CURRENT MEDICINE

GARY L. GITNICK

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Edited by

Gary L. Gitnick, M.D.
Professor of Medicine
Division of Gastroenterology
University of California, Los Angeles
School of Medicine
Los Angeles, California

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Sponsoring Editor: Robert J. Kosinski
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Contributors

Edgar Achkar, M.D.
Department of Gastroenterology
The Cleveland Clinic Foundation
Cleveland, Ohio

Paul E. Bellamy, M.D.
Professor of Medicine
Will Rogers Institute
Pulmonary Research Laboratory
UCLA School of Medicine
Los Angeles, California

William D. Carey, M.D.
Department of Gastroenterology
The Cleveland Clinic Foundation
Cleveland, Ohio

Doyt L. Conn, M.D.
Professor of Medicine
Chairman, Division of Rheumatology
Mayo Medical School
Rochester, Minnesota

Edward D. Crandall, Ph.D., M.D.
Professor of Medicine
Will Rogers Institute

Pulmonary Research Laboratory
UCLA School of Medicine
Los Angeles, California

Richard G. Farmer, M.D.
Chairman, Division of Medicine
Department of Gastroenterology
The Cleveland Clinic Foundation
Cleveland, Ohio

W. Leroy Griffing, M.D.
Assistant Professor of Medicine
Mayo Medical School
Rochester, Minnesota

David Heber, M.D., Ph.D.
Associate Professor of Medicine
UCLA School of Medicine
Los Angeles, California

M. Colin Jordan, M.D.
Professor of Medicine
University of Minnesota School of Medicine
Minneapolis, Minnesota

Martin Markowitz, M.D.
Assistant Professor
The New York Hospital–Cornell Medical Center
New York, New York

Clement J. Michet, Jr., M.D.
Assistant Professor of Medicine
Mayo Medical School
Rochester, Minnesota

Ralph L. Nachman, M.D.
Professor of Medicine
Chief, Division of Hematology-Oncology
The New York Hospital–Cornell Medical Center
New York, New York

Allen R. Nissenson, M.D.
Associate Professor of Medicine
Dialysis Program

UCLA School of Medicine
Los Angeles, California

Nigel K. Roberts, M.D.
Associate Clinical Professor of Pediatrics
UCLA School of Medicine
Los Angeles, California

Edward A. Ross, M.D.
Professor of Medicine
Dialysis Program
UCLA School of Medicine
Los Angeles, California

Robin L. Saltzman, M.D.
Professor, Section of Infectious Diseases
Department of Medicine
University of Minnesota School of Medicine
Minneapolis, Minnesota

Sheila Sherlock, M.D.
Professor, The Royal Free Hospital
London, England

Richard K. Winklemann, M.D., Ph.D.
Professor of Dermatology and Anatomy
Mayo Medical School
Consultant, Department of Dermatology
Mayo Clinic and Mayo Foundation
Rochester, Minnesota

Preface

In this third volume of *Current Medicine,* a group of leading medical researchers joined together to assess the most significant progress in American medicine during the past year. Experts from each medical specialty reviewed the literature in their respective fields and then reported on those emerging areas of greatest importance. They were asked to avoid extensive discussions of less significant studies and to concentrate on the interrelationships of different research trends and the potential importance of scientific programs. Because of our desire to make this book concise we had to make choices as to the material with the widest significance. In some instances we may have erred and to the authors whose work is not cited and to the readers we apologize. It is our hope that work of real significance and extensions thereof will again enter the medical literature in the years to come.

We sought to make this volume comprehensive enough to serve as a reliable up-to-date resource for a wide range of readers, including medical students as well as practicing physicians. Repetition is difficult to avoid and in some instances in which educational reinforcement seemed important and where there was appropriate overlap, some studies are mentioned in more than one chapter. We have placed much effort into the planning, writing, and editing of this book. We trust that the new information it contains will advance the teaching, care, and understanding of medical problems, and in this way may actually lead to stimulating further inquiry and research. As editor, I am indebted to each of the authors for the many hours of work they devoted to reviewing articles and writing chapters. I also wish to express my gratitude to Mrs. Susan Dashe for her invaluable editorial assistance and to Year Book Medical Publishers, Inc. for the efficient manner in which the text was compiled and produced.

