Schistosoma mansoni and *Biomphalaria*: past history and future trends

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SUMMARY

Schistosoma mansoni is one of the most abundant infectious agents of humankind. Its widespread distribution is permitted by the broad geographic range of susceptible species of the freshwater snail genus *Biomphalaria* that serve as obligatory hosts for its larval stages. Molecular phylogenetic studies suggest that *Schistosoma* originated in Asia, and that a pulmonate-transmitted progenitor colonized Africa and gave rise to both terminal-spined and lateral-spined egg species groups, the latter containing *S. mansoni*. *Schistosoma mansoni* likely appeared only after the trans-Atlantic dispersal of *Biomphalaria* from the Neotropics to Africa, an event that, based on the present African fossil record, occurred only 2–5 million years ago. This parasite became abundant in tropical Africa and then entered the New World with the slave trade. It prospered in the Neotropics because a remarkably susceptible and productive host, *B. glabrata*, was widely distributed there. Indeed, a snail similar to *B. glabrata* may have given rise to the African species of *Biomphalaria*. *Schistosoma mansoni* has since spread into other Neotropical *Biomphalaria* species and mammalian hosts. The distribution of *S. mansoni* is in a state of flux. In Egypt, *S. mansoni* has nearly completely replaced *S. haematobium* in the Nile Delta, and has spread to other regions of the country. A susceptible host snail, *B. straminea*, has been introduced into Asia and there is evidence of *S. mansoni* transmission in Nepal. Dam and barrage construction has lead to an epidemic of *S. mansoni* in Senegal, and the parasite continues its spread in Brazil. Because of competition with introduced aquatic species and environmental changes, *B. glabrata* and consequently *S. mansoni* have become less abundant on the Caribbean islands. Control of *S. mansoni* using praziquantel and oxamniquine has reduced global prevalence but control is difficult to sustain, and *S. mansoni* can develop tolerance/resistance to praziquantel, raising concerns about its future efficacy. Because of legitimate environmental concerns, snail control is unlikely to be an option in future control efforts. Global warming will impact the distribution of *Biomphalaria* and *S. mansoni*, but the magnitude and nature of the effects are poorly understood.

Key words: *Schistosoma mansoni*, *Biomphalaria*, evolution, distribution, control.

INTRODUCTION: *S. MANSONI*'S PRESENT ABUNDANCE, DISTRIBUTION AND HOST PREFERENCES

Schistosoma mansoni Sambon, 1907 has the distinction of being the most intensively studied of all members of the phylum Platyhelminthes. The number of papers published annually regarding this species is 3–4 times higher than for any other platyhelminth species, reflecting its importance as a laboratory model for studying schistosomiasis. It is likely that the first complete genome sequence obtained for a flatworm will be that of *S. mansoni* (Snyder *et al.* 2001). The scrutiny given this organism is well deserved for *S. mansoni* is the most widely distributed of all the schistosomes infecting humans, being found in sub-Saharan Africa where it is particularly abundant, in the valley and delta of the Nile, in parts of southwest Asia, in Brazil and other parts of northeastern South America, and in isolated foci on some of the Caribbean islands (Fig. 1). A recent estimate places the number of people infected with *S. mansoni* at about 83 million (Crompton, 1999), in 54 countries (Chitsulo *et al.* 2000). In addition to infecting humans, *S. mansoni* is also found in rodents (Théron & Pointier, 1995; D'Andrea *et al.* 2000) and in wild primates, particularly baboons (Ghandour *et al.* 1995; Müller-Graf *et al.* 1997; Munene *et al.* 1998).

The geographic distribution of *S. mansoni* is closely tied to that of freshwater pulmonate snails that serve as its obligatory molluscan hosts, susceptible species of the planorbid genus *Biomphalaria*. Although there are reports of successful experimental *S. mansoni* infections in another discoidal planorbid species, *Planorbarius metidjensis* (Barbosa, Barbosa & Morais-Rêgo, 1959), the extent to which *S. mansoni* is a specialist on *Biomphalaria* snails is remarkable. In sub-Saharan Africa, *S. mansoni* is predominantly transmitted through *Biomphalaria pfeifferi* even though all of the 12 African species of *Biomphalaria* are susceptible to infection and can play some role in transmission in certain situations (Brown, 1994). *Biomphalaria alexandrina* is the most

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Parasitology (2001), **123**, S211–S228.

DOI: 10.1017/S0031182001007703 Printed in the United Kingdom

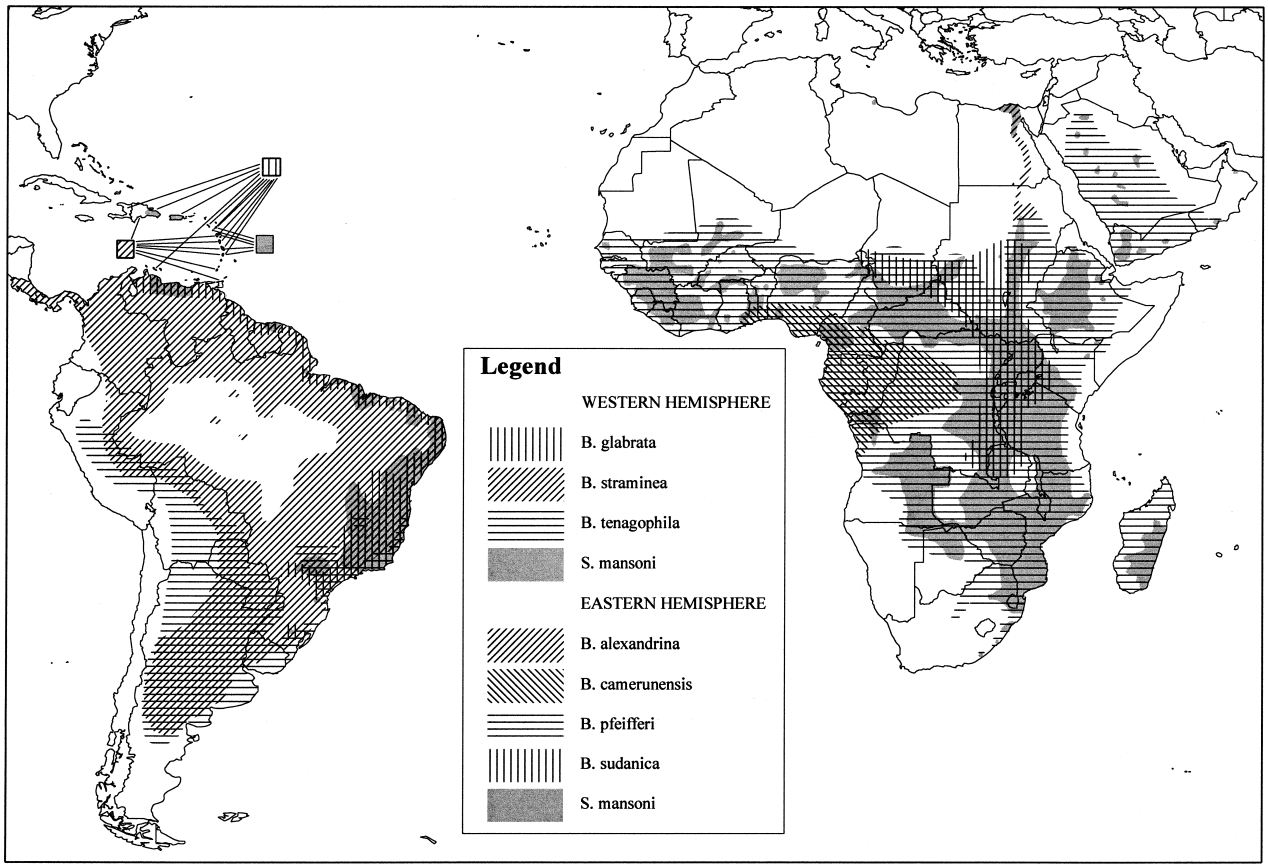

Fig. 1. Distributions of *Schistosoma mansoni* and *Biomphalaria* host species of major medical importance. After Brown (1994), de Souza & Lima (1997), Doumenge *et al*. (1987) and Malek (1985). Distributions are intended to indicate the main areas of occurrence; continuity of distribution is not implied and there may be significant discontinuities within these areas.

common host in Egypt. In South America and the Caribbean region, *B. glabrata* is the most important snail host, although *B. straminea* and *B. tenagophila* can also be found naturally infected. In South America there are six *Biomphalaria* species that have not been implicated in *S. mansoni* transmission but that are susceptible experimentally and eight species that are apparently refractory to infection (Malek, 1985).

