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Schistosomiasis then and now: what has changed in the last 100 years?

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Review

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Abstract

Only with the completion of the life cycles of *Fasciola hepatica* in 1883 and 30 years later those of *Schistosoma japonicum* (1913), *Schistosoma haematobium* and *Schistosoma mansoni* (1915) did research on schistosomiasis really get underway. One of the first papers by Cawston in 1918, describing attempts to establish the means of transmission of *S. haematobium* in Natal, South Africa, forms the historical perspective against which to judge where we are now. Molecular biology techniques have produced a much better definition of the complexity of the schistosome species and their snail hosts, but also revealed the extent of hybridization between human and animal schistosomes that may impact on parasite adaptability. While diagnostics have greatly improved, the ability to detect single worm pair infections routinely, still falls short of its goal. The introduction of praziquantel ~1982 has revolutionized the treatment of infected individuals and led directly to the mass drug administration programmes. In turn, the severe pathological consequences of high worm burdens have been minimized, and for *S. haematobium* infections the incidence of associated squamous cell carcinoma has been reduced. In comparison, the development of effective vaccines has yet to come to fruition. The elimination of schistosomiasis japonica from Japan shows what is possible, using multiple lines of approach, but the clear and present danger is that the whole edifice of schistosome control is balanced on the monotherapy of praziquantel, and the development of drug resistance could topple that.

Introduction

A paper titled 'Bilharziasis in Natal', published in *Parasitology* in 1918 by Dr F. G. Cawston, provides a window on the state of knowledge at the time (Cawston, 1918). He was a British physician and zoologist practising in South Africa, whose interest was aroused by a patient with 'bilharziosis' (most probably infected with *Schistosoma haematobium*) (Cawston, 1915). In fact, the very first volume of *Parasitology* had published an article on the same topic (Turner, 1909), with speculations on the mode of transmission but no mention of snails. Dr Cawston was of the opinion, echoing both Turner and Sir Patrick Manson in a lecture given in 1914, that the disease was caught by swimming in freshwater pools, an activity more common in boys than girls. Theodor Bilharz had identified parasitic trematodes as the cause of this disease in Egypt in 1851, hence the term bilharziasis (for a description of the discovery see: http://www.whonamedit.com/doctor.cfm/2829.html). However, the intestinal and urinary forms were not distinguished with any clarity. The disease had been recorded from South Africa as far back as 1864, associated with symptoms of haematuria and dysentery (= *S. mansoni* infection?). Dr Cawston's paper came at the trailing edge of a period of very intense research and to appreciate its context and significance we need to trace the developments that preceded its publication.

Historical perspective

Trematode cercariae emerging from molluscs were reported as far back as the 18th century and classified by taxonomists with the generic name *Cercaria* and suitable specific names. There was a vague realization that these cercariae might be the larval stages of the numerous species of trematodes parasitic in vertebrates. Indeed, in 1842 the Danish scientist Steenstrup put forward the idea of alternation of generations as a 'peculiar form of breeding among the lower animals'. He meant this not as the alternating haploid and diploid generations found in lower plants but as alternate generations reproducing sexually and asexually. The practical problem was making the link between mollusc and vertebrate and we know with hindsight that larval trematodes can have quite stringent species-specificity for their hosts. It is clear from the literature of the time that the colourful sporocysts packed with cercariae, seen in the tentacles of the snails *Succinea* sp, were the larval stages of *Leucochloridium paradoxum*, a bird intestinal fluke that took only six days to mature after ingestion. However, the route of transmission back to the snail was not confirmed.

Over the winter of 1879/1880 there was a massive mortality of sheep in the UK due to liver fluke (*Fasciola hepatica*) infection. Such was the consternation nationally that in April 1880 the outbreak occasioned that very British institution of letters to *The Times* newspaper (https://gdc.gale.com/gdc/artemis/home. In advanced search use 'fluke' as the search term in Entire