GARY L. GITNICK, M.D.

Contents

CHAPTER 1

Infectious Diseases

Robin L. Saltzman
M. Colin Jordan

THERE HAVE BEEN SEVERAL important developments in infectious diseases during the past year. In some instances, etiologic agents have been discovered for new diseases (acquired immune deficiency syndrome, Lyme disease), while the causative agent may also have been identified for such venerable disorders as cat-scratch fever. New pathogenetic concepts have evolved for virus-induced liver disease and infectious gastroenteritis. In terms of diagnosis, recombinant DNA methodologies and monoclonal antibody technology are proving to be powerful tools for detection and characterization of certain diseases. Finally, new information has become available concerning prophylaxis and treatment of certain infections.

NEW ETIOLOGIES: THE MYSTERY UNRAVELS

Acquired Immune Deficiency Syndrome

The first cases of acquired immune deficiency syndrome (AIDS) were reported to the Centers for Disease Control (CDC) in 1981,[1, 2] and to date the number of cases continues to increase exponentially. Over 4,000 cases have been reported to the CDC, and the overall mortality rate has been estimated at about 43%.[3] AIDS has a wide geographic distribution. Although cases have been reported from most states within the U.S., almost 70% are from New York City, San Francisco, Los

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Angeles, or Miami. In addition, over 150 cases of AIDS have been reported from 25 other countries; approximately 30% of these are from Haiti.

The occurrence of AIDS has been significantly associated with high-risk groups in about 94% of cases. These include homosexual or bisexual men (72%), IV drug abusers (16.5%), Haitian immigrants (5%), and hemophiliacs or transfusion-related cases (0.7%). In addition, there are several reports of the syndrome occurring in infants where one or both parents had AIDS, were in high-risk groups for the syndrome, or had had sexual contact with persons in a high-risk group but without AIDS. In approximately 6% of cases, there is no apparent risk factor association.[3, 4]

In a recent national case-control study of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma within the homosexual population, the syndrome was significantly associated with patients who were promiscuous and engaged in passive anorectal sexual intercourse. A history of syphilis was common in the AIDS patients. Other studies have alluded to an increased risk for homosexuals with a history of non-A non-B hepatitis, treatment for enteric parasites, and use of illicit substances.[5, 6] Over 90% of cases occurred in persons 20 to 49 years of age, and all primary racial groups have been affected. The incubation period is long, and is presumed to be several months up to two years in duration. Because transmission of the syndrome prior to the actual illness can occur, major efforts continue to identify these individuals as early as possible.[4, 7]

The initial clinical manifestations of AIDS can be extremely subtle because thus far there are no clear-cut symptoms indicating loss of immunity. Early symptoms may include unexplained weight loss (10 to 20 lb over several months), prolonged fever, generalized lymphadenopathy, flulike symptoms (malaise or fatigue lasting more than ten days), dyspnea on minimal exertion, violaceous nodular lesions of the skin suggestive of Kaposi's sarcoma, unresolved herpeslike lesions, persistent diarrhea, blurred vision, or severe prolonged headache. The presence of generalized lymphadenopathy in a homosexual person, once thought to be a benign entity, is now thought by some to represent part of the spectrum of AIDS.[8] Seventeen percent of homosexual persons with generalized lymphadenopathy followed prospectively developed life-threatening opportunistic infections, malignant lymphoma, or Kaposi's sarcoma.

