Clinical Pathologic Correlations of Lyme Disease by Stage

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INTRODUCTION

It is now known that erythema migrans disease (as described by Afzelius and Herxheimer[1]), acrodermatitis chronica atrophicans,[2] lymphocytoma of Bafverstedt,[3] meningopolyneuritis (Garin-Bujadoux-Bannwarth syndrome),[4,5] and Lyme disease (as described by Steere in North America)[6,7] are all one and the same disease caused by *B. burgdorferi*.[8] All of these disorders are histopathologically characterized by variable infiltrates of perivascular lymphocytes and plasma cells, and vascular damage and fibrin deposits in the synovia of arthritis patients.[9]

Primarily cutaneous and neural in involvement, the disease has come to be understood as a multisystemic infectious syndrome involving the cardiovascular system, central and peripheral nervous system, and reticuloendothelial and gastrointestinal systems.[10,11] Involvement of these and specialized systems produces clinical symptoms that can correlate with varying degrees of tissue damage caused by a complex interplay of cells of the immune system and humoral factors such as interleukin-1 (IL-1), circulating immune complexes, prostaglandins, collagenases, and possibly compounds derived from arachidonic acid.[12,13]

Experience in both hemispheres now points to ever-expanding clinical and pathologic lesions that heretofore have been referred to by a variety of seemingly unrelated terms. Many of these involve the skin in chronic phases. Increasing evidence points to the continuing presence of spirochetes in these lesions. This paper summarizes these alterations as seen histopathologically.

MATERIALS AND METHODS

Tissues of human patients infected with *B. burgdorferi* have been obtained by consultations and contributions from clinicians and pathologists from both hemispheres. Tissues largely have been submitted previously formalin fixed and embedded in paraffin from postmortem examinations, surgical biopsies, dermatologic punch biopsies, synovectomies obtained both from arthroscopy as well as open joint surgery, and endocardial biopsies by trans-venous catheterization. Tissue samples have been submitted from acute stage illness, chronic and convalescent stages, and from patients in quiescent periods of the disease. In some instances the material was confined to glass

slides and/or photomicrographs. Whenever available, paraffin blocks were recut for histochemical studies utilizing reticulin stains, Mallory trichrome stains, Giemsa stains for mast cells, Putt's fibrin stain for fibrin products and fibrinogen, Verhoeff Van Gieson stain for elastin, alcian blue stains at pH 1.8 and 2.4 for stromal mucopolysaccharides, modified Dieterle stain for spirochetes, and routine hematoxylin and eosin stains. Avidin-biotin immunohistochemistry utilizing monoclonal antibodies H5332, H3TS, and H9724 obtained from Dr. Alan Barbour and hyperimmune human polyclonal antibody obtained from Dr. Allen C. Steere was used to identify spirochetes in formalin-fixed tissue sections. Chromagen substrates used in the immunohistochemical analyses consisted of diaminobenzidine and alkaline phosphatases, chromagen I and III.

Tissue samples have been examined from the states of California, Minnesota, Wisconsin, Texas, Michigan, Pennsylvania, New Jersey, New York, Maryland, North Carolina, and Massachusetts. Countries in the Western Hemisphere include the Netherlands, Sweden, France, West Germany, Italy, and Austria.

Notes on Histogenesis

The spirochete disseminates by the vascular system following a variable period of time in the skin upon tick inoculation.[14] Humoral and cellular immune responses play a major role in all clinical pathologic stages as well as a number of enzymes, including collagenase and derivatives of the arachidonic acid pathway, namely prostaglandin, and biologic response modifiers such as IL-1. Circulating immune complexes and elevated IgM, IgA, and later IgG, become elevated in the circulation[15] as well as some deposition of IgG in the synovia of the joints. Lymphocytes—both B-cell and T-cell (helper and suppressor)—proliferate at one time or another in most of the organ systems that will be discussed subsequently, and are accompanied by varying numbers of macrophages, dendritic immune cells, and tissue mast cells. The plasma cell and its precursors are a mainstay inflammatory responder in most if not indeed all visceral and organ system sites of involvement. Visceral damage and alteration are caused by an interplay of these humoral and cellular elements, presumably in response to the continuing presence of spirochetal antigen(s),[14] either from viable and proliferating spirochetes or from degenerating forms. Although T cells seem to be a major responder in the central nervous system and elsewhere, B cells which differentiate into plasma cells comprise a major response in the deep dermis, fascia, soft tissues, myocardium, dermis, and synovium. Not only are plasma cells plentiful in the spleen, lymph nodes and bone marrow, they are also represented by large and somewhat atypical-appearing precursor B cells as well. Mild-to-moderate vasculopathies in the form of mild vasculitis and hypercellular vascular occlusion are often seen in multiple sites, and appear to be temporally related. These vascular alterations are not fully explained, but may reflect secondary damage by immune cells and possibly immune complexes. Tissue necrosis in any site appears lacking with one minor exception: lymphadenitis in stage I. Multinucleated giant cells, granulomas, gummas, and fibrin microthrombi of vessels appear not to be found in human Lyme disease thus far.

