ANIMAL MODEL OF HUMAN DISEASE

Lymphatic Filariasis

ADAM EWERT, PhD, and DEAN FOLSE, DVM, PhD

From the Departments of Microbiology and Pathology, University of Texas Medical Branch, Galveston, Texas

Biologic Features

Lymphadenitis and lymphangitis progressing to lymphatic dysfunction can be produced in the hind legs of domestic cats by inoculation of *Brugia malayi*. Infections are established in such a way that the filariae develop in the regional lymphatics. Within 24 hours after infection on the foot, the larvae, from appropriate laboratory-reared mosquito vectors, enter the afferent lymphatics and migrate to the periphery of the first intervening lymph node, the popliteal. The lymphatic vessels harboring growing larvae dilate and become tortuous, and the valves become incompetent. By 4–6 months after infection many of the worms are redistributed within the lymphatic vessels between the popliteal node and the foot.[1]

Pathologic changes occur as the worms moult, change location, and/or die in the afferent vessels. Endothelial cells hypertrophy (Figure 1), valves thicken and become distorted, and lymph thrombi sometimes form, partially occluding the lumen (Figure 2). Within the vessel walls elastic fibers and smooth muscle cells are disrupted and displaced by extensive collagen deposition.[2] Inflammatory cells accumulate along the inner lining of the lymphatic vessel, within the wall itself, and in aggregates in the surrounding connective tissue.

Affected lymph nodes and vessels may increase up to 10-fold in size. Lymphedema is seen at varying times after infection and may involve the entire lower leg and foot. If a *Brugia*-infected leg is concomitantly infected with a microorganism such as Group G *Streptococcus* or a lymphocutaneous fungus like *Sporothrix schenckii*, these organisms proliferate in the static lymph and cause an increase in inflammation, edema, and necrosis.[3,4] Chronic and repeated infections result in blockage, fibrotic lymph vessel walls, and the proliferation of fine collateral vessels that by-pass the malfunctioning node and vessels[5] (Figure 3).

Comparison With Human Disease

Early signs and symptoms of human lymphatic filariasis often include lymphadenitis and lymphangitis. However, many individuals have circulating microfilariae in the bloodstream without showing lymph node and vessel enlargement or inflammation.[6] A similar pattern is seen in experimental infection in cats. The popliteal lymph node usually enlarges soon after infection but eventually returns to normal size in most cases. In some animals progressive changes occur in the lymphatics. Worm movement or death causes irritation, tissue reaction, and lymph blockage. A spectrum of tissue response to lymphatic filariasis has been reported from human autopsy cases in which the parasites were positively identified.[7] Many of these changes, including lymphangiectasia, lymphangiohemorrhage, parietal lymphangitis, organizing lymphangitis, and granulomatous thrombolymphangitis, are also seen in the cat model.

In man, transient edema and acute inflammation of lymph vessels and nodes with febrile episodes are called "filarial fevers." Experimental infection with

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Address reprint requests to Adam Ewert, PhD, Department of Microbiology, University of Texas Medical Branch, Galveston, TX 77550.