The actual clinical presentations of AIDS most commonly include *Pneumocystis carinii* pneumonia (PCP) in 51%, Kaposi's sarcoma (KS) in 26%, other opportunistic infections in 16%, and the combination of PCP and KS in 7%.[3] The most frequently occurring opportunistic infections seen in patients with AIDS, in addition to PCP, are *Candida* esophagitis, disseminated cytomegalovirus disease often with pneumonitis, chronic and progressive herpes simplex ulcerations, disseminated *Mycobacterium avium-intracellulare,* chronic unrelenting cryptosporidial enteritis, and CNS disease with *Cryptococcus neoformans* and *Toxoplasma gondii.*[4, 7] With respect to the latter, recent studies have emphasized the difficulty in establishing this diagnosis in AIDS patients. They frequently exhibit only a modest serologic response to *Toxoplasma gondii,* and therefore the diagnosis of dis-

ease often relies on brain biopsy. Several studies have shown AIDS patients with documented CNS toxoplasmosis to frequently have low IgG titers. Many lack a fourfold rise in antibody titers, and they often lack an IgM response.[9, 10, 11, 12, 13] In addition, several patients have had negative brain biopsies.[9, 12] This has led some to recommend empiric therapy for certain high-risk individuals with a clinically compatible presentation.[12] However, because of the possibility of polymicrobial infection and the fact that different organisms may be isolated from separate mass lesions, most advocate the brain biopsy in the evaluation and appropriate treatment of CNS mass lesions.[14]

The primary immunologic abnormalities involve cell-mediated immunity and include skin test anergy, lymphopenia, decreased numbers and percentage of T-helper cells, increased percentage of T-suppressor cells, and reduced T-cell proliferative responses to mitogens and antigens. Defects in humoral immunity also occur, and these include a polyclonal gammopathy (usually IgG and IgA) as well as increased circulating immune complexes, usually seen in patients with opportunistic infections.[4, 6, 7]

The epidemiology of the syndrome is similar to that for hepatitis B, with its apparent spread through sexual contact, blood products, the sharing of needles, and within families.[4, 5, 7] Thus the focus of attention has been on a transmissible agent, presumably a virus. Extremely exciting data have been reported implicating HTLV-III, a human lymphotrophic RNA retrovirus that preferentially infects T-helper cells, as the etiologic agent of AIDS. Although almost 90% of AIDS patients and 79% of pre-AIDS patients were seropositive for HTLV-III,[15] the virus has only been isolated from 36% of adult and juvenile patients with AIDS (see reference 16, section on HTLV).

Further studies are definitely needed to ascertain the role of HTLV-III in AIDS. If found to be the etiologic agent, efforts can be aimed at finding appropriate therapy (antiviral agents and immunomodulators) to help alter the fatal progression of the disease. In addition, work can then begin on the development of a vaccine to protect high-risk individuals from the deadly acquired immune deficiency syndrome.

Human T-cell Lymphotropic Viruses

Human T-cell lymphotropic retroviruses have certain unique characteristics. They are RNA viruses with a high degree of tropism for the OKT_4 (helper) subset of human lymphocytes. After infection with the virus, T-cell function may be inhibited, and the lymphocytes may be killed or transformed. Thus far, four members of the virus family have been identified: HTLV-I, HTLV-II, LAV (lymphadenopathy-associated virus), and HTLV-III.

HTLV-I, commonly known as human T-cell leukemia lymphoma virus, was first isolated from a black American with an aggressive form of T-cell lymphoma.

Since that time, most isolates have been recovered from patients with mature T-cell malignancies. The characteristic syndrome consists of a fulminant T-cell disorder with hypercalcemia and opportunistic infections. Seroepidemiologic and nucleic acid hybridization studies indicate that HTLV-I may be associated etiologically with the T-cell malignancy of adults that is endemic in southern Japan, the Caribbean, and Africa. Twelve strains of HTLV-I have been isolated to date.[17–19] In addition, HTLV-I has been isolated from the T-cells of 10% to 15% of AIDS patients. HTLV-II has been recovered from one patient with a variant of hairy cell leukemia and from the T-cells of one AIDS patient.[16]

LAV, or lymphadenopathic/lymphadenopathy-associated virus, differs from HTLV-I or HTLV-II in that it is primarily associated with lymphadenopathy. It was first isolated from the lymph node of a homosexual man with lymphadenopathy.[20] Its link to AIDS was suggested by (1) the presence of antiviral antibody in both AIDS (37% to 41%) and pre-AIDS (72%) patients (Table 1), (2) the repeated isolation of the virus from both these patient populations, and (3) the isolation of the virus from a blood-donor recipient pair with AIDS.[21] LAV remains poorly characterized because of the lack of a cell line for propagation of the virus. Whether LAV is identical to the newly described HTLV-III remains to be determined.

