

Visceral Leishmaniasis

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Introduction

Definition

Visceral leishmaniasis (VL), a chronic disease caused by parasites of the *Leishmania donovani* complex, is characterized by irregular fever, enlargement of the spleen and liver, weight loss, pancytopenia, and hypergammaglobulinemia.

Synonyms

Visceral leishmaniasis is also known as kala-azar, a Hindi word meaning “black sickness”, although hyperpigmentation is not a common feature of the disease. Descriptive names for VL, such as Burdwan fever, Dumdum fever, and Shahib’s disease, are used infrequently.

General Considerations

The most common etiologic agents of VL are 3 species of the *L. donovani* complex: *Leishmania donovani donovani* and *Leishmania donovani infantum* in the Indian subcontinent, Africa, China, the Mediterranean littoral, and the Middle East; and *Leishmania donovani chagasi* in South America. (Hereafter, organisms will be identified only by genus and species; eg, *L. donovani* for *L. d. donovani*). Organisms with biochemical characteristics of *Leishmania tropica* have occasionally been isolated from bone marrow cultures of patients with systemic leishmanial infection in Kenya, the Middle East, and India.^{1,2,3}

Epidemiology

Visceral leishmaniasis is widely distributed and endemic in 82 countries (Fig 5.1). Estimated incidence of VL worldwide is at least 100,000 per year. Over 90% of patients come from 3 regions: the Ganges River basin in India, Bangladesh, and Nepal; the East African countries of Ethiopia, Sudan, and Kenya; and northeastern Brazil.⁴ Since the 1990s, southern Sudan and the Indian state of Bihar have been epidemic centers, with high rates of infection and tens of thousands of deaths. Civil strife, poor nutrition, population movement, and dire poverty are common factors contributing to the spread of disease in these regions.

Subspecies of *L. donovani* are transmitted by sandflies of the genera *Phlebotomus* in the Eastern Hemisphere and *Lutzomyia* in the Western Hemisphere. Epidemiology depends on the interaction of sandflies, reservoir hosts, and susceptible humans.^{5,6}

Reservoir Hosts

Humans. In India, where the domestic sandfly vector *Phlebotomus argentipes* feeds solely on humans, large epidemics spread continuously and discontinuously through population migrations. Transmission during the epidemic periods is largely person to person from active cases of visceral leishmaniasis. The contribution of the human reservoir of asymptomatic and oligosymptomatic infections to transmission is not known. Humans appear to be the only reservoir host, but it is possible that an unknown animal

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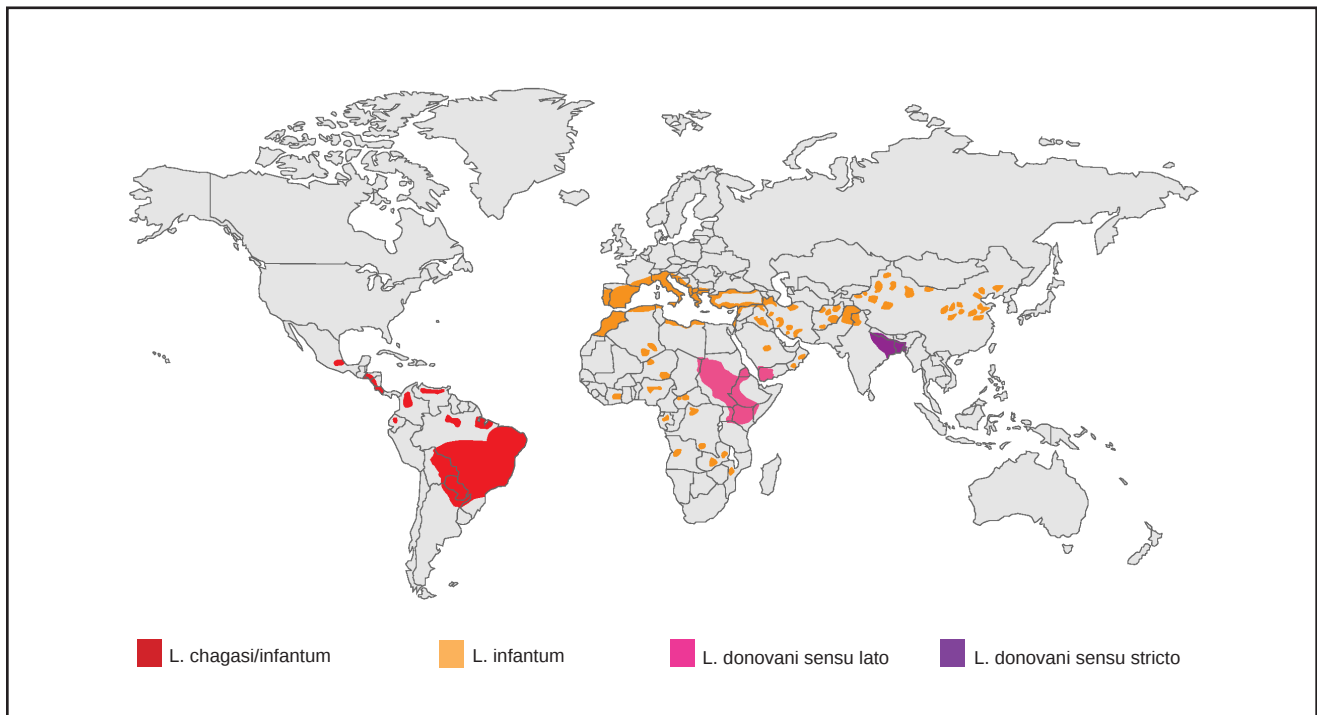


Figure 5.1 Geographical distribution of leishmaniasis

reservoir maintains the cycle between epidemics.

Domestic Canines. In Mediterranean countries, VL is urban and periurban and transmitted by *Phlebotomus perniciosus*, *Phlebotomus major*, *Phlebotomus simici*, and *Phlebotomus longicuspis*, with dogs as the main reservoir. Infants and young children are most commonly affected. Young dogs and certain breeds such as foxhounds and beagles are especially susceptible to infection with *L. infantum* and develop overt disease that is often fatal. In North America, rare outbreaks among foxhounds have been reported (Fig 5.2).^{7,8} Dogs are also important reservoirs in South America, where the main vector is *Lutzomyia longipalpis*.

