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Filaroides hirthi: Hyperinfective Lungworm Infection in Immunosuppressed Dogs

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Abstract. *Filaroides hirthi* is a pulmonary parasite found primarily in beagle dogs. The modes of transmission and the life cycle of this parasite have been described recently, and the possibility of an autoinfectious cycle has been suggested. In this paper, we report two cases of experimentally immunosuppressed beagles (4 mg/day of prednisolone for over four months) in which massive disseminated *F. hirthi* infections developed. Large numbers of *F. hirthi* adults were present in the lungs, and larvae were found in lungs, mesenteric nodes, intestinal walls, and liver. While only minimal cellular responses were associated with the adult worms, a conspicuous mononuclear cell reaction was found around the larvae in the tissues. Since our dogs were caged to minimize contact with their own feces, we suggest that autoinfection took place in these dogs. Heavy worm burdens probably were reached because the reduced immune responses against the larvae facilitated their successful penetration of the intestinal wall and their recirculation within the host.

Filaroides hirthi, a metastrongyloid nematode, is a pulmonary parasite commonly encountered in beagles reared in commercial breeding establishments.[5,7] The pulmonary lesions exhibit a broad pathological spectrum[11,12,13]: intact, viable adults may be found in the lungs without significant tissue responses, while dead and disintegrating worms may be associated with intense granulomatous reactions similar to drug-induced tumor-like growths.[11,12] The modes of transmission and the life cycle of this parasite have been clarified by experimental studies.[4,6,8] These authors found larvae in the mesenteric lymph nodes long after a single exposure to exogenous infection, and suggested the possibility of autogenous reinfectivity of *F. hirthi*,[6,8] a phenomenon known to occur in *Strongyloides stercoralis* infection of man[16] and primates.[10] Initially it was felt that the number of *F. hirthi* lungworms in naturally infected dogs rarely exceeded a few dozen[8]; however, subsequent reports of massive infections in a corticosteroid-treated Yorkshire terrier[2] and in a debilitated toy poodle[1] indicate that *F. hirthi* hyperinfection may occur like the disseminated *S. stercoralis* infections observed in immunocompromised patients,[16] dogs,[15] and primates.[3] We report two cases of massive lungworm infection in immunosuppressed beagles, and provide further circumstantial evidence to support the possibility of autogenous hyperinfection in *Filaroides hirthi* parasitism.

Case History

In June, 1982, several "helminth naive" beagle pups were acquired from a commercial breeder for a research project designed to evaluate the effects of chronic corticosteroid administration on dogs with experimental strongyloidiasis. After a short adjustment period, the pups were infected with 2000 *Strongyloides stercoralis* larvae each and caged individually. To minimize the possibility of reinfection, the cages of all dogs were steam-washed daily for the duration of the study. Three months after the initial infection, the dogs were started on a daily regimen of prednisolone (4 mg/day *per os*), a dose exceeding that found to be immunosuppressive in previous studies in our laboratory.[14] Four months after the steroid regimen began, dog GM-5 developed severe diarrhea, dehydration, and dyspnea, and euthanasia was done. Sixteen days later, in accordance with our project schedule, we sacrificed the remaining dogs. In the course of counting *S. stercoralis* at postmortem examination, numerous *F. hirthi* adults and larvae were found in the bronchi and trachea of dogs GM-5 and GM-6. Dog GM-6 had not exhibited clinical evidence of disease except for occasional mild diarrhea. In these two dogs, over 100,000 and 30,000 *S. stercoralis* adults were recovered from the intestine, respectively. This provides further indirect evidence of immunosuppression in these dogs.

Results

On gross examination of both dogs, lesions were confined to the lungs and to the mediastinal and mesenteric lymph nodes. The pleural surfaces were dark red and mottled with many tiny yellow dots which were confluent in some areas. The pulmonary parenchyma

was firm, with nearly complete consolidation. On cut surfaces, the lungs were hemorrhagic. Bronchial and tracheal mucosae were unremarkable. Both the mediastinal and the mesenteric lymph nodes were enlarged greatly; they were matted together to form large, fleshy aggregates. The other organs were unremarkable with the exception of the spleen, which was reduced in size (as expected after the long steroid therapy), and of the small intestine which had some areas of mucosal erosion. The latter finding is common in the presence of heavy *S. stercoralis* infection.