The factors underlying compatibility between *S. mansoni* and *Biomphalaria* are complex and have been the subject of a number of studies that have been reviewed elsewhere (Loker & Bayne, 1986; Richards, Knight & Lewis, 1992; Yoshino & Vasta, 1996; Adema & Loker, 1997). Suffice it to say here that both the resistance status of the snail host and the infectivity of the parasite are genetically controlled. Also because both snail and parasite are variable entities (Vidigal *et al*. 1994; Mulvey & Bandoni, 1994; Curtis & Minchella, 2000), tremendous variation in the compatibility of local host and parasite strains has been noted (Basch, 1976; Frandsen, 1979*b*).

For many of us, *S. mansoni* exists as a laboratory abstraction, yet it is vitally important to try to understand its existence in the real world. With this goal in mind, it is helpful to gain a perspective on where *S. mansoni* has been and where it is likely to go in coming years.

VIEWS ON WHERE *S. MANSONI* CAME FROM

Origin of the genus

Schistosomes have left no fossil record making it difficult to pinpoint where or when the genus originated. *Schistosoma mansoni* probably arose in Africa (Davis, 1980, 1992; Snyder & Loker, 2000) but how and when did its progenitors get there? Two theories are currently available to describe the origins of the genus.

Out of Africa theory. The African origin theory was proposed by George M. Davis and has been developed over a number of years (Davis, 1980, 1992). The theory proposes that the genus *Schistosoma* originated in Gondwanaland (the supercontinent consisting of Africa, Antarctica, India and South America) within both pulmonate and pomatiopsid snails and dispersed via continental drift and collisions, see Fig. 2A (Davis, 1980, 1992). Thus, the ancestor of all Asian *Schistosoma* rafted

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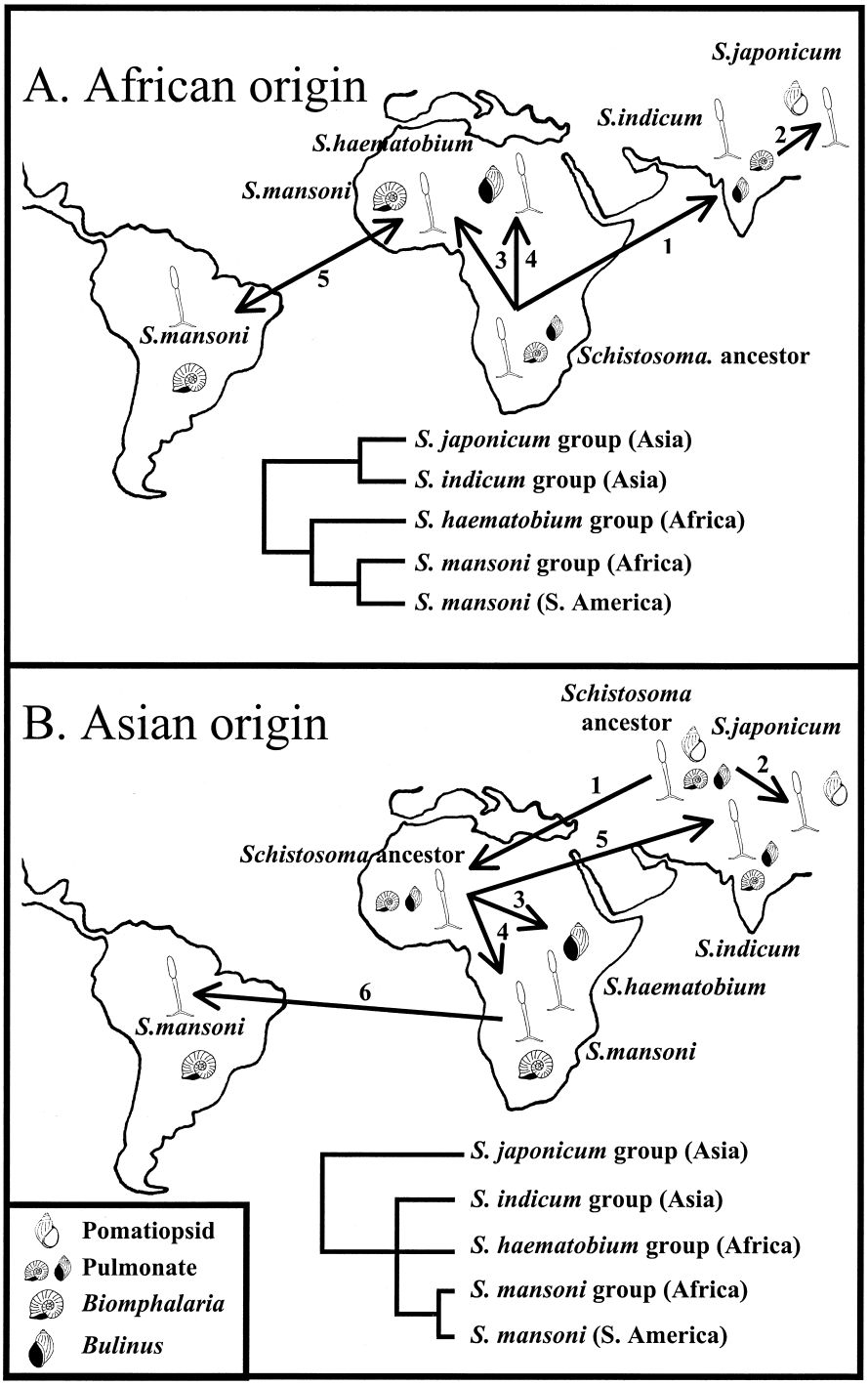

Fig. 2. Maps displaying the two hypotheses of origin of *S. mansoni*, A. the African origin and B. the Asian origin. Below each map is a tree depicting expected species group relationships given the theorized origin. (A) African origin (after Davis, 1980; 1992); 1 and 2 The ancestral African *Schistosoma* rafts to Asia on the Indian plate 70–148 MYA forming the *S. indicum* and *S. japonicum* groups. 3 and 4 The *Schistosoma* ancestor remaining in Africa diverges > 120 MYA to form the *S. mansoni* and *S. haematobium* groups. 5 *Schistosoma mansoni* disperses to South America 80–120 MYA, before continental drift splits Gondwanaland. (B) Asian origin (after Snyder & Loker, 2000 and other sources): 1 The ancestral Asian *Schistosoma* (likely a parasite of pulmonate snails) moves to Africa 12–19 MYA via widespread mammal migration. 2 The *Schistosoma* ancestor remaining in Asia becomes the *S. japonicum* group. 3 and 4 The African *Schistosoma* ancestor diverges 1–4 MYA to form the *S. mansoni* and *S. haematobium* groups. 5 An *S. indicum* ancestor also diverges from the African ancestor 1–4 MYA and migrates back to India, probably with early humans and their domestic animals (Barker & Blair, 1996). 6 *Schistosoma mansoni* disperses to South America 150–500 YA via the transport of African slaves.

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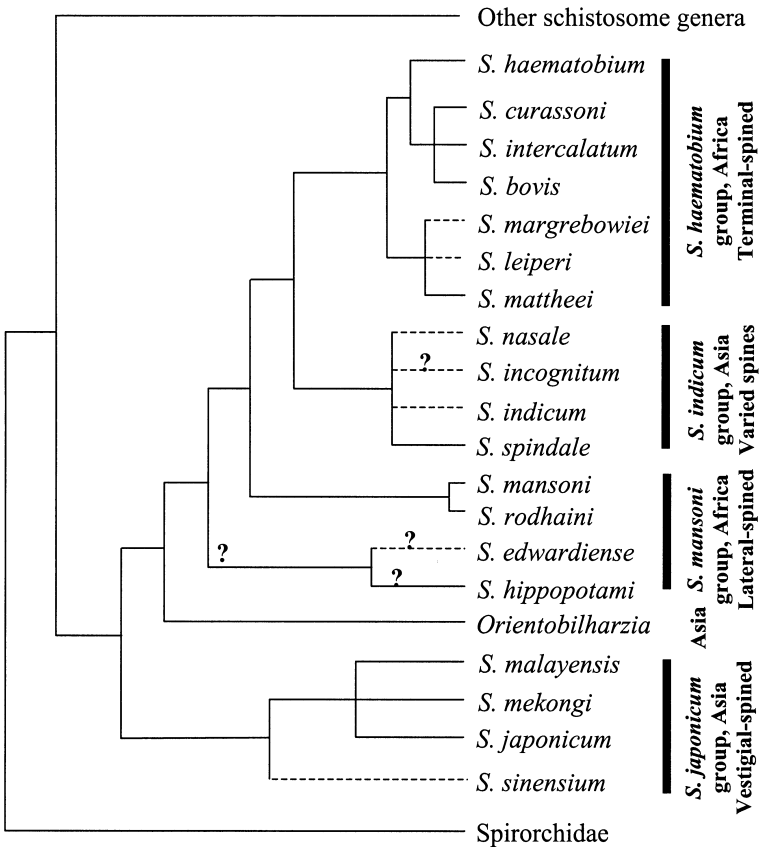