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Document, limited by Publication Dates 1 and 30 April 1880, and Document Type as Letter to the editor). It should be borne in mind that this was less than 20 years after Louis Pasteur proposed his 'germ theory' of disease and only four years after Robert Koch conclusively identified *Bacillus anthracis* as the cause of anthrax in cattle. On one side of the correspondence were a Mr Bowick who clearly saw flukes as some kind of germ that would only establish in unhealthy animals, a Mr Harley who was convinced that the transmission was direct *via* fluke eggs in animal droppings contaminating the pastures, and a Mr Gabb who thought that the flukes developed from the eggs of tapeworms! (This may be the same Mr J Harley who had reported on endemic haematuria in southern Africa the 1860s.) In 1880 the idea that snails might transmit disease was anathema to some people who disputed the existence of any intermediate host. Ranged against these correspondents was Professor Rolleston of Oxford whose contribution, apart from being dismissive of Harley, was to suggest that the fluke was very specific in its choice of larval host. Most telling was the contribution of Professor Cobbold of the Royal Veterinary College, who was aware of the *Leucochloridium* life cycle and quoted a letter he had received from Prof Leuckart in Germany saying that the latter had successfully infected the snail *Lymnaea* (= *Galba*) *truncatula* with miracidia of *F. hepatica* and obtained *cercariae*. The Royal Agricultural Society of England was prompted by Professor Rolleston to fund Algernon Thomas, working at the Oxford Museum, to investigate the causes of fluke disease. Thomas settled the question, describing the miracidium infecting the snail *L. truncatula*, the intramolluscan stages, and the metacercarial cyst on grass (Thomas, 1883). The infection of livestock by ingestion of metacercaria *via* the oral route had a rather unhelpful influence on later thinking about schistosomes.

Research on schistosomes progressed slowly after Bilharz's initial description. In 1893 Patrick Manson finally separated the two clinical forms with lateral- and terminal-spined eggs (Leiper, 1915), and a new species, *S. mansoni,* was erected by Sambon in 1909 for the lateral spined egg producer (Leiper, 1915). In spite of Thomas's publication, in 1884 Looss promoted the hypothesis that schistosome infection was direct, with miracidia hatching from eggs and penetrating the skin when humans entered water (Leiper, 1915). Unsurprisingly, heroic attempts to infect potential mammalian hosts using miracidia failed, but 25 years later Looss was still advocating human skin penetration by miracidia (Looss, 1909). (Ironically, he was an associate of Leuckart in Leipzig where the life cycle of *Fasciola* was well understood.) Such was the confusion that in 1914 Manson himself hedged his bets by suggesting that miracidia might enter a mollusc, crustacean or arthropod, and encyst, before oral ingestion and entry into human tissues across the gut wall (c.f. *Fasciola*) (Leiper, 1915). In spite of Looss being utterly mistaken, one beneficial outcome of the focus on schistosome transmission by an aquatic larva was the recommendation that urination and defaecation should not take place near water.

Independent of work in Europe, Japanese researchers were investigating six very focal diseases associated with rice paddies and nearby river banks (summarized by Tanaka and Tsuji, 1997). To deliberately misquote Pasteur, this was a case of 'fortune favours the unprepared mind' as the Japanese were not burdened by the misconceptions then prevalent in Europe. Initially, the cause was thought to be ingestion of a poison, but parasite eggs were observed in human livers at autopsy and in 1904 Katsurada described adult worms from a cat, with the same eggs *in utero*. Realizing the similarity with *S. haematobium* he proposed the name *Schistosoma japonicum* for the new species (Katsurada, 1904). It was felt that since worms were found in mesenteric vessels, infection was likely *via* the oral route, with penetration of the gut wall (c.f. *Fasciola* again). However, Miyagawa immersed dogs and rabbits in paddy field water and showed they became infected with schistosomes (he was helped in his quest by the fact that *S. japonicum* is a true zoonosis). He also performed histology on exposed skin and demonstrated the presence of schistosomula (Miyagawa, 1912). Finally the direct link between schistosomes and snails was made when Miyairi and Suzuki identified the snail *Oncomelania* in the paddy fields and showed that the emerging cercariae were the infective stage for mammals (Miyairi and Suzuki, 1913).

News of these rapid advances reached London and prompted the rather grandly titled 'Wandsworth Expedition' to Shanghai, China with a side trip to Japan, to investigate trematode diseases of humans. It was led by Professor Leiper of the London School of Hygiene and Tropical Medicine from February to August 1914 (Leiper and Atkinson, 1915). In their visit to Japan, the authors mention finding a small opeculate snail in Katayama (of Katayama Fever fame), now known as *Oncomelania hupensis nosophora*. Back in Shanghai these snails showed an extraordinarily marked attraction for *S. japonicum miracidia*, hatched from eggs shed by a heavily infected dog. Ultimately, a single mouse exposed to cercariae teased from *Oncomelania* snails yielded paired adult worms in the mesenteric veins. The findings of Miyairi and Suzuki were confirmed as one of the great discoveries of all time in parasitology.

