Erythema migrans of at least six weeks' duration with central lymphocytoma-like lesion in a 48-year-old woman. No tick bite was noted.

Spirochetal lymphocytoma of eight weeks' duration in a ten-year-old girl. A tick bite occurred six weeks prior to the beginning of the lymphocytoma.
PLATE III. Acrodermatitis chronica atrophicans of one year's duration in a 68-year-old man. Note the marked swelling and violaceous discoloration of right hand and arm.

PLATE IV. Acrodermatitis chronica atrophicans of two years' duration in a 77-year-old woman. Note the violaceous discoloration, infiltration, and atrophy of the skin.
European Erythema Migrans Disease and Related Disorders

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European erythema migrans disease, lymphocytoma, and acrodermatitis chronica are a group of disorders associated with the bite of ixodid ticks. These disorders are now thought to be due to a single, or closely related, ixodid tick spirochetes. European erythema migrans disease closely resembles Lyme disease. Serological evaluation may help to separate spirochetal lymphocytoma from other pseudolymphomas of nonspirochetal origin and from lymphoma. Acrodermatitis chronica atrophicans, so far observed mainly in Europe, is presumably a late manifestation of this group of spirochetal disorders.

ERYTHEMA MIGRANS DISEASE (EMD)

Erythema migrans following a tick bite was first described by the Swedish dermatologist Aftelius in 1909 [1]. A few years later, Lipschütz from Vienna gave a more detailed description of another case using the designation erythema chronicum migrans [2]. In 1922, Garin and Bujadoux described a case of meningopolyneuritis [3]. Several years later, Hellerström presented a case with meningitis or, more likely, meningoencephalitis [4]. In 1934, the German dentist Stadelmann included among his six erythema migrans patients the case of a patient with severe joint pain, myalgia, and fatigue [5]. A detailed description of meningopolyneuritis was given by Bannwarth in the early 1940s [6]. In 1951, Hollström observed the beneficial effects of penicillin for both erythema migrans and a patient with meningitis [7]. Binder et al. reported the successful transmission of erythema migrans from human to human four years later [8]. In the 1960s and early 1970s, erythema migrans was recognized as a systemic disease by Hauser and others ([9]; literature in [19]). Hörstrup and Ackermann published a well-defined retrospective study on meningopolyneuritis in 1973 [10]. One year later, a case report showed that low doses of penicillin cleared the erythema migrans but were not sufficient to prevent meningitis; a beneficial effect of high doses of parenteral penicillin was achieved in this patient. In the same paper, it was concluded that a hitherto unknown bacterium must be the cause of both erythema migrans and “erythema chronicum migrans meningitis” [11].

The description by Allen Steere and co-workers of a disease which they first called Lyme arthritis [12] has stimulated further work in Europe. One and a half years before the discovery of the causative organism, high doses of parenteral penicillin or another appropriate antibiotic were suggested for later manifestations of both Lyme disease and erythema migrans disease and for some patients with early manifesta-
tions of these disorders [13]. A turning point in the history of EMD and related disorders was the discovery by Burgdorfer and co-workers of a spirochete from ixodid ticks, cultivation of the spirochetes, elicitation of animal lesions, and positive serological reactions in patients with Lyme disease [14]. Recovery of spirochetes from patients with Lyme disease was reported by Steere et al. and Benach et al. a few months ago [15,16]. Ackermann, using Borrelia, and other spirochetes, and Neubert, using rodent blood spirochetes supplied by Dr. H.E. Krampitz, obtained positive serological reactions at the same time [17,18]. Soon afterwards, we described 31 patients with what we now call erythema migrans disease [19]. The serological evaluation of 42 patients was presented very recently [20].

European erythema migrans usually presents as an expanding annular lesion often accompanied by central clearing. This lesion is the hallmark of the disease. Sometimes, a central lymphocytoma-like lesion can also be seen [9,19] (plate 1). Erythema migrans can disappear after a short duration of up to four weeks; it can exist in its chronic form as erythema chronicum migrans, or it may be absent [19]. European erythema migrans may be accompanied by general symptoms such as headaches, fever and/or fatigue, arthritis or arthralgia, certain neurological findings, probable cardiac involvement, and possibly tracheolaryngitis [19].

To date, we have observed 49 patients; 41 of them have been followed prospectively since December 1978. In our study, 17 patients (35 percent) had joint symptoms; most had involvement of the elbow, the knee, and/or the joints of the fingers. All patients had pain on motion of joints, eight had swelling, and only one experienced redness. Joint symptoms were usually not intermittent. Nine patients (18 percent) had neurologic signs. Six showed clinical evidence of meningopolyneuritis, four had severe headaches, and three were mildly encephalopathic. Seven women (14 percent) had signs suggestive of cardiac involvement. Five experienced one to several attacks of palpitations, one had episodes of substernal chest pain, and one had bradycardia.

