What's Eating You? *Schistosoma mansoni*

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The life cycle of *Schistosoma mansoni* involves both invertebrate and vertebrate hosts. Humans may play the part of the vertebrate host. The larvae (cercariae) are released from fresh water snails and penetrate the skin of a vertebrate host. In a primate model of infection, the schistosomes travel to the lungs 2 to 5 days after skin penetration. By day 9, 60% of the adult worms have reached the hepatic vessels.[1]

Travelers to endemic areas (tropical and subtropical Africa and Asia) who swim in bodies of fresh water may experience intense pruritus as their skin dries and large numbers of cercariae penetrate the skin. Urticaria, periorbital edema, and, rarely, a purpuric eruption may occur 4 to 6 weeks later, shortly after oviposition by adult worms. These cutaneous changes probably reflect hypersensitivity to ova and other schistosome products. Papulonodular lesions of the perineum or distant sites are associated with granulomatous reactions to schistosome ova or, rarely, adult worms.[2]

Those who travel to endemic areas are advised never to swim in fresh water. One study of schistosomiasis among travelers to these areas reported an attack rate of almost 100% (28 of 29 travelers who could be evaluated) among those who swam in fresh water pools. One third of those infected presented with cercarial dermatitis. About half developed Katayama fever. Ova were recovered in either stool (*S mansoni* and *Schistosoma intercalatum*) or urine (*Schistosoma haematobium)* in 79% (22) of the 28 patients. Ten patients had mixed infection with more than one species.[3]

Cutaneous schistosomiasis may be associated with *S mansoni* infestation, even in the absence of preceding visceral disease.[4] Paragenital lesions are characteristic of schistosomiasis, but extragenital skin lesions may be seen during the acute phase or several years after treatment for schistosomiasis.[5] Abdominal papular lesions containing schistosome ova may be related to migration of adult worms from the portal circulation to the paraumbilical veins.[6] The diagnosis of cutaneous schistosomiasis due to *S mansoni* often is based on the discovery of eggs in the stool or in a skin biopsy specimen of a vertebrate host. The diagnosis may not be suspected clinically prior to performing a skin biopsy.[7] Schistosome ova are characterized histologically by a refractile chitinous wall and distinctive central basophilic stippling.

S mansoni ova have a thick refractile wall, unlike the thin delicate wall of *S haematobium*. The presence of a thick lateral spine (Figure) also helps differentiate *S mansoni* from *S haematobium*, which have a delicate apical spine. The ova of *Schistosoma japonicum* have a thick refractile wall, but the ova are round and smaller than other schistosome ova. *Schistosoma japonicum* ova usually demonstrate no visible spine, though some specimens will demonstrate an inconspicuous apical spine.

Serologic studies also can be helpful. Travelers who acquire schistosomiasis have often failed to take protective measures against other tropical diseases. It may be helpful to screen for a wider range of diseases, as concurrent acquisition of schistosomiasis, loiasis, and African trypanosomiasis has been described.[8]

Schistosomes infect their hosts through cutaneous penetration. The cutaneous immune response is key to understanding and controlling schistosome infections. In sensitized mice, the early cutaneous inflammatory response to schistosome penetration is characterized by edema and an infiltrate of neutrophils. Within 24 hours, eosinophils become more numerous.[9] Mice with established *S mansoni* infections demonstrate impairment of cell-mediated immunity, as evidenced by delayed