In 1915, as a result of the First World War, the British Government sent a mission, headed by Leiper, to Egypt where British troops were stationed. Its task was to obtain 'a clear appreciation of the factors and the conditions under which the disease (i.e. schistosomiasis) was contracted and propagated' (Leiper, 1915). In the Introduction to his report on the mission he was very critical of Looss whose direct infection theory had dominated all research on schistosomes in Africa for the previous 25 years. Apparently Looss even objected to the description of *S. haematobium* and *S. mansoni* as two distinct species (Leiper, 1915).

Armed with his knowledge from Japan and China, Leiper's plan was to collect and dissect large numbers of snails from districts near Cairo where schistosome infections were common. He knew that he was looking for a fork-tailed cercaria lacking a pharynx, and wanted to see if these could infect animals brought from the UK. He focused on El Marg village, with a *S. haematobium* prevalence of 91% in boys. He collected *Planorbis boissyi* (= *Biomphalaria* sp) *Melania tuberculata* and a *Bulinus* sp. snail. His problems were compounded by the observation of four trematode species with fork-tailed cercariae, namely 'both forms' of *S. haematobium* (i.e. *S. mansoni* as well), *S. bovis* and *Bilharziella polonica*. He infected rats, mice and other species, and concluded that infection was by skin penetration (or drinking cercarial-contaminated water). He also recorded that the worms took 6–7 weeks to develop after exposure of monkeys brought from London (probably sooty mangabeys, *Cercocebus atys*). What is notable in this and all preceding work was the total focus on *S. haematobium* to the almost complete exclusion of *S. mansoni*. Was it simply that haematuria and eggs in the urine were very visible manifestations, compared with eggs in faeces? Leiper subsequently published a note stating that *Bulinus contortus* (= *B. truncatus*) and *B. dybowski* (unknown) shed cercariae that gave rise to worms releasing terminal-spined eggs whilst cercariae from *Planorbis boissyi* (= *Biomphalaria* sp) gave rise to worms laying lateral spined eggs (Leiper, 1916).

Writing in 1918, Dr Cawston was aware of the discoveries about the life cycle of *S. japonicum*, and the results of the Wandsworth expedition. To investigate schistosome transmission in South Africa, in 1915 he first attempted to infect the abundant *Lymnaea natalensis* snails using *S. haematobium* miracidia, without success (ironically these snails are hosts of *Fasciola gigantica*).

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In 1916 he collected large numbers of *Physopsis africana* (= *Bulinus africanus*) from various parts of Natal. He described specimens shedding fork-tailed cercariae, and containing sporocysts. He subsequently made a study of the freshwater snails of Natal, noting additionally the presence of *Planorbis* (= *Biomphalaria*) *pfeifferi* but saying that *S. mansoni* was absent. (Today it is listed as endemic to KwaZulu-Natal, along with *S. mattheei* in livestock.) He also collected *Isidora tropica* and *Isidora forskali* (= *Bulinus tropicus* and *B. forskali*) which did not shed fork-tailed cercariae, but are known schistosome hosts elsewhere. He was successful in infecting *Bulinus africanus* with miracidia of *S. haematobium* and obtaining cercariae, but he failed to infect rats, guinea pigs and pigeons with these.

Cawston also took the standpoint of the medical practitioner, noting that in one school 76% of boys were infected and he lists symptoms such as renal calcium deposits, renal colic and haematuria. He did not consider the infection life-threatening or even life-shortening. Indeed his greatest concern was how catching schistosomiasis would affect the prospects for getting life insurance. His advice was to avoid bathing in freshwater pools and his list of treatments intended to relieve symptoms rather than cure patients, included diuretics and urinary antiseptics, such as hexamine, aspirin, the local herbal medicine Buchu, and tincture of henbane (*Hyoscamus*)!

What are the current gaps in schistosome knowledge?

Where are our research gaps in schistosomiasis 100 years after the publication of Cawston's paper? We now have a much greater understanding of the complexities of the disease, its impact on infected individuals and an appreciation that high worm burdens generate severe and life-threatening pathologies. In this update some recent advances are highlighted, but equally importantly there is a focus on what we still don't know in 2019.