By histologic examination, the lungs of dog GM-5 had many *F. hirthi* worms in most sections. They were not associated with any cellular reaction, but other areas of the pulmonary parenchyma had moderate fibrosis of the alveolar septa. A few hemosiderin-laden macrophages were seen in the alveolar spaces and small areas of intra-alveolar and interstitial hemorrhage also were observed. In dog GM-6, more than 50% of the pulmonary tissue in any given section was occupied by sections of adult *F. hirthi* (fig. 1). Many worms contained a brown pigment which stained by the Gomori technique for iron; embryonated eggs were seen within the uteri of many worms. Additionally, large numbers of larvae were present in the pulmonary parenchyma. In contrast to the lack of a cellular response to most adult worms, most larvae were surrounded by macrophages and histiocytes, and many actually were engulfed within young giant cells (fig. 2). Both adult worms and larvae also were seen in bronchioles and small bronchi, again with no inflammatory reaction around them. Innumerable hemosiderin-laden macrophages occurred in all sections and small areas of recent intra-alveolar and interstitial hemorrhage were present throughout the lungs.

The microscopic appearance of both mediastinal and mesenteric nodes was similar in the two dogs. There was almost complete depletion of the germinal centers (an effect of prolonged steroid administration) and sinus histiocytosis. Almost all nodes contained large numbers of *F. hirthi* larvae, both in the lymphatic vessels at the periphery of the node and within the parenchyma (fig. 3). While the larvae found within the vessels appeared to be free of cellular response, those within the node invariably were associated with macrophages and many were found within multinucleated giant cells (fig. 4).

Large numbers of *S. stercoralis* adults, larvae and eggs were seen within the intestinal mucosa in all portions of the intestine. In two sections of the colon of dog GM-6 and in one section of the colon of dog GM-5, cross sections of *F. hirthi* larvae were seen within the muscularis (fig. 5) and the submucosa (fig. 6) with a mononuclear cell reaction around them.

Numerous tiny granulomata with giant cells containing sections of *F. hirthi* larvae were seen in the liver of dog GM-6 (fig. 7), while none were seen in sections from the liver of dog GM-5.

Discussion

Transmission of *Filaroides hirthi* among cagemate pups occurs by the ingestion of first-stage larvae in recently passed stools, and it has been suggested that coprophagia is the parasite's principal mechanism of transmission.[9] As early as six hours after oral administration, these larvae appear in the lungs, suggesting that they migrate from the alimentary tract to the lungs by way of the hepatic portal vein, the mesenteric drainage, or both.[6] Our findings of larvae in the intestinal wall, mesenteric lymph nodes, and liver provide further support for this view. In addition, the massive infections observed in our immunosuppressed dogs and the anatomical distribution of the adult and larval lungworms allow us to propose a possible mechanism of host control in *F. hirthi* infection.

We suggest that after the initial infection has occurred in an immunocompetent dog and a few adult worms are established in the pulmonary parenchyma, a stage-specific immunity directed against the larvae develops. The migrating first-stage larvae, by virtue of their mobility, are likely to come in contact with tissues in larger numbers than the less mobile adults. Moreover, because of their comparatively small size, larvae can be surrounded and eventually engulfed by macrophages, as seen in our sections. The macrophages take up larval antigens and present them to lymphocytes, which, in turn, become specifically sensitized and may initiate the establishment of anti-larval immunity. Our finding of a florid granulomatous response to the larvae in the lungs, intestine, liver, and lymph nodes in the absence of a significant reaction to adult lungworms is consistent with the occurrence of a strong stage-specific immunity. Once such immunity is established, the immunocompetent dog will be able to resist further infection, whether it is endogenous (internal migration of larvae) or exogenous (ingestion of infective larvae by coprophagia).

This protective mechanism, which is likely to require the cooperation of antibodies and effector cells, is less effective in the immunosuppressed host in which the larvae are free to migrate and establish in the lungs, where they mature into adult worms. Our dogs had

