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GLOBAL HEALTH

Toward the Elimination of Schistosomiasis

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Related article, p. 121

 An interactive graphic on schistosomiasis is available at NEJM.org

Schistosomiasis remains one of the world's most prevalent diseases. Despite more than a century of control efforts and the introduction of highly effective antischistosomal drug therapy in the 1980s, the disease just will not go away. More than 207 million of the world's poorest people are currently infected with schistosomiasis, which is often a decades-long, chronic inflammatory disorder that is associated with disabling anemia and undernutrition as well as poor performance in school and at work.¹

Schistosomiasis, also known as bilharziasis, results from long-lived infection by multicellular intravascular parasites of one of five trematode species — *Schistosoma japonicum*, *S. mansoni*, *S. haematobium*, *S. intercalatum*, or *S. mekongi*. Parasite transmission and the consequent risk of human infection are strongly linked to specific geographic locations, because the parasite goes through several developmental stages that must occur in fresh water, including a period of growth within partic-

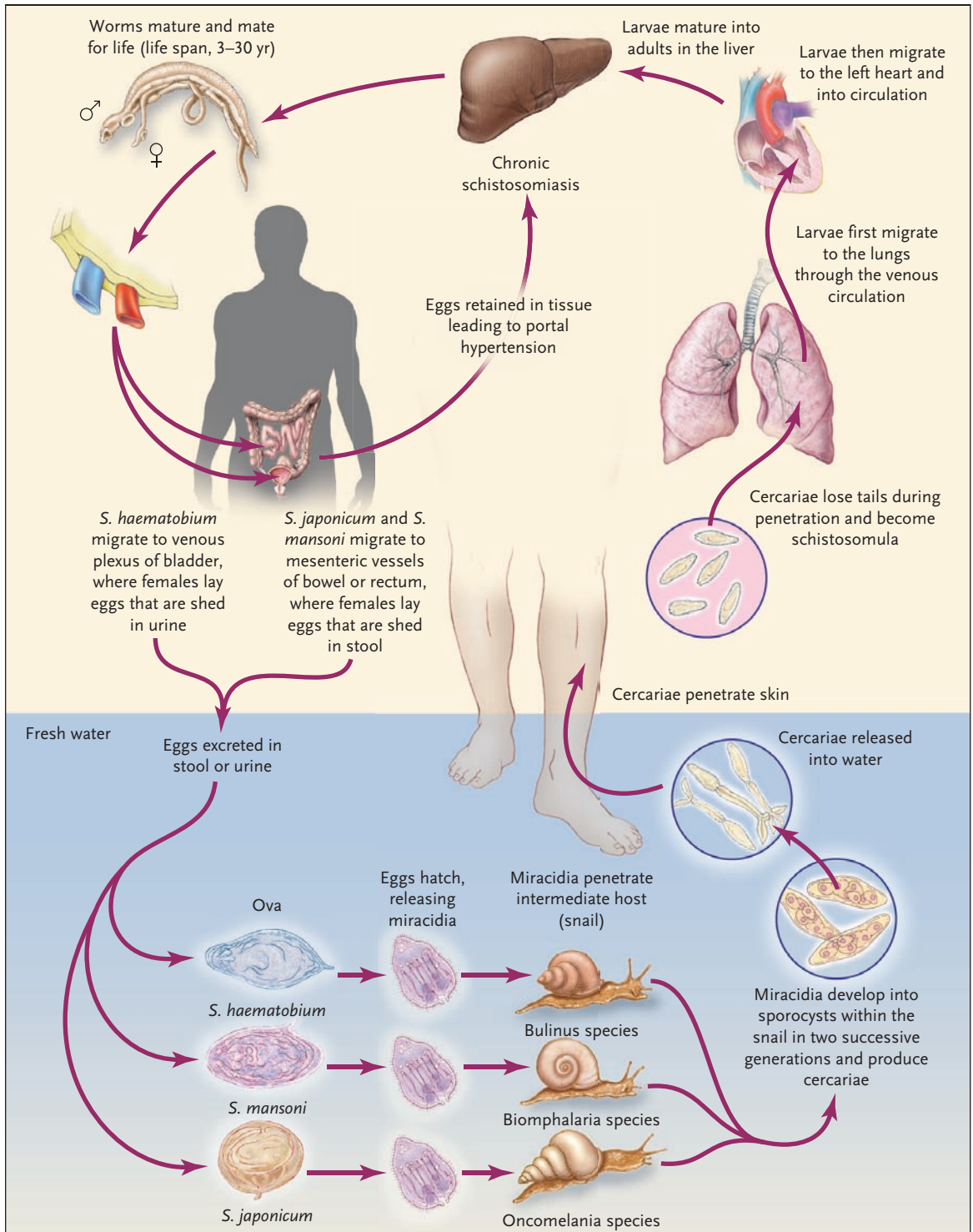
ular species of intermediate host snails (see diagram and interactive graphic).

Even after infection ends, disease persists. In some patients, especially those with intestinal schistosomiasis (see photo), the late fibrotic complications of schistosomiasis-associated inflammation lead to portal hypertension, which conveys a substantial risk of death due to variceal gastrointestinal bleeding. In patients with urinary schistosomiasis, late complications include irreversible urinary tract obstruction with an associated risk of renal failure and inflammation-induced bladder cancer. Arguably, the Asian form of intestinal schistosomiasis caused by the species *S. japonicum*, reported on by Wang et al. in this issue of the *Journal* (pages 121–128), carries the highest risks of infection-related inflammation and other complications.