CLINICAL PATHOLOGIC CORRELATION BY STAGE

Stage I

The tick bite site in the skin yields an ulceropapule consisting of partially denuded and peripherally hyperplastic epithelium, overlaying an inflammatory infiltrate in the dermis of lymphocytes, plasma cells, macrophages, and mast cells, acutely and

followed by plasma cells later on (TABLE 1). In some circumstances discrete, somewhat unusual appearing, hemorrhagic nodules are seen in the deep dermis below the inflammatory infiltrate. At this stage spirochetes are hard to see but are nevertheless present. Erythema chronicum migrans, the hallmark of stage I involvement, is reflected histologically by mild-to-moderate perivascular infiltrates of mostly lymphocytes and minor components of plasma cells and mast cells. Vasculitis is not seen at this stage, and there is no vascular proliferation. Spirochetes at this stage are seen randomly near the epidermis but appear preferentially in the reticular dermal collagen. We have also seen them in lymphstasis in the subcutaneous soft tissues. Spirochetes stain poorly with the specific monoclonal antibodies in the skin but stain readily with polyclonal human immune serum followed by an avidin-biotin immunohistochemical procedure. Collagen is intact in ECM in the first stage, and the infiltrate is confined to the immediate perivascular regions. The epidermis appears normal. In Europe mainly, and rarely in the U.S., cutaneous lymphoid hyperplasia may be seen in the earlobes or the nipple skin.[16] This consists of benign but remarkably hyperplastic and crowded lymphocytic follicles with discrete germinal centers in the dermis, yielding an

TABLE 1. Stage I

Tick papule
Erythema chronicum migrans
Secondary lesions
Lymphocytoma cutis (lymphadenosis benigna cutis)
Ear lobe
Nipple/areolae
Conjunctivitis; uveitis; pharyngitis
Interstitial pneumonitis
Myalgia-arthralgia
Early meningitis (meningismus)
Encephalopathy
Lymphadenopathy
Splenomegaly
Hepatitis
Orchitis
Hematuria; proteinuria

appearance of tonsillar tissue. Numerous names have been given to this stage, including pseudolymphoma, lymphoid hyperplasia, follicular hyperplasia, lymphocytoma cutis, Spiegler-Fendt lymphoid hyperplasia, and lymphadenosis benigna cutis of Baverstedt. Secondary lesions of ECM occur as the spirochete disseminates to other regions of the skin, and the perivascular infiltrate is the same in the secondary deposits. In later biopsies of ECM, mast cells become more numerous near the lymphoid cells.

Soon after the onset of ECM, the organism disseminates hematogenously, with what appears to be random dispersal throughout the body. The immune response involves virtually all of the organs and structures of the reticuloendothelial system including the bone marrow, and clinical pain and discomfort seems to correlate with hyperplasia of lymph nodes and spleen and bone marrow. Diffuse visceral involvement in this acute stage mimics infectious mononucleosis or disseminated viral syndromes. These include conjuctivitis, pharyngitis, pneumonitis with dry cough and mild pleuritic pain, hepato-splenic tenderness, lymph node swelling of the neck and groin, and orchitis. There is lymphoid hyperplasia of the lymph nodes and spleen consisting of prominent germinal centers and numerous perifollicular lymphocytes, with proliferation of plasma cell precursors and mature plasma cells. The plasma cell precursors are

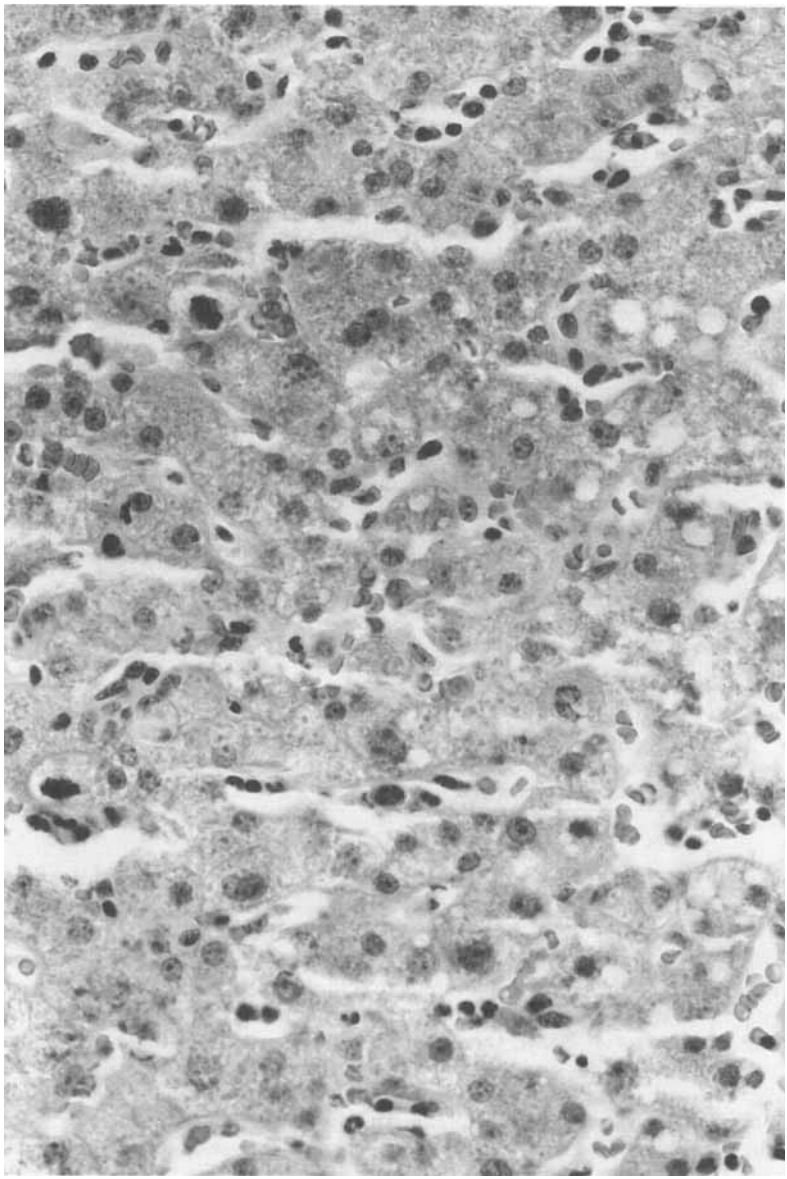

FIGURE 1. Photomicrograph of stage I Lyme hepatitis from an elderly woman. Liver cells are swollen with microvesicles of fat with numerous sinusoidal leukocytes. Near the top are two liver cells in mitosis. Hematoxylin and eosin stain; magnification 500×.

