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Schistosomiasis: Paleopathological Perspectives and Historical Notes.

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Chapter

Schistosomiasis: Paleopathological Perspectives and Historical Notes

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2.1 INTRODUCTION

The many different species of the digenetic flatworms of the genus *Schistosoma* in existence are generally adapted to a specific, mammalian definitive host and a snail intermediate host producing parasite/snail/mammal life cycles that only occasionally interact across the various species involved. *Schistosoma japonicum*, however, is uncharacteristically zoonotic with a large number of definitive hosts, though this trait is not followed through with respect to its snail host, where it depends completely on one genus, generally even on one species, *Oncomelania hupensis*. The great majority of human infections are caused by *S. mansoni* and *S. haematobium* in sub-Saharan Africa and *S. japonicum* in China, The Philippines and Indonesia. *S. mekongi* and *S. intercalatum* are not only in minority, they are also geographically limited, the former being exclusively found in foci near the border between Cambodia and Laos and the latter existing only in the vicinity of the Congo River and in Lower Guinea on the African continent.

Including the mechanism developed by this parasite to evade the definitive host's immune response, first described by Smithers and Terry (1969), the evolution of the schistosome 'double life', with the adult worm stage radiating into a terrestrial vertebrate, must have required thousands of years. Even if the worm's adaptation to a dioecious lifestyle in a homoeotherm mammal from a probable, previous, hermaphroditic situation in a poikilotherm mollusc seems improbable, an understanding of the intermediate steps is emerging (Platt and Brooks 1997). For example, the reproductive steps in the definitive host required a series of compensatory changes to offset progeny limitations, such as forming dioecious permanent worm pairs with pronounced longevity and strong fecundity. These worm-pairs further needed to colonize areas near conduits to the outside (intestines or bladder) to allow the eggs produced by the female worm to reach water. This is not only necessary for hatching and subsequently reaching the intermediate snail host, but also to ensure that cercariae, when released into the water from infected snails, seek and penetrate the skin of humans. Although an enigmatic chain of events, the result is continuation of the parasite's

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life cycle and is as much the key to schistosomiasis epidemiology now as it was in Antiquity and prehistory.

There is little doubt that schistosomiasis was a constant menace for people in the tropics, and humankind must have been associated with this infection long before civilizations first appeared. Water, the common link for humans, snails and schistosomes, satisfies mundane human needs for drinking, washing and fishing and has done so since times immemorial. With the development of fixed human settlements and agriculture, especially when combined with irrigation, the need for water expanded exponentially and so did its role in the transmission of schistosomiasis (Kloos and Thompson 1979). Although we know little about the intensity of the disease in ancient times, it must have been considerably lower before fixed human settlements emerged. Recent estimates suggest that over 250 million people are infected, which translates into a global burden of 3.3 million disability-adjusted life years (DALYs) (Murray *et al.* 2012; Hotez *et al.* 2014), figures even higher than the 200 million infected believed to have existed by the end of last century (Chitsulo *et al.* 2000).

It was not until the early 1900s that the discovery of the parasite's life cycle made it possible to entertain realistic ideas of counteractive measures. This discovery translated into prophylaxis and disease prevention, but it took another 70 years before a safe and reliable drug was introduced. Not long after extensive drug trials covering endemic areas in all continents had proved the efficacy and safety of praziquantel (Davis and Wegner 1979), mass drug administration (MDA) started to make strong inroads with respect to morbidity in previously highly endemic areas. Although reinfection remained commonplace, pathology due to chronic disease could now be managed through scheduled, repeated drug treatment.

The despair of people with schistosomiasis in the endemic areas, as well as that of scientists and clinicians just 40 years ago, is difficult to visualize today, now that praziquantel has enabled improved control of large areas. The focus of this chapter, however, is neither on control nor on chemotherapy but on the history of the disease and its ravages since Antiquity. Even though we cannot (yet) reach back to its very origin, we shall visit surviving written records, learn about parasite eggs found in human remains, envisaging the disease at the dawn of history and make an effort to tease out the loose ends of prehistoric times.

2.2 PARASITE DIVERSIFICATION

We lack hard evidence of the presence of schistosomiasis in prehistoric times. The parasite could first have adapted to various monkey species and baboons and then crossed over to humans, as advocated by Adamson (1976). It is more probable, though, that the parasite's life cycle was simultaneously established in primordial primates and hominids, giving credence to the idea that the origin of human schistosomiasis substantially predates recorded history. Deprès *et al*. (1992) have investigated development from the genetic point of view and propose that the schistosome might have captured the human host from other animal hosts in Africa 1–10 million years ago, coinciding with the time the first hominids invaded the savannas.

Geographical separation rather than choice of host appears to be the most important factor in the diversification of the parasite, as pointed out by Morgan *et al.* (2005). Beer *et al.* (2010) have suggested that the *Schistosoma* genus evolved 70–120 million years ago in Gondwanaland, i.e., the supercontinent consisting of today's Africa, Antarctica, Australia, India and South America. Davis (1992) developed this idea further based on the snail record, maintaining that *S. mansoni* and *S. haematobium* appeared in Africa from a common ancestor more than 120 million years ago and that the ancestral schistosome moved to Asia on the Indian plate 70–148 million years ago to produce the *S. indicum* group, which eventually diversified into the *S. japonicum* of the Far East.

More recent ideas based on genetic analysis of the parasite suggest that the original parasite instead appeared in what is today northern India (see also Littlewood and Webster, Chapter 1). According to this hypothesis, it spread eastward first developing into the *S. japonicum* ancestor (Snyder and Loker 2000; Lawton *et al.* 2011), then transporting itself in the opposite direction by the widespread mammal migration in the late Miocene epoch, eventually reaching Africa between 1 and 4 million years ago where it diversified into *S. mansoni* and *S. haematobium* (Lawton *et al.* 2011). An even later time for the *mansoni/haematobium* split is suggested by Morgan *et al.* (2005) based on the relatively recent, strong variation of East African schistosome specimens, indicating an East African origin for *S. mansoni* of only 0.30–0.43 million years ago. Interestingly, this timeframe not only follows the arrival of the snail host but also coincides with early human evolution.

Since the *S. indicum* group has a closer affinity with the African group of schistosomes than with the other Asian ones (Attwood *et al.* 2002), it would not be too farfetched to think that the Indian Plate ferried the first schistosomes to Asia from Africa as suggested by Davis (1992). This plate moved north after it disconnected from Africa as early as the Mesozoic Era 150–160 million years ago. However, it stayed together with Madagascar for another 90 million years before finally breaking off and coming into close contact with southern Asia some 25 million years ago (van Hinsbergen *et al.* 2012). This scenario produces an unbroken Madagascar-India-Asia connection but to satisfy the 'ferry hypothesis' there must also have been a mainland Africa-Madagascar connection within a suitable timeframe, demanding the origin of *Schistosoma* (or a Schistosomatidae ancestor) to be at least 30 million years older in order to fit this scenario. The snail record may provide this connection. Phylogenetic studies indicate that the three *Bulinus* species endemic in Madagascar, *Bu. obtusispira*, *Bu. bavayii* and *Bu. liratus*, are related to the sub-Saharan *Bu. africanus* group, *Bu. forskalii* group and the *Bu. truncatus/tropicus* group, respectively (Stothard *et al.* 2001). Further studies are required to evaluate the divergence of these species within the timeframe of the 'ferry hypothesis' Fascinating as this is, we will leave this discussion here in the absence of further evidence and instead move to the first hominids.

2.3 EVOLUTIONARY TRENDS IN HOST SELECTION

Australopithecus afarensis, better known as 'Lucy', may have provided the emergence of segmental DNA duplication, a mutation type that increased strongly in the primate genomes, most remarkably in the human one (Sassa 2013), leading to bipedalism, increased height and brain development. This hominid evolved in early Pliocene becoming extinct about three million years ago, with our own genus (*Homo*) thought to have split off from this evolutionary chain at least 1 million years before its demise (Kimbel and Delezene 2009). The australopithecines survived for about 1 million years in East Africa living close to freshwater bodies providing accessible food in the form of shellfish. Such areas were not only suitable for the intermediate snail hosts, whose prehistoric shells remain as evidence, but were most probably also frequented by baboons, which constitute an important *S. mansoni* reservoir to this day (Fenwick 1969; Wright 1970). In this case, there should have been ample possibilities for the transfer of schistosomes between definitive and reservoir host species, which is also indicated by evidence of host-parasite co-evolution in the snail-schistosome system (Webster *et al.* 2004). However, lacking any shred of paleoepidemiological evidence from the 10^5 to 10^6-year level, we may be left in a perpetual conundrum as to the fundamentals of human schistosomiasis ecology, in particular how the first chapter of the story unfolded.