Schistosome species and their snail hosts

The number of schistosome species known to infect humans now stands at six, with description in the intervening period of *S. intercalatum* (1934) and *S. guineensis* (2003) in Central Africa, and of *S. mekongi* (1978) is South-East Asia. However, the advent of molecular genetics has revealed a more complex situation with the discovery of hybrids between human and animal schistosomes (Webster *et al.*, 2013). The hybridization appears to be introgressive and may have an impact on the adaptation and evolution of the parasites. In Africa, there are two members of the *S. mansoni* clade and nine members of the *S. haematobium* clade. As molecular tools have become more discerning, the detection of hybrids has moved from laboratory experiments to human/snail populations in endemic areas. Hybrids between *S. mansoni* and *S. rodhaini* (rodent host) have been reported in East Africa and between various members of the *S. haematobium* group in West Africa (reviewed by Leger and Webster, 2017). The latest reports from Malawi using single aberrant eggs as starting material have revealed interactions between *S. haematobium* and the livestock schistosomes *S. mattheei* and *S. bovis* (Webster *et al.*, 2019). An appreciation of the importance of schistosome promiscuity was revealed when a new focus of schistosome infection in humans was identified in Corsica in 2013, where *Bulinus truncatus* is endemic (Boissier *et al.*, 2016). Molecular analysis showed that hybrids between *S. haematobium* and *S. bovis* were present, very likely originating in Senegal. Given the abundance of the snail host, the fear is that the hybrid could become established in rodents or livestock as reservoir hosts. Indeed, the range of schistosome species in animals sharing their habitat with humans, and their propensity for hybridization, could have long-term implications for attempts to eradicate the disease from the human population.

Before the molecular era, the classification of the snail intermediate hosts relied primarily on shell characteristics, a particularly plastic feature (Mandahl-Barth, 1965). A better definition of the snail hosts is now being achieved using molecular techniques. Thirty-six species within the genus *Bulinus*, hosts of several schistosome species, have been placed into four species groups by DNA barcoding, but substantial genetic diversity has been revealed within groups and individual species (Kane *et al.*, 2008). The same approach has been used with the genus *Biomphalaria*, the hosts of *S. mansoni* around the world (Zhang *et al.*, 2018). The molecular profile of 15 species of *Biomphalaria* in South America, four of which are hosts of *S. mansoni*, has also been established (Caldeira *et al.*, 2016). The genetic diversity of *Oncomelania hupensis*, the host of *S. japonicum* across China, has similarly been characterized (Guan *et al.*, 2016). However, the physiological basis for the compatibility between particular schistosome and snail species (or even isolates) remains something of a mystery.

There have been significant advances in our understanding of the snail immune system, and its ability to combat schistosome infection (Mitta *et al.*, 2017; Pila *et al.*, 2017). Most intriguing is the possibility that miracidia may locate snail hosts by latching onto molluscan pheromone/chemoattractant systems (Adema *et al.*, 2017; Wang *et al.*, 2019); this could provide a mechanism with sufficient inherent specificity to explain the often tight host preference displayed by the intramolluscan stages.

Diagnostics

The inaccessible location of adult schistosomes in either the veins of the vesical plexus or the hepatic portal system makes the direct estimation of their number (infection intensity) virtually impossible, yet it is the size of that population that is crucial both for the ensuing pathology and the capacity for onward transmission. Surrogate measurements of infection intensity therefore need to be used; egg output was the original measurement of choice, both because the egg is the principal agent of pathogenesis and also because a direct correlation with infection intensity was assumed.

For *S. haematobium*, the detection of eggs in urine was always a relatively simple matter, particularly when coupled with the visible presence of haematuria, and that has not changed in the last 100 years. Indeed, detection of haematuria by dipstick, and the counting of eggs in the urine after filtration or centrifugation may provide adequate estimates of infection intensity, and the method has a high specificity (reviewed by Le and Hsieh, 2017). However, a recent study using a urine-based up-converting phosphor-lateral flow assay for circulating antigen detected a considerably higher number of infections than egg counting (Knopp *et al.*, 2015). A research gap for *S. haematobium* infections is that calibration of egg excretion relative to actual worm burden has not been achieved. Unlike *S. mansoni* or *S. japonicum*, there is no large animal model where that parameter might be established. Even in a permissive host like the baboon very few or no worms reach the bladder wall and eggs are excreted through the gut wall. This is largely due to the limiting size of the anastomoses between the inferior mesenteric/rectal veins of the portal system and the vesical plexuses of the systemic circulation around the bladder, although it is also not understood why *S. haematobium* should take this route when *S. mansoni* and *S. japonicum* do not. The best information available on egg production remains that obtained from cystectomy and autopsy investigations on human patients in Egypt more than 40 years ago. A mean output of 203 eggs per worm pair per day was estimated (Cheever *et al.*,

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1975), and there was a positive correlation between number of female worms recovered from the urogenital system and the passage of viable eggs in the urine (Cheever *et al*., 1977). Taking the average human urine production per day as 1400 mL, the usual sample size of 10 mL urine ought to be adequate for single worm pair detection, although diurnal variation in egg excretion needs to be considered, together with the inhibition of egg excretion by tissue fibrosis.