large, appear tumor-like, and can resemble Reed-Sternberg cells. Others look like typical immunoblasts (FIG. 1). In one example, cervical lymph nodes show cell degeneration with karyorrhexis and nuclear debris of lymphoid elements. This patient had repeated high fevers and marked discomfort of neck nodes. Large atypical immunoblasts can also be seen in the spleen and bone marrow. The red pulp of the spleen is congested, not unlike that seen in infectious mononucleosis. Spirochetes can be demonstrated in the lymph nodes, spleen and bone marrow and liver. There is a transient hepatitis reflected by elevated liver cell enzymes such as SGOT, SGPT, and GGT. The liver can vary from a mild lymphocytic portal triaditis all the way to liver cell derangement that simulates acute viral hepatitis. The cells at this stage appear swollen with clear cytoplasm and microvesicles of fat (FIG. 2). Numerous leukocytes are seen in the sinusoids, and there is Kupffer cell hyperplasia. Plasma cells are present and randomly distributed throughout the sinusoids and portal tracts. One hepatitis case from Wisconsin showed a remarkable number of mitoses of liver cells, itself a very

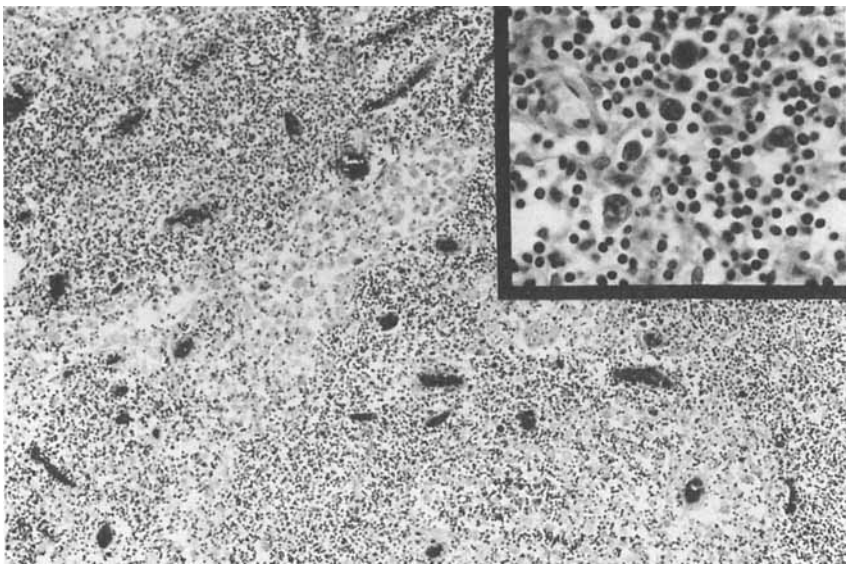

FIGURE 2. Peripheral lymph node from stage I Lyme disease patient with lymphadenopathy. An increase in macrophages is seen in the lymphatic spaces. High power shows the presence of moderately atypical-appearing immunoblasts and precursor B cells (inset).

unusual finding in non-neoplastic conditions of the liver. In stage I the lungs are involved by a hypercellular interstitial pneumonitis with irregular alveolar spaces (FIG. 3). The interstitial infiltrate is nonspecific and does not appear to resemble the interstitial lymphocytic pneumonitis of classic influenza. Cells are mixed with macrophages and tissue histiocytes in addition to lymphocytes. The alveolar spaces are irregular in shape.

Stage II

Stage II (TABLE 2) begins weeks to several months following the initial infection and is largely characterized by the involvement of the cardiovascular and central

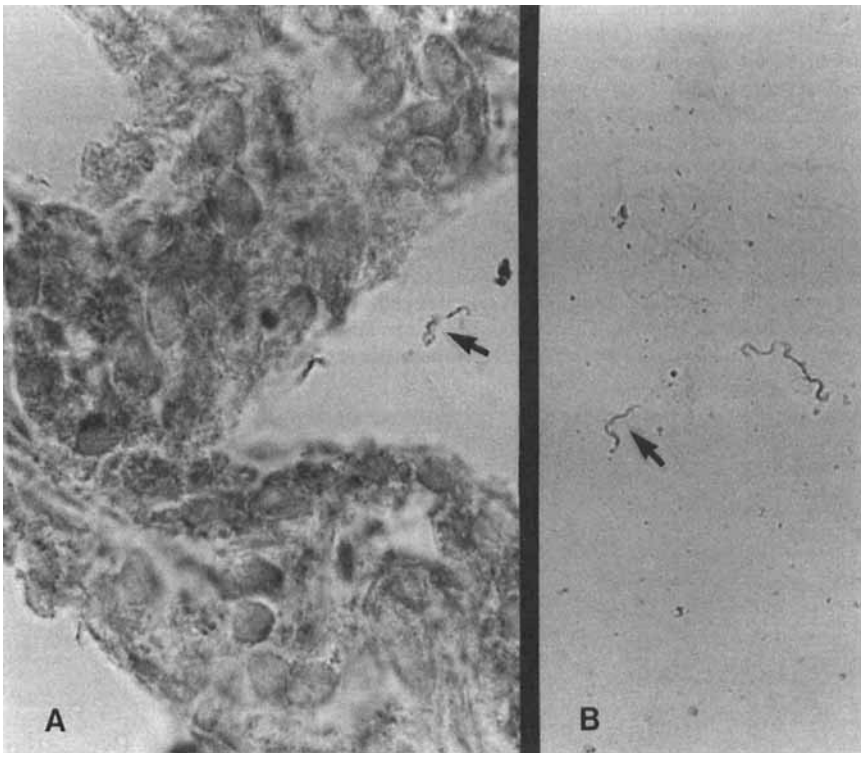

FIGURE 3. Photomicrograph of a stage I patient with interstitial pneumonitis. **(A)** Interstitial thickening by inflammatory cells. *Arrows* show spirochetes labeled with H5332 monoclonal antibody, specific for *Borrelia burgdorferi*. **(B)** Positive control from a culture of spirochetes. Avidin-biotin immunohistochemical technique; magnification 900×.