HTLV-III is 100 to 120 nm in diameter, and is produced in high number from infected cells by budding from the cell membrane (Fig 1). It is distinguished morphologically from HTLV-I or HTLV-II by the dense cylindrical core seen in mature virions by electron microscopy (Fig 2).[16] HTLV-III has been isolated from cultured lymphocytes of 48 subjects—18 of 21 (85.7%) with pre-AIDS, three of four clinically normal mothers of children with AIDS, 26 of 72 (36%) adult and juvenile patients with AIDS, and one of 22 normal homosexual subjects (Table 2).[16] The latter patient subsequently developed AIDS six months after virus isolation. No HTLV-III was isolated from 115 normal heterosexuals. The low yield

TABLE 1.—ANTIBODIES TO LAV IN SERUM FROM PATIENTS WITH AIDS, PRE-AIDS AND CONTROLS*

GROUP	NUMBER POSITIVE	NUMBER TESTED	PERCENTAGE
AIDS	51	125	41
Homosexuals	42	100	42
Intravenous Drug Abusers	5	16	31
Haitians	2	5	40
Others	2	4	51
Pre-AIDS	81	113	72
Controls			
Homosexual Men			
1978	1	100	1
1980	12	50	24
Blood Donors	0	189	0
Laboratory Workers	0	70	0

*Modified from Kalyanaraman V.S., Cabradilla C.D., Getchell J.P.[21]