In the 1980s, after the introduction of the highly effective antischistosomal drug praziquantel, it was believed that large-scale drug delivery through school-based or community-based

programs could solve the problem of schistosomiasis transmission and, in so doing, eliminate the risk of parasite-associated disease. Although such mass-treatment campaigns substantially reduced the infectious burden and the parasite-associated morbidity, they often failed to curb parasite transmission in high-risk communities. Since these efforts failed to prevent immediate reinfection itself, they also did not do a very good job of reducing the substantial rates of illness associated with reinfection.

Why didn't mass treatment stop transmission? As it turns out, the very complexity of the parasite's life cycle helps to ensure that its transmission continues within local ecosystems. Whereas public health planners had assumed that a treatment-related reduction in the excretion of parasite eggs by humans would stem the transmission of the parasite, the process of infection is, in fact, more complicated, being abetted by "superspreaders" (especially untreated children who do not attend school) and by social and hydrologic linkages



Life Cycle of the Schistosome.

Infection of humans with schistosome species causes chronic hepatic and intestinal fibrosis or fibrosis, stricturing, and calcification of the urinary tract. Infection follows contact with fresh water harboring larval parasites called cercariae, which penetrate humans' skin, become schistosomula, and enter capillaries and lymphatic vessels. The worms migrate to the portal venous system, where they mature and unite, and then to the superior mesenteric veins, the inferior mesenteric and superior hemorrhoidal veins, or the vesical plexus and veins draining the ureters. Eggs are produced and pass into adjacent tissues; many are shed in feces or urine. The eggs hatch, releasing miracidia that infect freshwater snails, which ultimately release cercariae.

among focal “hot spots” of transmission where the requisite human–snail interactions are most likely to occur. The problem of persistent transmission is compounded in the case of *S. japonicum*, because domesticated and wild animals can also be infected by this species, providing a persistent zoonotic reservoir that perpetuates local parasite transmission.

How, then, can we break the cycle of transmission? Clearly, in implementing any new schistosomiasis-control campaign, the first priority will always be to reduce the burden of illness and prevent deaths, and these objectives are usually achieved through the currently accepted mass-treatment strategies.² However, the next, more comprehensive and effective phase of disease control — the elimination of reinfection — will require efforts that are substantially more intensive and expensive. Yet the incremental expense of these additional control efforts would ultimately be offset by the greater health benefits achieved with complete elimination of parasite transmission. As Wang et al. show, in high-risk ecologic settings, drug treatment alone may suppress transmission only partially. In such environments, any program based solely on drug delivery will need to be continued for decades (or perhaps indefinitely) to prevent a reemergence of infection and disease. It is only through the incorporation of additional strategies for interruption of parasite transmission that all forms of schistosomiasis-associated disease can be prevented.

Because much schistosomiasis-associated illness remains sub-

clinical in resource-poor settings, it has effectively gone unmeasured and has often been overlooked in assessments of global burdens of disease.¹ The burden of illness due to schistosomiasis is, in fact, quite substantial, whether measured in terms of quality-



adjusted life-years³ or recalibrated disability-adjusted life-years⁴ or simply assessed through careful consideration of the process of schistosome infection and its known complications.¹

Schistosomiasis is a disease of chronic inflammation that substantially affects the daily performance of the millions of people who are or have been infected. In particular, *S. japonicum* has important effects on nutritional status, anemia, growth and development, and pregnancy outcomes.¹ The problem is due not only to fibrotic damage to specific organs but also to the constant process of granulomatous inflammation caused by the deposition of parasite eggs in host tissues. Chronically elevated levels of interleukin-6 and tumor-necrosis factor cytokines lead to the chronic el-

evation of acute-phase reactants, such as hepcidin, that impair iron uptake and mobilization, resulting in anemia of chronic inflammation. Even with low-intensity infection or reinfection, the process of new inflammation (manifesting as hepatosplenomegaly and anemia) in response to schistosomiasis can be substantial. Lapses in parasite-control efforts can result in a worsening of immunopathologic features when reinfection occurs.

It is becoming clear that the interruption of schistosome transmission in high-risk areas will require more complicated, integrated control strategies — that is, a combination of drug treatment, water management, snail control (through habitat modification, irrigation changes, and the use of molluscicidal sprays), and the control or treatment of sewage. In the case of *S. japonicum*, it will also require a reduction in the size of animal reservoirs. The community-based trial by Wang et al. suggests that such a combination strategy can work to significantly reduce or eliminate schistosome transmission in rural China. Moreover, their strategy has external environmental benefits — biofuel generation and improved water sanitation — that are likely to yield additional gains for the targeted community.

A good analogy for such integrated vector-control approaches to disease elimination can be found in the malaria-eradication efforts of the early 20th century in the United States and Europe,⁵ during which public health authorities came to realize that quinine would not eradicate malaria, since human treatment alone cannot prevent the environmental transmission of a parasitic dis-

ease. Nonetheless, long before the advent of synthetic insecticides and modern antimalarial-drug prophylaxis, malaria was effectively eradicated in many locales through combination interventions that interrupted vectorborne transmission. In the southern United States, these involved a combination of water management, reduction of habitats favorable to mosquitoes, introduction of mosquito-proof housing, and barrier screening.

Similarly, until now, preventive chemotherapy has been seen as the most appropriate means of controlling schistosome-related disease in resource-poor areas.² Now we are coming to realize that drug delivery may be only a stopgap measure. If the process of schistosome infection contin-

ues unchecked, its disabling effects in the context of rural poverty will always limit the potential benefits of drug-treatment programs while also necessitating that treatment continue indefinitely. Obviously, the elimination of schistosomiasis will be a long-term process requiring a long-term investment, but we must shoulder the necessary extra effort, including long-term planning, intersectoral government coordination, and decades-long commitment. Informed and locally adaptive prevention strategies for long-term control will be necessary. The integrated schistosomiasis-control strategies described by Wang et al. are clearly an important step in this direction.

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