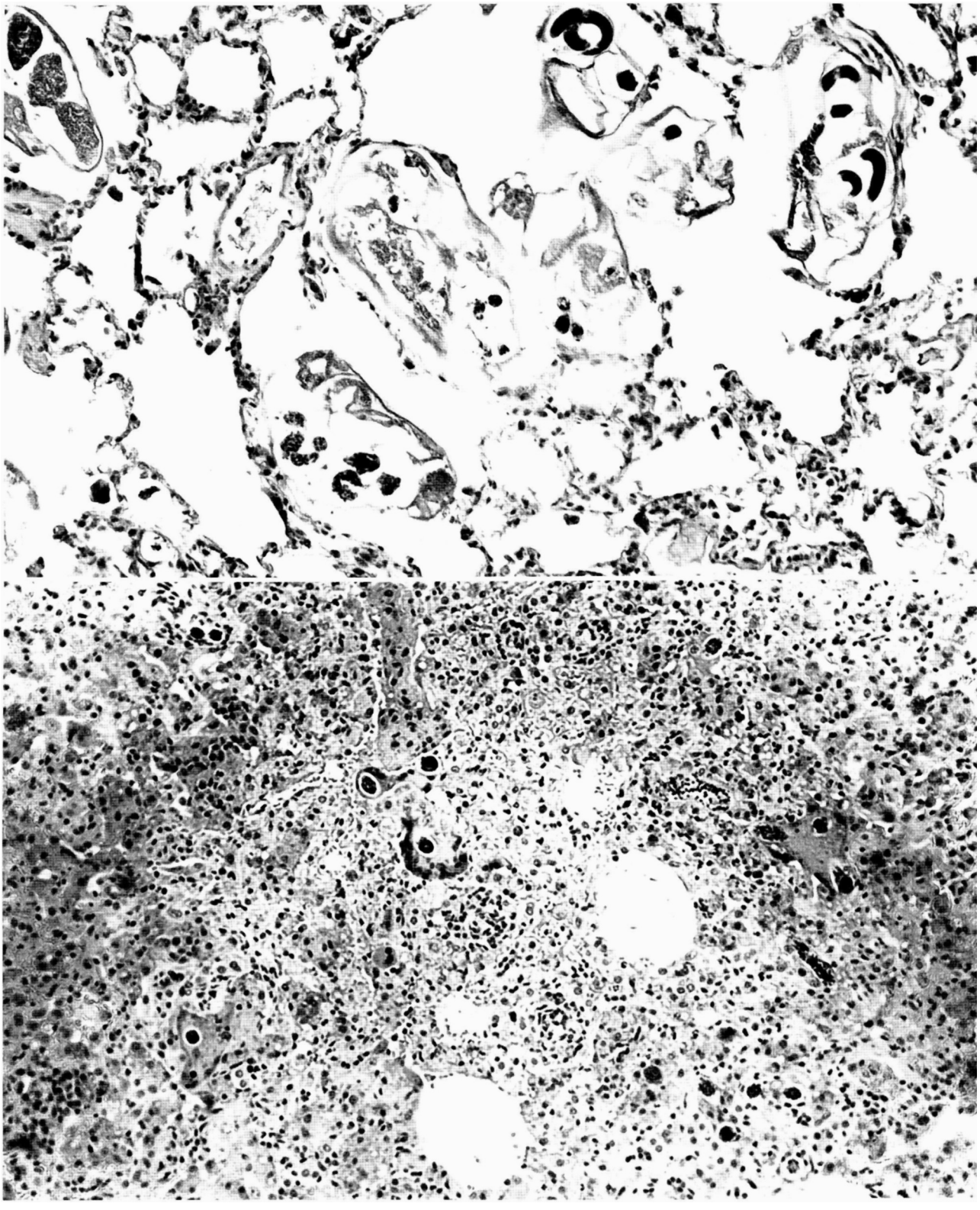

Fig. 1: Photomicrograph, lung from dog GM-6; adult female *Filaroides hirthi* in alveolar spaces. Many larvated eggs in uteri. Minimal cellular response. Hematoxylin and eosin (HE).

Fig. 2: Conspicuous mononuclear cell reaction, including giant cells, around *F. hirthi* larvae in some areas of lung parenchyma of dog GM-6. HE.