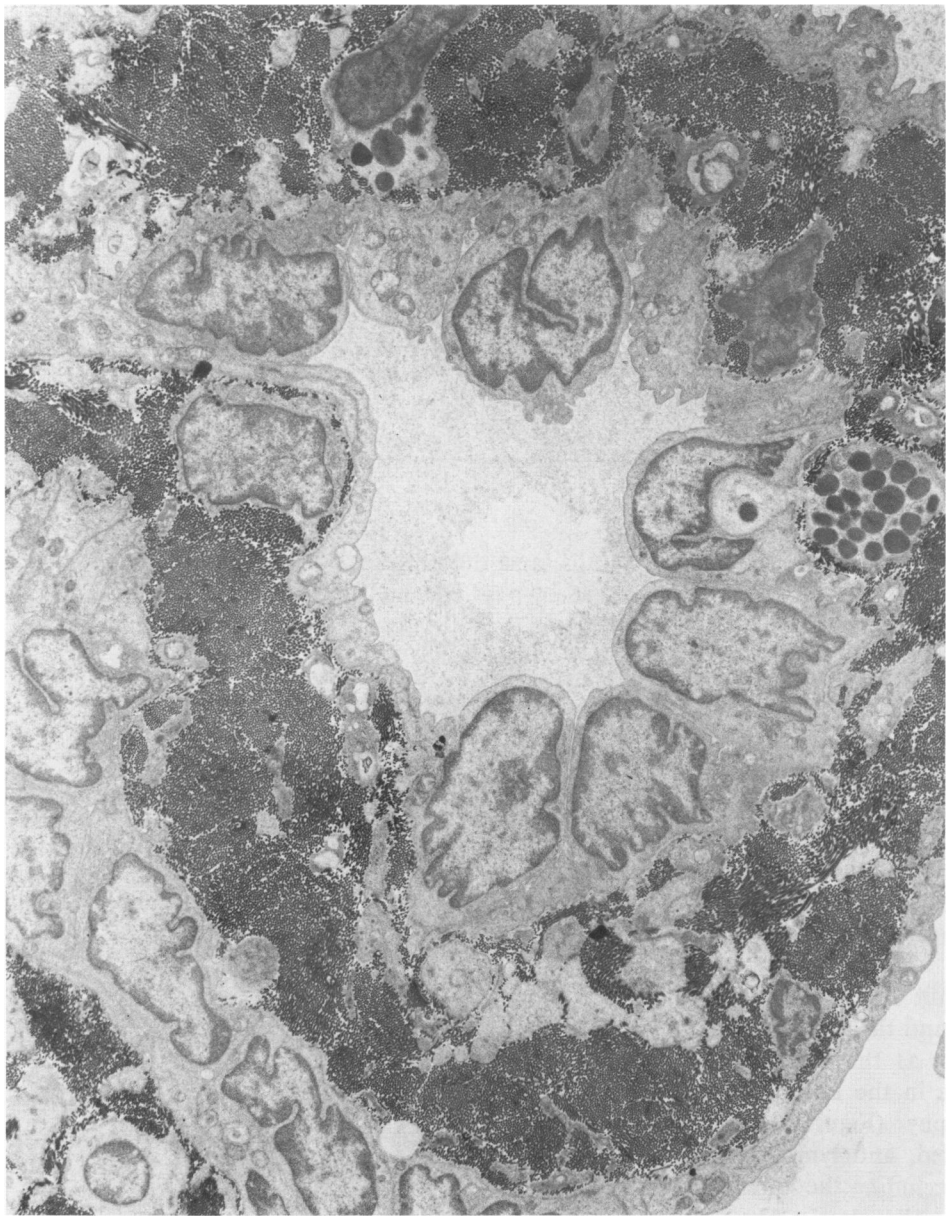

Figure 1—Hypertrophy of lymphatic endothelial cells. Deposition of collagen adjacent to endothelium. Notice the mast cells. (×5000)

Brugia malayi in cats results in temporary edema and lymphangitis demonstrable by dissection and histopathologic examination. Systemic fever is more difficult to demonstrate. Local elevation of temperature in the affected limb does occur. Permanent irreversible elephantiasis seen in a small proportion of human infection has not been produced experimentally, but an elephantoid condition persisting for several months can be produced in a proportion of infected animals[3] (Figure 4).

Usefulness of the Model

The onset of human filariasis can seldom be determined precisely because people in an endemic area are continuously exposed to the parasite. The extent of infection in an individual is also difficult to determine because the microfilaremia level is not necessarily related to the number of developing or adult worms present in the body. In the experimental model in cats the number of worms in a particular regional lymph vessel can be controlled by the number of infective larvae used to initiate the infection. By killing cats at different time intervals after infection, one can determine at necropsy the effect that each stage of the parasite has on the vessel and the number and conditions of worms present.