Wild Canines. In southern France and central Italy, VL is primarily a rural disease that affects older children and adults. *Phlebotomus ariasi* and *Phlebotomus perfiliewi* are the vectors, and foxes with no overt disease are the reservoir. Foxes are also reservoirs in Brazil. Jackals are probably an important source of the sporadic, mainly rural outbreaks in the Middle East and Central Asia.

Multiple Hosts; Rodents. The epidemiology of VL in Africa is incompletely understood. In Kenya, *Phlebotomus martini* is the probable vector, and epidemics of VL in the 1950s and 1970s suggested a human reservoir. However, domestic dogs in Kenya have occasionally been infected with *L. donovani*. In Sudan, there have been several epidemics of VL since the 1950s, but the disease is usually sporadic in nomads who occupy temporary villages in the dry season near patches of scrub that harbor the vector

Phlebotomus orientalis. *Leishmania donovani* has been isolated from Nile grass (or Kusu) rats (*Arvicanthis niloticus*) and other rodents in Sudan, which are probably important in maintaining enzootic foci in interepidemic periods. Parasite isolates from Sudan, Ethiopia, and Kenya all appear to be *L. donovani*, albeit a genetically diverse population.^{9,10}



Figure 5.2 American foxhound, one of the breeds susceptible to visceral leishmaniasis in North America.

Infectious Agents

Morphologic Description

See chapter 4.

Life Cycle and Transmission

See chapter 4.

Clinical Features and Pathogenesis

The incubation period for VL is generally 2 to 6 months, although disease occasionally develops many years after exposure. Following inoculation by a sandfly, *Leishmania* promastigotes enter cutaneous dendritic cells or macrophages through receptor-mediated phagocytosis. The parasites use host complement receptors to enter phagolysosomes, and survive and multiply despite low pH and activated proteinases. Experimental studies in mice have shown that sandfly saliva promotes transmission of *Leishmania* sp through anticlotting and antiplatelet factors, and by vasodilation and immunomodulation. Persistence and propagation of promastigotes and amastigotes in host macrophages are enhanced by the effect of these salivary components on cytokines and by inhibition of nitric oxide killing. These properties of sandfly saliva are the focus of current research on an antileishmania vaccine.¹¹

At the site of inoculation, a small granuloma develops, consisting of histiocytes filled with amastigotes and surrounded initially by epithelioid cells and later by giant cells. Parasites spread to local lymph nodes and then, hematogenously within macrophages, to the liver, spleen, and bone marrow. There they either stimulate a granulomatous cellular immune response that results in subclinical disease and spontaneous resolution, or they multiply and cause the clinical syndrome of VL. Pathogenesis depends to some degree on host genetic factors.

In naive adults, onset of disease is frequently acute, with high fever, chills, and malaise that are often mistaken for malaria.¹² Visceral leishmaniasis progresses more gradually in indigenous patients, with intermittent fever, progressive enlargement of the spleen and liver, and vague abdominal/splenic discomfort. Other common symptoms include weight loss, loss of appetite, epistaxis, diarrhea, and non-productive cough. Patients are often weak and emaciated on initial presentation.

On physical examination and at autopsy, the abdomen is usually distended by a markedly enlarged spleen and a moderately enlarged liver (Figs 5.3 to 5.5). The spleen is smooth, firm, and nontender. In acute VL, the spleen may be scarcely palpable. Femoral and inguinal lymphadenopathy are often noted, especially in African VL. Lymphatic leishmaniasis is frequent, and generalized and regional adenopathy may be present with or without systemic symptoms. Lymph nodes are painless and seldom greater than 2 cm in diameter. Trophic changes of the skin and hair of

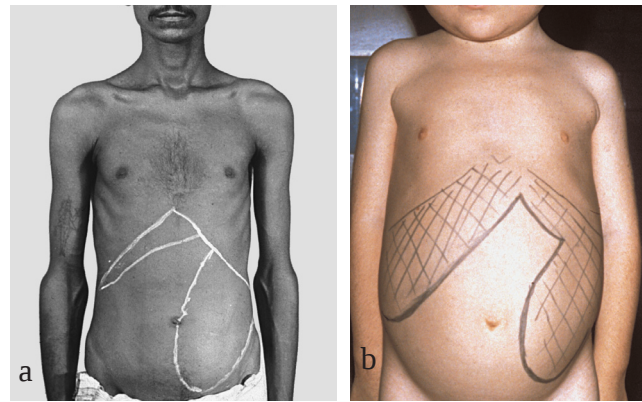


Figure 5.3 a,b
Hepatosplenomegaly a. Asian adult patient with visceral leishmaniasis b. Four year-old child from Natal, Brazil.



Figure 5.4
Hepatosplenomegaly in siblings from Natal, Brazil.

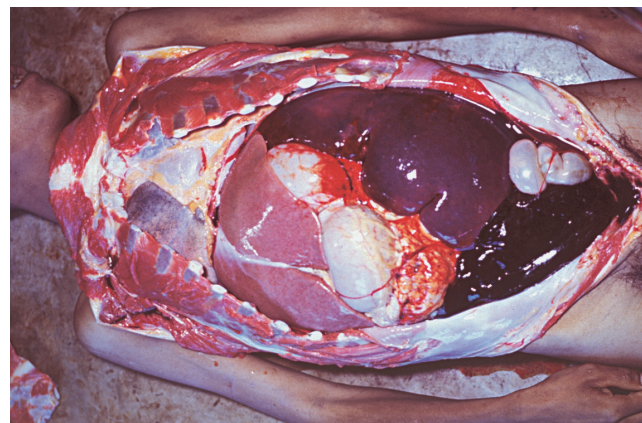


Figure 5.5
Autopsy of man with visceral leishmaniasis, hepatosplenomegaly, and intra-abdominal hemorrhage that followed percutaneous needle aspiration of spleen. Note wasting and cutaneous hyperpigmentation

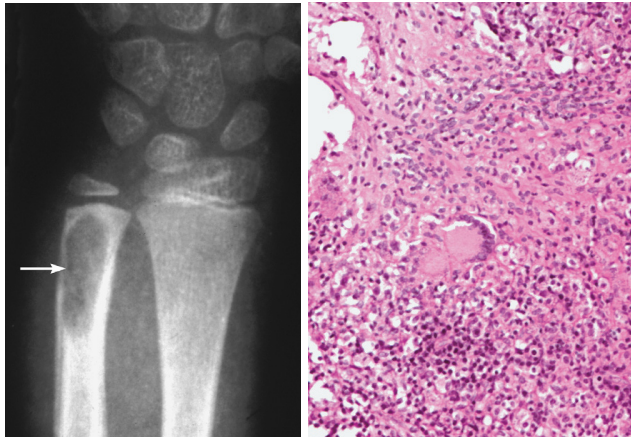


Figure 5.6. a,b

a. Radiograph of tender swollen wrist of 9-year-old Iranian patient with no clinical evidence of cutaneous or visceral leishmaniasis. Lesion in distal ulna (arrow) was originally diagnosed as Ewing's tumor.
b. Curettage of the bone lesion revealed visceral leishmaniasis. Note multinucleated giant cells. x110

the lower legs (thinning, dryness, hypopigmentation, loss of curl) are common. Cardiac failure from anemia often causes heart murmurs. Edema of the legs, jaundice, petechiae, and purpura develop in less than 10% of patients. Minor cutaneous, oral, and nasopharyngeal abnormalities are also seen.