Most experts on human evolution and early migration agree that early humans split into *Homo neanderthalensis* and *H. sapiens* about 1.8 million years ago and that the former dispersed into Eurasia at an early time. However, there is debate about how and when the latter gained a foothold in the Middle East, eventually replacing *H. neanderthalensis* and peopling the rest of the world. The

weight of current evidence favors the hypothesis that all present-day human populations descended from a common ancestor tribe in East Africa that first appeared 150,000 to 200,000 years ago and subsequently produced the small bands of humans who reached the Arabian Peninsula across Bab-el Mandeb at the southern end of the Red Sea (Finlayson 2005). The first move may have occurred as early as around 125,000 years ago, but there were probably several retrenchments with the earliest settlements being overrun by *H. neanderthalensis* from the North. It is now believed that the first *H. sapiens* established permanent communities in present-day Yemen, around 75,000 years ago (Armitage *et al.* 2011). If this hypothesis holds, it seems unlikely that human schistosomiasis originated in the Middle East, as argued by some, as this would set the upper time limit for the schistosome/human association at less than 75,000 years to develop. The longer period of 1.8 million years would be more plausible, but would have required a long-term, close relationship between *H. sapiens* and *H. neanderthalensis* in the Middle East, which is also unlikely.

An alternative hypothesis, based on biogeographic, paleohydrographic, archaeological and phylogenic evidence, has *H. sapiens* and schistosomiasis moving together from sub-Saharan Africa via a humid corridor that dispersed into both Egypt and the Middle East. Climatic conditions during the Holocene were associated with a "green Sahara" characterized by humid climatic conditions, which are increasingly considered to have permitted early modern man to move out of Africa via the Sahara and the Nile Valley during different pluvial periods around 120,000 years ago (Osborne *et al.* 2008; Castaneda *et al.* 2009; Drake *et al.* 2011).

2.4 THE SNAIL RECORD

The taxonomy and distribution of extant snail hosts is covered by Madsen (Chapter 4) while this overview deals exclusively with evidence of snails from previous times. Subfossil shells of *Bu. truncatus*, *Biomphalaria pfeifferi and Bi. alexandrina* have been recovered from at least 16 sites between Israel and the Saharan Desert as far west as Mali and as far south as Chad, Sudan and Kenya and of *Bu. truncatus* at two sites in the Upper Egyptian Nile Valley (Wendorf *et al.* 1976; Beadle 1981, p. 184; Mienis 1992, 2011; Bocxlaer and Verschuren 2011; Abou-El-Naga 2013). This, in combination with the known, heavy reliance by prehistoric populations on fishing, suggests that schistosomiasis transmission could even have occurred in those and other Neolithic Saharan settlements as recently as within the last 5,000-years (see Fig. 2.1 and Table 2.1). Molecular studies of the phylogeny of planorbid snails and fossil evidence strongly suggest that *Bulinus* originated in Africa and that *Biomphalaria* evolved from a neotropical *Bi. glabrata*-like ancestor (Morgan *et al.* 2002). Although earlier hypotheses stated that *Biomphalaria* existed in Africa prior to the breakup of Gondwanaland, recent phylogenetic studies indicate that African species of this genus colonized Africa from South America in the past 1–5 million years after the split of the continents (DeJong *et al.* 2001). The view that *Biomphalaria* colonized Africa from the Americas, attributed to birds and floating materials from those continents taking place long after the breakup of Gondwanaland, is supported by close links to the ancestral Planorbidae in the New World 200–300 million years ago, the significantly lower diversity of mitochondrial sequences of *Bi. pfeifferi* than *Bi. glabrata* and the fossil record of *Biomphalaria* in Africa from the last 1–2 million years (Morgan *et al.* 2002). The oldest *Bi. pfeifferi* haplotypes occurred in southern Africa and they appear to have expanded their range in East Africa less than 100,000 years ago (DeJong *et al.* 2003). Molecular studies also indicate that both *Bi. pfeifferi* and *Bu. truncatus* colonized North Africa and Egypt from sub-Saharan Africa via the humid Saharan corridor (DeJong *et al.* 2003; Kane *et al.* 2008; Zein-Eddine *et al.* 2014). *Bu. truncatus*, *Bi. pfeifferi* and *Bi. alexandrina* still live in oases, ponds and springs around many of their prehistoric sites (Brown 2005; Van Damme 1984; Van Bocxlaer and Verschurren 2011). Several putative *Biomphalaria* species, including *Bi. gaudi*, *Bi. rhodesiensis*, *Bi. stanleyi*, *Bi. sudanica* and the now extinct *Bi. barthi*, most of them found in East African lakes

and the Sahel regions (Fig. 2.1), are closely related to other *Bi. pfeifferi* populations (DeJong *et al.* 2003). The geographic range of these species and the *S. haematobium* intermediate host *Bu. globosus* was probably much more extensive in Central and East Africa in prehistoric times than the distribution of their fossils suggests (Fig. 2.1). This view is supported by the wide distribution of most of these species today and the confinement of their subfossil shells to geological strata from dry phases of the late Pleistocene, which provided good conditions for the preservation of their shells (Van Damme and Gautier 2013). Although we might get sufficient information to state whether human schistosomiasis came from the South or the East, we will never really know the details, so let us now focus closer to our own era where there is real evidence to be found, even if it is scattered and somewhat limited.

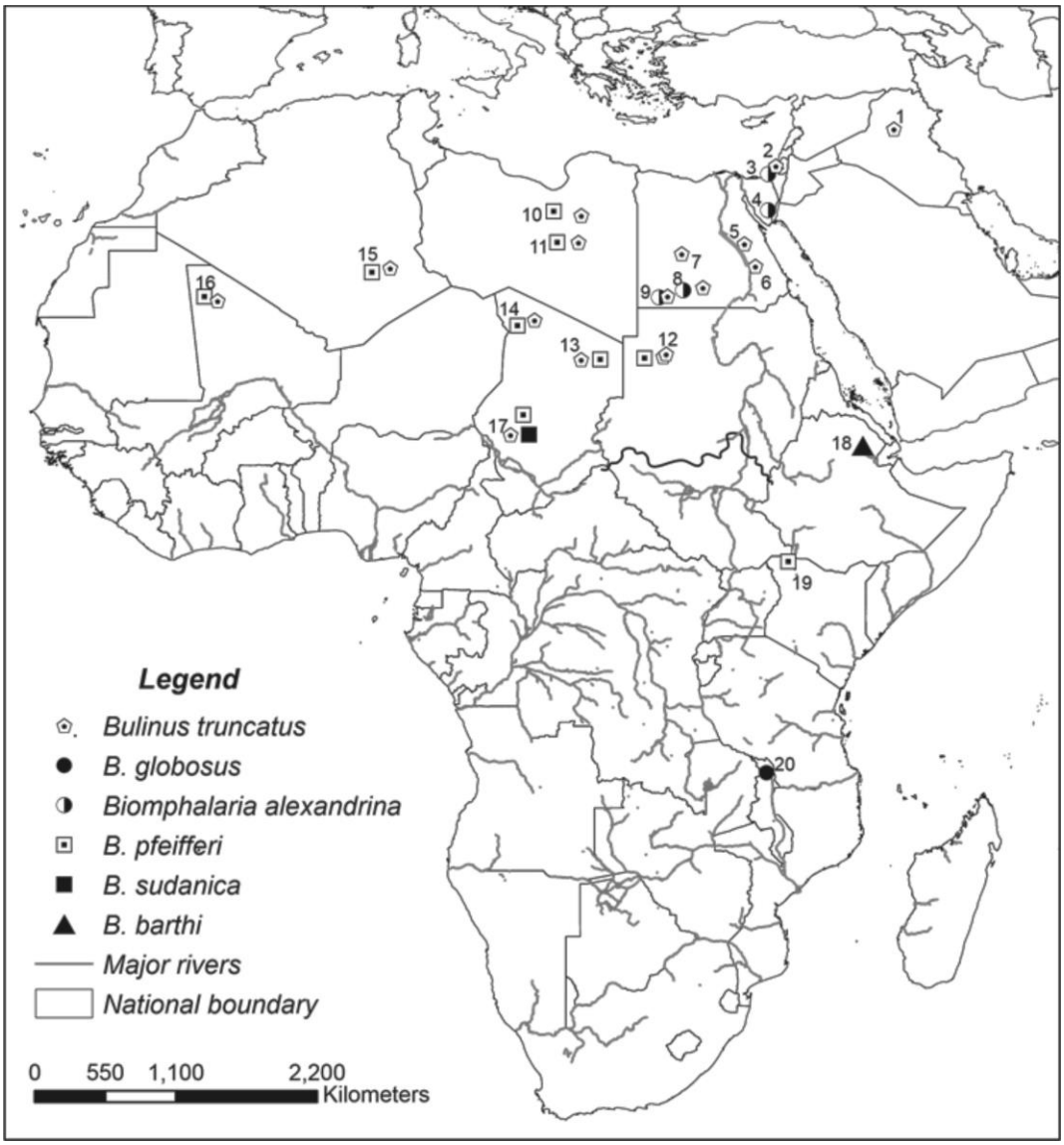

FIg. 2.1 Distribution of subfossil *Bulinus* and *Biomphalaria* species in Africa and the Near East (Sources: see Table 2.1).