TABLE 2. Stage II

Lymphocytoma cutis (LABC)
Iritis, panophthalmitis
Meningitis-pleocytosis
Encephalitis-like
Perivascular cuffs, vasculopathic
Mild spongioform changes
Focal microgliosis
No apparent abnormality
Cranial neuritis (bilateral Bell's Palsy)
Radiculoneuritis
Myelitis
Myocarditis
Endocarditis
Endomyocarditis, vasculitis
Fibrinous pericarditis
Myositis, perivascular cuffs
Fasciitis (Schulman-like)

nervous system. By this time the acute reactive phase with diffuse involvement of the reticuloendothelial system and elevated serum IgM levels have subsided. Cardiovascular system involvement is manifested by one or more forms of cardiac arrhythmia. Patients may have either an incomplete (first or second degree) AV block or a complete AV block. Some patients appear not to be aware of their arrhythmias during this stage. Fortunately most of these forms are benign and transient. Nevertheless severe forms do occur and can be manifested by slow idioventricular rhythms. We previously recorded a terminal case of Lyme myocarditis in a middle-aged man with refractory arrhythmia.[17] We examined several sections of the myocardium from this case, but had no opportunity to dissect the cardiac conduction system. Nevertheless a transmural inflammatory infiltrate involved all three layers of the myocardium including the endocardium. The infiltrate consisted of lymphocytes, plasma cells, and

FIGURE 4. Lyme myocarditis with perivascular lymphocytes and plasma cells and vascular damage with disruption of the endothelium and debris in the lumen.

macrophages. Scattered branches of intramyocardial veins showed sparse lymphocytes in the tunica media. Lymphocytes and scattered macrophages were also present in the tunica adventitia and the immediate perivascular stroma. The stroma showed laminations suggesting early obliterative vasculopathy. Necrotizing vasculitis was not present, but rare vessels showed luminal amorphic debris and vasculopathy (FIG. 4). The lymphocytes and plasma cells diffusely infiltrated the interstitium of the myocardium in all sections examined. The endocardium showed a band-like infiltrate of lymphocytes and plasma cells of more or less uniform thickness. In another case of myocarditis from a middle-aged woman in Pennsylvania, early traces of myocardial fiber degeneration were present along with neutrophils in addition to lymphocytes and plasma cells. This patient survived the myocarditis phase following intravenous penicillin therapy. Fibrinous pericarditis occurred in another case, wherein symptoms of pericardial

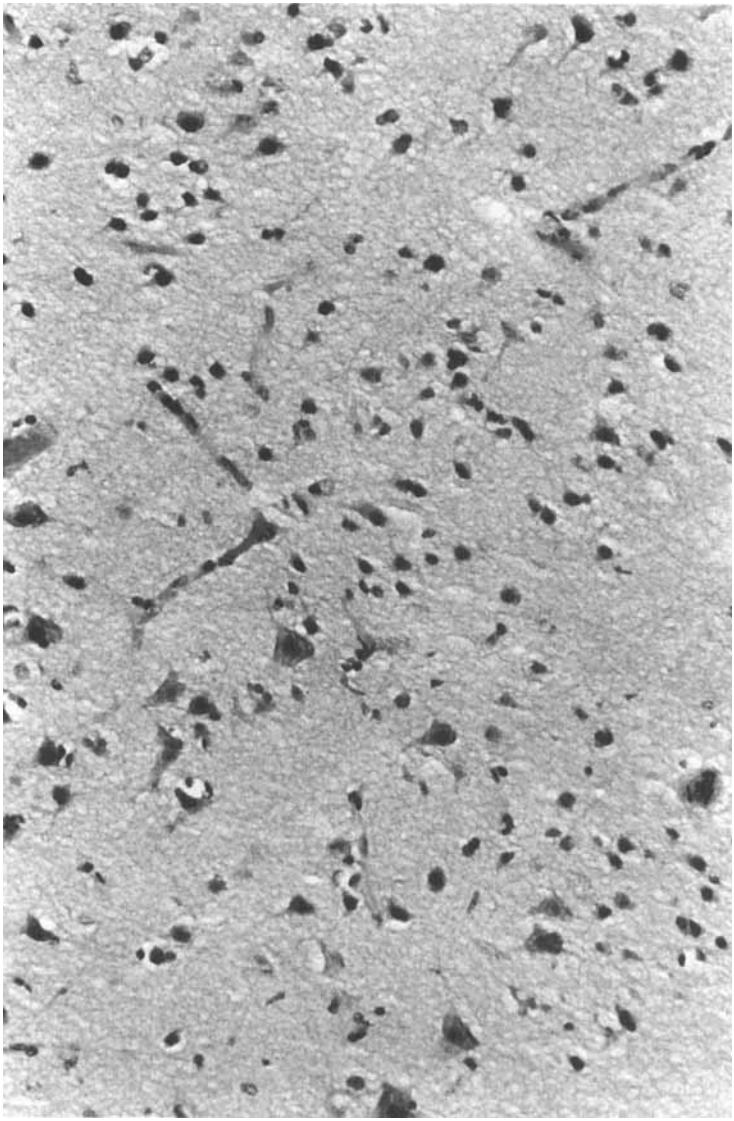

FIGURE 5. Stage II Lyme cerebritis demonstrated by an increase in microglial cells and round cells. Hematoxylin and eosin; magnification 250×.

constriction were clinically evident. That patient also survived. Spirochetes can be demonstrated in multiple sections of the myocardium, but they were absent in the fibrinous pericarditis samples. This characteristic band-like infiltrate of the endocardium can be demonstrated even in limited biopsies taken of the right ventricle by trans-venous catheter.