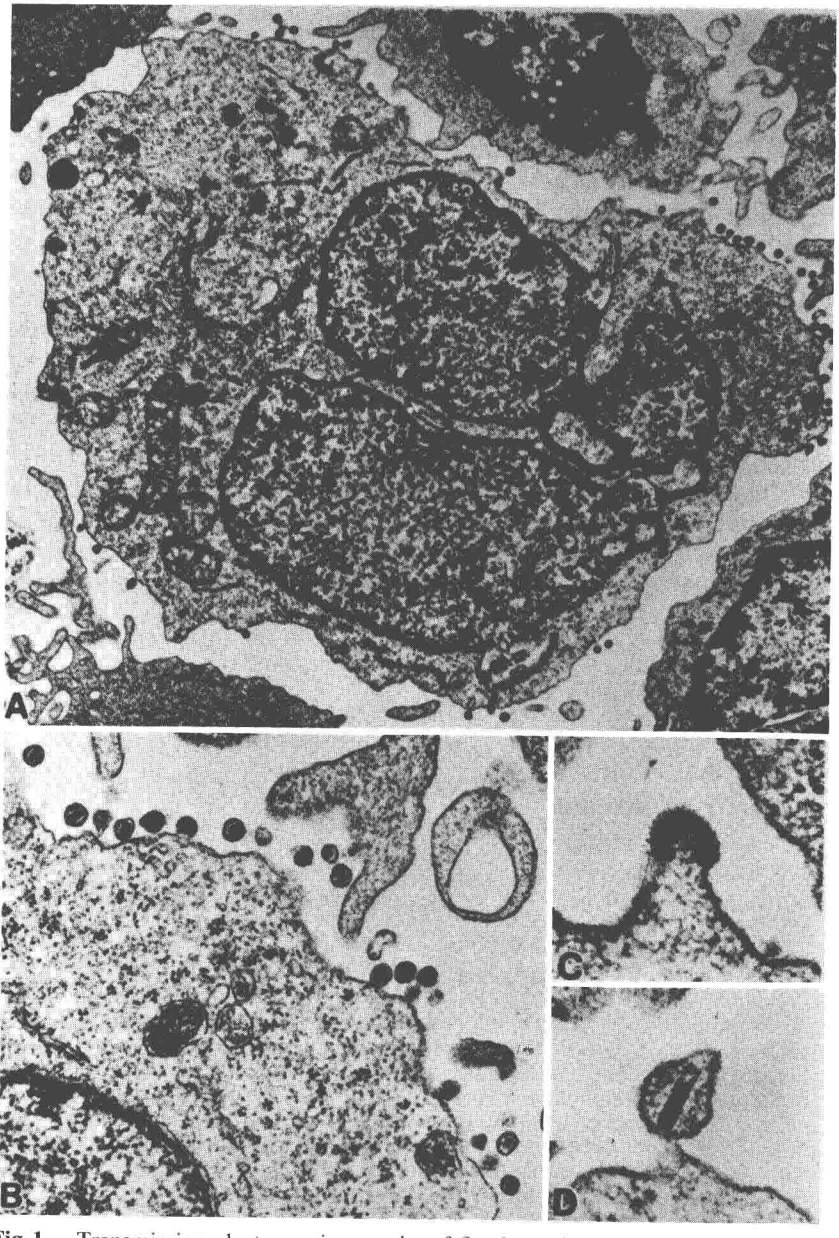

Fig 1.—Transmission electron micrographs of fixed, sectioned lymphocytes from a patient with pre-AIDS. **B** to **D** show production of HTLV-III via budding from the cell membrane of infected cells. **D** shows the characteristic dense cylindrical core of HTLV-III. (From Gallo R.C., Salahuddin S.Z., Popovic M.[16] Used by permission.)

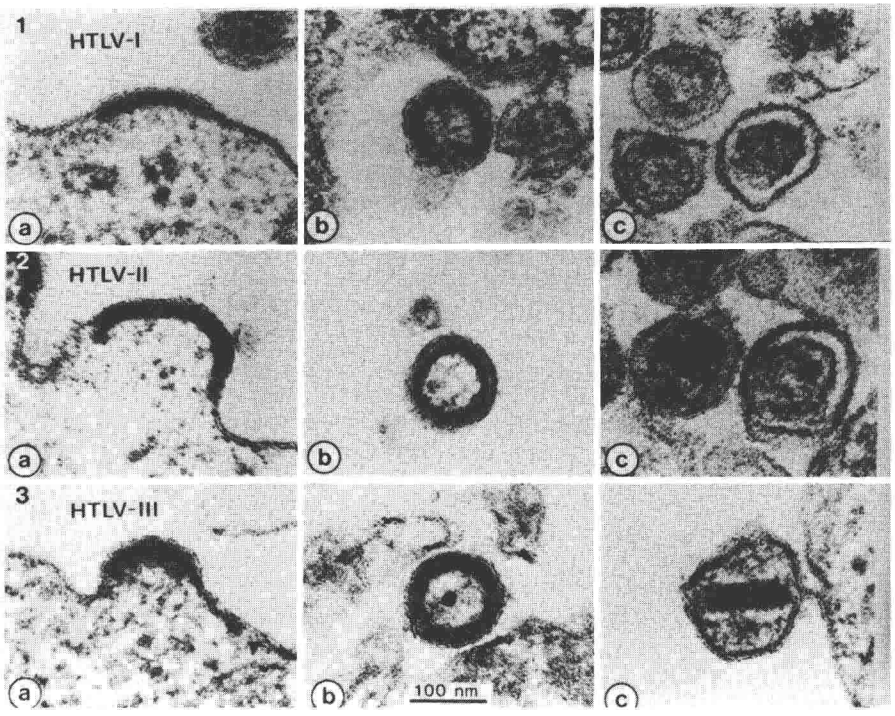

Fig 2.—Electron microscopy of thin sections of cells producing HTLV-I, HTLV-II and HTLV-III. **Top,** HUT 102 cells producing HTLV-I. **Middle** cells from AIDS patient producing HTLV-II. **Bottom,** cells from Pre-AIDS patient producing HTLV-III. **a,** Virus particles budding from the cell membrane. **b,** Free particles have separated from the membrane. **c,** Free particles sectioned in a different plane. Note the characteristic dense cylindrical core of HTLV-III. (From Schupbach J., Popovic M., Gilden R.W., et al.[130] Used by permission.)