Table 2.1 Chronology of subfossil *Bulinus* and *Biomphalaria* species in Africa and the Near East.

Site*	Locality	Species	Chronology	Source
1	Irrigated area, Iraq	*Bu. truncatus*	4,000 BC-300 AD	Zakaria 1959
2	Jericho, Israel	*Bu. truncatus*	1,650 BC	Biggs 1960
3	Ta'alat Soreq Stream, Israel	*Bu. truncatus*, *Bi. alexandrina*	Late Pleistocene-Holocene	Mienis 2011
4	Wadi Gibba, Sinai	*Bi. alexandrina*	Neolithic	Mienis 1992
5	Edfu, Egypt	*Bu. truncatus*	Upper Paleolithic	Gautier 1976
6	Isna, Egypt	*Bu. truncatus*	Upper Paleolithic	Gautier 1976
7	Kharga Oasis, Egypt	*Bu. truncatus*	Holocene	Wendorf *et al*. 1976
8	Bir Tarfawi, Egypt	*Bu. truncatus*, *Bi. alexandrina*	Paleolithic-Neolithic	Gautier 1993; Wendorf *et al*. 1976
9	Bir Sahara, Egypt	*Bu. truncatus*, *Bi. pfeifferi*	Paleolithic- Neolithic	Gautier 1976; Wendorf *et al*. 1976
10	Wadi Behar Belama, Libya	*Bu. truncatus*, *Bi. pfeifferi*	Paleolithic	Osborne *et al*. 2008
11	Wadi Quoduin, Libya	*Bu. truncatus*, *Bi. pfeifferi*	130,000-117,000 yrs B.P.	Osborne *et al*. 2008
12	Wadi Howar, Sudan	*Bu. truncatus*, *Bi. pfeifferi*	Late Quaternary	Kröpelin 1993
13	Ounianga, Chad	*Bu. truncatus*, *Bi. pfeifferi*	Early Holocene	Bocxlaer and Verschurren 2011
14	Tibesti, Chad	*Bu. truncatus*, *Bi. pfeifferi*	Late Quaternary	Van Damme 1984
15	Hoggar, Algeria	*Bu. truncatus*, *Bi. pfeifferi*	Late Quaternary	Van Damme 1984
16	Bassin de Taoudenni, Mali	*Bu. truncatus*, *Bi. pfeifferi*	Holocene	Rosso 1983
17	Lake Chad Basin	*Bu. truncatus*, *Bi. pfeifferi*, *Bi. sudanica*	Late Pleistocene-Early Holocene	Lévêque 1967; Malek 1958; Van Damme 1980
18	Assaita, Ethiopia	*Bi. barthi*	Pleistocene	Brown 2005 (p. 271)
19	Lake Turkana, Kenya	*Bi. pfeifferi*	No information	Beadle 1981 (p. 184)
20	Lake Malawi, Malawi	*Bu. globosus*	Early Pleistocene	Van Damme and Gautier 2013

*Codes are the same as in Fig. 2.1.

2.5 SCHISTOSOMIASIS IN ANTIQUITY

Not surprisingly, the oldest available records of schistosomiasis emanate from the Middle East, one of the first areas in the world to sustain larger numbers of people, starting to develop agriculture

and live together in more or less permanent communities. An archaeological excavation of the ancient cemetery Tell Zeidan in the valley of the Euphrates River in modern-day northern Syria recently reported the finding of a schistosome egg in the mummified remains of a child's corpse, buried between 6,000 and 6,500 years ago (Anastasiou *et al.* 2014). This represents the oldest case of the disease so far, but additional, useful information may appear once all the material has been sifted through. It is clear that the egg emanates from a schistosome, but the authors leave the exact species open. Although they seem sure that the egg belongs to the *S. haematobium* clade, they have not been more precise, suggesting only that it is either *S. haematobium* or *S. intercalatum* (Anastasiou *et al.* 2014). Apart from the fact that the latter species exists exclusively in the western part of the African continent, at least nowadays, there are also several other reasons that speak in favor of *S. haematobium*, e.g., the fact that a disease causing blood-stained urine is mentioned in ancient medical texts from this part of the world (Adamson 1976) and the recovery across the Middle East of ancient *Bulinus* shells (Kloos and David 2002; Mienis 2011), i.e., the remains of the intermediate host of modern-day *S. haematobium.* Acid-fast staining (Ziehl-Neelsen) might provide supporting, biological evidence since *S. intercalatum* eggs are the only kind of schistosome egg stained red by this technique (Southgate 1976).

There is still no hard evidence of *S. mansoni* infection in humans during Antiquity in the Middle East. However, fossilized (*Bi. alexandrina* Mienis 2011) and *Bi. pfeifferi* and *Bi. arabica* transmitted *S. mansoni* in most countries on the Arabian Peninsula and in the Levant until very recently, with transmission continuing in Oman, Yemen and Saudi Arabia (Abdel Azim and Gismann 1956; IAMAT 2015). Molecular and ecological studies indicate that *Bi. pfeifferi* has been endemic in the Arabian Peninsula for a long time and that this snail is well adapted to the harsh desert environment (Mintsa-Nguema *et al.* 2013), further arguing for its potential role as a host of *S. mansoni* in Antiquity.

2.5.1 Egypt

Available data support the presence of schistosomiasis in the Nile Valley as early as 5,000 years ago. After Ruffer's first report (1910) of the disease in 3,000 years old mummies, other authors demonstrated similar results in mummies of variable time periods (Deelder *et al.* 1990; Miller *et al.* 1992; Contis and David 1996; Kloos and David 2002; Coon 2005; Hibbs *et al.* 2011). However, the disease must have had a much wider distribution in Antiquity, as intermediate snail hosts were then widely spread both south and east of the Mediterranean. Although the disease has been a scourge for millennia and the symptoms must have been well-known, it was not perceived as a specific, medical entity until a French army surgeon under Napoleon reported the symptoms of urinary schistosomiasis in soldiers during the French Egyptian campaign 1798–1801 (Renault 1808). His pathognomonic description only lacked the cause of the problem, whose uncovering would take another half century and include many arguments put forward by famous scientists of the period.

Theodor Maximilian Bilharz's observations in 1851 in Egypt ensure the perpetual connection of this German pathologist's name with schistosomiasis. The disease is also associated with Bilharz's mentor Carl Theodor von Siebold and his supervisor Wilhelm Griesinger at the University of Tübingen, Germany. When Griesinger was named Director of the Egyptian Department of Hygiene in 1850, he accepted on the condition that his assistant Bilharz accompany him. Thus, the then 25-year old Bilharz (Fig. 2.2) started his work at the medical school in Cairo connected with the prestigious Kasr el Aïn Hospital that should lead to his great discovery only because autopsies could be carried out there despite general religious resistance in the country at the time.

