- Asymptomatic microfilaremia
- Recurrent lymphadenitis
- Chronic lymphadenitis with swelling of the dependent limb or scrotum (elephantiasis)
- Tropical pulmonary eosinophilia.

As is the case with leprosy and leishmanial infections, some of the different disease manifestations caused by lymphatic filariae are likely related to variations in host T-cell responses to the parasites.

Pathogenesis. Infective larvae released by mosquitoes into the tissues during a blood meal develop within lymphatic channels into adult males and females, which mate and release microfilariae that enter into the bloodstream. When they bite infected individuals the mosquitoes can take up the microfilariae and transmit the disease. The filarial genome project has led to the identification of a number of filarial molecules that enable the organism to evade or inhibit immune defenses. *Brugia malayi* produces:

- Several surface glycoproteins with antioxidant function, which may protect from superoxide and free oxygen radicals
- Homologs of cystatins, cysteine protease inhibitors, which can impair the MHC class II antigen-processing pathway
- Serpins, serine protease inhibitors, which can inhibit neutrophil proteases, critical inflammatory mediators
- Homologs of TGF-β, which can bind to mammalian TGF-β receptors and downregulate inflammatory responses.

In addition, symbiotic *Wolbachia* bacteria infect filarial nematodes and contribute to pathogenesis of disease. *Wolbachia* are required for nematode development and reproduction, and antibiotics that eradicate *Wolbachia* impair nematode survival and fertility. It has been hypothesized that LPS from *Wolbachia* also stimulates inflammatory responses.

Immunologic responses to the filarial worms produce damage to the human host. In chronic lymphatic filariasis, damage to the lymphatics is caused directly by the adult parasites and by a T_H1-mediated immune response, which stimulates the formation of granulomas around the adult parasites. There may be an *IgE-mediated hypersensitivity* response to microfilariae in *tropical pulmonary eosinophilia.* IgE and eosinophils may be stimulated by IL-4 and IL-5, respectively, secreted by filaria-specific T_H2 helper T cells. Tropical pulmonary eosinophilia is seen most commonly in either individuals of Southern Asian or northern Latin American descent, suggesting that host factors contribute to this disorder (Chapter 15).

MORPHOLOGY

Chronic filariasis is characterized by **persistent lymphedema** of the extremities, scrotum, penis, or vulva (Fig. 8-56). Frequently there is hydrocele and lymph node enlargement. In severe and long-lasting infections, chylous weeping of the enlarged scrotum may ensue, or a chronically swollen leg may develop tough subcutaneous fibrosis and epithelial hyperkeratosis, termed

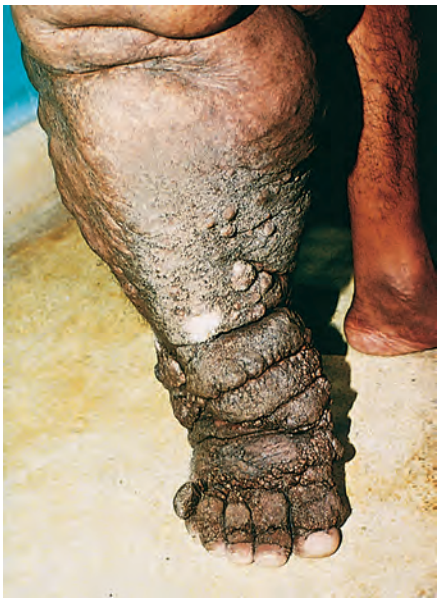

Figure 8-56 Massive edema and elephantiasis caused by filariasis of the leg. (Courtesy Dr. Willy Piessens, Harvard School of Public Health, Boston, Mass.)

elephantiasis. Elephantoid skin shows dilation of the dermal lymphatics, widespread lymphocytic infiltrates and focal cholesterol deposits; the epidermis is thickened and hyperkeratotic. Adult filarial worms—live, dead, or calcified—are present in the draining lymphatics or nodes, surrounded by (1) mild or no inflammation, (2) an intense eosinophilia with hemorrhage and fibrin (recurrent filarial funiculoepididymitis), or (3) granulomas. Over time, the dilated lymphatics develop polypoid infoldings. In the testis, hydrocele fluid, which often contains cholesterol crystals, red cells, and hemosiderin, induces thickening and calcification of the tunica vaginalis.

Lung involvement by microfilariae is marked by eosinophilia caused by T_H2 responses and cytokine production (tropical eosinophilia) or by dead microfilariae surrounded by stellate, hyaline, eosinophilic precipitates embedded in small epithelioid granulomas (Meyers-Kouwenaar bodies). Typically, these patients lack other manifestations of filarial disease.

Onchocerciasis

Onchocerca volvulus is a filarial nematode **that is the leading cause of preventable blindness in sub-Saharan Africa**. It is transmitted by black flies and affects 18 million people in Africa, South America, and Yemen. An aggressive campaign of ivermectin treatment has dramatically reduced the incidence of *Onchocerca* infection in West Africa. Since vector's preferred habitat is near fast moving water there is higher incidence of human disease near rivers, accounting for the name *river blindness* given to this disease. It is estimated that there are 270,000 people who are blind due to onchocerciasis.

The disease attributable to onchocerciasis is primarily due to inflammation induced by microfilaria. Adult *O. volvulus* parasites mate in the dermis, where they are surrounded by a mixed infiltrate of host cells that produces a characteristic subcutaneous nodule (onchocercoma). Inseminated females produce microfilariae, which accumulate in the skin and disseminate to the eye chambers.