1 of 20 immunocompromised patients and in none of 21 immunocompetent patients who had positive Borrelia culture from an EM lesion before treatment and were rebiopsed 2–3 months later at the same site. As stressed by the authors of the study, these results should be interpreted with caution because the causes of immune deficiency were somewhat heterogeneous. The findings in the small numbers of patients with individual underlying diseases could give only a hint of potential differences between distinct immunocompromised settings, but could not permit reliable statistical analysis; 1 of 7 patients (14%) with cirrhosis of the liver, 4 of 22 (18%) patients treated for diabetes, 2 of 8 (25%) with autoimmune disease, and 4 of 14 patients with underlying malignant disease presented with signs of disseminated Lyme borreliosis or developed treatment failure during the observational period of 1 year. The various types and levels of altered immunity in patients within individual immunocompromised subgroups might also have considerably influenced the results. Nevertheless, according to the results of the study, it appears that in patients with underlying malignant disease the likelihood of developing disseminated infection or treatment failure may be higher among those with hematologic malignancies: signs of disseminated borrelial infection or development of treatment failure were present in 3 of 7 patients (2/3 with chronic lymphatic leukemia, 1/2 with lymphoma and 0/2 with myeloproliferative disorders), in contrast to 1 of 7 patients with nonhematologic malignancies. The authors concluded that although in the majority of immunocompromised patients with EM the management can be the same as in immunocompetent patients with early Lyme borreliosis, more aggressive initial antibiotic treatment might be appropriate for some subgroups of patients with altered immunity; for example, in patients with hematologic malignancy [259].

A second study [260] investigated the impact of immunosuppression on EM in 33 patients with malignant or autoimmune disease, chronic infection or immunosuppressive therapy for organ transplantation by comparing findings in the immunosuppressed patients with those in 75 otherwise healthy patients with EM. The 2 groups were matched for sex, age and antibiotic therapy. Comparison did not reveal any significant difference between the 2 groups in pretreatment clinical parameters, such as presentation of the skin lesion and presence of extracutaneous signs and symptoms, in the disease course during a median follow-up of 9 months after treatment, or in serum borrelial antibodies before treatment and at the end of follow-up. Further, it appeared that immunosuppression did not influence clinical presentation, response to therapy or production of B. burgdorferi antibodies in patients with EM. The au-
thors concluded that it is not necessary to treat immunosuppressed patients with EM differently from immunocompetent patients [260]. Again, one of the several drawbacks of this retrospective study was the pronounced heterogeneity in types and levels of altered immunity.

The third report comprised 6 adult recipients of solid-organ transplants who had chronic drug-induced immunosuppression and presented with solitary EM. These patients appeared to have only localized infection of the skin, even though they were immunosuppressed; all had a mild and smooth course of illness, as well as a favorable outcome of the illness after treatment with antibiotics administered at the same dosage and for the same duration as used in treatment of early localized Lyme borreliosis in immunocompetent patients. However, the number of patients in the study was too small to enable valid generalization of the findings. Potential application of the observations might be appropriate for European patients with solitary EM caused by *B. afzelii* (in this study 3 of 4 *Borrelia* isolates from lesional skin were typed as *B. afzelii* and 1 as *B. garinii*; a skin sample from 1 patient was culture negative), but the observations may not apply to patients with *B. burgdorferi* infection in the USA (localized infection of the skin is more commonly associated with *B. afzelii* infection in Europe than with *B. burgdorferi* infection in the USA [15]) or to patients with disseminated *Borrelia* infection [261].

**Laboratory Diagnosis of Lyme Borreliosis**

An important observation in Lyme borreliosis is that there is usually no clinical laboratory parameter in the peripheral blood that is indicative of this infectious disease. Almost all patients have normal CRP values and usually normal white blood cell counts [1–3, 16, 18].

The marked impression of EM on the skin could be expected to represent a typical histologic reaction, but the histologic picture in EM is generally nonspecific with some perivascular infiltration, mainly of lymphocytes and sometimes plasma cells. In borreial lymphocytoma, the respective skin area, in contrast to EM, frequently shows lymphocytic infiltration in the dermis with plasma cells, macrophages and eosinophils. The histopathologic picture of ACA is also characterized by a lymphocytic infiltration, and also by telangiectases. The cellular infiltration is again mixed with plasma cells and is present not only in the dermis, but also not infrequently in the subcutis. Histology in ACA may be supportive of the diagnosis, but it is not typical enough to be exclusive, and in borreial lymphocytoma the histologic picture is not unique and may be difficult to differentiate from malignant lymphomas.