Clinical signs and symptoms of meningoencephalitis are fully developed in stage II. Patients have headache, photophobia, and signs of meningismus. This stage is paralleled by CSF pleocytosis. In terminal cases seen thus far, band-like infiltrates of lymphocytes and plasma cells are seen in the leptomeningeal layers. Some cases have shown mild spongioform changes of the cerebral cortex, and others have shown an increase in oligodendrocytes, which at times are situated in cuffs around small vessels. Microgliosis of a focal nature was seen in one young male in coma who responded to intravenous penicillin therapy (FIG. 5). Spirochetes were demonstrated in that case. Patients have either severe encephalopathy including stupor and coma, or varied forms of psychoneurosis including depression. Many of these are also found in stage III disease. These encephalopathic stages may be entirely absent, and patients present with various combinations of cranial neuritis.[30] Bilateral Bell's palsy is a prominent feature in some stage II patients, and almost constitutes a firm clinical sign that a given patient in an endemic area with bilateral Bell's palsy has Lyme disease until proven otherwise. Also the clinical triad of cranial neuritis, meningitis, and radiculoneuritis also constitutes Lyme disease in an endemic area unless proven otherwise.[18] Aggregates and groups of lymphocytes are found infiltrating the autonomic ganglia directly as well as the afferent and efferent rootlets. Plasma cells are not so prominent as are the lymphocytes in this stage. We have not seen spirochetes in the ganglia, but the assumption is that they are directly present.

We have had recent experience with a lesion that is not uncommonly seen in late stage II in Europe, and that consists of a lesion manifested clinically by extreme pain in one or more proximal muscle groups such as the musculature of the thigh or forearm. This pain is not that of the stage I myalgia but is one of pain at rest as well as in motion. Clinically there is swelling and tenderness of involved muscle groups. This lesion appears to be independent of peripheral neuropathy or central nervous system involvement, although they may coexist. Biopsy shows perivascular infiltrates of lymphocytes and plasma cells of vessels within the muscle itself. The myocardial fibers show minimal swelling but no sarcoplasmic degeneration or direct myopathy such as peripheralization of nuclei. In one case we demonstrated spirochetes in the interstitium and overlying muscle fibers. These perivascular lymphoid infiltrates within muscle are virtually identical to those found in polymyositis and dermatomyositis. The duration of Lyme myositis is not known, but it probably can persist for variably long periods.

Stage III

Stage III (TABLE 3) is the chronic phase of Lyme disease, usually beginning months after initial onset, and lasting into many years. Stage III is characterized by involvement of the joints (intermittent oligoarthritis), peripheral nervous system, skin and subcutaneous soft tissue. The arthritis is one of an intermittent nature with periods of activity alternating with quiescence. Knee, wrist, and shoulder are more common, with the knee joint being the most characteristically involved.[19] Clinically there is swelling and pain of the involved joint, and unlike rheumatoid arthritis rarely will more than three joints be involved. It is now well known that Lyme arthritis is reflected by varying degrees of hypertrophic, proliferative synovitis, consisting of aggregates of lymphocytes in the subsynovium, with admixtures of plasma cells, macrophages, and

numerous mast cells. Neutrophils are found in the synovial fluid, and with only minor exception are not usually seen in the synovium in Lyme arthritis. They probably are present in acute stages of the arthritis but give way within a short period of time to lymphocytes and plasma cells. Well-defined germinal centers are usually not seen in the synovia as they were in lesion of the skin called lymphadenosis benigna cutis. Synovial cells are hyperplastic, often more than four cells thick, and accompany the villous hypertrophy. Vessels are prominent and may actually be angiomatoid in appearance. Deposits of fibrin and fibrinogen are found not only on the surfaces of some villi, but also within the stroma of villi, and sometimes compose 50% or more of the total tissue volume as obtained by synovial curetting specimens. Putt's fibrin stain yields a rose-to-pink color against a background of blue collagen, confirming that fibrinogen and fibrin are present in this material. Despite this deposition, fibrin microthrombi are not seen within the vessels (FIG. 6). Not every case of Lyme arthritis shows this fibrin deposition, but it is prominent in some patients and exceeds the amount seen as a rule in rheumatoid arthritis or Reiter's disease.[9] This material is not seen in every example, and is not a requirement for Lyme synovitis.

TABLE 3. Stage III

Arthritis-synovitis vasculitis
Lymphoplasmacellular hyperplasia
Fibrinaceous deposits
Occlusive vessels
Myositis, fasciitis
Peripheral neuropathies: motor, sensory
EPI and endoneural vasculitis
Wallerian degeneration
Demyelination
Acrodermatitis chronica atrophicans, occluded vessels
Lymphocytoma cutis?
Linear scleroderma, morphea, fasciitis, vasculopathy
Ulnar fibrous nodules, occluded vessels
Lichen sclerosus

The small vessels in some cases have obliteration as a result of a hypercellularity of the inner lining of the vessels (FIG. 6). In some cases this produces the appearance of "onion skinning" of the type classically seen in the vasculopathy of vessels of the spleen in lupus erythematosus. This is also not seen in every case of Lyme arthritis, but when coexisting with prominent deposits of fibrin suggests the presence of Lyme arthritis, if the patient is in an endemic area.[9] Spirochetes are very sparse and are demonstrated in histologic sections only with great difficulty and in only a minority of cases (FIG. 6). A large number of cases show prominent hemosiderin deposits, especially in the deeper subsynovial regions. It is possible that exacerbations and flairs of the arthritis are heralded by stromal hemorrhages, leading to the hemosiderin and fibrin and fibrinogen depositions.