TABLE 2.—ISOLATION OF HTLV-III FROM THE PERIPHERAL BLOOD LEUKOCYTES OF PATIENTS WITH AIDS, PRE-AIDS AND CONTROLS*

GROUP	NUMBER POSITIVE	NUMBER TESTED	PERCENTAGE
AIDS	26	72	36
Pre-Aids	18	21	85.7
Controls			
Homosexuals	1	22	4.5
Heterosexuals	0	115	0

*Modified from Gallo R.C., Salahuddin S.Z., Popovic M.[16]

of virus isolation from AIDS and pre-AIDS patients may reflect (1) the age and poor handling of the specimens, (2) the depletion of permissive OKT_4 cells in patients with advanced AIDS, or (3) the insensitivity of current methods for viral detection. Serologic studies revealed that 87.7% of AIDS patients and 78.5% of pre-AIDS patients were antibody-postive for HTLV-III (Table 3).[15]

Further studies will be necessary to determine whether HTLV-III and LAV are identical viruses and whether either is, in fact, the cause of AIDS. If so, characterization of the pathogenesis of the disease should be possible, and perhaps vaccine development will be feasible.

Lyme Disease

Lyme disease, first described in the United States in 1975, has been reported in 14 states as well as in Europe and Australia. The disease is now known to be caused by a spirochete and is transmitted via the tick vector, *Ixodes dammini*. These tick vectors are endemic along the northeast coast of the United States from Massachusetts to Maryland, and in Wisconsin, California, and Oregon.

A spirochetal etiology was suggested after the isolation of spirochetes from 61% of *Ixodes dammini* ticks from endemic Shelter Island, New York. In addition, inoculation of spirochetes into rabbits produced erythema chronicum migrans (ECM)-like lesions, which are classic in Lyme disease.[22, 23] The spirochetal etiology was confirmed after the recovery of the organisms from three of 56 patients with Lyme disease. One isolate was from blood, one from an ECM skin lesion, and another from cerebrospinal fluid (CSF).[22] In addition, a spirochete similar both morphologically and immunologically was isolated from approximately 20% of nymphal or adult *Ixodes dammini* ticks in areas endemic for Lyme disease.[22]

Since the first report, others have isolated the spirochetes from the blood of two of 36 patients,[24] and from the CSF of one of 12 patients[25] with Lyme disease. This low yield in recovery of organisms suggests that the spirochetemia is tran-

TABLE 3.—ANTIBODIES TO HTLV-III IN SERUM FROM AIDS, PRE-AIDS AND CONTROLS*

GROUP	NUMBER POSITIVE	NUMBER TESTED	PERCENTAGE
AIDS	43	49	87.8
Pre-AIDS	11	14	78.6
Controls			
Homosexuals	6	17	35.3
Intravenous drug users	3	5	60
Random Volunteers	1	164	0.6

*Modified from Sarngadharan M.G., Popovic M., Bruch L., et al.[15]

sient and of low density.[24] Each patient from whom spirochetes were recovered had a rise in the specific antispirochetal antibody.

The disease usually begins in summer, with more than 80% of cases occurring in June or July.[26] Although presumably initiated from a tick bite, only 31% of patients with Lyme disease recall such an event.[26] The disease has early and late manifestations. Classically the skin lesion, erythema chronicum migrans, which occurs in about 75% of patients, appears first. It is defined as a red macule or papule, often at the site of the tick bite that expands to form a large annular lesion, usually with a bright red outer border and partial central clearing. The skin lesions may occur anywhere but are particularly common on the thigh, groin, and axilla. In addition, approximately 50% of patients experience multiple secondary annular lesions, with evanescent red blotches or circles, malar or urticarial rash, conjunctivitis, periorbital edema, or diffuse erythema. Commonly associated with the ECM are flulike symptoms consisting of headache, stiff neck, myalgias, arthralgias, fever, malaise, and occasionally lymphadenopathy. Migratory polyarthritis, usually without significant joint swelling, may also occur. Late manifestations may occur weeks to months after the initial presentation and usually involve the CNS (meningoencephalitis, cranial or peripheral nerve palsies, and sensory radiculopathy) or the heart (myocarditis or conduction abnormalities).