Laboratory findings in up to 37 of the 49 patients included a moderate elevation of ESR in 32 percent of the patients (mean value, 16 mm/h), elevation of IgM (13 percent; mean value 316 mg/dl), IgG (10 percent; 1,432 mg/dl), or IgA (3 percent; 394 mg/dl), slight increase of SGPT (19 percent; 26 U/l) or SGOT (6 percent; 21 U/l), and mild cryoglobulinemia in one patient (12.6 mg/dl).

Forty-two patients were evaluated serologically [20]. We found IgG and/or IgM antibody titers against Ixodes dammini spirochetes (kindly supplied by Dr. Burgdorfer) to be significantly elevated in only 40 percent of our patients (Table 1). Treatment in these patients was begun a mean of eight weeks (0.5–26) after the tick bite or the beginning of the erythema migrans. The highest antibody titers were detected in some patients with more severe disease. Thus, it is possible that antibiotic therapy aborted the antibody response in some patients or that the disease was too mild to allow for significant rise in antibody titer. Seven patients with EMD, three with acrodermatitis chronica atrophicans (ACA), and two with lymphocytoma were also tested at the Rocky Mountain Laboratory for IgG antibodies against both the Ixodes dammini and the Swiss Ixodes ricinus spirochete. There was no significant difference in the titers between these spirochetes, and the results were basically comparable to those obtained by the Max von Pettenkofer-Institut in Munich [20].

LYMPHOCYTOMA (LYMPHADENOSIS BENIGNA CUTIS)

The first description of a solitary cutaneous lesion with follicles resembling those seen in lymph nodes was published by the Swiss pathologist Burckhardt in 1911 [21].
He clearly separated his case from true lymphoma. The term lymphadenosis benigna cutis was introduced by Bäverstedt in 1943 [22]. Seven years later, Bianchi noticed the beneficial effect of penicillin [23]. In 1957, Paschoud succeeded in transmitting lymphocytoma from human to human [24]. Braun-Falco and Burg noted the polyclonality of the lymphocytes within the lymphocytoma [25]. Histological [26,27], enzyme cytochemical [25,27], immunocytological [25,27-29] and ultrastructural [29,30] studies have provided more insight into our understanding of lymphocytoma and its differentiation from lymphoma in recent years. We recently reported a serological evaluation of patients with lymphocytoma [20].

Lymphocytoma occurs most often as a solitary lesion but several grouped or even more widespread lesions can sometimes be seen. Its size varies from a small nodule to rather large plaques several centimeters in diameter. The red or violaceous lesions have a firm consistency and are sometimes sensitive to touch (PLATE II). The histological diagnosis of lymphocytoma is aided by the follicular arrangement [31]. Such a follicle consists of small lymphocytes and central larger cells some of which represent centrocytes or centroblasts such as are found in true lymph nodes [27]. Unlike lymphoma, B and T lymphocytes are present in lymphocytoma [25,27-29]. Macrophages are present in follicular and non-follicular structures, and a few plasma cells and eosinophils may also be seen [25-27,31]. Electron microscopic studies have revealed the presence of various lymphoid and reticulum cells with many cytoplasmic processes [Weber K: unpublished two cases, 1974; 29,30].

The clinical features and laboratory findings of what we now call spirochetal lymphocytoma are exemplified by the findings in our four patients. All had their lesions on the ear; two-thirds of lymphocytomas are found on the head [9]. Our patients had their lesions for a mean of nine (6-12) weeks. However, if untreated, the lesions may last months and even years. Although our patients had regional lymphadenopathy, general symptoms were absent except for occasional headaches in two. However, meningitis has been reported [32], and a six-year-old boy had six erythema migrans lesions for four weeks. We observed elevations of alpha2 globulins in all four patients, beta globulin, in one, and IgM, in another patient (322 mg/dl). Serological examination of our patients revealed that they had a significantly elevated titer of either IgG or IgM antibodies against ixodid tick spirochetes [20] (Table 1). Thus, spirochetal lymphocytoma may now be diagnosed serologically.

### Table 1

Significantly Elevated Antibody Titers by Indirect Immunofluorescence Test in Patients with EMD, ACA, and Spirochetal Lymphocytoma Compared to Controls

| Diagnosis         | Number of Patients (%) | Unabsorbed Absorbed with | Unabsorbed Absorbed with | Unabsorbed Absorbed with |
|-------------------|------------------------|--------------------------|--------------------------|--------------------------|
|                   |                        | T. phagedenis ≥ 64 (%)   | T. phagedenis ≥ 64 (%)   | T. phagedenis ≥ 64 (%)   |
| EMD               | 42 (100)               | 7 (17) 11 (26)           | 19 (45) 14 (33)          |
| ACA               | 9 (100)                | 9 (100) 3 (75)           | 6 (67)* 5 (56)*          |
| Lymphocytoma      | 4 (100)                | 2 (50) 1 (2.5)           | 3 (75) 1 (2.5)           |
| Healthy controls  | 40 (100)               | 1 (2.5) 1 (2.5)          | 1 (2.5) 1 (2.5)          |