Fig. 3. Manually constructed schistosome tree summarising published phylogenies. Tree is a compilation of trees published by Snyder & Loker (2000), trees reviewed in Rollinson *et al*. (1997) and a super-tree generated by Morand & Müller-Graf (2000). Dotted lines mark predicted branch positions for species with no available data. The question marks (?) indicate branches that vary in different publications and are placed speculatively on this tree.

there from Africa on the Indian plate, which split from Africa 70–148 million years ago (MYA; Després *et al*. 1992). On reaching Asia the ancestors of *Schistosoma japonicum* radiated along with their pomatiopsid snail hosts. Schistosomes remaining in India retained their association with pulmonate snails and became the ancestors of the *S. indicum* group. The ancestral *Schistosoma* remaining in Africa, diverged over 120 MYA to form the ancestors to today's *S. mansoni* and *S. haemotobium* groups. *Schistosoma mansoni* had to be present in Gondwanaland at least 80 MYA, within *Biomphalaria*, to enable them both to access South America before the continents separated.

Out of Asia theory. A more recent theory on the origin of *Schistosoma* suggests that the genus arose in Asia and was introduced to Africa (Fig, 2B; Snyder & Loker, 2000). The Asian ancestral *Schistosoma* may have had either a pomatiopsid or a pulmonate snail host. Davis (1992) has linked the diversification of the *S. japonicum* group to the radiation of their pomatiopsid hosts in the mid-Miocene. Based on this link, Snyder & Loker (2000) reasoned that the colonization of Africa by *Schistosoma* occurred no earlier than this time (15 MYA), well after the fragmentation of Gondwanaland. On reaching Africa, the descendants underwent extensive radiation becoming exclusive parasites of pulmonate snails in the family Planorbidae. According to this theory, *Schistosoma mansoni* was not in Gondwanaland when Africa separated from South America; thus the species must have utilized an alternative method for dispersal.

Molecular data support Asian theory

Taking a closer look at relationships among members of the genus *Schistosoma* at a molecular level may help us to understand the origins of *S. mansoni*. Predicted phylogenetic trees based on the two theories outlined above are drawn in Fig. 2.

A tree summarizing the genetic relationships among members of the genus *Schistosoma* is shown in Fig. 3. The tree has been compiled from a number of published phylogenies generated from both mitochondrial and nuclear genes (Snyder & Loker, 2000, trees reviewed in Rollinson *et al*. 1997 and a super tree generated by Morand & Müller-Graf, 2000). Predicted branches leading to species for which sequence is lacking are indicated with dotted lines. With the exception of *S. hippopotami*, the genetic phylogenetic trees produced agree with the four general groupings within the genus (*S. mansoni*

https://doi.org/10.1017/S0031182001007703 Published online by Cambridge University Press

group, *S. haematobium* group, *S. japonicum* group and *S. indicum* group), which were originally based on morphology and life history characteristics. To date only one representative of the *S. indicum* group has been sequenced. The level of genetic diversity among species within the *S. japonicum*, *S. haematobium* and *S. mansoni* groups appears to be very low compared to that measured between the species groups (reviewed in Rollinson *et al*. 1997).

The position of *S. hippopotami* is the one exception. The rDNA ITS2 from a single specimen has been sequenced and despite *S. hippopotami* displaying *S. mansoni* group characteristics (lateral-spined eggs and thought to infect *Biomphalaria*) it fails to cluster with the *S. mansoni* clade (Després *et al*. 1995; Rollinson *et al*. 1997). Thurston (1963) indicated that *S. hippopotami* resembles *S. incognitum* in egg size, egg morphology (subterminal-spine) and adult morphology. Efforts to complete the life cycle of *S. hippopotami* have been unsuccessful (Thurston, 1971) and to date its intermediate host remains unknown. *Schistosoma incognitum* infects lymnaeid snails and adults are common in pigs and dogs from India (Sinha & Srivastava, 1960) and rodents from Indonesia (Carney *et al*. 1977). Sequence data for *S. incognitum* are currently unavailable so its position within the *S. indicum* group (Fig. 3) is questionable. In the future it may in fact be recognized as separate from the *S. indicum* group, all other members of which infect the planorbid snail *Indoplanorbis exustus*, and show a closer affiliation to *S. hippopotami*. The ancestral African *Schistosoma* might have been a *S. incognitum*-like parasite, transmitted by a pulmonate (lymnaeid or planorbid ?) snail, that made the passage from Asia in pigs, or their close relatives, hippos. The position of *S. edwardiense* is even less clear. This species infects hippos, has *S. margrebowiei*-shaped eggs and appears to infect *Biomphalaria*. It is intriguing that *S. edwardiense* also has cercariae with long tail-stems, like those of *S. incognitum*.

The Asian origin theory is based on molecular evidence. Snyder & Loker (2000) generated a tree from rDNA 28S sequences representing ten of the 13 genera belonging to the family Schistosomatidae. The tree depicts the genus *Schistosoma* as a paraphyletic assemblage with the Asian genus *Orientobilharzia* positioned as sister taxon to the African *Schistosoma* with *S. japonicum* more distant (Fig. 3). The African clade appears to be the most derived of the *Schistosoma* species, supporting the Asian origin theory. It is interesting to note that, like *S. incognitum*, *Lymnaea* snails are also intermediate hosts for *Orientobilharzia*.

Trees constructed from rRNA 18S (Johnston, Kane & Rollinson 1993) and 28S (Barker & Blair, 1996) sequences place *S. spindale*, a member of the *S. indicum* group, within the African species clade as a sister taxon to the *S. haematobium* group. Barker & Blair (1996) suggested that the position of *S. spindale*, and its lack of genetic divergence reflected a more recent introduction into Asia, probably with early humans and their domestic animals as they dispersed from Africa. Unfortunately sequence data are currently unavailable for comparisons with other members of the *S. indicum* group.

In favour of the Asian origin theory, the *S. japonicum* group displays the greatest divergence in all of the molecular studies to date. Species variation within the group (sequence data available for *S. japonicum*, *S. malayensis* and *S. mekongi*) is also higher than that observed among species within the *S. haematobium* and *S. mansoni* (excluding *S. hippopotami*) groups (Bowles, Blair & McManus, 1995; Rollinson *et al*. 1997).

Recent research has discovered changes in the mitochondrial gene order of Asian versus African schistosomes (Le *et al*. 2000). Their results add further support to an Asian origin for the genus. The Asian species, represented by *S. japonicum* and *S. mekongi*, display a gene order similar to that observed in other trematodes and cestodes while the African species (*S. mansoni*, *S. rodhaini*, *S. haematobium*, *S. bovis*, *S. curassoni*, *S. intercalatum*, *S. mattheei* and *S. margrebowiei*) have a rearranged mitochondrial genome. Although mitochondrial gene order cannot in itself be used as evidence for an Asian origin it does suggest that the African taxa may be more derived. The *Schistosoma* Genome Network has undertaken a collaborative study to sequence and analyse the entire mitochondrial genome of *S. mansoni* and *S. japonicum* (Franco *et al*. 2000).

Resolving the origins of *Schistosoma* may require additional sequences from those rarer species and genera missing from current studies: *S. sinensium*, *S. indicum*, *S. nasale*, *S. incognitum*, *S. hippopotami*, *S. edwardiense*, *S. leiperi*, *Griphobilharzia*, *Bivitellobilharzia* and *Macrobilharzia*.