Manipulation of the onset and degree of infection permits evaluation of host responses during any phase of the disease process. Tissues for study by

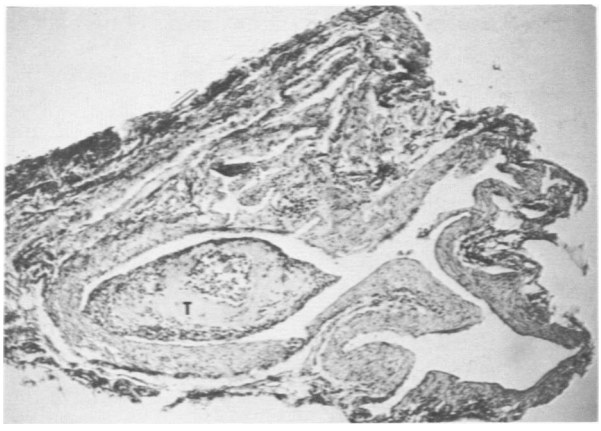

Figure 2—Cross-section of lymph vessel with thickened walls and thrombus (*T*) within the lumen. (H&E, ×300)

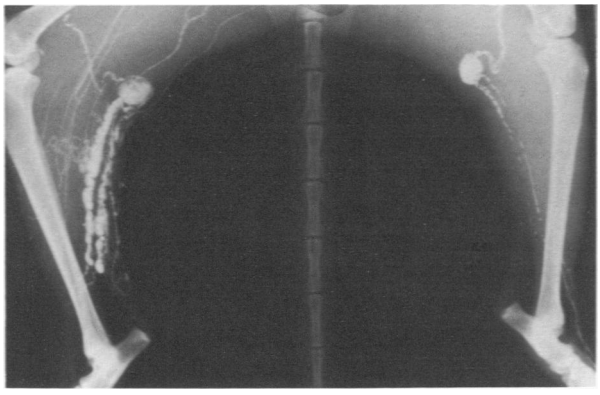

Figure 3—X-ray of the hind legs of a cat experimentally infected with *Brugia malayi* in left leg, which shows dilated tortuous major lymphatic vessels with numerous fine collaterals. The uninfected right leg is normal in appearance (ethiodol injection).

light and electron microscopy, chemical analysis, or other laboratory procedures may be easily obtained by necropsy whenever desired. Kinetic studies using radiolabeled colloids can be done in intact animals and correlated with the lymphatic pattern delineated by X-ray or lymph-staining dye. Because the parasites are localized in regional lymphatics, they can be detected and examined following treatment with filaricides. Thus an efficient model is established for evaluating the efficacy of various treatment regimens and

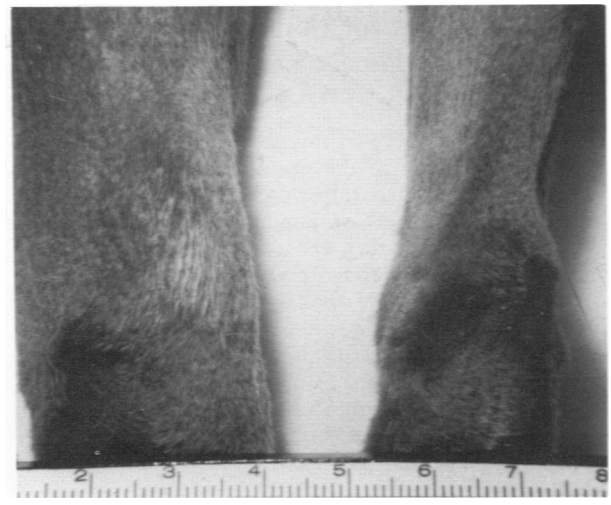

Figure 4—The hind legs of a cat. The elephantoid (*left*) leg was infected with *Brugia malayi*. The normal (*right*) leg was not infected.

for examining the changes in the disease process both before and after treatment.[8]

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