During the first year and a half of their stay in Egypt, Bilharz and Grisinger performed over 400 *post mortems*. Already within one year, Bilharz was able to report back to von Siebold about the discovery of three new flatworm species capable of infecting humans as well as noting the presence of other parasites, including hookworm and guinea-worm. He wrote to Siebold:

> *"As helminths in general and those who attack humans in particular are concerned, I think Egypt is the best country to study them. Nematodes in particular populate the intestines of the indigenous population in unimaginable quantities. It is not unusual to encounter 100 individuals of Strongylus duodenalis, 20–40 Ascaris, 10–20 Trichocephalus and close to 1000 Oxyuris. My attention soon turned to the liver and associated structures; in the blood from v. portae I found a number of long, white worms that with the naked eye appeared to be nematodes. A look in the microscope revealed an excellent Distomum with flat body and a twisted tail. These are a few leaves of a saga as wonderful as the best of Thousand and One Nights – if I succeeded in putting it all together".*

Realizing the difference from nematodes and that the 'twisted tails' were in fact two tails of paired worms, he wrote slightly later:

> *"I have not told you yet about the new phases into which my worm of the portal vein has entered. This has not developed into a fairy tale, as I had assumed, but something more miraculous—a trematode, with separate sexes. The worm which I had described to you in my last letter was the male. When I examined the intestinal veins more carefully..., I soon found samples of the worm which harboured a grey thread in the canal of their tails. You can picture my surprise when I saw that a trematode projected out of the anterior opening of the canal".*

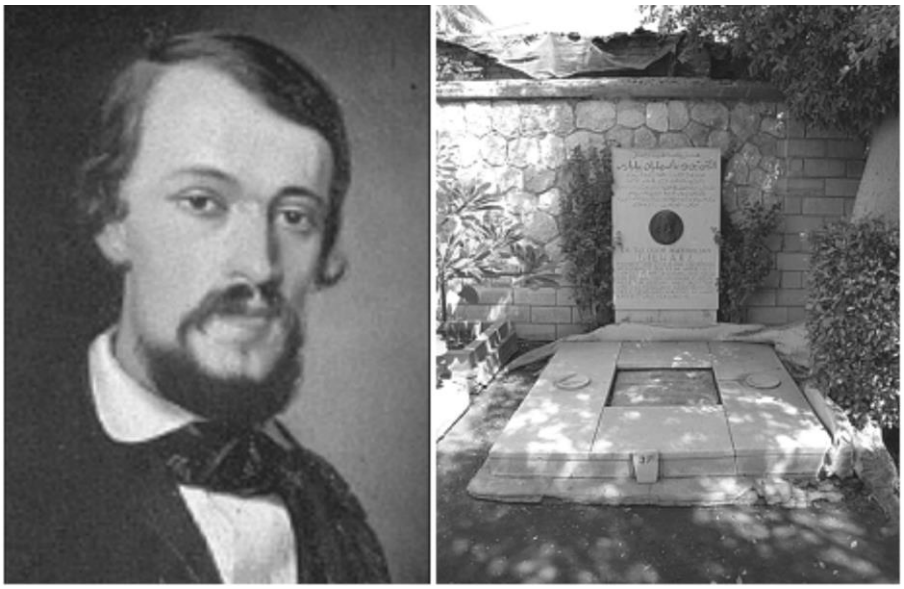

FIg. 2.2 Portrait of Theodor Bilharz and his grave in the Cairo German Cemetery.

The letters received from Bilharz were published by von Siebold, together with extensive editorial comments, in the journal for which he was the editor (Bilharz 1853). Bilharz produced drawings of paired flatworms as well as eggs and attributed them to '*Distoma*', a currently obsolete genus that was used for various digenetic flukes, whose members are now placed in different genera.

When Griesinger returned to Germany in 1852, Bilharz became head physician at the Department of Internal Medicine at Kasr el Aïn Hospital. He was appointed Professor of Clinical Medicine three years later, but the death in 1856 of Egypt's ruler Abbas I, who supported the German side in the ongoing scientific competition between Germany and France, resulted in a change from

German to French hegemony in the Egyptian academic sphere. Bilharz was more or less forced to leave his position and move to the 'calmer' chair of Descriptive Anatomy, which tenure he held until his death (from typhus) in 1862 at the age of 37. The genus *Bilharzia* was created in his honor in 1856, but only two years later the name *Schistosoma* (meaning split body) was officially adopted by the International Commission on Zoological Nomenclature based on the morphology of the parasite. The parasite discovered by Bilharz thus became known as *Schistosoma haematobium* and remained the supposedly only species in Africa for half a century.

The idea of there being only one schistosome species in Africa that was present in both the mesenteric veins and those around the bladder, held sway until Louis Westenra Sambon described *S. mansoni* (Sambon 1907) and named it after his teacher Sir Patrick Manson of the London School of Tropical Medicine. Manson had already noted that the eggs passed in the urine from schistosomiasis patients invariably had a terminal spine, whilst those found in the feces had a lateral one. Interestingly however, Bilharz had already 50 years earlier reported on worms that looked different from the ones he first had reported on. Although he just took them for abnormal worms, he was bothered by the many different types of eggs seen in these cases. As both worms and eggs, as well as the pathology produced, were difficult to decipher and as he did not encounter this picture very often, neither Bilharz nor anyone else discussed this further. In retrospect one understands that the bewildering picture Bilharz reported must have been due to double-infection by both species.

There can be no doubt that what Bilharz discovered was *S. haematobium*, not only because of his description of the adult worm and the eggs, but also because this species was predominant in the Nile at that time. However, his discovery of *S. mansoni* must also be accepted even though considerably less detail was given and it is unclear whether or not he realized that it was a separate species. This should not be as surprising as it might at first seem since *S. mansoni* was uncommon in Egypt in the 18th century and did not become more frequent there until the 20th century (Jobin 1999). *Bu. truncatus*, the sole transmitter of *S. haematobium* in Egypt, appears to have existed in the Nile since ancient times, as evidenced by its recovery from palaeolithic sites in Upper Egypt (Fig. 2.1) (Abou-El-Naga 2013). It was widespread in the river until the construction of barrages north of Cairo, the Low Dam at Aswan in 1900 and the Nasser Dam in 1964, the associated extension of perennial irrigation and increasing urban-based water pollution. The changing ecology of the Nile facilitated the spread of *Bi. alexandrina* from the Nile delta to Upper Egypt and caused the near disappearance of *Bu. truncatus* from the Delta (Watts and El Katsha 1995; Kloos and David 2010; Abou-El-Naga 2013).

Importantly, Bilharz not only described the worms he discovered in generous detail, but he also associated them with the 'white exuberances of cancerous aspect' in the mucous membranes of the bladder, intestines, ureters and seminal glands that he saw during his numerous dissections of the human hosts. The idea of infection thus dawned on him much ahead of its time. The parallel to Snow (1855) stopping the cholera epidemic in London 1854 is interesting in this connection, as the bacterial origin of the epidemic was not demonstrated until 1883. In contrast to Snow, Bilharz was fortunate that he could actually see the agent that he linked to the pathology at the *post mortem* investigations. By realizing the possibility of a connection between the parasites invading the body and the pathology observed, Bilharz should correctly be described as the father of the discipline we now call Infectious Diseases. It took a rather long time for this to become mainstream knowledge, but the idea of the nature of infection was quickly accepted after Pasteur's and Koch's work in the 1870s.

With regard to schistosomiasis, investigations centered on how the parasite entered the human body. However, this would remain an open question for more than 60 years after Bilharz's discovery and his early thoughts about parasitic infections. Indeed, the question was not be settled until Robert Leiper (1916) at the London School of Tropical Medicine and Hygiene not only demonstrated the parasite's life cycle, but also confirmed Bilharz's and Sambon's idea of two different species. In his

ground-breaking paper, Leiper further showed that the two species had different snail intermediate hosts. Naturally, all these conclusions did not arise out of the blue in a short span of time, but previous contributions by others, notably Cobbold (1872) and Looss (1908), played a significant role in the direction that Leiper's research was to take. The uncovering of the life cycle of a related parasite, the liver fluke *Fasciola hepatica* (Thomas 1883), should also be mentioned as this was an important catalyst for Leiper. The proposed theories by and controversies between, these researchers as well as other eminent scientists of the day that proceeded the unravelling of the schistosome life cycle are vividly described by Jordan (2000) in his account of the scientific work on the various aspects of schistosomiasis that followed.

Another towering figure in the history of diseases in the Egypt of old is Sir Armand Ruffer who worked there in the early 1900s. The discipline of paleopathology was ascribed to this British physician after he had subjected mummies from the Egyptian Twentieth Dynasty to autopsy and found calcified *S. haematobium* eggs in the kidneys of two of them (Ruffer 1910). Not only was this the very first example of retrospective diagnosis of individuals who had lived many thousands years ago, but it also indicated that the disease was already common in ancient Egypt. Paleopathology, supported by the advent of modern diagnostic methods, grew in fits and starts and eventually this new discipline began to provide information on social and ecological aspects of ancient infections (Brown *et al.* 1996). Results presented by Hibbs *et al.* (2011), based on a test for the presence of schistosome antigens in the remains of 237 bodies from three cemeteries from the Ballana period (350–550 AD) in present-day Sudanese Nubia, confirmed the positive results of an earlier study of 23 human remains from the same period in the same area (Miller *et al.* 1992). Although Hibbs *et al.* (2011) found varying prevalence rates according to the area (cemetery) investigated, the overall prevalence was similar in both studies. Together with the references above on the presence of schistosomiasis in the Nile Valley in Antiquity, the conclusion must be that schistosomiasis has been common there for at least 5,000 years, and continued to be so until the advent of praziquantel.