Visceral leishmaniasis can be disseminated to virtually any organ or tissue, often mimicking other diseases (Fig 5.6). Uncommon manifestations such as bacteremia, acute hepatitis, and Guillain-Barré syndrome may precede the development of the classic signs and symptoms of VL. Uncommon systemic manifestations associated with classic VL include retinal hemorrhages, massive hepatic necrosis, pancytopenia without splenomegaly, cholecystitis, and paresthesias of the distal extremities.

Laboratory findings typically include hemoglobin concentrations of 5 to 9 g/dl, leukocyte counts of 2,000 to 4,000/mm³, and platelet counts of 50,000 to 200,000/mm³, although lower counts are sometimes seen in advanced disease. Erythrocyte survival time is shortened by hypersplenism and, possibly, by autoimmune mechanisms. Anemia is multifactorial and may result from bone marrow depression, iron deficiency, or a combination of these factors. Coombs' test is usually positive, with both C3 and IgG present on erythrocytes, but does not correlate with the severity of anemia. Neutrophil survival time is shortened, and the leukocyte differential demonstrates neutropenia, relative lymphocytosis, and a near absence of eosinophils. Agranulocytosis is rare.

Liver transaminases are mildly elevated in the majority of patients (ALT more than AST), but elevations of serum bilirubin are uncommon. Prothrombin time is usually 2 to 4 seconds longer than in controls, and serum albumin is generally less than 3 g/dl. A polyclonal hypergamma-

globulinemia of 5 to 10 g/dl, most of which is IgG, is usual. Albuminuria is common in some patients; in others, urinalysis and renal function are normal.

Complications. Intercurrent illness is common and varies by season and geographic area. Bacterial pneumonia may be present on admission or may develop during treatment. Pulmonary tuberculosis, a common coinfection, should be suspected when response to therapy is unsatisfactory. Severe diarrhea, measles, and malaria can be present. Noma, a necrotizing oral infection, may develop in late stages of VL when neutropenia is severe. Hepatic cirrhosis is an uncommon sequela. Portal hypertension sometimes leads to persistent splenomegaly despite successful treatment. Post-kala-azar anterior uveitis may follow treatment for VL.¹³ Other rare ocular complications include retinal hemorrhages, keratitis, central retinal vein thrombosis, and optic neuritis. Disseminated intravascular coagulation, immune complex-mediated glomerulonephritis, and renal amyloidosis with nephrotic syndrome are rare. Death often results from concurrent or intercurrent infections such as tuberculosis, dysentery, measles, or bacterial pneumonia. Severely anemic patients may die from cardiac failure. (See topic 4 for a discussion of post-kala-azar dermal leishmaniasis.)

Differential diagnosis of late-stage VL is limited. Hematologic and lymphatic malignancies, disseminated histoplasmosis, tropical splenomegaly syndrome, and hepatosplenic schistosomiasis can mimic late stage VL. Early disease has a much broader differential, including malaria, African trypanosomiasis, brucellosis, enteric fevers, bacterial endocarditis, generalized histoplasmosis, chronic myelocytic leukemia, Hodgkin's disease and other lymphomas, sarcoidosis, hepatic cirrhosis, and tuberculosis. Multiple myeloma and Waldenström's macroglobulinemia occasionally present with findings suggesting VL.

Subclinical or Oligosymptomatic Infections. In endemic areas, inhabitants with no history of overt clinical disease often have a positive leishmanin skin test (Montenegro test). Such individuals appear to be resistant to naturally occurring and experimental infection with *L. donovani*. The difference between true asymptomatic infection and oligosymptomatic disease is difficult to establish in most endemic areas because nonspecific illness is rarely diagnosed and usually not evaluated due to cultural factors and inadequate health care facilities. In a prospective study in Brazil, 33% of children with antibodies to *L. donovani* developed classic VL within a few weeks to 15 months after seroconversion, 23% remained asymptomatic for up to 5 years, and 44% had prolonged, mild constitutional symptoms and intermittent hepatomegaly that resolved without treatment after an average of 35 months.¹⁴

Viscerotropic Leishmaniasis. Viscerotropic leishmaniasis differs from VL in that the infecting organism is *L. tropica* rather than *L. donovani*, and patients do not have the classic signs or symptoms of VL. In the 1990s, 9 cases of

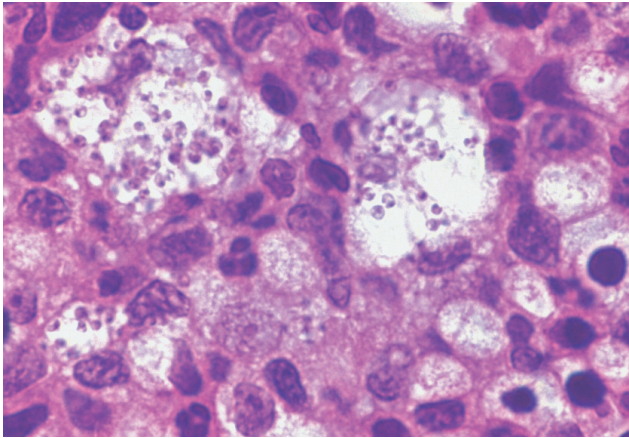


Figure 5.7
Bone marrow from 32-year-old AIDS patient who had traveled to Europe and Mexico. Note macrophages containing numerous amastigotes. Specimen also contained mycobacteria. x780