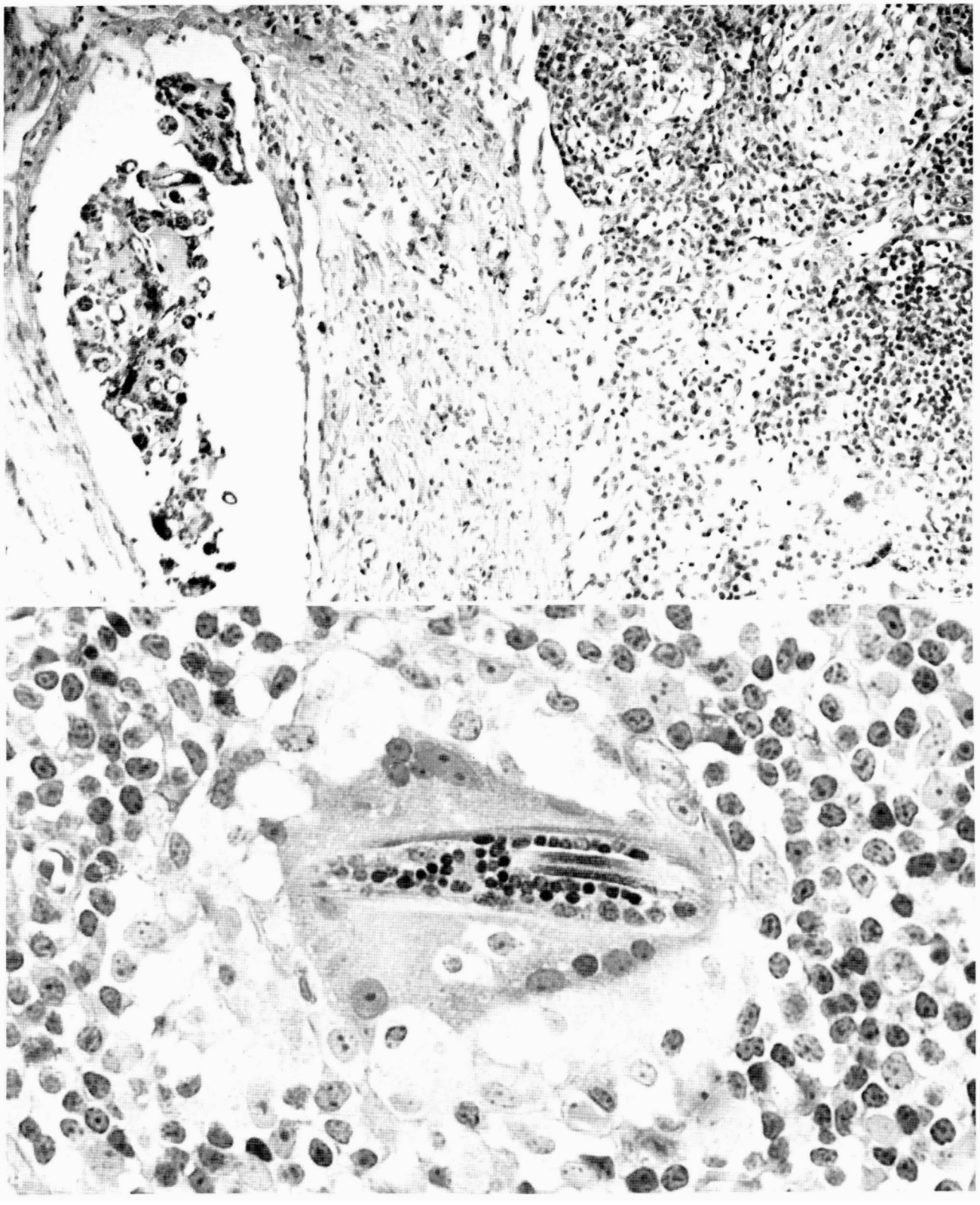

Fig. 3: Numerous *F. hirthi* larvae in dilated lymphatic vessel in mesenteric node from dog GM-5. HE.

Fig. 4: Photomicrograph from mesenteric node of dog GM-6; short longitudinal transverse section of an *F. hirthi* larva engulfed within giant cell. HE.