For *S. mansoni* and *S. japonicum*, diagnosis of light infections currently presents a significant problem. The introduction of the standardized Kato/Katz fecal smear test did much to improve detection rates (Katz *et al*., 1972). However, a single smear has an intrinsic limit of 20 eggs per gram, based on the standard ~50 mg capacity of the test chamber. Combining this information with an egg output for *S. mansoni* of ~300 per female per day, and a human fecal production of 250 grams shows that detection of one egg in a single smear is equivalent to 17 worm pairs (Ogongo *et al*., 2018). Using data from *S. mansoni* vaccination studies in baboons to calibrate the Kato/Katz method, based on nine replicate smears, the threshold of detection was determined as 16 worm pairs (Wilson *et al*., 2006). Given the low sensitivity of the smear technique, other surrogate measures have come to the fore, including the detection of glycoproteins from the worm gut, released into the bloodstream, and also parasite DNA in serum, faeces and urine (reviewed by Weerakoon *et al*., 2015; Ogongo *et al*., 2018). The emphasis is now on detection of schistosome antigens in the bloodstream and urine, especially using reagent strip assays (Corstjens *et al*., 2014). In areas of low *S. mansoni* endemicity, direct comparison of a lateral flow cassette assay to detect circulating cathodic antigen in urine with the Kato/Katz fecal smear, reveals a 1.5–6-fold higher prevalence (Kittur *et al*., 2016). The increased sensitivity has led to the realization that there is much more low-intensity schistosomiasis than previously thought (Colley *et al*., 2017). However, the detection of a single *S. mansoni* worm pair still requires sample concentration (Corstjens *et al*., 2014) and cannot be considered routine. That goal is crucial if eradication of the disease is to be achieved. Much is now known about the secretions of adult worms and eggs released into the host bloodstream and tissues. There is a need for biomarker studies on blood and especially urine of infected humans and laboratory hosts like the baboon to identify those markers of the live worm and egg secretomes that might be developed as new diagnostic targets (Ogongo *et al*., 2018).

Chemotherapy

The first chemotherapeutic agent against an infection (arsenic-containing salvarsan for syphilis and later human trypanosomiasis) was introduced in 1910, eight years before Cawston's paper. Early therapies against schistosomes used equally toxic compounds like antimony potassium tartrate (tartar emetic) injected intravenously, and it took many decades for therapeutics with only mild side-effects to emerge that would eliminate the adult schistosome population from infected individuals (reviewed by Cioli *et al*., 1995). The introduction of modern chemotherapeutics dates to the 1960s and 1970s but there were a number of false starts. Niridazole (1964) was the first orally administered compound, activated by passage through the liver, but it proved to have serious side-effects (including psychoses), especially in *S. mansoni*-infected hepatosplenic patients with porta-caval shunts (see below). Hycanthone (1975) provided a salutary warning, as the compound was found to have a long list of undesirable properties, causing frameshift mutations in microbial systems while its mutagenicity, teratogenicity and carcinogenicity were demonstrated in mammalian experiments. Amoscanate (1980) proved highly effective against *S. japonicum* but caused liver toxicity; the use of all the above compounds was ultimately discontinued.

On the positive side, metrifonate (1967), an organophosphorous insecticide derivative, is active against *S. haematobium* with an unusual mode of action. It is an inhibitor of acetylcholinesterase, and acts by paralysing worms so that they release their hold and transit through the venous system to the lungs from where they cannot return to the bladder (Cioli *et al*., 1995). This provides a clear distinction from *S. mansoni* and *S. japonicum,* which if paralysed only travel as far as the liver, and can then re-migrate back up the portal veins. Oxamniquine (1972), active only against *S. mansoni*, gives a 80–90% cure rate with only mild side-effects. Unfortunately, drug resistance was reported in Brazil and Kenya and the drug was superseded by praziquantel. However, efforts are currently underway to design oxamniquine derivatives that can treat infection caused by all schistosome species, as a hedge against resistance emerging to current therapy (Taylor *et al*., 2017).