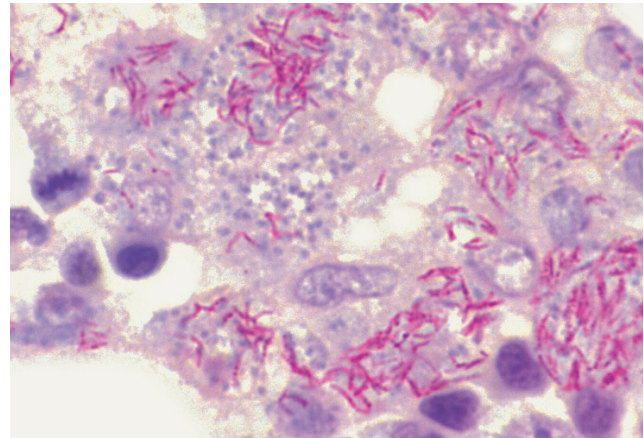


Figure 5.8
Acid-fast stain of bone marrow from patient described in Figure 5.20 showing macrophages containing amastigotes and mycobacteria. Ziehl-Neelsen x935

a mild, nonspecific illness characterized by cough, malaise, chronic fatigue, abdominal pain, and intermittent fever and diarrhea were documented in returning American veterans of Operation Desert Storm in the Middle East. All were parasitologically confirmed from bone marrow or lymph node aspirates; 6 of the 9 isolates were characterized as *L. tropica* by isoenzyme analysis.³ One of the soldiers presented more than 2 years after leaving an endemic area.¹⁵ Nonspecific chronic illness associated with viscerotropic leishmaniasis has also been reported from India and Italy.¹⁶

Immunocompromised Hosts. In the early years of the HIV/AIDS epidemic, visceral leishmaniasis emerged as an important opportunistic infection in HIV-positive patients, especially those with AIDS.^{17,18} (Figs 5.7 & 5.8) Coinfection with *Leishmania* sp and HIV is a recognized problem in East Africa, France, Italy, Portugal, and Spain and has been reported in 20 other countries. In the Mediterranean region, it is estimated that up to 70% of cases of VL in adults are associated with HIV, and that approximately 10% of AIDS patients have newly acquired or reactivated VL. In Europe, intravenous drug abuse is thought to be the most significant risk factor for leishmaniasis. As HIV infection spreads in India, Brazil, and East Africa, the number of people at risk for coinfection with VL will increase dramatically.

In coinfecting patients, clinical signs and symptoms of VL usually develop in late-stage AIDS. CD4 counts are usually less than 50 and almost always less than 200. In general, AIDS patients with VL have very high parasite burdens but tend to tolerate the coinfection. Many clinicians feel that leishmaniasis does not cause severe symptoms in these patients, but is merely one of many opportunistic infections that plague patients with markedly depressed CD4 counts. Numerous viscerotropic, dermatotropic, and novel *L. infantum* strains (zymodemes) have been isolated from coinfecting patients in Europe.¹⁹

The clinical presentation of VL in AIDS patients is similar to that in non-HIV-infected hosts and includes fever, splenomegaly, and pancytopenia. Involvement of the gastrointestinal tract is more common in AIDS patients. Parasite-laden macrophages are abundant in the submucosa from the esophagus to the rectum. Coinfected patients may have atypical presentations, including a variety of pulmonary radiographic findings such as pleural effusion and pulmonary nodules. Patients with minimal splenomegaly are sometimes afebrile.

Because parasite burdens tend to be higher and serologic tests may be negative in HIV-coinfecting patients, classic parasitologic diagnostic methods are preferred. For example, cultures or amplification of parasite specific DNA by PCR of the buffy coat of peripheral blood may be positive in AIDS patients. Fever or hepatosplenomegaly in an HIV-infected patient who has resided in or visited an area endemic for VL should prompt an examination of the bone marrow by both smear and culture for *Leishmania* sp.

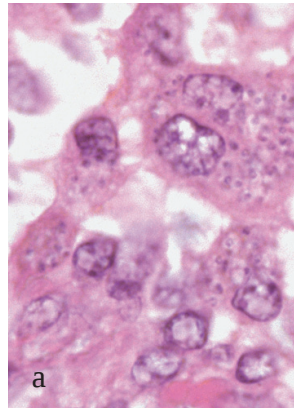
Visceral leishmaniasis may occur as an opportunistic infection in patients receiving immunosuppressive drugs or chronic corticosteroids.²⁰ In solid-organ transplant recipients, VL characterized by fever, splenomegaly, and cytopenia may appear several months following transplantation. Again, in these patients, standard parasitologic diagnostic methods are satisfactory. In endemic areas, VL should never be overlooked in the differential diagnosis of immunocompromised patients.

Pathologic Features

In the less common acute VL, the spleen is smooth and friable and splenic follicles are small. Patients with progressive VL develop marked splenomegaly (Fig 5.5). Splenic infarcts are common. In chronic VL, the spleen is firm, red,

**Figure 5.9**

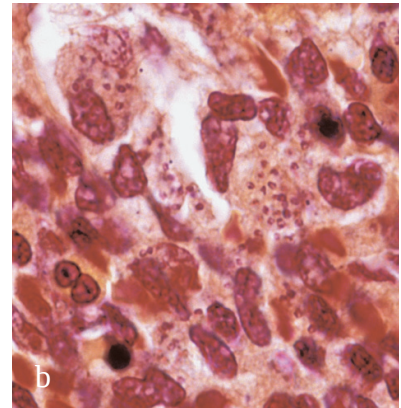
Splenomegaly in 7-year-old Ugandan patient who died of visceral leishmaniasis after several courses of treatment. Spleen was 970 g and lobulated, with firm red cut surface.