Timing of events

The time frame placed on the divergence of the African and Asian *Schistosoma*, given an African origin, is 70–148 million years (Després *et al*. 1992). According to the Asian origin hypothesis, if the time of diversification of the *S. japonicum* group in the mid-Miocene is correct, then Africa was colonized no sooner than 15 MYA. The obvious question is: Is 15 million years enough time to account for the diversification of African *Schistosoma*? Barker & Blair (1996) completed a log likelihood ratio test on their rDNA 28S trees to determine if a molecular clock could be used to describe the evolution of the data set. Unfortunately, the molecular clock was rejected and they were unable to speculate about the age of the genus. Després *et al*. (1992) estimated divergence times by calibrating their nuclear rDNA ITS2 and mitochondrial 16S sequence based trees

against rodents, which have a clear fossil record. They estimated a divergence for 16S of 1–2% per million years and for ITS2, 0·3–0·8% per million years. Based on these rates, the African and Asian schistosomes split 24–70 MYA. Separation of the two African groups (*S. mansoni* and *S. haematobium*) was dated 10–30 MYA and divergence within the African clades was 1–10 MYA for the *S. mansoni* group and 1–6 MYA for the *S. haematobium* group.

The mammalian fossil record shows an influx of Asian mammals into Africa 12–19 MYA during a series of collisions between Arabia and Turkey (Cox, 2000). Lowered sea-levels and a continuous tropical environment encouraged the transfer of carnivores, pigs, bovids and rodents from Asia into Africa (Cox, 2000). The conditions were probably well suited for the transfer of a *Schistosoma* ancestor within one of these hosts.

Origin of the species

The ancestral African *Schistosoma* species diverged to form the two African clades known today, the lateral-spined *S. mansoni* group and the terminal-spined *S. haematobium* group. The basal position of *S. hippopotami*, with respect to the African species, suggests that the African ancestor had a subterminal-spined egg. Note that the evidence to support the position of *S. hippopotami* is not strong, it relies upon a 300 base pair sequence from a single animal. Sequence data from *S. incognitum* may provide additional support for a subterminal-spined ancestor. A snail other than *Biomphalaria* must have been susceptible to the African ancestor as evidence presented below suggests *Biomphalaria* was not in Africa at this time.

The *S. mansoni* ancestor radiated into at least two, and possibly four, species and the *S. haematobium* ancestor radiated into seven. The human acquisition of African schistosomes is believed to be the result of independent lateral transfers from other animals (Combes, 1990). It is unlikely that primates were the ancestral host because no *Schistosoma* specific to non-human primates have been described (Combes, 1990). Ungulates are thought to be the original hosts of the *S. haematobium* group and Combes (1990) suggested that primates acquired *S. mansoni* from rodents. The lack of genetic differentiation detected between *S. mansoni* and *S. rodhiani* (0·56% difference through ITS2) suggests a recent separation of these species, and divergence rates indicate it could be as little as 1 MYA (Després *et al*. 1992). Given that hominids have been present in Africa for considerably longer than this, it is possible that they acquired the ancestor of *S. mansoni* from other mammals and that the parasite has since undergone a lateral transfer into rodents. Further research is required to resolve the origin and diversification of the *S. mansoni* group.

Despite greater speciation within the *S. haematobium* group, it was *S. mansoni* that radiated geographically. Populations of *S. mansoni* now occur in the New World and have spread throughout the Neotropics. Analysis of RAPD data has shown that *S. mansoni* isolates display considerably less intraspecific variation than is observed within *S. intercalatum* and *S. haematobium* isolates despite greater geographic separation (Rollinson *et al*. 1997). The current distribution of *S. mansoni* is strongly correlated to that of *Biomphalaria*, which is outlined in the following section.

Biomphalaria *fossil record and phylogenetics*

To fully understand the past history and future trends of *S. mansoni*, it is important to place this parasite in the context of the origin and evolutionary history of *Biomphalaria*. The current distribution of *Biomphalaria*, primarily in South America and Africa, can be described as Gondwanian. The geographic distributions of the most important intermediate hosts for *S. mansoni* are shown in Fig. 1. Given this distribution, it is reasonable to consider the possibility that *Biomphalaria* originated in Gondwanaland more than 100 MYA, and as the African and South American continents split apart, two lineages of *Biomphalaria* were formed: one South American and the other African (Pilsbry, 1911; Davis, 1980, 1992; Meier-Brook, 1984). Davis (1980, 1992) proposed that schistosomes existed along with pomatiopsid, bulinid and biomphalarid snail hosts before the breakup of the two continents. However, it is perplexing why bulinids, if Gondwanian in origin, are neither extant nor have a fossil record in South America.

A Gondwanian origin for *Biomphalaria* is challenged by the fossil record as well. Although *Biomphalaria*-like shells are represented in South America as early as the Paleocene (55–65 MYA; Parodiz, 1969), there is no corresponding record in North Africa. The oldest known occurrence of *Biomphalaria* in Africa is only mid to late Pleistocene (1–2 MYA; Van Damme, 1984). In fact, the African fossil record is relatively devoid of planorbids until the Pleistocene, with the exception of *Planorbis*, which has possible fossils dating to the Lower Eocene (42–55 MYA; Van Damme, 1984).

The pre-Pleistocene fossil record of *Biomphalaria* is not restricted to South America, however, but appears to include North America and Eurasia. Due to the sub-tropical and tropical conditions that existed over much of North America extending as far north as southern Canada during the Eocene and Oligocene (23–55 MYA), fossil *Biomphalaria* are quite common in sediments of this age (Pierce, 1993). Similar conditions presumably existed in Eurasia where such fossils have been described from Eocene strata (34–55 MYA; McKenna, Robinson &

Taylor, 1962) These tropical conditions waned in the late Oligocene and early Miocene (16–29 MYA), and *Biomphalaria* fossils are less common, restricted to western Montana (Pierce, 1993). This fossil literature is less frequently considered by medical malacology, but there is a need for incorporating this extensive fossil evidence, only touched upon here, into the discussion of existing *Biomphalaria* species and distribution. Caution is certainly warranted when interpreting these records; not all specimens may be correctly identified. Clearly though, the past distributional and evolutionary history of *Biomphalaria* may be more complex than the current distribution would imply.

In 1997 some striking new possibilities regarding the continent of origin and subsequent diversification for *Biomphalaria* were proposed. Based on allozyme studies, Woodruff & Mulvey (1997) concluded that *Biomphalaria* was of South American (not Gondwanian) origin. According to their theory, *Biomphalaria* underwent a west-to-east trans-Atlantic colonization event, either by rafting or via aquatic birds, between 2·3 and 4·5 MYA, suggesting the 12 extant species of African *Biomphalaria* must have diverged since this colonization event. Woodruff & Mulvey (1997) suggest that the fossil record (as discussed above) is consistent with this theory. They also note that the morphological differences amongst African *Biomphalaria* species are small compared to those amongst South American species (Mello, 1972), suggestive of a more recent origin of the African species. In light of the extensive, albeit uncertain, North American fossils, the concept of a South American origin should perhaps be modified to a concept of an American origin, allowing for a North American or South American origin. We suggest that a longer existence in the Americas, than in Africa, is also supported by: (1) there are more recognized species in the Neotropics; (2) these species exhibit a greater range in size than do the African *Biomphalaria*; and (3) the Neotropical species show greater diversity with respect to *S. mansoni* susceptibility (Paraense, Ibañez & Miranda, 1964; Paraense & Corrêa, 1982; Malek, 1985).

A Pliocene (2–5 MYA) colonization of Africa by *Biomphalaria* is significant because it raises the possibility that *S. mansoni* did not differentiate from its immediate ancestor until this time. The ancestor, possibly a pulmonate-transmitted schistosome similar to *S. hippopotami* or *S. incognitum*, might have switched to *Biomphalaria* when it became available, and given rise to the *S. mansoni* species group.

Woodruff & Mulvey (1997) also provide some provocative suggestions regarding the most important host of *S. mansoni* in the Neotropics, *B. glabrata*. This snail occurs in Venezuela, French Guiana, Surinam, Guyana, eastern Brazil and on some of the Caribbean islands (Fig. 1). The analyses of Woodruff & Mulvey (1997) supported a close relationship between this species and the 3 African species included in their study. In fact, their analyses indicated *B. glabrata* to be derived from African ancestors, prompting them to suggest that the presence of this species in the Neotropics is the result of colonization with the slave trade, with *B. glabrata* or proto-*B. glabrata* carried to the Caribbean and South America via water casks aboard slave ships (though they also allowed for an earlier east-to-west trans-Atlantic event). If *B. glabrata* is a recent colonist (< 500 years ago), one would expect that this species might still be extending its range, which has been documented (Paraense 1983; Paraense & Araujo, 1984). However, the presence of *B. glabrata*-like shells at two Upper Pleistocene sites in Brazil (Lima, 1984, 1987) suggests that *B. glabrata* existed in Brazil before the slave trade.