Praziquantel (1982) is well tolerated and active against adult worms of all schistosome species, as well as other flukes and tapeworms. It does have some limitations, such as inactivity against schistosomula, but now underpins mass drug treatment programmes aimed at controlling and ultimately eradicating the disease (Fenwick *et al*., 2006; Colley, 2014). As with any mass drug administration programme there is a danger that resistance will arise. The selection for Praziquantel resistance by *S. mansoni* was first demonstrated in the laboratory by serial passage through mice treated with multiple subcurative doses (Fallon and Doenhoff, 1994), although its occurrence in the field is unclear (Stelma *et al*., 1995). The slow rate of replication of schistosomes (a minimum of about 12 weeks for one turn of the cycle) is not a protection against drug resistance arising, witness the situation with *F. hepatica* which has a similar or even slower replication rate. The drug triclabendazole was introduced in the early 1980s, but reports of treatment failure and the isolation of resistant flukes are now widespread (Kelley *et al*., 2016). Combination therapies can be adopted to circumvent the problem, but treatment of schistosomiasis is currently a monotherapy. Panic and Keiser (2018) have reviewed the topics of praziquantel usage and potential resistance. They note that the research community has been active in preclinical research to identify novel or resurrected candidates but record that 'the landscape for novel antischistosomal clinical candidates is, to put it bluntly, a desert'. The timeline from laboratory bench through clinical trials to field application calls for extreme vigilance in the mass treatment programmes to detect any signs of praziquantel resistance.

As of December 2018, the World Health Organization (WHO) estimated that preventive chemotherapy was required in 52 countries for ~100 million adults and 120 million school-aged children infected with one of the six species of schistosomes (World_Health_Organization, 2018). It is not clear if these estimates took account of the findings on prevalence reported by Kittur *et al*. (2016) and Colley *et al*. (2017); if not then the number of doses required may be appreciably higher. For 2017, WHO estimated that ~17 million adults and 82 million children were treated. For adults in particular this represented only 17% of global needs; taken together, about 45% of the global need was met. It should be emphasized that annual treatments may be required for some time to come to prevent resurgence. The good news is that since 2017, Merck has been donating 250 million tablets annually.

Pathogenesis/Pathology

It seems remarkable that Cawston (1918) did not consider schistosomiasis life-threatening or life-shortening: does that reflect

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relatively low worm burdens in the infected populations at the time? The disease was certainly prevalent in Egypt in ancient times (1250–1000BC), doubtless as a consequence of the reliance of that civilization on irrigation agriculture. Indeed, Symmers described the peri-portal pipe stem fibrosis associated with heavy *S. mansoni* infections, while working in Egypt (Symmers, 1904). As the 20th century progressed it seems probable that multiple factors generated a greater overall parasite burden, and an increased awareness of the potential serious consequences of schistosome infection. There has been a marked increase in human populations over the last 100 years, and hence a greater density of potential hosts (e.g. KwaZulu/Natal: 1.1 million in 1904 to 11.3 million in 2018; Egypt: 11.7 million in 1910 to 83 million in 2009). Over the same period irrigation schemes have been developed throughout Africa, providing ideal conditions for the expansion of snail intermediate host populations. The Gezira scheme in Sudan (1925) is an early example, while Scott reported on the effects of moving from basin (intermittent) to perennial irrigation in Egypt (Scott, 1937). He found that almost half the total population was infected with one or both species, with huge differences in prevalence between the two irrigation systems (6% *vs* 60% for *S. haematobium* in Upper Egypt). The impact of the more recent construction of the Diama Dam on the Senegal River in 1986 on increased schistosome transmission has also been documented (Picquet *et al*., 1996).