Jordan (2002) brings up the speculation about the meaning of the Egyptian word '*aaa*', depicted in Egyptian hieroglyphs as a urinating phallus and commonly referred to in surviving ancient texts of medical interest, e.g., the Hearst Papyrus (9 times), the Berlin Papyrus (11 times) and the Ebers Papyrus (20 times), as mentioned by Colley (1996). Some authors argue that '*aaa*' should be taken to mean haematuria and specifically haematuria due to schistosomiasis (Pfister 1913; Ebell 1927; Jonckheere 1944) but this contention is now deemed unfounded (Westendorf 1992; Nunn 1996; Nunn and Tapp 2000). Today's preferred interpretation of '*aaa*' is that it refers to the way a disease gains entry to the body, i.e., it was believed that evil spirits impregnated victims with poison during the night (von Deines 1961; Nunn 1996). The correct interpretation of '*aaa*' remains an open question and even if it is obvious that haematuria must have been observed in the endemic areas along the Nile, it must have been so common that it was not regarded as a sign of disease. Ebbell (1927) also mentions '*hrrw*', that could possibly mean worms but it must be regarded as highly unlikely that this word would implicate schistosomes, as they could only have been observed *post mortem* and even then been difficult to recognize by the naked eye.

2.5.2 Sub-Saharan Africa

Although the earliest evidence of African schistosomiasis comes from Egypt, sub-Saharan Africa is, and has probably always been, the most heavily infected part of the world with respect to schistosomiasis. This situation has worsened in modern times due to dam constructions, widespread irrigation schemes and strong population growth. It makes no sense to try to pin down the first publications of schistosomiasis country by country, but it is of interest to note that *S. intercalatum*, one of the five schistosome strains capable of causing human infection, is found only in this region. The first description of this species was described by Fisher (1934) and relates to findings in the former Belgian Congo. We now know that there are two strains of this species

in West Africa, one in Zaire and one in Cameroon (Bjorneboe 1978) with most of the relevant research performed in the latter country (Tchuem Tchuenté *et al.* 2003). Two species of freshwater snails act as the intermediate host, *Bu. forskalii* in Cameroon and *Bu. africanus* in Zaire (Tchuem Tchuenté *et al.* 2003).

2.5.3 The Far East

The disease we now recognize as schistosomiasis japonica was first known as Asiatic schistosomiasis and had been found in several countries in Southeast Asia. Mortality was high and morbidity was generally more pronounced than that due to other schistosome species: patients presented with marked liver enlargement, often accompanied by bloody diarrhea, itching skin and occasionally fever. These early, serious symptoms are due to the higher egg output from the *S. japonicum* worms, which often induce intensive tissue reactions since the eggs commonly are released in aggregates (Chen and Mott 1988).

The endemic areas today include China and The Philippines with three minor foci in Sulawesi, Indonesia (*S. japonicum*) and along the Mekong River near the border between Laos and Cambodia (*S. mekongi*). The snail hosts transmitting *S. japonicum* and *S. mekongi* belong to two sub-families of the family Pomatiopsidae, which appears to have originated in Gondwanaland and radiated via Australasia to The Philippines, Japan, China and finally to Southeast Asia (Liu *et al.* 2014). According to estimates based on the molecular clock, *S. japonicum* and *S. mekongi* were already adapted to the pre-human host about 3.8 million years ago, more than 2.8 million years prior to *S. mansoni* and *S. haematobium* (Standley *et al.* 2012). We have no records of *S. mekongi* before 1957 but ample documentation of *S. japonicum* covering more than 2,000 years is available from China and there is interesting information on how the causative organism was discovered in Japan, the only country where the disease has been officially eradicated. The Japanese schistosomiasis control programme has been described in great detail by Kajihara and Hirayama (2011), demonstrating that once the epidemiology had been determined, elimination followed by eradication was a straightforward affair. Chinese control specialists, on the other hand, having a more complicated situation with both large stretches of flooded lowlands and mountainous areas, some of which difficult to reach, are just coming to the elimination stage based on a very well managed control programme that has had an uninterrupted run since the mid 1950s (Utzinger *et al.* 2005).

Very recent phylogenetic reconstruction based on complete mitochondrial genome sequences has shown that *S. japonicum* originated in the lake area of China and radiated (together with its human host) to the mountainous areas about 5,000 years ago, to Japan around 7,000 years ago and to The Philippines and Indonesia about 4 kya (Yin *et al.* 2015).

2.5.3.1 China

Symptoms resembling those of *Katayama disease* in Japan (see below) can be found in old books of traditional Chinese medicine referring to times more than 2,400 years ago (Mao and Shao 1982). In addition, splenomegaly and ascites (possibly due to chronic schistosomiasis) are mentioned in *Ling-Su*, a treatise claimed to be written by Huang-Di, a mythical Emperor said to have lived about 4,700 years ago (Mao 1986). More tangible evidence appeared when two corpses from around 2,100 years ago were discovered in the Chinese provinces of Hunan (1971) and Hubei (1975). The *S. japonicum* eggs identified in both these human remains, presumably from well-to-do persons, indicate that the disease cannot have been uncommon at that time (Wei *et al.* 1980; Chen and Feng 1999; Chen 2014). For the time being, this represents the oldest hard evidence of the disease in ancient China.

The first confirmed Chinese schistosomiasis patient was diagnosed in 1905 by Oliver Tracy Logan, an American physician working in a missionary hospital in Hunan Province (Logan 1905). However, there seems not to have been any immediate follow-up, at least not according to available

literature, which is somewhat curious since there is no reason to believe that the high prevalence (60%) reported by Totell (1924) 18 years later should have been unexpected. The time lag before Totell's follow-up of Logan's original finding is, however, surprising when one learns that both Logan and Totell worked at the same hospital. Totell perhaps thought that Logan's patient was atypical and the findings unconvincing until the first large systemic study on the disease appeared (Faust and Meleney 1924). This study, covering the three provinces Jiangsu, Zhejiang and Guangdong, also provided evidence that the intermediate snail host was *Oncomelania hupensis*, the same genus (but different species) of snail that played this role in Japan. The work by Faust and Meleney was published as a monograph and obviously had a large readership, since many papers related to the prevalence, morbidity and control of schistosomiasis japonica were published soon afterwards, both in Chinese and in international medical journals (Chen 2014). Hsu and Wu (1941) also reviewed the literature and summed up the distribution of schistosomiasis based on their wide experience of field surveys. At this time, schistosomiasis was shown to be common in 12 provinces in central and southern China with the number of people infected estimated at around 10 million.

One of the first actions of the new Government that took over in 1949 was to create a programme tasked with responsibility for schistosomiasis control in all endemic areas. The Chinese national schistosomiasis control programme was initiated in 1955 and not long afterwards, Maegraith (1958) pointed out the huge public health impact and economic significance of this disease underlining the importance of recognizing the problem. He noted the strong political will to do something about the situation and witnessed the founding of a working control strategy based on local resources (community participation). The national control programme established offices at all administrative levels, each linked to an expert advisory committee for schistosomiasis. At the provincial level, there was a 'Leading Group of Schistosomiasis (Endemic Diseases) Control', while special institutions were created at the prefecture, county and township levels. The latter offices had the responsibility to carry out local day-to-day control measures according to the higher-level plans of action. Provincial institutes for parasitic diseases still exist in all endemic provinces, with the Shanghai National Institute for Parasitic Diseases, now part of the Chinese Center for Disease Control and Prevention (China CDC) coordinating all field activities (Zhou *et al.* 2012).

We understand from later publications (Mao and Shao 1982) that the schistosomiasis control programme worked well from the start and has continued to do so by successfully reducing the endemic areas as well as the number of new cases year by year. Effective delivery and intersectoral collaboration between all governmental ministries that had connection with the disease, i.e., those dealing with health, agriculture, education, forestry and water conservancy, constituted an important part of this success story. Crucially, as in Japan, there was a strong emphasis on environmental management for the control of the intermediate snail host. In addition, interventions were usually implemented in an integrated fashion and readily adapted to local eco-epidemiological settings. However, there was a long pause in the written literature until the update by Mao and Shao, referred to above, that provided information regarding the human and the zoological distribution of the disease as well as an attempt to estimate its incidence. Although schistosomiasis must have played a big role in the panorama of Chinese ailments since time immemorial, one wonders why the medical literature lacks continuity until the latest 30 years. Possible answers must include the obvious probability that much of the literature was not translated. However, it might also be a reflection of the fact that scientific reporting in scientific journals developed quite late in China and that many of the records were personal notes, which are difficult to retrieve or have in fact not survived.