A particularly puzzling question that arises from the Woodruff & Mulvey (1997) hypothesis is: which particular African taxon might be the immediate ancestor of *B. glabrata*? There is no obvious answer based on morphology. If the colonization event is as recent as the slave trade, one expects there to be a reasonably similar snail somewhere in West Africa. Based on its relatively large size, and West African distribution (Fig. 1), *B. camerunensis* may be a candidate. However, *B. camerunensis* lacks a renal ridge, a defining character for *B. glabrata* (Malek, 1985; Paraense & Deslandes, 1959). It is also a rainforest species, unlike *B. glabrata*, and is less susceptible to *S. mansoni* infection (Frandsen, 1979*a*, *b*: Greer *et al* 1990). Furthermore, if the slave trade commonly facilitated colonization of African *Biomphalaria* to the Neotropics, why wasn't *B. pfeifferi*, the most common species in Africa (including West Africa; Fig. 1), or *Bulinus* introduced? West Africa has been surveyed for *Biomphalaria* (Doumenge *et al*. 1987), so the existence of a yet undescribed species as conspicuous as *B. glabrata* seems unlikely.

Bandoni, Mulvey & Loker (1995) also found a close association between *B. glabrata* and the African species, yet the results of the two studies differ in an important way. Bandoni *et al*. (1995) found *B. glabrata* to be the sister group of the African species and therefore a proto-*B. glabrata* could be the possible ancestor of the African lineage they found to be monophyletic. This scenario requires only a single colonization event, that of a proto-*B. glabrata* colonizing Africa, with subsequent radiation giving rise to the African species. The success of *S. mansoni* in so many different locations in South America and on several Caribbean islands is more easily explained under this scenario, since a suitable endemic host in *B. glabrata* would be present before the arrival of the parasite. If *B. glabrata* is of African origin, and colonized South America via water casks, the establishment of *S. mansoni* in multiple locations

would require the introduction and rapid success of the African snail in each location, which seems somewhat unlikely. However, we credit Woodruff & Mulvey (1997) for demonstrating the close association of *B. glabrata* with the African species and providing a thought-provoking suggestion regarding its origin. Both of the above studies were based on allozyme data, and were limited by low numbers of species (9 and 11), high frequencies of laboratory populations instead of field-derived populations, and poor representation of populations from West Africa.

Recent molecular studies, which have incorporated field-derived and West African taxa, are consistent with Bandoni *et al*. (1995). A study of 7 *Biomphalaria* species (Campbell *et al*. 2000) and data obtained from 23 species in our laboratory (DeJong *et al*., unpublished observations) support an American origin for *Biomphalaria*, and a relatively recent colonization of Africa by proto-*B. glabrata*.

COLONIZATION OF THE NEW WORLD BY *S. MANSONI*

If the fossil record is correct in suggesting that *Biomphalaria* has been in Africa for less than 5 million years and that *S. mansoni* originated in Africa less than 4 MYA, the New World colonization by *S. mansoni* must have occurred since then. Files (1951) suggested a recent introduction of *S. mansoni* into the New World via the extensive 16th to 19th centuries slave trade. Enzyme electrophoresis studies by Fletcher, Loverde & Woodruff (1981) supported this theory as they detected very little variation between South American and African isolates. A comparison of nuclear and mitochondrial ribosomal gene sequences detected greater variation within South American isolates than could be measured between isolates originating from the two continents (Després *et al*. 1992). They concluded that the South American *S. mansoni* was a recent introduction and that the relatively high level of genetic diversity observed among South American isolates was a consequence of multiple transfer events originating from many parts of Africa. Further research, by Després and her co-workers, characterizing *S. mansoni* mitochondrial DNA, produced similar results providing additional support for the recent introduction theory (Després, Imbert-Establet & Monnerot, 1993).

Although intraspecific variation among *S. mansoni* isolates appears to be low compared to other *Schistosoma* species (Rollinson *et al*. 1997), localized strain differences have been recorded among New World isolates. An RFLP study focusing on the intergenic spacer and 18S rRNA was able to detect differences among isolates from Brazil (Vieira *et al*. 1991). Isolates from the southeast showed less variation than those from the northeast, suggesting *S. mansoni* is radiating from the northeast of the country.

More sensitive markers are now being sought to detect *S. mansoni* population differences. A repeating element within the mitochondrial genome of *S. mansoni* is being targeted. The number of copies of this element can cause length polymorphisms among isolates that can vary up to 8400 bases (Minchella *et al*. 1994; Minchella, Sollenberger & Desouza, 1995; Johnston *et al*. 1993; Curtis & Minchella, 2000; Després *et al*. 1993). A set of microsatellite markers has also been identified for *S. mansoni* but they are yet to be applied to populations outside of Guadeloupe (Durand, Sire & Theron, 2000).

Definitive host capture appears to be more common in the New World with *S. mansoni* frequently recovered from rodents while more strictly primate transmitted isolates occur in East Africa (Combes, Léger & Golvan, 1975; Jourdane, 1978). Isolates of *S. mansoni* recovered from humans and rodents originating from Brazil could not be distinguished using mitochondrial DNA 16S sequences (Després *et al*. 1992). The authors suggested that, rather than co-evolving with a single host, *S. mansoni* is simply expanding its host range. A similar transfer into rodents has been observed in Guadeloupe (Bremond *et al*. 1993; Théron & Pointier, 1995). In Guadeloupe, differences between human and rodent transmitted isolates of *S. mansoni*, including egg morphology and patterns of cercarial shedding, are suggestive of incipient speciation (Théron & Pointier, 1995). If the origin of *S. rodhaini* in Africa was a result of a lateral transfer by *S. mansoni* from humans into rodents, then we may be seeing the start of a similar event in the New World.

CHANGES IN SNAIL DISTRIBUTIONS AND IMPLICATIONS FOR *S. MANSONI*

The transmission of *S. mansoni* is restricted to freshwater habitats in geographic regions where susceptible species of *Biomphalaria* are present and where the specific local ecological circumstances enable biomphalarids to exist. Not surprisingly, with increasing human demands placed on the world's supplies of freshwater, pervasive changes have occurred in tropical freshwater habitats that influence *Biomphalaria* and consequently *S. mansoni*. Each of the countries/geographic regions discussed below provides its own insights regarding changing patterns of snail distributions and the attendant impacts on *S. mansoni*.

S. mansoni *ascendant – the example of Egypt*

Egypt presents several intriguing observations and questions regarding *S. mansoni*. The first systematic studies of the abundance of *S. mansoni* in Egypt were

https://doi.org/10.1017/S0031182001007703 Published online by Cambridge University Press

by Scott (1937) who noted that this parasite was restricted to the northern and eastern part of the Nile Delta and was rare south of Cairo. By comparison, *S. haematobium* was not only much more abundant in the Delta, but also found in Upper Egypt. *Biomphalaria alexandrina*, the Egyptian snail host for *S. mansoni*, was apparently then confined to the Nile Delta. In 1955, the snail was reported for the first time south of Cairo, and by 1979 had been reported as far south as Aswan (Vrijenhoek & Graven, 1992). Studies of allozyme variation in *B. alexandrina* suggested that colonization of the upper Nile involved a series of stepwise founder events originating from the Delta, each marked by a loss of some allelic diversity (Vrijenhoek & Graven, 1992). Not surprisingly, focal transmission of *S. mansoni* from regions such as Fayoum south of Cairo began to occur (Abdel-Wahab *et al*. 2000). Judging from the increased abundance of *S. mansoni* in the Delta, *B. alexandrina* has also become relatively more abundant there as well. At the same time, the prevalence of *S. haematobium* throughout the Nile Delta has declined sharply, and reduced numbers of *Bulinus truncatus* have been noted from the region.

