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PLOS | NEGLECTED TROPICAL DISEASES

Editorial

Will All Scientists Working on Snails and the Diseases They Transmit Please Stand Up?

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If this request had been made during the presidential address at the ASTMH meeting in Philadelphia in 2011, even though the room was filled beyond capacity, only a few people would have stood up. Yet, 300 million disadvantaged people suffer from snail-transmitted infections, with consequences ranging from life-threatening cholangiocarcinoma to subtle morbidity effects that stunt physical and mental development. The disability-adjusted life year (DALY) scores for these diseases have long been underestimated. The term "*neglected* tropical diseases" truly applies to all snail-borne infections, including schistosomiasis, fascioliasis, fasciolopsiasis, paragonimiasis, opisthorchiasis, clonorchiasis, and angiostrongyliasis [1–7]. The prevalence of most of the parasites involved has scarcely diminished in recent decades. The resilience of the snails that transmit them, such as *Biomphalaria* hosting *Schistosoma mansoni* in Africa, Yemen, or South America, or lymnaeid snails supporting *Fasciola hepatica* in Bolivia and elsewhere, provides a remarkable stability to the life cycles involved. Snail-borne infections provide a worthy challenge for any young parasitologist looking for an exciting career.

The recent World Health Organization (WHO) announcement of a global effort to eliminate human schistosomiasis by 2025 [8] is an inspiring clarion call that underscores the need for more emphasis on snail-related research. Future control of snail-borne parasites needs to be considered outside of the box of current, almost exclusive, reliance on chemotherapy. Although it is essential and surely must continue, chemotherapy alone may never achieve transmission control or elimination [9], and resistance is an ever-present possibility [10–12], especially when drug options are few, the extent of treatment is broadened, and the size of drug-sensitive parasite refugia diminishes [13].

So, how can study of relevant snails contribute to eliminating schistosomiasis and other snail-borne parasites? A detailed grasp of the role of snails in transmission is essential for developing *integrated* control strategies that also target the intramolluscan larval stages of parasites. For example, what determines the population structure and geographical distribution of snails that define endemic areas for parasite transmission, and how will global warming affect these [14]? To what extent is the number of infected snails dictated by immuno-compatibility between parasite and snail versus ecological factors that limit infections? Precise information *from the field* is lacking for how long infected snails continue to shed cercariae, and the number of cercariae produced per snail. Deciphering properties of immunity and virulence that have evolved to influence snail–parasite compatibility reveals determinants of host competence that will facilitate monitoring, predicting, and ultimately modifying transmission of schistosomiasis and other snail-borne parasites.

Exciting science can be done! Snails (and trematodes parasites) are lophotrochozoan protostomes, an animal lineage to which little attention has yet been paid—fundamental discoveries consequently lie ahead in a field that is not cluttered by many competing research groups. Recent novel basic insights into host–parasite interactions include the discovery of somatic diversification of immune molecules in invertebrates (*Biomphalaria*); the involvement of antigenic variation by *Schistosoma* to survive in snails; and the epigenetic modification of snail host chromosomes during the course of infection [15–17]. Much work is needed to clarify the mechanisms involved, work that can in

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Dr. Coen Adema, Associate Professor, studies snail immunity and genomics at the Center of Theoretical and Evolutionary Immunology, Biology, University of New Mexico. Dr. Christopher J. Bayne is a comparative immunologist with interests in the evolution of immunity. His research focuses on gaining a deeper understanding of innate immune systems and their modulation, and exploits two model organisms: the rainbow trout, in which he studies the inflammatory components of the acute phase response and effects of stress on innate immunity, and molluscan schistosomiasis, in which he investigates the mechanisms that determine susceptibility and resistance in this host–parasite system. Dr. Joanna Bridger is a Reader and a group leader at Brunel University in London, UK, has spent over 20 years studying the spatial relationship between the structures in cell nuclei and the regulation of genome behavior and gene expression in a variety of organisms, including the schistosome snail host. Dr. Matty Knight is a principal investigator at the Biomedical Research Institute. For over 20 years, her research has focused on elucidating the molecular and genetic mechanisms underlying snail–schistosome interactions. Dr. Eric Loker (Sam) has interests in the biological interplay between larval schistosomes and the snails that serve as their intermediate hosts, particularly as they influence the epidemiology of schistosomiasis in Africa. In addition, his research focuses on the use of the snail as a model system to provide new insights into the nature of invertebrate defense responses. Dr. Loker also investigates the diversity inherent among both mammalian and avian schistosomes using molecular phylogenetic and other methods. He is also involved in promoting and developing genomic resources for snails involved in the transmission of schistosomiasis. Dr. Timothy Yoshino currently is a Professor of Parasitology and Director of the NIH-supported Cellular and Molecular Parasitology Training Program in the Department of Pathobiological Sciences, School of Veterinary Medicine, at the University of Wisconsin-Madison. His research is focused on the molecular mechanisms regulating larval schistosome–snail interactions. Dr. Si-Ming Zhang, Research Associate Professor, is interested in immunological and genetic mechanisms of snail and parasite interactions, and works at Center for Evolutionary & Theoretical Immunology, University of New Mexico.

today's difficult funding climate be justified by its applicability to alleviating the largely undiminished burden of snail-borne diseases. An excellent modern research toolkit justifies optimism that novel insights into *Biomphalaria*'s role in schistosomiasis transmission will be forthcoming. Microarray platforms [18,19], next-generation sequencing [20], and RNA interference enable functional transcriptomic studies of *Biomphalaria* snails [21–23]. A draft assembly of the *B. glabrata* genome sequence is fully available [24], comprising the third component of the genome triad—human definitive host, parasite, and snail intermediate host—pertinent to schistosomiasis. The prospects for rapid development of similar tool kits for other important snail such as *Bulinus*, *Lymnaea*, *and Oncomelania* [25] are excellent.

Such new molecular capabilities have great potential for application to field investigations and disease control. These include identifying genetic markers for compatibility, developing sensitive means to detect transmission in areas subjected to control, and assessing receptors involved in chemoattraction of parasite to host. Next-generation sequencing can identify third party symbionts (bacteria or viruses) influencing snail-trematode interactions. The characterization of regulators of parasite transmission in natural snail population can contribute to the development of novel, ecologically friendly snail control methods (e.g., feeding or pheromone traps), and open up new lines of study such as introduction of snail transgenes capable of disrupting larval growth/differentiation. With so many snail-transmitted infections still at large, and so many obvious approaches awaiting investigation, we sincerely hope that the decline in snail-related funding, with a concomitant decline in the number of trained investigators, can be reversed. The availability of young workers even able to identify medically relevant snails has dropped to a shockingly low level.

To conclude, it is an unchanging reality that snails are essential for the continued flourishing of snail-borne parasites, including those that cause schistosomiasis. Given the recent call for global elimination of schistosomiasis, it is imperative we pursue a broader agenda that incorporates basic and applied snail research. From such efforts can emerge integrated and more sustainable control strategies. This will also help to arrest the alarming decline in young investigators, particularly in endemic countries. Given the considerable attention currently focused on other parasitic diseases such as malaria, could it be that the greatest opportunities to make significant new advances in parasitology now lie in other fields that have been truly neglected?

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