In contrast to the other schistosome species, *S. japonicum* is a zoonosis infecting a wide spectrum of wild and domestic animals and the reservoir in domestic animals keeps large swathes of land endemic, which might be more to blame for human infection than anything else. In the early 1950s, there were an estimated 14,300 km^2 of *Oncomelania* snail habitats in China and about 1.2 million infected cattle, which translates into more than 100 million people at risk (Chen and

Feng 1999). The historic peak of human prevalence of the disease that Mao Zedong gave the name 'God of Plague' was between 10.5 million (Mao and Shao 1982) and 11.8 million (Chen and Feng 1999). We will never know which estimate is closest, but it is safe to say that both prevalence and intensity of disease in the endemic areas were unusually high in those days. Numerous deaths, broken families and destroyed villages followed in the wake. There were many tales of the toll and names like "big belly village", "no man's village", "widows' village" or "village without villagers" were once common in the endemic areas (Chen 2014). Indeed, schistosomiasis was the major cause of death in the endemic areas, accounting for as much as 90% of the mortality and according to a local survey in Jiangxi Province from the 1950s, a total of 1,362 villages were destroyed, 26,000 families passed away and 310,000 residents left their homes (Chen 2014).

In the early 1990s, the World Bank committed a US$ 71 million loan for schistosomiasis control in China with the Chinese Government providing USD 82 million as counterpart funds (Yuan *et al.* 2000). This World Bank Loan Project (WBLP), at the time the largest amount of money ever allocated for one disease, ran for 10 years (1992–2001) with the stated goal of enhancing morbidity control through large-scale praziquantel administration to humans and bovines. This key strategy was complemented with health education and limited environmental management to control the snail population. The specific objectives were to reduce the *S. japonicum* prevalence in both humans and bovines by at least 40% and to lower the snail density by 50%. An important feature of the WBLP was standardized implementation, monitoring of control measures and careful documentation of the achievements made over time plus economic evaluation (Yuan *et al.* 2000; Utzinger *et al.* 2005). The progress achieved included reduction of the human prevalence from 10% in 1989 to 5% six years later, while the average bovine infection rate decreased from 13% to 9%. In the remaining time of the project, the number of those infected continued down from an estimated 865,000 people in 1995 (MOH 1998) to about 700,000 in 2001 (Utzinger *et al.* 2005). In addition, transmission had been controlled in many counties of the seven endemic provinces. The final evaluation, carried out in 2002 comparing outcome measures with baseline ones, revealed that most of the specific project objectives had been met except that the diminishing trend of snail infections stalled and rates kept fluctuating at a low level rather than disappearing completely (Chen *et al.* 2005).

After the WBLP, the snail-infested areas started to expand again and the number of people infected with *S. japonicum* increased somewhat with higher numbers of acute cases. As these trends were picked up by the surveillance system, schistosomiasis control was upgraded to the highest priority level for communicable diseases in 2004 (Engels 2005). The State Council issued new plans for prevention and control marking the shift from morbidity control to an integrated strategy. For example, farmers were given mechanized farm equipment in exchange for the removal of cattle from the snail-infested areas in a move to reduce contamination of the fields (Wang *et al.* 2009). These activities involved a number of governmental sectors such as those dealing with agriculture, forestry, water conservancy, environment, education and others as needed, with the combined actions resulting in a reduction of the number of infected cases to an estimated 325,800 in 2010 and the total area of snail habitats estimated at 3,700 km^2, i.e., less than a quarter of the 1955 estimate (Lei *et al.* 2010). The most recent data published estimate that there were only 250,000 infected people in 171 counties in 2012 (Li *et al.* 2013), which supports the current aim to achieve elimination of schistosomiasis by the early 2020s (Zhou *et al.* 2012).

2.5.3.2 Japan

Although the historical roots of schistosomiasis in Japan cannot be followed as far back as in China and Egypt, several Japanese warlords of the 16th and 17th century apparently had symptoms typical of schistosomiasis and the Kofu basin was almost certainly endemic in the Edo period (1600–1867) (Kajihara and Hirayama 2011). From the discovery point of view, the Japanese situation parallels

Bilharz's work, but the enigma caused by the infection was unraveled from a direction opposite to that in Egypt. Long before the cause was known, schistosomiasis was clinically well characterized, mainly due to the higher egg output from the *S. japonicum* species. Maki *et al.* (2001) remind us that just a few years before Bilharz arrived in Egypt, Dr. Yoshinao Fujii had reported (in 1847) signs of a 'new' disease in a relatively limited area in Hiroshima Prefecture along the south-eastern coast of Honshu, the main Japanese island:

> *"During the past 2 or 3 years, farmers have had small eruptions on their legs when they entered the water to cultivate the rice field. The eruptions are unendurably painful and itchy. Cows and horses also show the same symptoms. Most of the residents suffer from this disease and they consider that the symptoms are due to the lacquer spread out in this area in ancient times".*

Fujii had not seen these pathological signs before but realized that it was a serious disease that often led to death. He also noted that it was not exclusively infecting humans but that various animals were also affected and frequently died. He came to understand that the disease was geographically focal and existed in various parts of southern Japan, often along rivers or in low-lying areas that were frequently flooded. Several counties in the Chūgoku region south of Honshu, among them Katayama (that gave the disease its first name), were particularly hard hit. In Japan, in contrast to the situation in Egypt, disease was limited to only three main endemic areas: 1) the Hiroshima and Okayama Prefectures in the Chūgoku region; 2) the northern part of Kyushu island, situated south of Honshu and only separated from Chūgoku by a narrow strait of the sea; 3) the Kofu Basin in the centre of Honshu (Tanaka and Tsuji 1997). In addition, there were a few smaller endemic areas northeast of Tokyo, mainly scattered around what is present day Narita Airport (Tanaka and Tsuji 1997).

While it took more than 60 years from Bilharz's discovery until the life cycle and route of infection was determined, it took almost as long until the disease in Japan was understood. Fujii's presumption that the disease he had discovered was due to a poison reflects the universal lack of the concept of infection in his day. The time for a paradigm shift was not ripe until the end of the 19th century when scientists finally started to hypothesize that the cause of *Katayama disease* could be a parasite. Some imagined an agent similar to that causing malaria (Nakahama 1884), while others' thoughts went in the direction of the liver fluke (Oka 1886), the latter idea being quite close to the mark. However, the correct explanation was not reached until 1904 – not long before *S. mansoni* was discovered in the West. Fijiro Katsurada, Professor of Medicine at the Okayama Medical School, had been investigating the *Suishuchoman disease* in patients from Yamanashi in the Kofu Basin when he noted eggs in the feces of five of his twelve patients, the symptoms of whom were reminiscent of those described by Fujii 40 years earlier. Katsurada thought that the eggs looked similar to those seen by Bilharz in Egypt, making him suspect that the disease was caused by a related parasite. Although he had at that time no opportunity to carry out human *post-mortem* examinations, he was able to investigate the disease in household animals:

> *"Since I had previously ascertained that trematodes (e.g., P. westermani) which most often invade humans are also not infrequently found in cats and dogs, I therefore believed that a trematode causing our disease could be found in these animals. I therefore autopsied two dogs and a cat and in the latter I found a part of a male trematode. I later received a second cat from the county of Yamanashi and found in the portal vein as well as in its tributaries numerous trematodes which were in the exact form as that discovered in the first cat".*

Katsurada soon realized that *Suishuchoman disease* was identical to *Katayama disease* and described the morphological features of the worms he found, including the eggs and pointing out differences from those described in Egypt (Katsurada 1904). He later described the eggs in the liver and intestinal walls in deceased humans, making a number of observations on the pathology and

noting that the new schistosome species never caused the bladder pathology seen in *S. haematobium* infections. Based on these findings, he named the 'new' trematode *Schistosoma japonicum*.

In Europe, speculation abounded on how the schistosome entered the human host. Looss, for example, did not accept the need for intermediate hosts, believing instead that the miracidium was the infective agent. In contrast, Manson correctly felt that this was a two-step procedure with the miracidium passing into an intermediate snail host to eventually transform into cercariae, infective for humans. However, this was purely guesswork based on the similarity to *Fasciola*, whose life cycle had recently been determined by Thomas (1883). Although Katsurada originally agreed with Loos, he changed his mind when Kan Fujinami and his assistant Hachitaro Nakamura of Kyoto University heard that local people in Katayama attributed their disease to wading in muddy rice paddies. Fujinami and Nakamura carried out a series of experiments exposing calves taken from disease-free areas of Japan to local water making it clear that the infection had to be percutaneous (Fujinami and Nakamura 1909). Finally, Miyairi and Suzuki (1913) found the small, intermediate snail host *O. nosophora*, which brought the discussions to a close.

