are released into the host dermis along with the sandfly saliva, which potentiates parasite infectivity. The promastigotes are phagocytosed by macrophages, and the acidity within the phagolysosome induces them to transform into round amastigotes that lack flagella but contain a single mitochondrion with its DNA massed into a unique suborganelle, the kinetoplast. Amastigotes proliferate within macrophages, and dying macrophages release progeny amastigotes that can infect additional macrophages.

How far the amastigotes spread throughout the body depends on the *Leishmania* species and host, and determines the extent of disease. There are several forms of disease and that are caused by different species of *Leishmania*.

- Cutaneous disease
  - Old World—*Leishmania major* and *Leishmania tropica*
  - New World—*Leishmania mexicana* and *Leishmania braziliensis*
- Mucocutaneous disease (also called *espundia*)
  - New World—*L. braziliensis*
- Visceral disease involving the liver, spleen, and bone marrow
  - Old World—*Leishmania donovani* and *Leishmania infantum*
  - New World—*Leishmania chagasi*

Tropism of *Leishmania* species seems to be linked in part to the optimal temperature for their growth. Parasites that cause visceral disease grow best at 37°C, whereas parasites that cause mucocutaneous disease grow better at lower temperatures. However, cutaneous *Leishmania* species often are viscerotropic in HIV patients.

Leishmania manipulate innate host defenses to facilitate their entry and survival in macrophages. Promastigotes produce two abundant surface glycoconjugates that contribute to their virulence.

- Lipophosphoglycan forms a dense glycocalyx that both activates complement (leading to C3b deposition on the parasite surface) and inhibits complement action (by preventing membrane attack complex insertion into the parasite membrane). Thus, the parasite becomes coated with C3b but avoids destruction by the membrane attack complex. Instead, the C3b on the surface of the parasite binds to Mac-1 and CR1 on macrophages, targeting the promastigote for phagocytosis.
- Gp63 is a zinc-dependent proteinase that cleaves complement and some lysosomal antimicrobial enzymes. Gp63 also binds to fibronectin receptors on macrophages and promotes promastigote adhesion to macrophages.

Leishmania amastigotes also produce molecules that facilitate their survival and replication within macrophages. Amastigotes reproduce in macrophage phagolysosomes, which normally have a pH of 4.5. However, the amastigotes protect themselves from this hostile environment by expressing a proton-transporting ATPase, which maintains the phagolysosome pH at 6.5.

The primary mechanisms of resistance and susceptibility to *Leishmania* are mediated through T_H1 and T_H2 responses. Parasite-specific CD4+ T_H1 cells are needed to control *Leishmania* in mice and humans. *Leishmania* evade host immunity by impairing the development of the T_H1 response. In animal models, mice that are resistant to *Leishmania* infection produce high levels of T_H1-derived IFN-γ, which activates macrophages to kill the parasites through reactive oxygen species. By contrast, mouse strains that are susceptible to leishmaniasis mount a dominant T_H2 response. T_H2 cytokines such as IL-4, IL-13, and IL-10 prevent effective killing of *Leishmania* by inhibiting the microbicidal activity of macrophages.

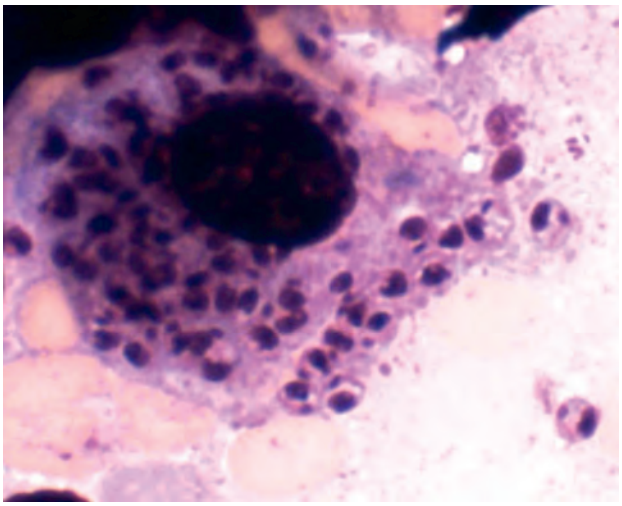

Figure 8-49 Giemsa stain of a tissue macrophage with *Leishmania donovani* parasites.

MORPHOLOGY

Leishmania species produce four different types of lesions in humans: visceral, cutaneous, mucocutaneous, and diffuse cutaneous. In **visceral leishmaniasis**, parasites invade macrophages throughout the mononuclear phagocyte system (Fig. 8-49), and cause severe systemic disease marked by hepatosplenomegaly, lymphadenopathy, pancytopenia, fever, and weight loss. The spleen may weigh as much as 3 kg. Phagocytic cells are enlarged and filled with *Leishmania*, many plasma cells are present, and the normal architecture of the spleen is obscured. In the late stages, the liver becomes increasingly fibrotic. Phagocytic cells crowd the bone marrow and also may be found in the lungs, gastrointestinal tract, kidneys, pancreas, and testes. Often there is hyperpigmentation of the skin in individuals of South Asian ancestry, which is why the disease is called *kala-azar* (*black fever* in Hindi). In the kidneys there may be an immune complex-mediated mesangioproliferative glomerulonephritis, and in advanced cases there may be amyloid deposition. People with advanced leishmaniasis can develop life-threatening secondary bacterial infections, such as pneumonia, sepsis or tuberculosis. Hemorrhages related to thrombocytopenia may also be fatal.

Cutaneous leishmaniasis is a relatively mild, localized disease consisting of ulcers on exposed skin. The lesion begins as a papule surrounded by induration, changes into a shallow and slowly expanding ulcer, often with heaped-up borders, and usually heals by involution within 6 to 18 months without treatment. On microscopic examination, the lesion shows granulomatous inflammation, usually with many giant cells and few parasites.

Mucocutaneous leishmaniasis is found only in the New World. Moist, ulcerating, or nonulcerating lesions develop in the