In Lyme neuroborreliosis, the CSF usually shows moderate-to-intense lymphocytic pleocytosis, but some patients have only elevated CSF protein. Lymphocytic pleocytosis is absent in several patients with peripheral facial palsy and in patients with isolated peripheral neuropathy, and may be absent very early in CNS involve-
ment particularly in children [262]. Intrathecal IgM and IgG production and oligoclonal IgG bands are common findings in patients with CNS involvement of a few weeks or longer and are supportive of the diagnosis. Concentration of CSF glucose is usually normal. Patients with ‘chronic’ peripheral polyneuropathy, usually a feature of ACA, have normal CSF findings.

Thus, without a specific marker, full proof of the borrelial etiology of any of the given disorders in Lyme borreliosis is missing. The specific etiology of any infectious disease is usually best documented by direct detection of the agent, but this is not straightforward in suspected Lyme borreliosis.

Direct Detection of the Agent

Culture
Culture of B. burgdorferi s.l. strains is possible in complex media [263, 264], with success depending on the type of specimen. For example, cultivation of B. burgdorferi s.l. from skin biopsies of EM is usually very successful, at 60–80% [38, 77, 108]. However, the clinical conditions EM and ACA will mostly be identified by inspection, to some extent with the help of histology in the latter case, and cultivation is only rarely requested. In CSF the success of culture is usually around 10% or less, possibly increasing to 30% in children in the very early phase of neurologic disorders [262]. Borreliae have also been isolated from the blood of patients with EM, most successfully in the USA by using high-volume blood cultures [64], from cardiac tissue of patients with dilated cardiomyopathy [180], and from synovial fluid of patients with Lyme arthritis [265]. Although some results suggest that even early Lyme borreliosis such as EM is very frequently a disseminated infectious disease, most medical laboratories would not be able to manage the relatively sophisticated demands of Borrelia culture. Thus, blood, cardiac tissue and synovial fluid are less suitable sources for culture of B. burgdorferi s.l.

Nucleic Acid Amplification Techniques
Genus- and species-specific PCR methods can be used to detect low copy numbers of B. burgdorferi s.l. Unlike culture, PCR detects borrelial DNA of both viable and non-viable organisms, which means that a positive PCR cannot explicitly establish whether an infection is active or not. PCR appears to be a valuable tool, particularly in the diagnosis of patients with arthritis, since it can detect borrelial DNA in 85% of synovial fluid samples and even more if the synovial membrane is examined [224].

Urine has been investigated by several groups [266]; however, results are contradictory and studies indicate that more attention to methods of DNA extraction may help improve this situation [267]. A further problem is illustrated by a study in which a proportion of urine samples of healthy individuals whose serum contained Borrelia-specific antibodies also reacted positive in a Borrelia-specific PCR. Thus, as with se-
rologic findings, PCR results should always be interpreted with caution and the clinical significance of a PCR-positive finding in urine remains to be established.

Lastly, reference should be made to the fact that a negative result for culture and/or PCR does not exclude active infection.

**Indirect Detection of Borrelial Infection: Serology**

Currently, there are almost uncountable numbers of commercial test kits on the market for detection of IgG and IgM antibodies against *B. burgdorferi* s.l. The test systems comprise immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA) and immunoblot.

IFA were the first serodiagnostic tests used for detection of antibodies against *B. burgdorferi* s.l., and are still used in many countries. Nevertheless, although IFA can be automated today, ELISA are the most frequently used tests. Since the two-tier testing principle was introduced, ELISA has become the most commonly used serodiagnostic screening method for Lyme borreliosis. Sonicate and recombinant ELISA are in use. Most assays are either enriched with VlsE (variable-like sequence expressed) antigen or use VlsE or C6 as a single antigen for detection of specific IgG antibodies. OspC antigen as a single ELISA antigen is used for detection of specific IgM antibodies in serum. VlsE and C6 were originally considered markers for active infection; however, the strong immune reaction to these antigens is also present in convalescent and healthy persons and thus does not differentiate between active and past infection.