**Figure 5.10 a,b**

Spleen with clusters of amastigotes in phagocytic cells. x720

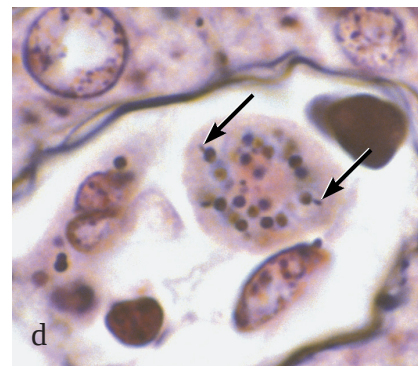
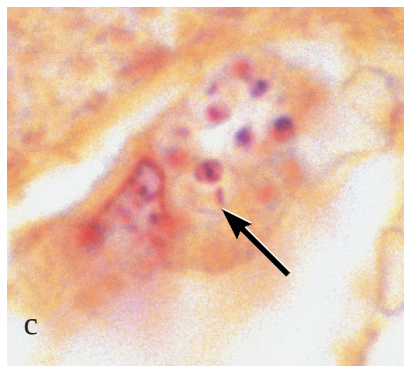
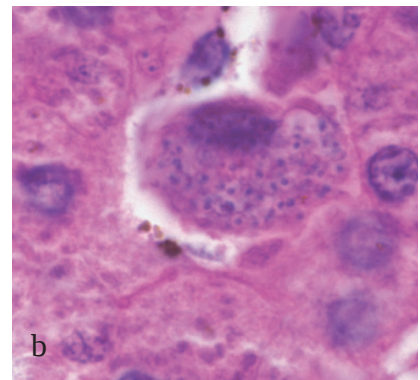
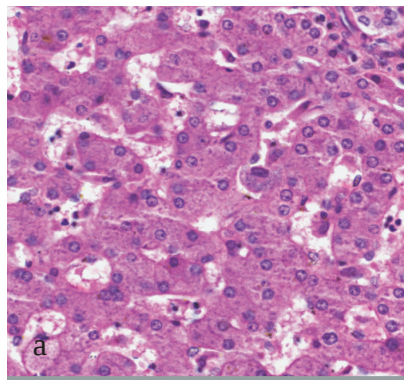
a. Hematoxylin and Eosin

b. Brown Hopps (B-H).



and lobulated, and has a thickened capsule. The spleen can weigh up to 3 kg even in children (Fig 5.9). Hyperplasia and hypertrophy are caused by parasite-filled reticuloendothelial cells (Fig 5.10a,b). In our experience, amastigotes in VL appear slightly smaller and less distinct than those observed in cutaneous leishmaniasis. Because kinetoplasts are much more difficult to identify, special stains such as Brown-Hopps and Wilder's reticulum are recommended (Fig 5.11b to 5.11d).

The liver is usually enlarged and has a smooth capsule (Fig 5.5). Microscopically, liver sinusoids are dilated, show prominent amastigote-laden Kupffer's cells and little or no cellular reaction (Figs 5.11a & 5.11b). Sections stained by Brown-Hopps and Wilder's reticulum show features of intracellular amastigotes more clearly (Figs 5.11c & 5.11d). In subclinical infections, non-caseating granulomas with few parasites are scattered throughout the liver (Figs 5.12 & 5.13). Lymph nodes may be enlarged and contain macrophages filled with amastigotes, usually with surrounding lymphocytes (Fig 5.14). Tonsillar lymphoid tissue may contain parasites. In subclinical

**Figure 5.11 a,b,c,d**

a. Liver with dilated sinusoids and enlarged Kupffer's cells. x250.

b. Numerous amastigotes in Kupffer's cell. x700

c. Amastigotes in Kupffer's cell. Note kinetoplast (arrow). B-H x2200

d. Numerous black amastigotes in Kupffer's cells. Note kinetoplasts (arrows). Wilder's reticulum x1900

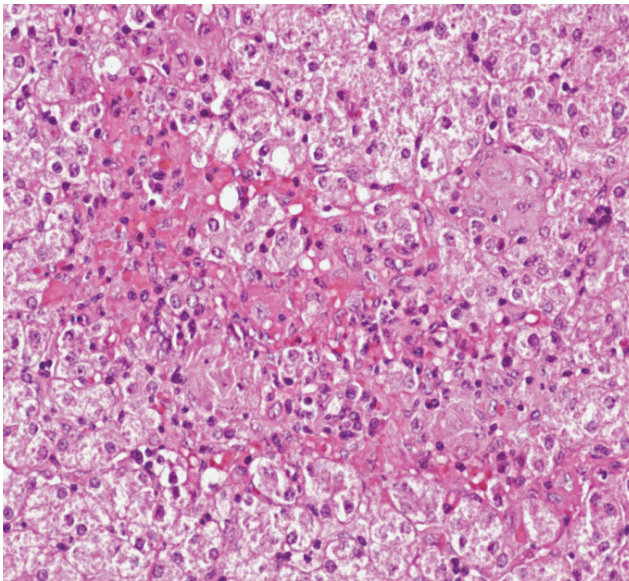


Figure 5.12
Nonnecrotizing granuloma in liver. x160.

VL and lymphatic leishmaniasis, there is a granulomatous reaction, with giant cells resembling tuberculosis but without caseation.

Although nasal mucus is an unlikely route of transmission, in Sudan, East Africa, and India, VL sometimes presents with oral and nasopharyngeal lesions. These lesions vary histologically from numerous parasitized histiocytes to granulomas with few parasites. Parasites are less abundant in nasopharyngeal tissues than in oral lesions, but may be demonstrated in secretions from these areas.

In the gastrointestinal tract, there is proliferation of reticuloendothelial cells in the duodenum and jejunum, infiltration of the submucosa with parasitized cells, and, occasionally, villous atrophy with hyperplasia of crypt cells (Fig 5.15). There may be small ulcerations with demonstrable parasites.

The bone marrow is hyperplastic and contains numerous parasite-laden macrophages in acute infections, but few in chronic disease (Fig 5.7). The skin may contain parasites. In fatal VL, all levels beneath the epidermis are often heavily infiltrated, with masses of parasitized cells concentrated around sweat glands and small blood vessels.

Parasites have been identified in virtually all organs, including cardiac muscle (Figs 5.16 & 5.17), adrenals (Figs 5.18a,b), parotid glands, and kidneys (Fig 5.19a,b,c). The kidneys may show an interstitial nephritis (Fig 5.19b) or a mild proliferative glomerulonephritis (Fig 5.19c) and may contain immune complexes. Renal amyloidosis is an uncommon complication of late-stage VL.