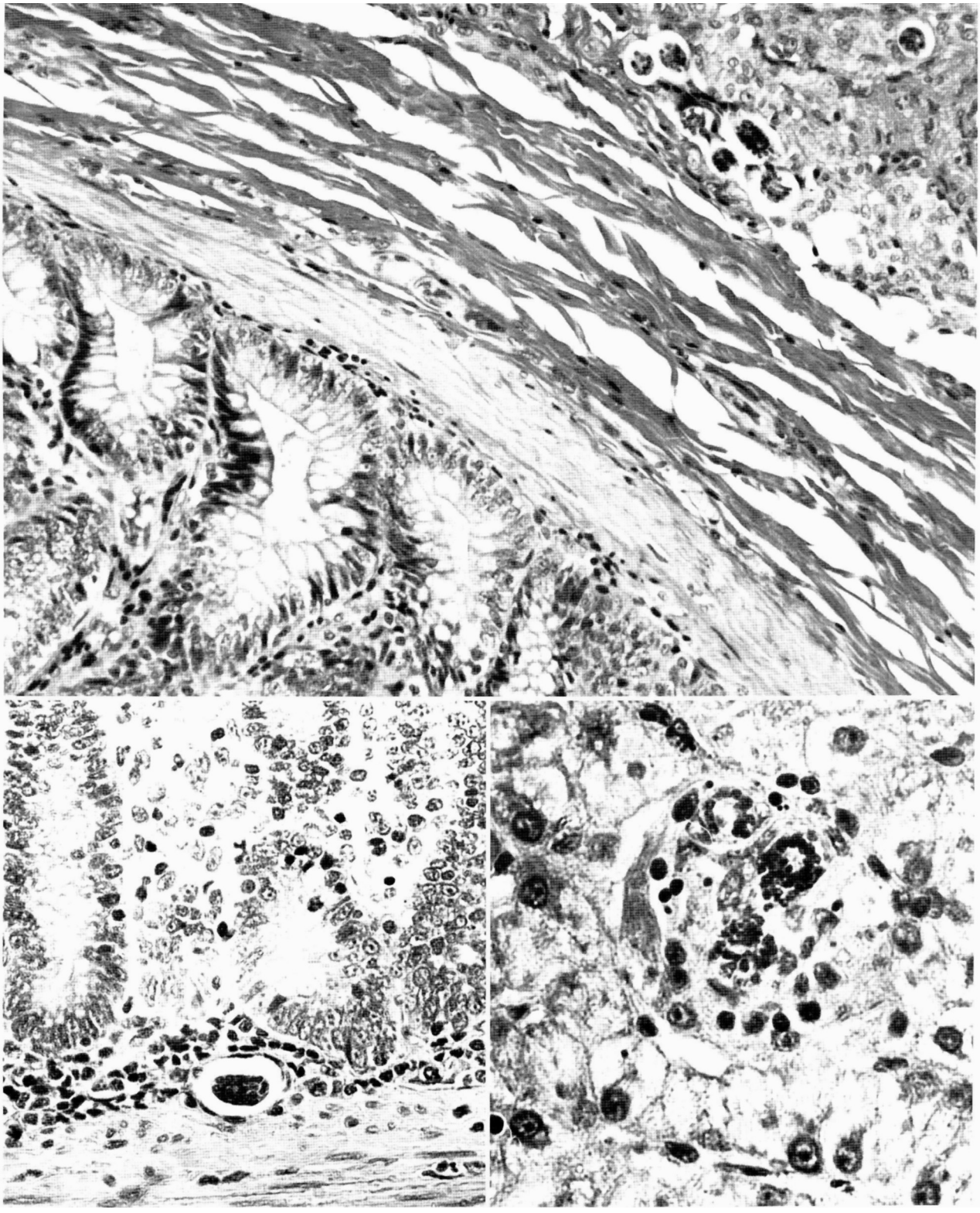

Fig. 5: Numerous cross sections of *F. hirthi* larvae in muscularis of colon of dog GM-6. Marked histiocytic response around larvae. HE.

Fig. 6: Cross section of an *F. hirthi* larva in lamina propria of colon of dog GM-5. Modest lymphocytic response in vicinity of larva. HE.

Fig. 7: Small early granuloma containing cross section of an *F. hirthi* larva; photomicrograph of liver of dog GM-6. HE.

been receiving immunosuppressive doses of prednisolone for more than four months; therefore, the effector cell system must have been incapacitated greatly, as shown by the paucity of lymphocytes or plasma cells in the proximity of larvae. Those larvae which were not trapped by macrophages were able to reach the lungs and amplify the infection.

It has been suggested that autoinfection accounts for the very large *F. hirthi* burdens found in apparently immunocompromised dogs. However, if our proposed explanation of the control of this parasite in normal dogs has merit, then the great increase in worm burden in the immunocompromised dog also could be attributable to an unusually great degree of successful development after larval ingestion. Coprophagia also might contribute to this process by providing unusually large doses of infective larvae.

With reference to the two dogs discussed in this report, it is likely that autoinfection, leading to hyperinfection, was responsible for the heavy worm burdens. It is improbable that our dogs could have ingested their diarrheic feces, most of which immediately would have passed through the wire floors of their cages. It is more probable that the *F. hirthi* larvae (L_1), which are already infective as they leave this host in the feces, would have re-infected by invading the intestines directly. If this occurred in the small intestine, invasion could have been facilitated by mucosal damage caused by the massive population of adult *Strongyloides stercoralis*. Furthermore, if penetration occurred in the large intestine, invasion could have been facilitated by *S. stercoralis* autoinfection, with numerous infective larvae of the latter providing portals of entry for *F. hirthi* larvae.

The increasing use of immunodepressive therapy in human medicine has led to a notable increase in the occurrence of clinical disease attributable to infections by opportunistic or facultatively opportunistic parasites. This trend also may occur in veterinary medicine with the increasing therapeutic use of corticosteroids and other immunosuppressants. Indeed, one case of disseminated filaroidiasis already has been reported from clinical practice, and we have confirmed experimentally that both disseminated filaroidiasis and strongyloidiasis[15] will occur in dogs following steroid administration.

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