The peripheral nervous system can be involved in stage III, manifested mainly by peripheral neuropathies. There is overlap from stage II neural involvement. Most neuropathies in stage III appear to be cranial.[21,22] These neuropathies are sensorimotor, and involve the infiltration of predominantly lymphocytes and a few plasma cells along the perineurium. Fewer lymphocytes can infiltrate the internal segment of the nerves, where they can be clustered around small vessels. The vessels and the perineural

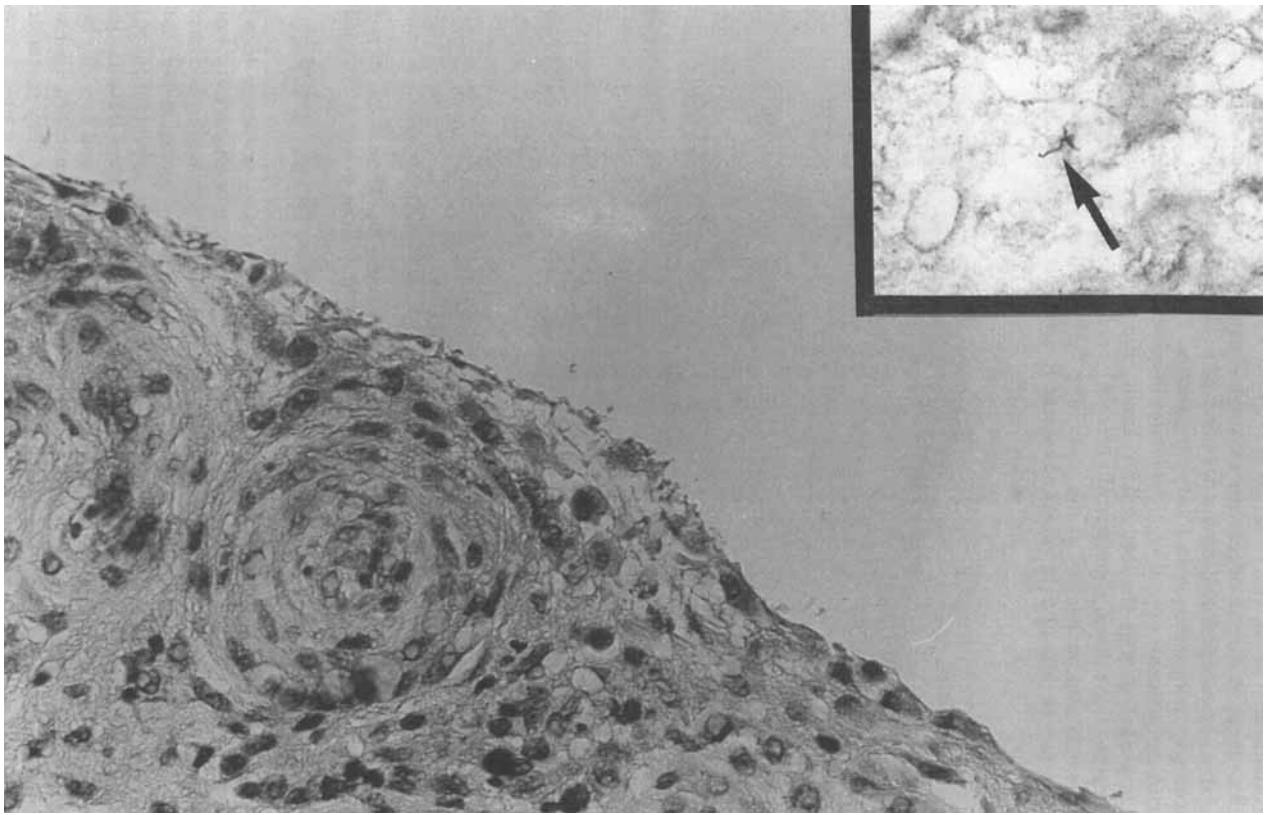

FIGURE 6. Stage III Lyme synovitis with hypercellular occluded vessel with perivascular plasma cells and lymphocytes. A synovial spirochete is seen by silver stain in the inset (magnification 1000×).

regions as well as within the nerve proper show a vasculopathy in the form of variable occlusion and lymphocytes. These changes also can be found in stage II involvement. In chronic and severe forms, there may be nerve fiber loss, demyelination, and changes not unlike that of Wallerian degeneration. Amyloid deposits are not seen.

The skin and subcutaneous tissues are involved in chronic, stage III Lyme disease, and seemingly more common in European patients. The hallmark is acrodermatitis chronicum atrophicans, a peculiar, often bilaterally symmetrical, reddish discoloration of the acral skin such as the feet, ankles, hands, and wrists, often with scaling and hyperkeratosis.[23] At times, a peripheral neuropathy accompanies this dermal change. The joints may also be involved at the same time.[24] The histology is characteristic in that there can be loss of rete ridges subjacent to which is a dermis infiltrated by

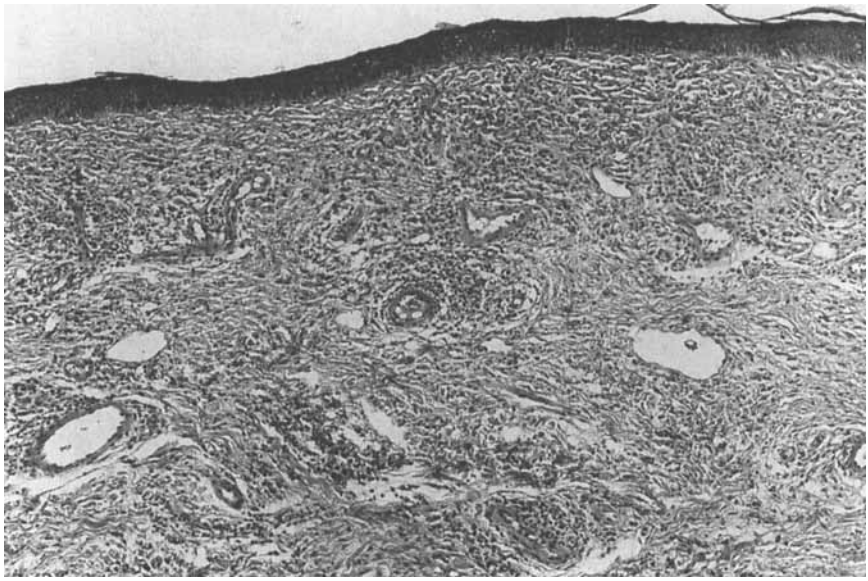

FIGURE 7. Photomicrograph of acrodermatitis chronicum atrophicans. There is loss of rete ridges followed by dilatation of the dermal vessels and a persistent infiltrate of lymphocytes and plasma cells.