The underlying reasons for these twentieth century changes in snail abundance are not known. There is a general sense that construction of the Low and High dams at Aswan, and the resultant shift from inundative to perennial irrigation, has had the effect of creating more impounded water bodies with a sufficient degree of stability to favour the proliferation of *B. alexandrina* (Malone *et al*. 1997; El Khoby *et al*. 2000). The role of other factors such as extensive pollution of the irrigation canals and the introduction there of exotic species has not been assessed. Whatever the underlying causes, *S. mansoni* has now nearly completely replaced *S. haematobium* in the Nile Delta and appears likely to continue to increase in other areas as well. To make matters worse, the Neotropical *B. glabrata* has been introduced into Egyptian canals, possibly as early as 1981 (Pflüger, 1982), and there is evidence that it is hybridizing with *B. alexandrina* (Kristensen, Yousif & Raahauge, 1999). As *B. glabrata* is such an excellent host for *S. mansoni*, it seems its presence can only favour increased transmission.

It is also interesting to contemplate the history of *S. mansoni* in Egypt on a longer time-scale. Although studies of mummified remains and numerous references to hematuria in ancient writings clearly place *S. haematobium* in Egypt as early as the Middle Kingdom (1500 BC) (Ruffer, 1910; Contis & David, 1996) a definitive presence at that time for *S. mansoni* is less certain. *Schistosoma mansoni*'s symptomatology is less dramatic than for *S. haematobium* so its presence would have been understandably overlooked by the ancients. It is intriguing, however, that there are no clear demonstrations of *S. mansoni* eggs from Egyptian mummies.

A better understanding of the biogeography of *Biomphalaria* in Egypt would help to clarify the duration of the presence there of *S. mansoni*. In this regard, the relatively restricted, fragmented and disjunct geographic range of *B. alexandrina* is noteworthy. It is abundant in the Delta and as noted above, has been found south of Cairo only in recent years. Populations of *B. alexandrina* are also reported from northern Sudan, nearly 1000 km to the south (Fig. 1; Williams & Hunter, 1968). Also inhabiting the Nile drainage in the Sudan is *B. sudanica*, a species that according to our ongoing phylogenetic studies is a very close relative of *B. alexandrina*. For reasons that are not clear, perhaps because of annual flooding, the course of the Nile between Khartoum and Cairo was apparently not heavily colonized historically by *Biomphalaria* snails. One scenario is that *B. sudanica*-like snails from the Sudan managed to colonize the favorable habitat of the Nile Delta, perhaps by downstream or avian-mediated dispersal. The intervening stretch of the Nile may have served as a barrier sufficiently strong to enable this founder population to diversify into the endemic taxon recognized today as *B. alexandrina*. The scarcity of *Biomphalaria* in Upper Egypt could also have been a significant barrier that delayed the colonization of Egypt by *S. mansoni* from large endemic foci to the south. Thus, to a certain extent, the increase in *S. mansoni* noted in Egypt today, could represent part of a longer term colonization that has been underway potentially for thousands of years.

Epidemic schistosomaisis in Senegal – 'If you build it, they will come' (slightly modified from *Field of Dreams*, MCA Universal Films)

Senegal provides a striking modern example of the rapidity and extent to which large water development projects can favour colonization by *Biomphalaria* and transmission of *S. mansoni* (Southgate, 1997). In 1985, a large barrage was built about 40 km from the mouth of the Senegal River to prevent the intrusion of salt water into the river during times of low flow. Prior to construction of the barrage, *S. haematobium* existed at a low level along the lower stretches of the river. It was thought that the temperature was too high to allow *B. pfeifferi* to survive there and *S. mansoni* was not present. By as early as 1988, for the first time in the area, *S. mansoni* infections were being reported in the town of Richard Toll, 140 km upstream of the barrage (Talla *et al*. 1990). By 1989, 49·3% of patients examined were infected with *S. mansoni* and *B. pfeifferi* had become very common in the area. By 1994–5, mean prevalence in villages around Richard Toll had reached 72% (Picquet *et al*. 1996). Construction of the dam reduced salinity and increased irrigation as expected, but also had the unforeseen effect of increasing the pH of the river

https://doi.org/10.1017/S0031182001007703 Published online by Cambridge University Press

water (Southgate, 1997). All of these changes favoured colonization by both *Biomphalaria* and *Bulinus* snails. To make matters worse, compatibility between the local *B. pfeifferi* and *S. mansoni* was shown to be extraordinarily high (Tchuente *et al.* 1999).

The lower Senegal river basin is now considered to be one of the world's most intense foci of *S. mansoni* infection; mean values of 1793 ± 848 eggs/g of faeces have been reported from the area near Richard Toll (Picquet *et al.* 1996). Further compounding the problem, rates of treatment success with praziquantel in this area have been low. Several factors contribute to poor response to treatment (Southgate, 1997), and among them must be included the observation that the Senegalese isolate of *S. mansoni* is inherently less responsive to the drug (see below).

Ongoing conquest of a new world – S. mansoni *in Brazil*

Today we are witnessing a large-scale, ongoing colonization event by *S. mansoni* that began four to five hundred years ago when African slaves were brought to Brazil. This colonization is a complex process, one favoured by the built-in presence (Lima, 1987) of populations of a very susceptible snail host, *B. glabrata*, around the coastal areas originally inhabited by infected slaves. Since the time of the original introductions, massive human-imposed changes in the environment have favoured the spread of *B. glabrata* and other indigenous *Biomphalaria* species. For example, locally-acquired cases of *S. mansoni* have been reported for the first time from Brazil's most southern state, Rio Grande do Sul (Graeff-Teixeira *et al.* 1999), thus fulfilling a prediction made by Paraense & Corrêa (1987). The *S. mansoni* cases are associated with the recent first report of *B. glabrata* from Rio Grande do Sul. The sequence of events leading to the colonization of this area by *B. glabrata* is not known. Range extensions of *B. glabrata* have probably occurred elsewhere in Brazil (Paraense, 1983; Paraense & Araujo, 1984), creating new opportunities for *S. mansoni* transmission.

Another major factor contributing to the spread of *S. mansoni* has been the host capture of other species of *Biomphalaria* that initially were poorly susceptible to the parasite. Paraense & Corrêa (1963; 1987) noted that A. Lutz, during his pioneering work on schistosomiasis in Brazil in 1916, was unable to infect *B. tenagophila*. Since that time, the parasite has adapted to this snail species which is now an efficient host along the southeastern coastal region of the country. Similarly, to the northeast, the parasite has adapted to *B. straminea*. The adoption of different intermediate host species has been accompanied by the differentiation of isolates of *S. mansoni* (Paraense & Corrêa, 1963, 1981). The parasite has also shown a remarkable ability to adapt to new mammalian hosts, most particularly the aquatic rodent, *Nectomys squamipes* (D'Andrea *et al.* 2000). One of the interesting questions for the future is whether *S. mansoni* will continue its Neotropical spread. *Biomphalaria straminea* is known from as far north as Costa Rica (Paraense, Zeledón & Rojas, 1981) and has disseminated widely throughout the Caribbean (Pointier, Paraense & Mazille, 1993). A *B. straminea*-like snail is known from Uruguay and is susceptible to *S. mansoni* (Paraense & Corrêa, 1989). *Biomphalaria peregrina* from Equador (Paraense & Corrêa, 1973) and *B. tenagophila* from Peru (Paraense, Ibañez & Miranda, 1964) have been shown to be susceptible to *S. mansoni*.

One of the factors that may work to reduce the prevalence of *S. mansoni* in Brazil and other parts of South America is the introduction of thiarid snails such as *Melanoides tuberculata* (e.g. Junior, 1999). Thiarids are now present in Minas Gerais and also in the Rio de Janiero area. As noted below, for reasons that are still not well understood, following their introduction thiarids often become staggeringly abundant, and displace native snail species, including *Biomphalaria*.

Biomphalaria, S. mansoni *and Asia – will long-range colonization events result in endemicity in tropical Asia*?

In addition to the introduction of *B. glabrata* into Egypt noted above, other potentially troublesome long-range introductions of *Biomphalaria* are known. The Neotropical snail *B. straminea* was first noticed in a small stream in Hong Kong in 1973 (Meier-Brook, 1974). This introduction was likely aided by the trade in aquarium plants and fishes. The exact source of the introduced specimens has not been determined. Since that time the snail has spread into several adjacent habitats and it has become locally abundant (Woodruff *et al.* 1985*a*; Yipp, 1990). Yipp (1990) noted that *B. straminea* is likely to colonize organically polluted sites where other freshwater snails have been eliminated. Woodruff *et al.* (1985*b*) provided allozyme evidence to indicate that a second, separate introduction of *B. straminea* occurred in Hong Kong in 1981–1982. They commented that there is every reason to expect additional introductions of *B. straminea* to occur, and once established in Asia, that it was likely to be spread secondarily, both to other Asian localities and elsewhere. They also indicated surprise that *B. glabrata* had not yet colonized Asia. Walker (1978) noted that *B. straminea* was found among fishes imported into Australia from Hong Kong, but fortunately the snails were intercepted, and there still is no indication of the presence of *Biomphalaria* in tropical Australia. Although there is no evidence

for *B. straminea*-mediated transmission of *S. mansoni* in China, the snail is found naturally infected in Brazil and can maintain transmission there, so the potential exists for Asian transmission of *S. mansoni* by *B. straminea*.