*IGM fraction negative
This condition was first described by the German physician Alfred Buchwald 100 years ago [33]. In 1902, Herxheimer and Hartmann introduced the designation ACA [34]. Jessner described a patient with arthralgia and biopsy-proven laryngitis in 1921 and, three years later, together with Loewenstamm, mentioned 66 patients, nine of whom had joint and bone involvement [35,36]. Soon afterward, Ehrmann and Falkenstein suggested an infectious etiology [37]. In 1942, Kahle reported positive pallida reactions in six out of seven patients; the pallida antigen used was a protein fraction of *Treponema phagedenis* [38]. Two cases were successfully treated with penicillin by Nanna Svartz in Sweden in 1946 [39]. Three years later, Thyresson reported on the successful therapy of 57 cases [40]. Tetracycline, chloramphenicol, erythromycin, and streptomycin were also found to be effective [41–43]. Grünberg, referring to the report of Kahle, performed pallida reactions in 104 patients, almost 10 percent of whom gave positive results compared to 0.6 percent of the controls; he suspected a group-specific reaction due to a special ACA spirochete [44]. In 1954, Götz reported on the successful transmission of ACA from human to human [45]. Walter Hauser introduced the concept of ACA as a generalized disease. He observed regional lymphadenopathy, reactive hyperplasia in the bone marrow, and electrophoretic changes. Many of his patients gave a history of tick bite, and he found the geographical distribution of ACA to be concordant with the distribution of *Ixodes ricinus*. He was also impressed by the relationship among ACA, erythema migrans, and lymphocytoma [46]. Several cases have been described with both ACA and erythema migrans or erythema migrans-like lesions [43,45,46] and with ACA and lymphocytoma [46]. In addition, in some patients ACA has been found to follow erythema migrans [46,47], and lymphocytoma [48]. Peripheral neuropathy was established as a manifestation of ACA by Hopf in 1966 (cited in [49]). Cryoglobulinemia and changes in the immunoelectrophoresis have been observed in some patients [50–52]. Among the malignancies associated with ACA, monoclonal gamopathy of Waldenström and lymphoma seem to be most remarkable [53,54]. Very recently, we reported the serological findings in six patients [20].

ACA is a chronic disorder usually with characteristic skin lesions [9,55,56]. In the initial stage, the patient has violaceous discoloration and infiltration of the skin, sometimes associated with marked swelling (PLATE III); in the atrophic stage, the skin becomes thin and shows loss of appendages (PLATE IV). The lesions usually spread from distal to proximal sites. In some instances, one finds periarticular fibrous nodules and pseudosclerodermiform plaques or bands. Regional lymphadenopathy is common [9,46]. Some patients have peripheral neuropathy [49]. There have been several reports demonstrating joint and bone involvement [35,36,45,55]. Sometimes, patients experience arthralgia before and together with the appearance of the skin lesions; the joint involvement may lead to severe impairment of joint function [36,57]. Hövelborn believed that the same process which caused the skin involvement also affected the joints [57].

Systemic symptoms are usually lacking, but three of our nine patients had symptoms such as fatigue, sensitivity to cold, cough, rhinorrhea, irritability, abdominal pain, and epistaxis during the illness. While skin involvement was present, three of the patients experienced palpitations, dizziness, chest pain and/or syncope (one episode in one patient). Five of the patients had a history of tick bite, but in none did the bite directly precede the appearance of the skin lesions. All patients had skin involvement of the limbs and three of the face. Fibrous nodules were present in three,
obtaining Joswig for Frau meningitis, the daily been manifestations have developed despite penicillin, of spirochete and/or early forms, ACA only activity may occur. ACA spirochetal and/or lymphocytoma, and/or spirochetal lymphocytoma. However, many patients with ACA seem to lack a history of erythema migrans disease or spirochetal lymphocytoma.

THERAPY

We recommend penicillin or tetracycline in appropriate dosage for therapy of European ixodid tick spirochetosis. Erythema migrans can recur after the injection of small doses of penicillin, 300,000 to 600,000 U for two to five days [58,59]; the later manifestations of EMD are not prevented by low doses of oral phenoxymethyl penicillin, 400,000 to 600,000 U for eight to ten days [11,19], and ACA has developed despite injections of procaine penicillin, 300,000 U daily for two or three days [59]. High doses of oral phenoxymethyl penicillin, 1.5 million U three times a day for eight to twelve days, did not prevent arthralgias, but, to date, severe manifestations have not developed in 12 patients with EMD followed prospectively since May 1982 [Weber K: unpublished data]. Intravenous penicillin G, 10 to 20 million U daily for eight to 14 days, were found to be effective in a few EMD patients with meningitis, meningopolyneuritis, and polyarthritis [11,19]. The favorable effect of the tetracyclines, usually 500 mg three to four times a day for seven to ten days, has been observed by many physicians, including ourselves.

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