Immunoblot, or Western blot, is important in characterization of immune responses to specific *B. burgdorferi* s.l. proteins, and is generally used in the two-tier testing procedure. The interpretation criteria for immunoblot results are based on diagnostic antigens. Standardization of criteria for interpretation of immunoblot results in Europe was the subject of a study by EUCALB [268]. This multicenter study, involving 6 European laboratories using different immunoblot protocols, identified 8 bands that were discriminatory in all the laboratories, though with variations in significance. From these bands, 5 closely related European rules were formulated giving acceptable sensitivity and specificity, though there was no single rule that could be applied in all laboratories. This panel of European rules provides a framework for immunoblot interpretation that may be adapted in relation to the characteristics of Lyme borreliosis in local areas. Another source for the selection of diagnostic antigens is the work of Wilske and colleagues [269, 270]. Since complete standardization of immunoblotting protocols in Europe cannot be achieved, there was hope that new recombinant immunoblots would help to solve this problem [271]. However, even this hope was not fulfilled, particularly with recombinant IgM blots, which proved to be more sensitive than recombinant IgM ELISA.
With the introduction of VlsE and C6 peptides in the serology of Lyme borreliosis and the similar success in detecting *Borrelia*-specific IgG and IgM antibodies by using VlsE and OspC as single antigens in ELISA systems, it appears logical to replace the two-tier test principle, as indicated by results of recent studies [272]. However, even if the two-tier principle is abandoned, there is still no method or technique for identification of active infection. In addition, the high seroprevalence of specific antibodies in the general population in highly endemic areas will cause the problem of relevance to clinical disease. Moreover, persons such as hunters continuously exposed to ticks show an age-related seroprevalence as high as 83% in those over 70 years old [273]. Thus, physicians must take local seroprevalence into account when interpreting the clinical relevance of positive serology in patients. After more than 20 years of

**Table 3. Laboratory support in the diagnosis of Lyme borreliosis; modified according to the EUCALB clinical case definitions in Lyme borreliosis [12]**

<table>
<thead>
<tr>
<th>Initial clinical diagnosis</th>
<th>Essential laboratory evidence</th>
<th>Supporting laboratory evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM</td>
<td>none if typical</td>
<td>culture from skin biopsy; significant change in levels of specific antibodies or presence of specific IgM&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Borrelial lymphocytoma</td>
<td>specific IgG antibodies</td>
<td>histology; culture from skin biopsy</td>
</tr>
<tr>
<td>ACA</td>
<td>high level of specific serum IgG antibodies</td>
<td>histology; culture from skin biopsy</td>
</tr>
<tr>
<td>Early Lyme neuroborreliosis</td>
<td>lymphocytic pleocytosis in CSF; intrathecally produced specific antibodies&lt;sup&gt;2&lt;/sup&gt;</td>
<td>intrathecal total IgM and IgG; specific oligoclonal bands in CSF; significant change in levels of specific antibodies&lt;sup&gt;1&lt;/sup&gt;; culture from CSF</td>
</tr>
<tr>
<td>Chronic Lyme neuroborreliosis</td>
<td>lymphocytic pleocytosis in CSF; intrathecally produced specific antibodies&lt;sup&gt;2&lt;/sup&gt;; specific serum IgG</td>
<td>specific oligoclonal bands in CSF</td>
</tr>
<tr>
<td>Lyme arthritis</td>
<td>high level of specific serum antibodies</td>
<td>detection of borrelial DNA in synovial fluid and/or tissue (culture from synovial fluid and/or tissue)</td>
</tr>
<tr>
<td>Lyme carditis</td>
<td>significant change in levels of specific IgG antibodies&lt;sup&gt;1&lt;/sup&gt;</td>
<td>culture from endomyocardial biopsy</td>
</tr>
</tbody>
</table>

<sup>1</sup> Specific antibody levels in serum may increase in response to progression of infection or treatment, or may decrease due to abrogation of the infection process. Samples collected a minimum of 3 months apart may be required in order to detect a decrease in IgG levels.

<sup>2</sup> Intrathecally produced specific antibodies are determined by investigating simultaneously drawn samples of CSF and serum.
‘Lyme serology’ it appears that for diagnostic purposes serology has created more problems than it has solved. It is possible that the immune response to *Borrelia* infection still requires further elucidation. The results of a recent study appear to offer reasons for optimism with respect to diagnostic support [274].

Nevertheless, serologic tests for detection of intrathecal production of specific antibodies are very beneficial in the diagnosis of Lyme neuroborreliosis. Differing concentrations of immune globulins and specific antibodies in serum and CSF must be taken into account in detection of intrathecally produced specific antibodies; this is expressed as the CSF/serum index as follows:

\[
\text{CSF/serum index} = \frac{\text{ELISA units in CSF} \times \text{total IgG in serum}}{\text{ELISA units in serum} \times \text{total IgG in CSF}}
\]

Thus, the index expresses the proportion of pathogen-specific IgG antibodies in the total IgG content in the CSF compared with the serum. An index >1.0 would, strictly mathematically, prove the intrathecal production of specific antibodies. With respect to small volume variations when diluting samples, an index ≥1.5 is considered significantly elevated.

Table 3 refers to EUCALB recommendations listing the suspected clinical conditions and the weight of laboratory results required to confirm the clinical suspicion [12].

### References

Clinical Manifestations and Diagnosis of Lyme Borreliosis


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