The schistosome egg is the principal agent of pathogenesis, taking around 5–6 days to develop in the tissues where it is deposited; only then does it begin to secrete the glycoproteins that trigger the host inflammatory response to the embolized egg (Ashton *et al*., 2001). That response is an essential aid to egg escape from the intestine or bladder wall since excretion is much reduced in immunocompromised animal hosts (Doenhoff *et al*., 1981) and humans (Karanja *et al*., 1997). This provides a classic example of a parasite recruiting a host immune response to its own ends. Proteases have been conjectured in egg secretions (Costain *et al*., 2018) but none were identified in proteomic analyses (Mathieson and Wilson, 2010). Approximately 90% of the secretions from live eggs comprised two proteins, IPSE and omega-1 ribonuclease (Mathieson and Wilson, 2010), and their immunogenicity was overwhelmingly associated with the glycan moiety (Kariuki *et al*., 2008). The granulomatous response that accumulates around the egg is dominated by macrophages but with other leucocytes and fibroblasts recruited. The associated immunological processes are complex (Costain *et al*., 2018) and must perform a balancing act, promoting a response that aids egg passage through the gut or bladder wall but not the fibrosis that would immobilize it *in situ*; this balance is poorly understood (Costain *et al*., 2018). However, a proportion of eggs fail to escape and remain in the tissues or travel downstream to lodge in the liver (*S. mansoni*, *S. japonicum*) or lungs (*S. haematobium*), with consequences for morbidity.

The embolized eggs are strongly fibrogenic and initiate a chain reaction of pathology (von Lichtenberg, 1987), best characterized in *S. mansoni* infections but becoming better understood for *S. haematobium*. The intensity of *S. mansoni* infection undoubtedly plays a major role in generating the severe pathology, but other factors such as genetic background may be important (Andrade, 2009). The majority of patients in a classic study from Brazil showed few symptoms, mostly related to the digestive tract (intestinal or hepatointestinal form), but in areas of high transmission up to 7% had damage to the liver, spleen and lungs (hepatosplenic form) (Coutinho and Barreto, 1969). Pipe-stem fibrosis reduces blood flow through the liver, causing portal hypertension and the development of anastomoses with the esophageal veins. These allow escape of eggs to the venous circulation and lungs, leading in turn to pulmonary fibrosis, hypertension and hypertrophy of the right side of the heart. The peri-portal fibrosis takes many months to develop (so is not replicated in the mouse model), but experiments with baboons indicate that repeated exposures, associated with TGFβ and IL-4 production predispose to its development (Farah *et al*., 2000).

The pathogenesis associated with *S. haematobium* infection is rather different and until recently has received less attention. The deposition of eggs in the urinary system is focal and residual eggs in these 'patches' have a tendency to calcification; in the ureters this can lead to obstruction of flow and hydronephrosis. However, egg deposition is not confined to the urinary system and bladder but also occurs in all parts of the male and female genitalia; female genital schistosomiasis is now recognized as a specific condition (Christinet *et al*., 2016). An important consequence of female genital schistosomiasis may be the greater susceptibility to infection by HIV and other viruses (Kjetland *et al*., 2012). The analogous male genital schistosomiasis is even less well understood, having a range of effects on sexual function and male fertility (Kayuni *et al*., 2019).

The association of bladder cancer with *S. haematobium* infection is arguably the most important pathological sequela. In a large autopsy study in Egypt, a quarter of all deaths attributed to schistosomiasis resulted from bladder cancer (Cheever *et al*., 1978). This study also drew attention to a major feature of *S. haematobium* infection, where the tissue egg burden reflects the cumulative past infection intensity, compared to *S. mansoni* infection where eggs are cleared more rapidly. *S. mansoni* and *S. japonicum* infections are not associated with cancer in the intestinal mucosa or liver so the bladder site must be an important determinant while the greater persistence of the egg as an irritant provides another component. This is comparable with the suggestion that long-term indwelling catheters may be a trigger for bladder cancer (Groah *et al*., 2002). The bladder and ureters are lined by a specialized transitional epithelium, termed urothelium, which has both a very low turnover rate and a very low passive permeability for electrolytes and other compounds. In the intact bladder this barrier excludes toxic urine constituents but can be breached in bacterial infections permitting leakage into the underlying lamina propria (Lewis, 2000). It is clear that the urothelial barrier is breached by egg excretion during chronic *S. haematobium* infection, as evidenced by the accompanying haematuria from burst blood vessels. It can be inferred that the damaged urothelium may allow greater entry of carcinogenic chemicals from the bladder lumen. Associated chronic bacterial infections, generating nitrites and nitrosamines in the bladder wall and lumen, may also be a contributory factor (Tricker *et al*., 1989).