The complete schistosome life cycle remained unknown and this question was as high on the agenda in Europeas in Egypt and Japan. Manson, at the London School of Tropical Medicine and Hygiene, proposed that investigations should focus on *S. japonicum* as the parasites could be transmitted to experimental animals. He suggested that Leiper (who would later elucidate the *S. mansoni* and *S. haematobium* life cycles) travel to Shanghai in China to find out more about the oriental schistosome. This was also of some concern to the Royal Navy, which had been informed that some of its officers stationed on the River Yangtze in China had been affected by a mysterious disease that might have something to do with this parasite. The Advisory Committee of the Tropical Disease Research Fund and the British Admiralty agreed to send a joint team consisting of Robert Leiper and Edward Atkinson, a Royal Navy surgeon famous for his part in Scott's 1910–1913 Antarctic 'Terra Nova' expedition, to Shanghai to investigate the validity of the disease. The two men arrived in Shanghai in late 1913 and immediately began to set up a laboratory in a native house-boat. However, before they could start their investigation, World War I broke out and Atkinson was ordered back to England with immediate effect. Leiper, however, had time to travel to Japan, where he carried out some animal experiments before he too had to return home.

It fell to two Japanese investigators, Keinosuka Miyairi and his assistant Masatsuga Suzuki, to elucidate the first complete life cycle of a species of schistosome (Miyairi and Suzuki 1913). Their initial report describes how they had mixed cow dung containing eggs of *S. japonicum* with water to stimulate egg hatching and noted activation of the miracidia within the egg shells followed by wriggling of the larval worm and finally hatching as the egg shell broke open. They then went on to repeat these observations using human feces containing eggs, noting the same picture.

Epidemiological surveys began in 1910 in Kofu. The total number of cases of schistosomiasis japonica detected in Japan in 1920 was about 8,000, a figure reduced year-by-year down to 438 cases in 1970 (Tanaka and Tsuji 1997). Reflecting the strong focality of the infection in Japan, the number of infected people was rather modest compared to the situation in Egypt and China. The low number in Japan is peculiar when one considers the parasite's zoonotic character and it is difficult not to speculate that the topography must play an important role. Indeed, very similar conditions to Japan's endemic areas can be seen in China's mountainous endemic areas in the Sichuan and Yunnan provinces.

Various control activities were instituted, e.g., storing 'night soil', i.e., fecal matter intended for use as fertilizer in the fields, for at least two weeks to make sure that no live eggs remained. Cows and buffaloes were replaced with horses, which are more resistant to this infection. Sodium pentachlorophenate (NaPCP) was extensively sprayed in the fields in an effort to control the snail intermediate host and when sodium tartar emetic (Stibnal) became available in 1921, drug treatment of infected people started. However, environmental management was probably the most effective approach as the *Oncomelania* snail host is amphibious and cannot survive long without

water. Snail habitats were destroyed by wetlands being drained to reclaim land for agriculture and ditches around the rice fields were cemented to keep snails out of the paddies. Taken together, these activities were successful. Although positive results did not occur immediately, the political will did not waver in demanding long-term, rigorous adherence to the approach chosen. Naturally, some areas were freed of the infection more rapidly than others but it took more than 50 years before final success. However, once the goal of elimination (defined as reducing the disease prevalence to a point where it is no longer a public health threat), had been achieved the control programme swiftly moved to eradication, which refers to the permanent reduction to zero of new cases in a defined geographical area. The last new human infection in Japan was in Kofu in 1977 and although snails were eradicated in most areas by 1983, a limited number of uninfected snails still remained at Kofu and Obitsu at the end of the last century (Tanaka and Tsuji 1997).

2.5.3.3 The Philippines

Schistosomiasis was first reported in The Philippines as a supplementary observation of schistosome eggs in the large intestinal wall and the liver at the autopsy of a man, who had died of other reasons (Wooley 1906). Eggs were now actively looked for with many positive findings, both at autopsy and stool examination. The disease was later shown to be endemic in many of the Philippine islands, with 25,000 to 30,000 people estimated to be infected in 1921, a number that had increased to 300,000 in 1948 (Garcia 1976). The Second World War disrupted epidemiological surveying initially, a situation that was reversed when an outbreak of schistosomiasis occurred among soldiers of the Allied Armed Forces under the command of General McArthur on the island of Leyte in 1945. Twenty years later, 24 endemic provinces had been identified with about one million people infected and five million at risk (Garcia 1976). Since the early 1980s, MDA with praziquantel has become the mainstay of control. According to recent studies the prevalence ranges from 1% to 50% in different endemic zones and the situation is complicated by sustained disease transmission due to water buffaloes and cattle contaminating the fields (Olveda *et al.* 2014).

2.5.3.4 Indonesia

Schistosomiasis had not been reported from Indonesia until Muller and Tesch (1937) described the disease in a 35-year old male from a village near Lake Lindu, situated in an isolated valley with the same name in Central Sulawesi. The patient died shortly afterwards and tissue sections taken at autopsy subsequently revealed eggs identified belonging to *S. japonicum* (Brug and Tesch 1937). Soon after the discovery of this first case, the disease was also found in Napu, another Sulawesian valley but the strain of the intermediate snail species (*O. lindoensis*) was not demonstrated until 35 years later (Davis and Carney 1973). Satrija *et al.* (2015) have recently reviewed the schistosomiasis situation in Sulawesi, including the Bada Valley, a third endemic area that was not discovered until 2008. The first prevalence survey around Lake Lindu indicated that as many as 56% of the population were infected by *S. japonicum*, while a survey in 1973 in Napu Valley showed a prevalence as high as 72% in some places (Garjito *et al.* 2008). In contrast, the prevalence in Bada Valley was only 0.8% at the time when it was first detected (2008). The disease in these three valleys is believed to be sustained by *Rattus* spp. reservoir hosts whose prevalence rates range from 0 to 20% (Garjito *et al.* 2008). Although an integrated control approach reduced the human prevalence to an average of 0.5% in Lindu and 1% in Napu by 2006, more recent data indicate that it is increasing again (Satrija *et al.* 2015).

2.5.3.5 Continental Southeast Asia

The first human case of *S. mekongi* infection was reported in Laos (Vic-Dupont *et al.* 1957) and later also in Cambodia (Audebaud *et al.* 1968). This 'new' schistosome strain was, however, not

designated as a separate species until 1978 (Ohmae *et al.* 2004). *S. mekongi* causes severe intestinal and hepatosplenic disease with high mortality rates (Muth *et al.* 2010). Infections in the provinces of northern Cambodia and southern Laos were common in the early 1970s and 1990s but the disease has since been partly controlled (Muth *et al.* 2010).

Neotricula aperta is the only known intermediate host of *S. mekongi* (Attwood *et al.* 2001), which is exclusively found in the Mekong River Basin at the border between these two countries, where an estimated 1.5 million people live (Campbell 2004). Two separate clades of *N. aperta* have been found: a spring-dwelling form in northern Laos and another that prefers the ecology produced by the Mekong River in southern Laos and Cambodia; this divergence is dated at 9.3 million years ago with further radiation into sub-clades across Cambodia and Laos around 5 million years ago (Attwood *et al.* 2008). Historical events, rather than ecology, might best explain the absence of *S. mekongi* from most of Laos (Attwood *et al.* 2008).

2.5.4 Latin America

The relatively recent colonization of Brazil, Surinam, Venezuela and the Caribbean islands by *S. mansoni* from West Africa is supported by strong genetic similarities between schistosomes from both continents (Desprès *et al.* 1993; DeJong *et al.* 2001; Morgan *et al.* 2005). The infection is supposed to have been introduced by the African slave trade which in Brazilian ports started in the 16th century (Guimarães *et al.* 2012). However, the parasite could only get a foothold where the imported parasites could be supported by indigenous intermediate snail hosts, e.g., *Bi. glabrata*. The Northeast of Brazil became endemic first, since the ports of Salvador and Recife received the highest number of African slaves, but as there were also shipping routes to other parts of the New World from Africa, it is unclear whether the infection reached all of today's endemic areas directly or if there were also transfers within the New World. In Brazil, schistosomiasis soon spread to the South with large-scale population movements in the early 18th century, mainly due to the discovery of gold and diamonds in the Minas Gerais State in southeastern Brazil (Guimarães *et al.* 2012).

The first case description of schistosomiasis in Brazil was unequivocally demonstrated in 1904 in a patient in the State of Bahia in the Northeast, but this finding did not appear in the literature until four years later (Pirajá da Silva 1908). In this paper, the author reported that using stool microscopy he found eggs with lateral spines; this roused his curiosity but he was at a loss to explain what they were. Only after reading about the discovery of *S. mansoni* by Sambon (1907) did he realize what he had found, making it possible to publish the paper with full explanations. Pirajá da Silva performed three autopsies on suspected cases, finding schistosomes in all of them. He described their characteristics concluding that they were not *S. haematobium.* All this is described in great detail by Katz in a recent paper (2008).