lymphocytes, plasma cells, macrophages, scattered mast cells, and prominent blood vessels (FIG. 7). The vasculature shows a dilation which appears to be characteristic of ACA. The infiltrate can extend into the subcutaneous fat where a panniculitis becomes prominent. Scattered blood vessels in the involved dermis can show occlusion like that seen in the synovia and peripheral nerves. The blood vessels of the subcutaneous fat show increasing numbers of plasma cells and more severe damage than those in the upper dermis. Spirochetes can be demonstrated in sections of ACA and can also be cultured from ACA. It is becoming clear that lesions resembling morphea (linear scleroderma) can be found in stage III Lyme disease. Histologically they resemble scleroderma strongly, with a thickened dermis by excess collagen which extends below the eccrine sweat glands and into the fibrous septae that support the pannus. Perivascular lymphocytes and plasma cells are also present in these cases. Another

sclerodermoid manifestation of stage III Lyme disease is related to linear scleroderma and has the clinical and histologic appearance of eosinophilic fasciitis. Here there are more perivascular plasma cells, especially in the deeper dermis, and there is an underlying lymphocytic and plasmacytic fasciitis. Perhaps fewer eosinophils than are found in classic eosinophilic fasciitis are present in this form, but they can be found. Two cases of lichen sclerosus (et atrophicus) have now been seen in chronic Lyme disease patients by us and by others.[23] Both had the upper papillary dermal homogenization of the collagen with an edematous appearance as seen in classic LSEA, and also had the band-like mid-dermal lymphocytic infiltration. Again in both of these cases, the deeper dermal vessels showed occlusive changes.

Recent experience in Europe shows that some patients with evidence of exposure to *B. burgdorferi* have skin lesions that histologically are identical to granuloma annulare.[25,26] Granuloma annulare may indeed be another chronic cutaneous manifestation of stage III Lyme disease, but we have had no experience with this in North American cases so far.

Another European lesion, not uncommon in West Germany, is the condition referred to as ulnar fibrous nodules.[27] These peculiar thickenings found over the outer aspect of the forearms near the elbow joints consist of homogenized nodular collagen deposits which contain thickened and occluded blood vessels, with perivascular infiltrates of macrophages and plasma cells. We have seen spirochetes by silver staining in our examination of these nodules, supporting the premise that the spirochete survives for long periods of time in skin and soft tissue structures.

LYME DISEASE IN MATERNAL INFECTIONS

It is clear that *B. burgdorferi* can be transmitted in the blood of infected pregnant women across the placenta into the fetus. This has now been documented with resultant congenital infections[28] and fetal demise.[29] Spirochetes can be recovered or seen in the infant's tissues including the brain, spleen and kidney. The chorionic villi of the placenta show an increase in Hofbauer cells as in luetic placentitis. Inflammatory changes of fetal or neonatal changes are not as pronounced as in the adult, but cardiac abnormalities, including intracardiac septal defects, have been seen.[28,29] It is not known why inflammatory cells are so sparse from maternal transmission, but it is possible that an immature immune system plays a role.

SUMMARY

Lyme disease is capable of producing a wide variety of clinical pathologic conditions and lesions having in common histologic features of collagen-vascular disease. The plasma cell is an omnipotent inflammatory responder in most tissues involved by Lyme disease, ranging from relatively acute to lesions that have gone on for years. Vascular thickening also seems to be prominent, and in the dermis is accompanied by scleroderma-like collagen expansion. The disease in some ways resembles the responses seen in lupus erythematosus such as mild cerebritis with lymphocytes and plasma cells in the leptomeninges. Lymphoplasmacytic panniculitis of Lyme disease resembles lupus profundus, both in the infiltrate and the plasma cell-blood vessel relationship. The onion skin thickened vessels of the synovia resemble the vessels of lupus spleens, while the scleradermoid thickening of the dermis and various skin lesions of stage III Lyme disease suggest a collagen-vascular disorder. Finally, the perivascu-

lar lymphoid infiltrate in clinical myositis does not differ from that seen in polymyositis or dermatomyositis. All of these histologic derangements suggest immunologic damage in response to persistence of the spirochete, however few in number.