Another more recent and troubling report concerns the discovery of eggs resembling those of *S. mansoni* from human stool samples in southern Nepal (Sherchand & O'Hara, 1997). A serological study found 18·1 % of the 518 sera examined to be positive for antibodies to *S. mansoni* (Sherchand *et al*. 1999). Very little is presently known about this focus, but there has been extensive environmental change in the region, including deforestation and construction of irrigation schemes. It is conceivable that *Biomphalaria* has been introduced into these schemes and that this has been followed by the unfortunate introduction of *S. mansoni*, possibly with immigrant workers. An alternative possibility is that the eggs observed in Nepal are those of *Schistosoma sinensium*, a species with lateral-spined eggs known from southern China (Greer, Kitikoon & Lohachit, 1989). Eggs of this species may have been ingested and then passed by humans.

'*No worm is an island …*' – *the rise and fall of* S. mansoni *in the Caribbean*

The relatively brief history of *S. mansoni* in the Caribbean islands, although poorly documented, is nonetheless instructive in several regards: *Biomphalaria glabrata* is either present or used to be present on 17 of 31 Caribbean islands, and *S. mansoni* at one time or another colonized 10 of the 17 islands (Bundy, 1984). Significant foci of infection occurred in St. Lucia, Guadeloupe, Martinique, Puerto Rico and the Dominican Republic, and limited transmission also occurred on St. Martin, St. Kitts, Vieques, Antiqua and Montserrat. Today, although the overall status of human schistosomiasis in the area is remarkably poorly known, it is likely that transmission to humans is marginal at best throughout the islands. Puerto Rico provides a good example of this trend. In 1945, the overall prevalence of *S. mansoni* in Puerto Rico was 13·5 %. A limited survey carried out in previously endemic areas by Giboda, Malek & Correa (1997) revealed only 3 cases, all in older individuals. The cane-growing areas of the Dominican Republic may be the largest remaining foci of human infection on the Caribbean islands (Vargas, Malek & Perez, 1990). Thriving but highly focal areas of infection involving *Rattus rattus* as definitive host are known from the island of Guadeloupe (Théron & Pointier, 1995).

The failure of *S. mansoni* to persist in the region following colonization with the slave trade is due to several interacting factors. The first, and likely most important, is simply that these foci existed on islands. Populations on islands are inherently more vulnerable to extinction events, particularly if the islands are small. Islands like St. Martin and St. Kitts are tiny with few habitats to support snails and deforestation and water diversion projects altered these few habitats sufficiently to terminate transmission. Control programmes are more likely to succeed on islands because the target populations are small and confined to start with, and are less likely to be replenished from surrounding areas by immigration. Thus, a concerted schistosomiasis control programme, featuring the use of molluscicides and chemotherapy, succeeded in eliminating *S. mansoni* from the relatively small island of Vieques in 1962 (Ferguson, Palmer & Jobin, 1968). Human-induced changes in the islands have also contributed to the demise of *S. mansoni*. In Puerto Rico, the channeling of streams through enclosed cement viaducts, as part of a pervasive trend of urbanization, has played a role in reducing *B. glabrata* populations there. 'Economic development and well being' are described as the control strategy in Puerto Rico leading to eradication (Hillyer & deGalanes, 1999).

Natural catastrophic events also influence *S. mansoni* in the Caribbean. Hurricanes, such as Georges that devastated Puerto Rico in 1998, may interrupt local electric and water services, forcing people to wash clothing in streams. The attendant water contact would favour transmission (Hillyer & deGalanes, 1999). Hurricanes can eliminate freshwater snails by inundating habitats with saltwater. Another reality for the Caribbean is volcanism, dramatically demonstrated most recently in Monserrat. The volcano there, after being dormant for 400 years, erupted in 1995. As late as 1978, 14 % of people in two local villages were serologically positive for *S. mansoni* (Tikasingh *et al*. 1982). Ash and lava flows may have altered or obliterated habitats occupied by *B. glabrata*, but little is known of the eruption's effects.

Of all the factors influencing the decline in prevalence of *S. mansoni* in the Caribbean, probably the most important has been the introduction, both accidental and deliberate, of exotic snails that compete with and/or prey upon *Biomphalaria* (Pointier & Giboda, 1999). *Marisa cornuarietis*, an ampullariid snail indigenous to the Orinoco drainage of Venezuela, was introduced in 1958 into 30 of Puerto Rico's water reservoirs and by 1976, only 5 of these reservoirs still harboured *B. glabrata* (Jobin *et al*. 1977). The ampullariid both competes for resources with *B. glabrata* and preys upon its egg masses and young. A focus of murine schistosomiasis in Grand Etang lake in Gaudeloupe was also eliminated by the combined actions of ampullariids *Pomacea glauca* and *M. cornuarietis* (Pointier *et al*. 1991).

The islands of the Caribbean have experienced a remarkable biological invasion that began in the 1940s, probably as a consequence of the trade in

aquatic plants and fishes (Pointier & Giboda, 1999). In 1954, the Oriental snail *Thiara granifera* was first reported in Puerto Rico, and by 1968 had spread throughout the island (Chaniotis *et al*. 1980). Butler *et al*. (1980) documented the ability of *T. granifera* to displace *B. glabrata* from permanent streams in Puerto Rico. Similar results were obtained by Prentice (1983) in St. Lucia, and by Perez, Vargas & Malek (1991) in the Dominican Republic. Giboda, Malek & Correa (1997) concluded that the main reason for the decline of *S. mansoni* in Puerto Rico was the lack of *B. glabrata* and attributed this to the probable competitive impacts of thiarid snails. In St. Lucia, where *S. mansoni* prevalence was once as high as 57 % in some villages, *B. glabrata* is now scarce in former transmission sites. The related thiarid snail *Melanoides tuberculata*, an African species, was introduced in 1978, and only two years later had displaced *B. glabrata* where introduced (Prentice, 1983). Pointier (1993) found *B. glabrata* to be abundant in only two of 26 sites where it was formerly abundant. These two sites lacked *M. tuberculata*.

In Martinique, the introduction in 1983 of *M. tuberculata* into watercress beds, where *S. mansoni* was still transmitted, resulted in practically complete elimination of *B. glabrata* and *B. straminea* by 1990, and the reduction of *S. mansoni* transmission to a handful of cases (Pointier & Guyard, 1992). The thiarid has since colonized the entire island, and successive waves of colonization of the island by different morphs have been noted (Pointier *et al*. 1993). This species has since largely been replaced, although not eliminated, on Martinique by *T. granifera* (Pointier *et al*. 1998). *Melanoides tuberculata* did not effectively eliminate *B. glabrata* from the marshy forest transmission foci of Guadeloupe (Pointier, Theron & Borel, 1993) and, as noted above, *S. mansoni* is still actively transmitted there by rats.

Although *S. mansoni* is clearly on the wane in the Caribbean, it is premature to assume its eventual extinction. The situation on Guadeloupe indicates that in some locations thiarids are not able to displace *B. glabrata*, and that the parasite has exhibited a remarkable adaptability for infecting rats. Although thiarids are present to stay in the Caribbean region, it is conceivable that with time their abundance may diminish and that biomphalarids will come to coexist with them. In East Africa, where both *M. tuberculata* and *B. pfeifferi* are normal components of the snail fauna, the two species are known to occupy the same habitat for extended periods, without one species eliminating the other (Mkoji *et al*. 1992). Schistosomiasis thrives in regions of Africa where *M. tuberculata* is present (Brown, 1994). The same human behaviours that have introduced thiarids everywhere will also favour the colonization or re-colonization of some Caribbean islands or habitas by either *B. glabrata*, or the more peripatetic species, *B. straminea*. Whether *S. mansoni* can continue to exist on such shifting biological terrain remains to be seen, but its ability to adapt to introduced populations of *B. straminea* may prove to be critical to its survival.