2.6 CHANGE OVER TIME

The number of people infected with schistosomiasis increased naturally with the numbers of humans as we move from Antiquity and pre-Antiquity reaching a plateau by around 1980, after which morbidity declined sharply thanks to large-scale use of praziquantel. Although overall prevalence has not yet declined correspondingly, some countries have made impressive progress, e.g., China, Brazil and Egypt. In addition, the disease has disappeared from Japan and seemingly also from Puerto Rico and most Caribbean islands. In the Middle East there are only a few foci left, which is also the case for Africa north of the Sahara. The set of three pictures shown here (Fig. 2.3) summarizes this situation although, admittedly, the situation in Antiquity cannot be better than speculation, mainly based on Figure 2.1.

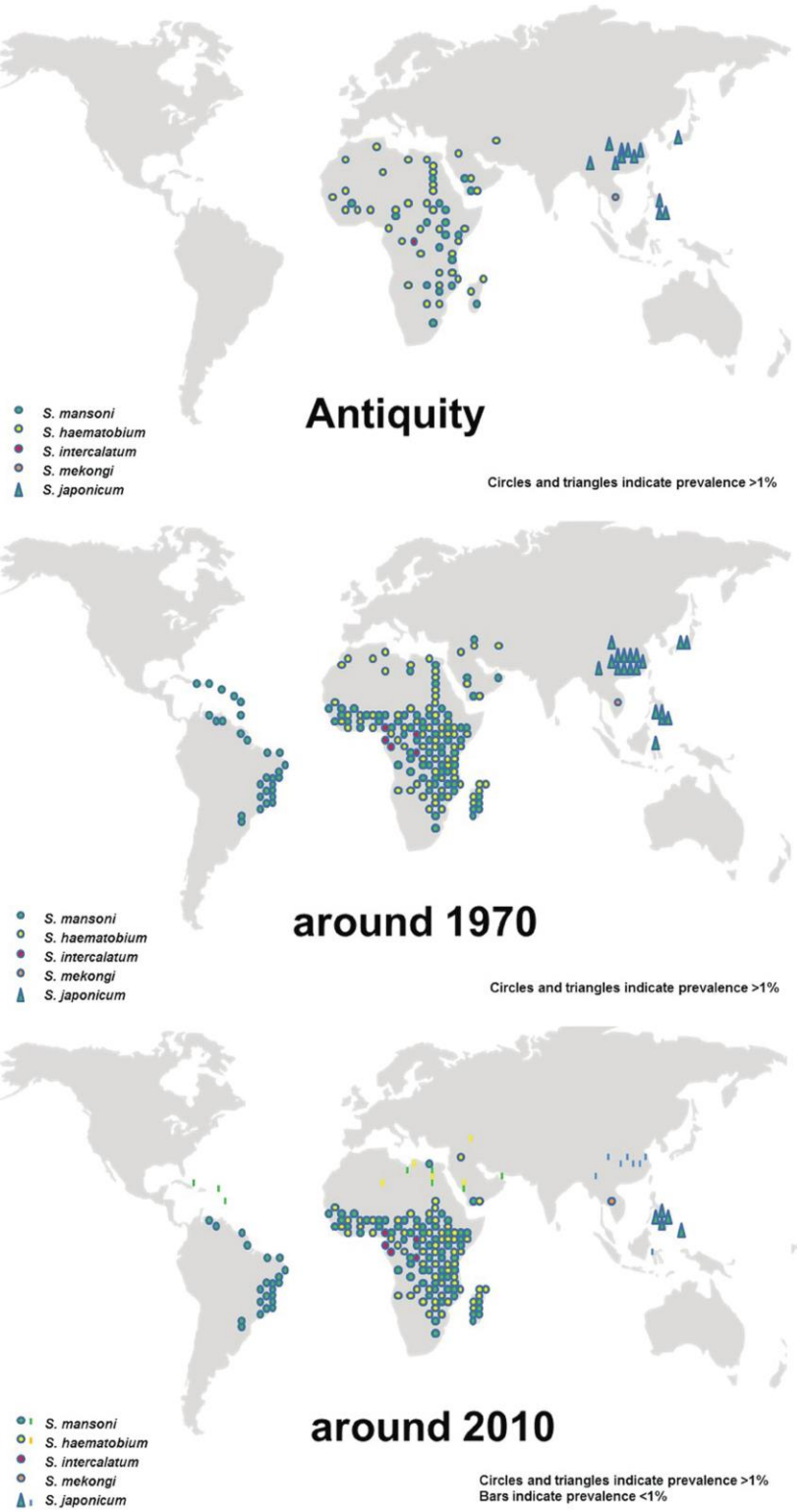

FIg. 2.3 Estimates of the distribution of schistomiasis in Antiquity, and in recent times.

2.7 CLOSING COMMENTS

All we know about schistosomiasis in ancient times is based on the finding of a limited number of schistosome eggs in mummies from Egypt, Middle East and China in combination with fossilized shells of snails that could have acted as intermediate hosts. It might still be safe to say that the general geographical distribution, with exception of the New World and Madagascar (that was still without human settlements at the time of Antiquity), has changed only little over the succeeding 5,000 years. Exceptional progress in countering this parasite has been achieved in Japan and China in modern times and the total number of schistosomes (as an expression of human prevalence and intensity of infection) probably passed its peak in the 1980s when large-scale MDA with the then new broad-spectrum anthelmintic drug praziquantel got under way. Surprisingly, however, the total number of those infected in the world is still increasing, a fact that must be ascribed to the ongoing population explosion and the creation of new transmission sites in areas characterized by land colonization and expanding irrigation in the tropical areas.

Table 2.2 *Schistosoma*: overview of ancient and historical findings.

Year	Indications/species	Country/place	Reference
Prehistoric		Unspecified conjecture	
6,000 BC	*S. haematobium*?	Mesopotamia (Euphrates)	Anastasiou *et al.* 2014
4,700 BC	Symptoms	China (written records)*	Mao 1986
2,100 BC	*S. japonicum*	China (Hubei Province)	Chen 2014
350–550	*S. mansoni*	Egypt (Ballana cemetery)	Miller *et al.* 1992; Hibbs *et al.* 2011
15–1800s	Symptoms	Japan (written records)**	Kajihara and Hirayama 2011
1500s	*S. mansoni*	Latin America	Guimarães *et al.* 2012
14–1500s	*S. mansoni*	France (medieval latrine)	Bouchet *et al.* 2002
1808	Symptoms	Egypt	Renault 1808***
1851	*S. haematobium*	Egypt	Bilharz 1853
1847	Symptoms	Japan (Fujii)	Tanaka and Tsuji 1997
1904	*S. japonicum*	Japan	Katsurada 1904
1905	*S. japonicum*	China	Logan 1905
1906	*S. japonicum*	The Philippines	Wooley 1906
1907	*S. mansoni*	England	Sambon 1907
1908	*S. mansoni*	Brazil	Pirajá da Silva 1908
1913	*S. japonicum* life cycle	Japan	Miyairi and Suzuki 1913
1916	*S. mansoni* life cycle	England	Leiper 1916
1916	*S. haematobium* life cycle	England	Leiper 1916
1934		Zaire (Belgian Congo)	Fisher 1934
1937	*S. japonicum*	Sulawesi, Indonesia	Müller and Tesch 1937; Brug and Tesch 1937
1957	*S. mekongi*	Laos	Vic-Dupont *et al.* 1957
1971	Snail host in Sulawesi	Sulawesi, Indonesia	Davis and Carney 1973

*Physicians at the Court of Emperor Hung-Di
**Contemporary physicians
***French Army physician

Schistosomiasis can be ascertained to have existed for at least 6,000 years, but the discovery of the causative infectious agent is recent; dating back less than 165 years (Table 2.2). The early 1980s marked a turning point as it was then that the large-scale effect of praziquantel turned out to be so profound and it now makes sense to think of the elimination of schistosomiasis as a public health threat.

Strangely, in Europe and the Middle East, there is a gap of about 1,300 years between the youngest Egyptian mummies shown to have been infected and the earliest description of schistosomiasis as a distinct disease by Renault (1808). As there was a constant exchange between Europe and the Near and Middle East, it is surprising that we have virtually no records covering this long period. The single exception is a *S. mansoni* egg found in the remains from a French latrine dating from AD 1450–1550, supposedly emanating from a European traveler or an early African immigrant (Bouchet *et al*. 2002). However, the existence of written, medieval records in China and Japan, although few, give hope that similar, yet unrecognized medical records from Greco-Romans times, might exist.

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