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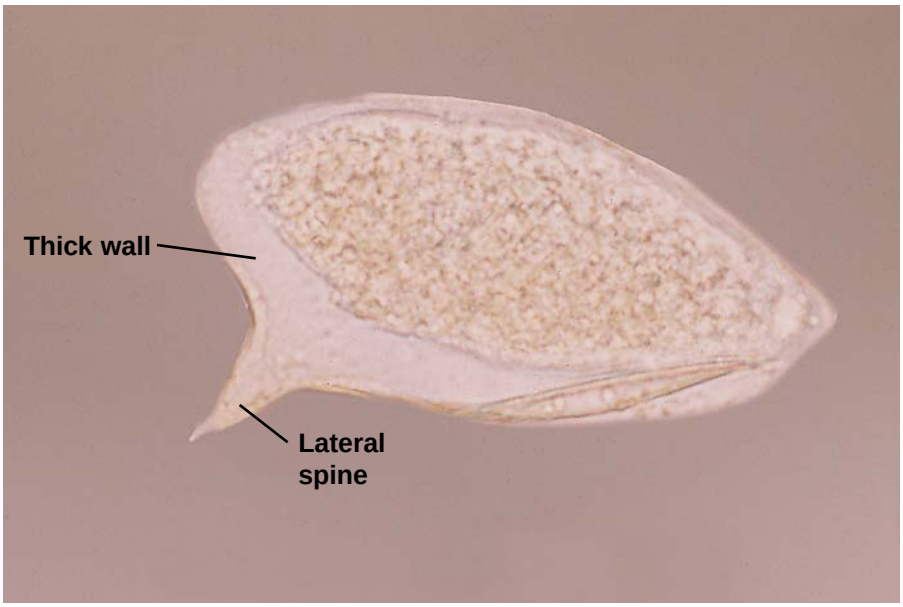

Schistosoma mansoni ova are oval with a thick refractile wall and lateral spine.

skin graft rejection.[10] Studies with human skin grafted onto immunodeficient mice with autologous lymphocytes have shown an infiltrate of CD4+ T cells 6 days after penetration of *S mansoni* cercariae. IL-7 was expressed in the epidermis and vascular endothelium. It appears that *S mansoni* larvae directly trigger IL-7 production by human skin endothelial cells but not by keratinocytes.[11] In mice, IL-7 is associated with a decrease in the production of interferon gamma and aggravation of the disease.[12] Generation of interferon gamma–producing T cells is associated with protective immunity against *S mansoni*.[13]

Human skin demonstrates both immediate and late-phase reactivity to schistosomal antigens in patients infected with *S mansoni*.[14] Treating *S mansoni* infection during the cutaneous phase results in protective immunity in mice, produced by the presence of dead schistosomes in the skin.[15] Cutaneous immunity may be key to protection against schistosomes. Immunity induced by treatment during the skin stage of infection is stronger than that produced by treatment during the lung or hepatic stages.[16] The immune response includes enhanced expression of IgG1 and tissue infiltration with lymphocytes and eosinophils.[17] Locally produced histamine also hinders the passage of viable schistosomes through skin.[18] A vaccine based on radiation-attenuated cercariae of *S mansoni* consistently elicits high levels of protective immunity in mice.[19] The immunity is protective even in the absence of B cells, suggesting that cell-mediated immunity alone can prevent infestation. Interestingly, the immunosuppressant agent cyclosporine A has been shown to be larvicidal for *S mansoni* in mice.[20] This appears to be a direct effect of the drug that is unrelated to its effects on the immune system.

Topical agents to prevent the penetration of schistosome cercariae offer another method of control. Schistosome cercariae secrete a serine protease in response to skin lipids. The serine protease facilitates penetration of human skin. Topical preparations of both peptide-based irreversible serine proteinase inhibitors and nonpeptide reversible inhibitors have demonstrated potential as topical schistosome antipenetrants.[21] N,N-diethyl-m-toluamide (DEET), also known as N,N-diethyl-3-methylbenzamide, is the most commonly used ingredient in insect repellents. When incorporated into liposomes, the lipsome-encapsulated DEET demonstrates minimal loss due to absorption or washing off. The product demonstrates a potent antiparasitic effect against *S mansoni* and has potential as a topical agent for preventing schistosomiasis.[22] Another insect repellent known as 1-(3-cyclohexen-1-yl-carbonyl)-2-methylpiperidine (AI3-37220) also demonstrates promise as a topical antipenetrant agent against *S mansoni* infection.[23] Topical niclosamide also has been studied for this purpose.[24] Although topical antipenetrant agents are ideal for preventing disease in travelers to endemic areas, this approach is likely to be too expensive to control disease in the indigenous population. Vaccination programs and efforts to control snail populations are more likely to be cost-effective in this setting.

Research of agents to control the intermediate host includes the use of plant extracts such as *Apodytes dimidiata* that are toxic to snails but not to mammals.[25] Such extracts are used to treat bodies of water. Other plant extracts that are both molluscicidal and cercaricidal show promise for intermediate host control and as topical antipenetrant agents.[26]

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