Finally, with respect to *S. mansoni* in the Caribbean, both Haiti and Cuba present interesting situations. Although *S. mansoni* is present in the Dominican Republic, and *B. glabrata* is known to be present in parts of Haiti (Raccurt *et al*. 1985), there is still no definitive evidence for the presence of schistosomiasis in Haiti. Thiarid snails may be increasingly limiting the distribution of *B. glabrata* in both countries, making it improbable that new foci of transmission will appear in Haiti. Cuba is of interest simply because *B. glabrata*, and hence *S. mansoni*, do not exist on the island. This raises the more general issue of what are the underlying determinants of *B. glabrata*'s distribution throughout the Caribbean region? It seems unlikely that islands as large as Cuba and Jamaica, which also lacks *B. glabrata*, were never colonized by this snail. Other species of *Biomphalaria* occur in Cuba, so it also seems unlikely that the hydrogeography of the island is unsuitable. Perhaps Cuba's more northernly latitude renders its climate too cool to support the tropical *B. glabrata*? Thiarids are also present in Cuba and so may prevent future colonization of the island by *B. glabrata*.

The impact of introduced aquatic species on snail intermediate hosts has been most dramatic with thiarids in the Caribbean region, but in Africa other introduced species are also likely to affect the distribution of *S. mansoni*. In Kenya, the North American crayfish *Procambarus clarkii* has become common in some drainage systems and where present, schistosome intermediate hosts are not found (Hofkin *et al*. 1991). The crayfish is a voracious predator of snails and other aquatic organisms. Where the crayfish establishes it has the potential to stop transmission of schistosomiasis (Mkoji *et al*. 1999). It is also present in the irrigation canals of the Nile Delta, and is known from the Sudan, Uganda, South Africa, Zimbabwe and Zambia (Hobbs, Jass & Huner, 1989). Unfortunately, the aggressive and omnivorous tendencies of this species pose a threat to the integrity of African freshwater ecosystems. Also, now widely present in Africa is another North American invader, the snail *Physa acuta*. This species has several attributes including high fecundity (Brackenbury & Appleton, 1991), effective defense against predators (Wilken & Appleton, 1991), upstream migratory tendencies (Appleton & Branch, 1989) and a high tolerance for polluted waters that seem to give it a competitive advantage over endemic species. These attributes may eventually favor the displacement of indigenous African *Biomphalaria* species.

CONTROL OF *S. MANSONI* AND SOME OF THE IMPLICATIONS

The most effective means to control *S. mansoni* has been the use of chemotherapy. In particular, use of praziquantel has been associated with an overall decline in the global prevalence of this parasite (Chitsulo *et al*. 2000). The experience in Egypt has shown, however, that control of *S. mansoni* based purely on chemotherapy is very hard to sustain, and prevalence rates have remained stubbornly high (El Khoby *et al*. 2000). Furthermore, evidence from a variety of sources suggests that resistance to praziquantel may be developing. In the laboratory, isolates of *S. mansoni* with a significant degree of resistance can be developed by simply exposing infected mice to subcurative doses of praziquantel. After seven generations of selection 93% of the worms were unresponsive to high doses of praziquantel (Fallon & Doenhoff, 1994). In field situations, in both Senegal and Egypt, there is evidence for the presence of *S. mansoni* isolates that are relatively unresponsive to the drug, although the underlying basis for this seems to be different in each case. In Senegal, the poor response of *S. mansoni* in the new focus on the delta of the Senegal River has been partially explained by the presence of very high worm burdens and the lack of immunity in this newly-exposed human population (see discussion in Southgate, 1997). Nonetheless, laboratory studies (Fallon *et al*. 1995) suggest that the Senegalese isolate is intrinsically less responsive to praziquantel. The underlying reasons for the presence of a tolerant isolate in Senegal remain poorly understood. The presence in this area of individuals with relatively heavy infections of both *S. haematobium* and *S. mansoni* has lead to some unforeseen situations with respect to treatment. Egg counts for *S. haematobium* were shown to decline sharply in such individuals following treatment, whereas *S. mansoni* egg counts increased seven-fold. One explanation for this result was that *S. haematobium* males had paired with *S. mansoni* females, and following the praziquantel-induced demise of the *S. haematobium* males, the relatively drug tolerant *S. mansoni* females were then freed to pair with *S. mansoni* males (Ernould, Ba & Sellin, 1999).

Considerably more troubling is the situation in the Nile Delta of Egypt, where praziquantel has been used aggressively for more than 10 years. Here it is probable that drug selection has favoured the emergence of resistant genotypes. *Schistosoma mansoni* isolates derived from patients that continued to pass eggs following treatment were, when passaged through mice, less responsive to praziquantel (Ismail *et al*. 1996, 1999), indicating that the diminished responsiveness was not somehow due to patient-related factors. *Schistosoma mansoni* from the Lake Albert region of Uganda may also becoming less responsive to praziquantel (Doenhoff, Kimani & Cioli, 2000). Fortunately, praziquantel resistance has not yet become pervasive and praziquantel-resistant worms are still susceptible to oxamniquine. Regarding the latter drug, resistance has also been produced experimentally and a recent study from Brazil suggests that *S. mansoni* isolates recovered from patients, that did not respond to oxamniquine, were less susceptible to the drug when in mice (Conceição, Argento & Corrêa, 2000).

One of the cornerstones of past schistosomiasis control programmes has been snail control, usually achieved with molluscicidal chemicals, although biological control and environmental control measures have also been employed in some contexts. One of the realities for schistosomiasis control programmes of the future will be an increasingly strong resistance to the use of measures to kill snails. About two-thirds of the 330 species of freshwater and brackish snails of Africa, are classified as ''threatened'' and programmes to control snails that serve as intermediate hosts for parasites of medical and veterinary importance can be perceived as a threat to this diversity (Kristensen & Brown, 1999).

Given that snail control is not economically feasible or environmentally acceptable, and that some cracks in the chemotherapy façade are showing, development of alternatives to praziquantel should be encouraged, and the much anticipated schistosomiasis vaccine would certainly be useful. Other effective methods of control including improved sanitation, provision of piped water, and health education all need to be encouraged as well.

Whither S. mansoni?

Several interacting factors will influence the future prevalence of *S. mansoni*. The continued application of chemotherapeutic and other (new?) control measures and a hoped-for overall rise in the standard of living in the developing world can be expected to lower both intensity and prevalence of infection. Deliberate control efforts will probably be unwittingly abetted by increased industrial water pollution, urbanization and continued introductions of exotic aquatic competitor/predator species, all of which will limit the distribution of biomphalarid snails. In the future, species of *Biomphalaria* once considered pestiferous and whose eradication was actively sought, will be regarded as endangered and in need of protection.

On the other hand, the traditional hand maidens of parasitic disease – poverty, over-crowding and civil war in developing countries – will conspire to prevent access to clean water and proper sanitation and favour *S. mansoni*. Although the effects of global warming are presently difficult to ascertain with any real degree of accuracy, some models predict an expansion of geographic areas susceptible to schisto-

somiasis (Martens *et al*. 1995) whereas others predict a decrease in transmission (Martens, Jetten & Focks, 1997). By eliminating dense vegetation cover and opening up potential snail habitats to colonization, deforestation can favour the spread of schistosomiasis (Walsh, Molyneux & Birley, 1993). The destruction of the forests of the central highlands of Madagascar followed by the encroachment of *S. mansoni* provides a bleak example (Ollivier, Brutus & Cot, 1999). Major new areas of endemicity may thus arise in rainforest areas like West Africa and Brazil. Construction of massive water development schemes favour transmission and continued application of drug pressure may favour the emergence of drug-resistant parasites. Human-mediated spread of snails such as *B. straminea* and *B. glabrata* will also favour *S. mansoni*. Much of the future success of this parasite may hinge on its ability to adapt to non-human hosts, as has happened in Guadeloupe and Brazil and in its ability to colonize invasive species of snails, particularly *B. straminea*. The coming years will prove to be fascinating in deciphering the net impact of these contrary trends.

ACKNOWLEDGEMENT

We would like to thank Wade Wilson, Nicole Rupple and Pascale Léonard for their editorial assistance in preparation of the manuscript. Thanks also go to Lynn Hertel for her map-womanship. We also wish to thank David Blair for his informative comments on the manuscript. This project was supported by NIH grant AI44913.

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