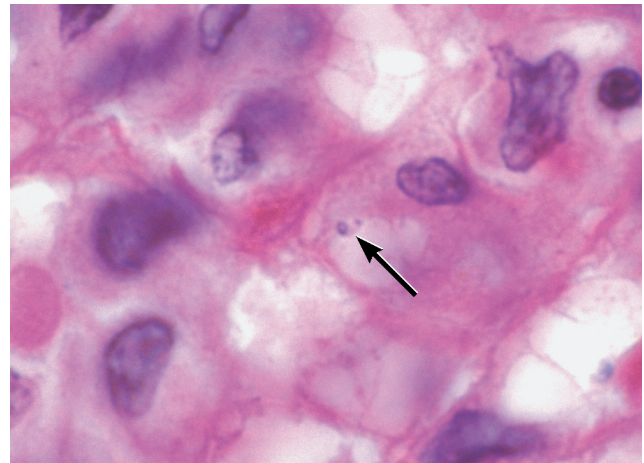


Figure 5.13
Higher magnification of liver shown in Figure 5.12 showing rare amastigote in Kupffer's cell (arrow). x1750

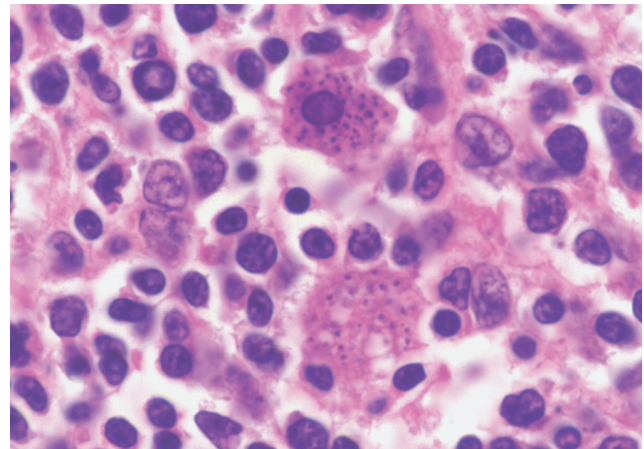


Figure 5.14
Lymph node with granular-appearing macrophages containing amastigotes. x620

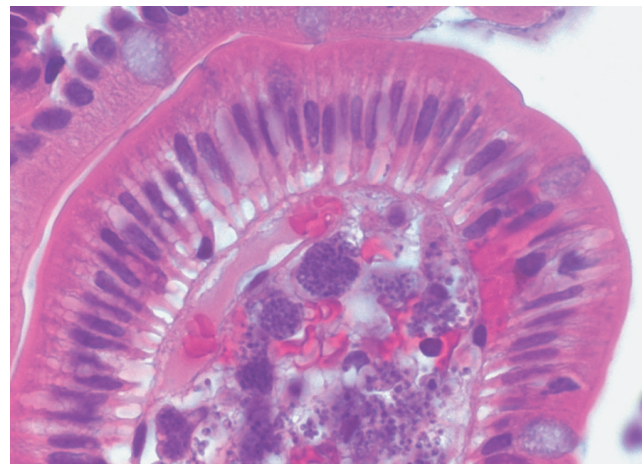


Figure 5.15
Numerous amastigotes within histiocytes in lamina propria of duodenum from 46-year-old patient with HIV infection who had traveled to Spain 10 years previously. x600

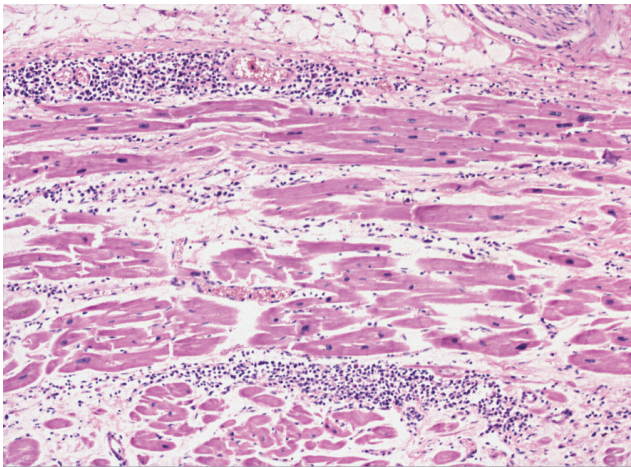


Figure 5.16
Chronic myocarditis caused by visceral leishmaniasis. x60

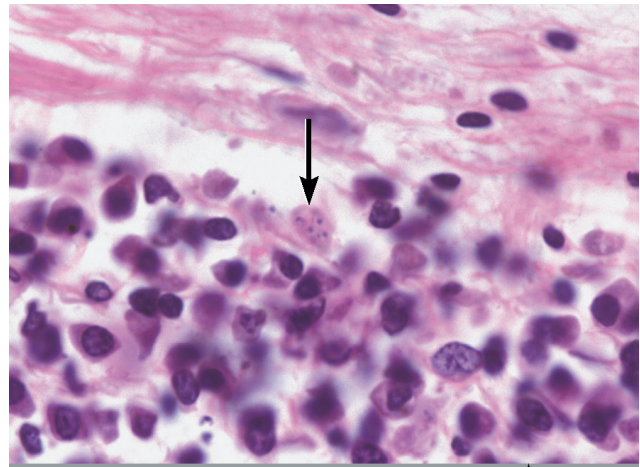


Figure 5.17
Amastigotes within histiocyte (arrow) in myocardium. x730

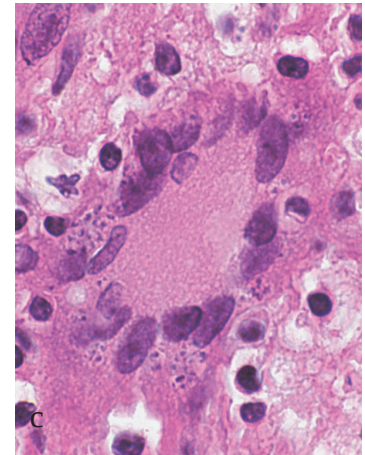
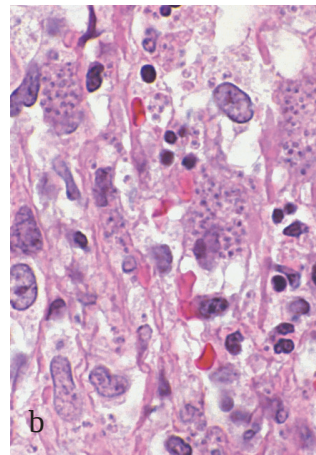
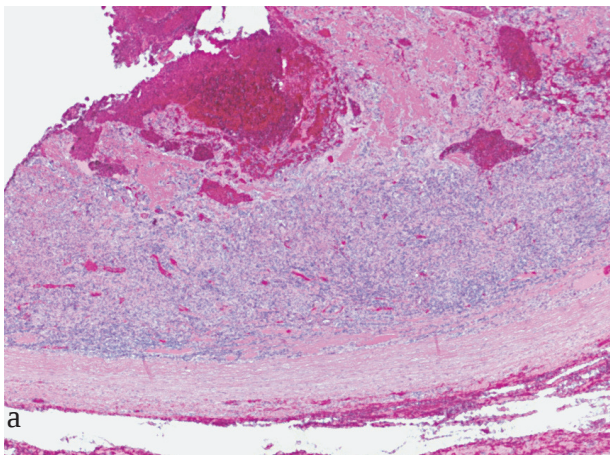