The classic Lyme arthritis can occur as early as weeks after the initial presentation, but reports of frank arthritis occurring years later are well documented. The arthritis is often intermittent and recurrent, and a chronic form with actual erosion of the cartilage and bone has been described. A genetic predisposition has been suggested for those with the more protracted and severe disease. These individuals frequently have been found to have the B-cell alloantigen, DR2.[25, 26]

Laboratory abnormalities early in the disease consist primarily of an elevated erythrocyte sedimentation rate, increased IgM levels, and occasionally elevated liver blood tests.[26] With the later manifestations, the expected abnormalities are seen (CSF pleocytosis with meningoencephalitis, ECG abnormalities in myocarditis, etc.). Specific IgM antibody occurs in 90% of patients with early disease (ECM alone), with titers greater than or equal to 1:128. It peaks three to six weeks after the onset of the disease. In contrast, specific IgG antibody is seen in 94% of patients with late disease, peaking months after the initial presentation. This often coincides with the appearance of arthritis. False-positive IgM titers may be seen in infectious mononucleosis.[22]

The diagnosis of Lyme disease is usually made clinically when the dermatologic manifestations and rapidly changing systemic involvement occur. Although the diagnosis can be made serologically, testing is not generally available and is usually unnecessary.[26]

The drug of choice for treatment of early Lyme disease in adults is tetracycline (1 gm daily) for ten days. In a prospective study, ECM and associated symptoms resolved faster in patients treated with penicillin or tetracycline than in those given erythromycin.[27] None of 39 patients treated with tetracycline developed late man-

ifestations as opposed to three of 40 penicillin-treated patients, or four of 29 treated with erythromycin.[27] Fourteen percent of patients, usually those with more severe disease, had an intensification of signs and symptoms within 24 hours after the start of treatment. This Jarisch-Herxheimer–like reaction was worse with penicillin and tetracycline than with erythromycin, and was usually manifested by higher fever, a redder rash, and increased pain. Penicillin (2 gm daily) can also be used and is the drug of choice in children at a dosage of 50 mg/kg daily with a minimum dosage of 1 gm daily. Erythromycin should be used in patients who are allergic to penicillin. Retreatment or continuation of treatment for 20 days should be considered in patients with recurring or persisting symptoms.

The neurologic manifestations, particularly meningoencephalitis, should be treated with high-dose parenteral penicillin (20 million units daily) for ten days.[25] Tetracycline, 2 gm daily for 30 days, is recommended for penicillin-allergic patients, although there is no experience with this regimen. In patients with cranial nerve palsies alone, if no previous antibiotics have been given, oral antibiotics as previously described for the treatment of early disease are recommended. In addition, a short course of prednisone is advocated if the patient is seen within 24 hours of the onset of the palsy.[25]

The pathogenesis of Lyme disease is not clearly delineated to date. The disease presumably begins with the bite of an infected tick. The spirochetes are injected into the skin or the bloodstream via the saliva of the tick, or are deposited onto the skin in the fecal material. After an incubation period of up to one month, the organisms migrate outward in the skin, resulting in the typical ECM lesion. In addition, blood-borne organisms have access to other organs, particularly the brain, liver, and spleen, or to other skin sites causing the secondary annular lesions.[26] Further work is required to determine the pathogenesis of the ''late disease.'' The following questions have yet to be answered: (1) Do the whole organisms persist months to years later when the arthritis appears? (2) Are the live organisms actually present in the joints, or do they live long enough to simply trigger a self propagating inflammatory host response? (3) Lastly, could it be that late disease is actually due to retained poorly degradable antigens of the spirochete that initiate a host response?

Cat-Scratch Disease

The etiology of cat-scratch disease (CSD) has remained a mystery for over 30 years. Some 2,000 cases occur annually,[28] predominantly in children. Characteristically, the disease presents with fever, malaise, and tender lymphadenopathy.[29, 30] The majority of patients have a history of contact with cats, and an erythematous papule, vesicle, or pustule is frequently noted at the primary site of inoculation.[29, 31] Less commonly, an oculoglandular syndrome consisting of con-