REFERENCES

1. AFZELIUS, A. 1910. Verhandlungen der dermatologischen Gesellschaft zu Stockholm. Arch. Dermatol. Syph. (Berlin) **101:** 405–406.
2. FRITZ, A. & B. LANGERHOLM. 1983. Acrodermatitis chronica atrophicans, erythema chronicum migrans and lymphadenosis benigna cutis—spirochetal diseases? Acta Derm. Venereol. (Stockholm) **63:** 432–436.
3. BAFVERSTEDT, B. 1950. Lymphadenosis benigna cutis (LABC): Its nature, course and prognosis. Acta Derm. Venereol. (Stockholm) **40:** 10–18.
4. GARIN, C. & C. BUJADOUX. 1922. Paralysie par les tiques. J. Med. Lyon **71:** 765–767.
5. BANNWARTH, A. 1941. Chronische lymphocytare Meningitis, entzundliche Polyneuritis and "Rheumatismus." Arch. Psychiatr. Nervenkr. **113:** 284–376.
6. STEERE, A. C., S. E. MALAWISTA, D. R. SNYDMAN, *et al.* 1977. Lyme arthritis: An epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis Rheum. **20:** 7–17.
7. STEERE, A. C., S. E. MALAWISTA, J. A. HARDIN, S. RUDDY, P. W. ASKENASE & W. A. ANDIMAN. 1977. Erythema chronicum migrans and Lyme arthritis: The enlarging clinical spectrum. Ann. Intern. Med. **86:** 685–698.
8. BURGDORFER, W., A. G. BARBOUR, S. F. HAYES, J. L. BENACH, E. GRUNWALDT & J. P. DAVID. 1982. Lyme disease—a tick-borne spirochetosis? Science **216:** 1317–1319.
9. JOHNSTON, Y. E., P. H. DURAY, A. C. STEERE, *et al.* 1985. Lyme arthritis: Spirochetes found in synovial microangiopathic lesions. Am. J. Pathol. **118:** 26–34.
10. STEERE, A. C., S. E. MALAWISTA, N. H. BARTENHAGEN, *et al.* 1984. The clinical spectrum and treatment of Lyme disease. Yale J. Biol. Med. **57:** 3–14.
11. DURAY, P. H. 1987. The surgical pathology of human Lyme disease. An enlarging picture. Am. J. Surg. Pathol. **11** (Suppl. 1): 47–60.
12. STEERE, A. C., C. E. BRINKERHOFF, D. J. MILLER, H. DRINKER, E. D. HARRIS JR. & S. E. MALAWISTA. 1980. Elevated levels of collagenase and prostaglandin E2 from synovium associated with erosion of cartilage and bone in a patient with chronic Lyme arthritis. Arthritis Rheum. **238:** 591–599.
13. HABICHT, G. S., G. BECK & J. L. BENACH. 1987. Lyme disease. Sci. Am. **257:** 78–83.
14. STEERE, A. C., R. L. GRODZICKI, A. N. KORNBLATT, *et al.* 1983. The spirochetal etiology of Lyme disease. N. Engl. J. Med. **308:** 733–740.
15. HARDIN, J. A., A. C. STEERE & S. E. MALAWISTA. 1984. The pathogenesis of arthritis in Lyme disease: Humoral immune responses and the role of intraarticular immune complexes. Yale J. Biol. Med. **57:** 139–143.
16. ÅSBRINK, E., A. HOVMARK & I. OLSSON. 1987. Lymphadenosis benigna cutis in Sweden. Presented at Lyme Borreliosis: Update Europe, Baden, Austria. June 2–4, 1987.
17. MARCUS, L. C., A. C. STEERE, P. H. DURAY, A. E. ANDERSON & E. B. MAHONEY. 1985. Fatal pancarditis in a patient with co-existing Lyme disease and babesiosis. Ann. Intern. Med. **103:** 374–376.
18. PACHNER, A. R. & A. C. STEERE. 1985. The triad of neurologic abnormalities of Lyme disease: Meningitis, cranial neuritis, and radiculoneuritis. Neurology **35:** 47–53.
19. STEERE, A. C., A. GIBOFSKY, M. E. PATARROYO, R. J. WINCHESTER, J. A. HARDIN & S. E. MALAWISTA. 1979. Chronic Lyme arthritis: Clinical and immunogenetic differentiation from rheumatoid arthritis. Ann. Intern. Med. **90:** 286–291.
20. HERZER, P. & B. WILSKE. 1986. Lyme arthritis in Germany. Zbl. Bakt. Hyg. A **263:** 268–274.
21. PACHNER, A. R. & A. C. STEERE. 1986. CNS manifestations of third stage Lyme disease. Zbl. Bakt. Hyg. A **263:** 301–306.

22. BAUMWACKL, U., W. KRISTOFERITSCH, E. SLUGA & G. STANEK. 1986. Neurological manifestations of *Borrelia burgdorferi* infections: The enlarging clinical spectrum. Zbl. Bakt. Hyg. A **263:** 334–336.
23. ÅSBRINK, E., E. BREHMER-ANDERSSON & A. HOVMARK. 1986. Acrodermatitis chronica atrophicans—A spirochetosis: Clinical and histopathological picture based on 32 patients. Course and relationship to erythema migrans Afzelius. Am. J. Dermpathol. **8:** 209–219.
24. HOVMARK, A., E. ÅSBRINK & I. OLSSON. 1986. Joint and bone involvement in Swedish patients with *Ixodes* ricinus-borne borrelia infection. Zbl. Bakt. Hyg. A **263:** 275–288.
25. ABERER, E., R. NEUMANN, H. KLODGE & G. STANEK. 1987. Antibodies against *Borrelia burgdorferi:* Serological screening of dermatological patients. Presented at Lyme Borreliosis: Update Europe, Baden, Austria, June 2–4, 1987.
26. KUSKE, B., J. SCHMIDLI, T. HURZIKA, M. CUENI & T. RUFLI. 1987. Antibodies against *Borrelia burgdorferi* in patients with granuloma annulare. Presented at Lyme Borreliosis: Update Europe, Baden, Austria, June 2–4, 1987.
27. WEBER, K., G. SCHIERZ, B. WILSKE & V. PREAC-MURSIC. 1984. European erythema migrans diseases and related disorders. Yale J. Biol. Med. **57:** 15–21.
28. SCHLESINGER, P. A., P. H. DURAY, B. A. BURKE, A. C. STEERE & M. T. STILLMAN. 1985. Maternal fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi.* Ann. Intern. Med. **103:** 67–68.
29. MACDONALD, A. 1986. Human fetal borreliosis, toxemia of pregnancy, and fetal death. Zbl. Bakt. Hyg. A **263:** 189–200.
30. REIK, L., A. C. STEERE, N. H. BARTENHAGEN, R. E. SHOPEY & S. E. MALAWISTA. 1979. Neurologic abnormalities of Lyme disease. Medicine **58:** 281–294.