Figure 5.18 a,b,c
Adrenal from 69-year-old patient who developed abdominal pain and adrenal enlargement after travel to Greece. a. Note thickened capsule and chronic inflammation. x30 b. Macrophages containing numerous amastigotes. x600 c. A multinucleated giant cell containing amastigotes. x715

Diagnosis

While parasitologic diagnosis and confirmation is always desirable, it is sometimes unfeasible because of the need for invasive procedures, expert microscopy, and adequate health care infrastructure. Depending upon local epidemiological considerations and clinical presentation, VL can be clinically diagnosed with a fair amount of certainty. In an endemic area, the positive predictive value of a clinical diagnosis of late-stage VL with classic signs and symptoms is likely to be high. Clinical diagnosis early in the course of infection when the classic features of disease are not yet established is much less certain. Favorable clinical response to appropriate therapy virtually confirms a clinical diagnosis of VL.

Parasitologic diagnosis is based on demonstrating amastigotes in tissues or clinical specimens, visualizing promastigotes in *in vitro* cultures, or amplification of parasite specific DNA via the polymerase chain reaction (PCR). Splenic

aspiration is the surest method of parasitologic diagnosis, but carries the risk of splenic laceration (Fig 5.5). Careful observation of the patient after the procedure is essential.²¹ Giemsa stained splenic smears demonstrate amastigotes in 98% to 100% of patients, and quantitation of splenic smears is helpful in measuring response to therapy.²² Promastigotes can be seen within 2 to 7 days in Schneider's medium or 7 to 21 days in NNN medium after incubation at 25° C.

For clinicians unfamiliar with splenic aspiration or concerned about its risks, there are satisfactory alternatives. Bone marrow smears usually contain amastigotes, though fewer than in splenic smears; parasites are found in up to 85% of patients.

Amastigotes are frequently found in aspirates or biopsies of liver or lymph nodes. In India and Kenya, buffy coat smears have demonstrated amastigotes in some cases, but this is an uncommon diagnostic method.

A minimally invasive test that would confirm diagno-

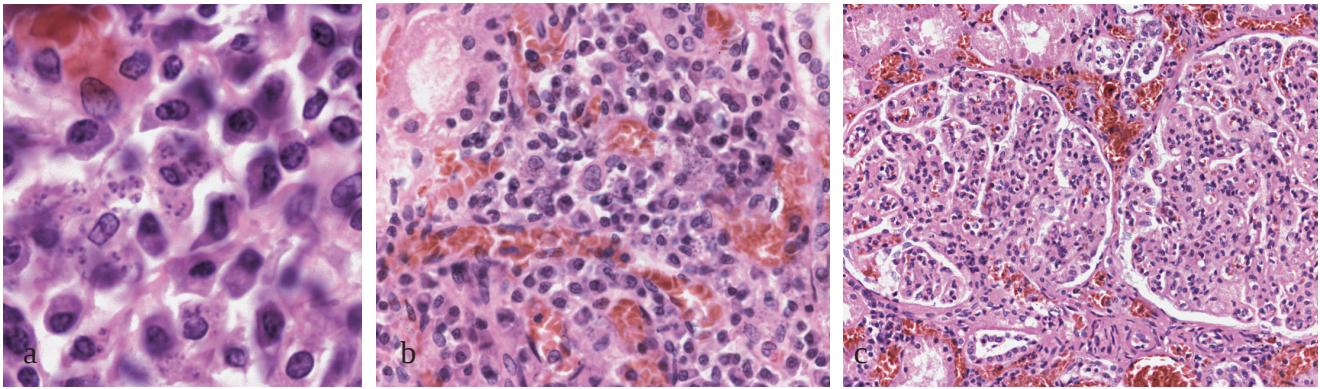


Figure 5.19 a,b,c

Kidney. a. Amastigotes in histiocytes. x730 b. Interstitial chronic inflammation. x315 c. Renal glomeruli with features of mesangioproliferative (mesangiocapillary) glomerulonephritis, including thickened basement membrane. x125

sis would be a great asset. Antigen detection assays using whole blood and PCR amplification of *Leishmania* sp DNA from peripheral blood have been used, but these methods are not as sensitive as splenic or bone marrow aspiration.

A variety of serologic tests are available worldwide, many of which however are available only in certain geographic areas. Few have been used extensively enough to compare sensitivity and specificity, but in general, serologic tests for VL currently in use are more than 90% sensitive; specificity tends to be lower. False positive results for VL may be seen in some patients with other infectious diseases. Leishmanial antibodies may also persist for many months following treatment hence are not generally useful to assess response to treatment.

The indirect fluorescent antibody (IFA) test is positive in more than 95% of patients with VL, with titers usually higher than 1:256. These positive IFA tests are readily distinguishable from the low-titer positive tests occasionally seen in malaria, typhoid fever, and other diseases. IFA testing is somewhat subjective and requires expertise and expensive equipment.²³

Enzyme-linked immunosorbent assay (ELISA) using whole or soluble promastigote antigens appears to be as sensitive and specific as IFA. Economy and convenience make ELISA especially useful for large-scale epidemiologic studies of human and canine leishmaniasis. Both IFA and ELISA can be performed on sera eluted from filter papers impregnated with 50 µl of capillary blood. A direct agglutination test is widely available. Its ease of use, economy, and high sensitivity are offset by poor reproducibility between field sites and the need to establish a cutoff titer for positivity based on local epidemiologic considerations.^{24,25}

ELISA and rapid “dipstick” formats for detecting serum antibodies to purified *Leishmania* sp antigens (such as rK39) in patients with VL have improved the

sensitivity and specificity of serologic testing for VL. Titers to rK39 decrease following successful chemotherapy and rise during relapse, making this test useful for recognizing treatment failure.²⁶

Skin test reactivity is a useful indicator of past infection in epidemiological studies. Intradermal injections of fixed whole promastigotes or a solubilized fraction of parasite antigens (Montenegro or leishmanin test) are negative in symptomatic VL, but become positive in over 90% of patients 6 weeks to a year after recovery. A meta-analysis of the diagnostic performance of the direct agglutination test and rK39 dipstick for visceral leishmaniasis showed comparable sensitivity and specificity of about 95% and 90% respectively.²⁷

Treatment and Prevention

Patients with VL should receive dietary support and antimicrobial agents for concurrent pneumonia, tuberculosis, or other bacterial infections as clinically indicated. Blood transfusion may be indicated in severely anemic patients, and iron or vitamin deficiency may require specific treatment.

Pentavalent antimony compounds (SbV), sodium stibogluconate (SSG) (Pentostam®) and meglumine antimoniate (Glucantime), have been effective drugs for the treatment of VL since the 1930s. SbV is efficacious in East Africa and Brazil and remains one of the first line treatments recommended by the World Health Organization for the treatment of visceral leishmaniasis.²⁸ However, in the mid-1990s, reports from India of increasing primary treatment failures with SbV led to trials of lipid-associated amphotericin B as initial therapy for Mediterranean and Indian VL.²⁹ Today, lipid-associated amphotericin B is frequently the first-line therapy for VL.

In the United States, SSG can be obtained from the Centers for Disease Control and Prevention under a clinical protocol by an Investigational New Drug application because

Pentostam is not an approved drug in the United States. The recommended treatment regimen for primary VL is 20 mg/kg body weight/day for 28 days.³⁰ Longer durations may be required for patients who are slow to respond and for Indian VL.

SSG is safe if used under close medical supervision but can produce side effects such as nausea, anorexia, abdominal pain, malaise, headache, arthralgias, myalgias, and lethargy.³¹ These side effects, which frequently appear 3 to 7 days into therapy, are poorly tolerated and more apparent in patients with cutaneous and mucocutaneous leishmaniasis, which have no associated systemic symptoms.³² Serious adverse events include renal failure, pancreatitis, hepatic failure, and sudden cardiac deaths likely caused by drug induced ventricular dysrhythmias have been documented.

Amphotericin B (either deoxycholate or liposomal encapsulated) has a cure rate of nearly 100% in VL patients who have failed treatment with SbV and pentamidine. It is not widely used, however, because of well documented infusion-related side effects of fever, chills, thrombophlebitis, long-term problems of renal insufficiency, anemia, hypokalemia, and poor tolerability (anorexia, nausea). Furthermore, sudden cardiac death has been reported following the first dose of amphotericin B deoxycholate in patients previously treated with SbV,³³ possibly because conduction abnormalities associated with SbV therapy predispose patients to cardiac events. It is prudent to obtain a baseline ECG and wait until any abnormalities normalize, usually within 10 days of terminating SbV therapy, before administering amphotericin B deoxycholate.

Lipid-associated amphotericin B preparations are the least toxic and best tolerated chemotherapeutic agents for VL. Liposomal amphotericin B (AmBisome®) was approved in 1997 by the United States Food and Drug Administration (FDA) for treatment of VL. A series of trials proved the drug to be safe and active against VL acquired in Brazil, India, Kenya, and Mediterranean countries.³⁴⁻³⁶ The current FDA-approved regimen for immunocompetent patients, based on data from Mediterranean countries and Brazil, is 3 mg/kg body weight daily on days 1 to 5, a 6th dose on day 14, and a 7th dose on day 21 (total dose: 21 mg/kg body weight). The overall cure rate with this regimen approaches 100%. The current FDA-approved regimen for immunosuppressed patients is 4 mg/kg body weight daily on days 1 to 5, 10, 17, 24, 31, and 38 (total dose: 40 mg/kg body weight). Even with the higher total dose, relapse is common in those individuals whose immunosuppression cannot be reversed or improved. These regimens have few infusion-related side effects and renal insufficiency is uncommon.

The relatively high cost of AmBisome has limited its adoption and use in resource poor countries and stimulated interest in lower-dose and shorter course regimens, many of

which have been shown to be effective in trials in Brazil, India, and Kenya. For example a single 10 mg / kg dose of AmBisome was shown to be > 95% efficacious in Indian VL.³⁷

In HIV coinfecting patients, the efficacy of SbV is 50%, however the efficacy of liposomal amphotericin B is 100%. Relapse is common after treatment with either drug. The optimal drug, dose, and duration of induction and intermittent maintenance regimens for the various infecting species are not known. Where feasible, the optimal therapy is immune system reconstitution through highly active antiretroviral therapy (HAART). Although data are lacking, it is reasonable to recommend an initial course of induction therapy using liposomal amphotericin B to decrease parasite burden, followed closely by HAART to raise the CD4 cell count.

Infection with *L. donovani* comprises a spectrum of diseases, and spontaneous resolution of subclinical infection is more common than was formerly realized. In contrast, the established syndrome of VL is almost always fatal without specific chemotherapy. With specific chemotherapy, such as SbV or amphotericin B, the death rate is relatively low. For example, in Bihar, India in 1990, mortality from VL was 1%. In war-torn southern Sudan, one of the most difficult environments for VL management, mortality during the VL epidemic of the 1990s was only 11%.³⁸ Outside of India, failure to respond to initial SbV therapy is uncommon in previously untreated, immunocompetent patients.

Where humans are the reservoir of VL (India and perhaps some areas of East Africa), finding and treating VL patients may interrupt epidemics. In regions where dogs are the reservoir (Mediterranean countries, China, South America), conventional wisdom states that identifying and destroying infected dogs reduces the incidence of VL. Although a recent interventional trial in Brazil failed to support that hypothesis,³⁹ some authorities strongly recommend continued control of zoonotic VL in Brazil, based on the results of a meta-analysis of the interventional trial.⁴⁰ In India in the early 20th century, vector control was maintained by burning houses that were microfocal for *L. donovani*. During malaria eradication campaigns that employed DDT to control the vector, VL virtually disappeared from India. With the termination of these campaigns, incidence has returned to high levels.

No VL vaccine is currently licensed or commercially available. A variety of vaccine preparations, including killed promastigotes with and without adjuvants, parasite fractions, recombinant antigens, genetically engineered “avirulent” live parasites, and vaccines based on sandfly saliva are in various stages of development and clinical trials.⁴¹⁻⁴⁶

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Acknowledgement

Figure 5.2
American Foxhound Club