S. haematobium-related cancers may be differentiated from non-schistosome bladder cancers by their younger age of onset, a greater male-to-female ratio and by their pathology and clinical presentation (Brand, 1979; Salem *et al*., 2011). *S. haematobium* infection predisposes to aggressive squamous cell carcinoma in contrast to the more widespread transitional cell carcinoma, for which smoking is the highest risk factor. The nature of the mechanism linking high *S. haematobium* prevalence, chronic fibrotic inflammation and the development of squamous cell carcinoma has not yet been established (Brand, 1979; Ishida and Hsieh, 2018). Recent attempts to identify transcriptional pathways by co-culture of *S. haematobium* and *S. mansoni* eggs with human cell lines, found no marked differences in oncogenesis, epithelial to mesenchymal transition and apoptosis pathways between the two species (Nacif-Pimenta *et al*., 2019). The major egg secretion ShIPSE has also been proposed as an aetiological agent due to its ability to enter host cells, and its possession of a nuclear localization motif (Pennington *et al*., 2017), but it shares those properties with non-carcinogenic SmIPSE glycoprotein (Kaur *et al*., 2011), which argues against. Whatever the cause, the capacity of *S.*

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haematobium to elicit bladder cancer is the strongest argument for not tolerating even low levels of infection in human populations, especially when fibrosis in the urogenital tract may diminish egg excretion, preventing detection of infection by urine filtration.

There can be no doubt that the introduction of praziquantel has been the great success story for schistosomiasis treatment and control, considerably reducing morbidity and causing a sharp decline in the severe life-threatening pathologies. The application of the disability-adjusted life year (DALY) concept has provided a rational method to assess disease impact (King *et al.*, 2005) and the achievement of mass treatment programmes has been to reduce overall worm burdens and hence morbidity. However, for *S. mansoni* in particular, the diagnostic deficit means that there are many individuals in endemic areas with low worm burdens, which may not cause detectable clinical disease but are still able to facilitate transmission. Recent work in East Africa suggests this may be also true for *S. haematobium* (Rollinson *et al.*, 2013; Secor and Colley, 2018).

Vaccines

An effective vaccine would be a great addition to the toolbox of control measures, not least because schistosomiasis is such a cryptic disease and chemotherapy does not prevent reinfection. The development of a vaccine against a helminth that can live for decades in the host bloodstream is *a priori* a tough proposition. In comparison with the advances in other areas, progress towards a vaccine has been painfully slow. A Medline search with the terms schisto* and vaccine reveals very little work before 1970, with an almost linear increase thereafter to a peak of 75 papers in 2015, before a downturn. We now have a better understanding of how adult worms can live in the bloodstream, yet survive immune attack (Skelly and Wilson, 2006; Wilson and Coulson, 2009). Thus far, only Bilhvax incorporating 26 kDa glutathione-*S*-transferase from *S. haematobium* underwent Phase III trials in humans, but failed to elicit significant protection in Senegalese recipients (Riveau *et al.*, 2018). Other candidates are in earlier phase human trials and results are eagerly awaited (Hotez *et al.*, 2019). In evaluating the obstacles to successful immunization against helminths, Hewitson and Maizels have pointed out that there is no reason to expect a single protein to be a sufficient target to disable a sophisticated parasite with a large number of coding genes (Hewitson and Maizels, 2014). Indeed it would be a remarkable weak spot if one could be identified. In that context, Crosnier *et al.* tested 96 cell surface and secreted schistosome proteins, expressed in mammalian cells, for protective efficiency in mice, including some candidates where protection was obtained by other groups (Crosnier *et al.*, 2019). Although the approach has worked well with *Plasmodium falciparum* (Douglas *et al.*, 2015), no schistosome antigen induced any protection in their experimental system, underscoring the problems underlying schistosome vaccine development.

Protective immunity against schistosomes can be induced in rodents and primates by radiation-attenuated cercariae, whilst both the brown rat and the rhesus macaque are able to terminate infections around 4 and 12 weeks, respectively (Wilson *et al.*, 2008; Li *et al.*, 2015). The effector mechanism of the partial protective response elicited in mice by the attenuated vaccine involves blocked migration in the lungs, likely mediated by lung stage secretions (Wilson and Coulson, 2009). Elimination of liver stage worms in the rat is associated with hepatic mastocytosis and high levels of specific IgE; more recently, nitric oxide levels have been demonstrated as a key component (Shen *et al.*, 2017). The worm antigens triggering these responses in the rat are not well explored. The rhesus macaque may be unique in its ability to eliminate established mature schistosomes, beginning about 10 weeks after infection. The mechanism appears to involve sustained immunological pressure over a period of weeks to months, manifested as a sequence of degenerative changes in the worms, involving cessation of feeding, starvation and ultimately organ failure. Multiple tegument surface and alimentary tract proteins are targets of the IgG response (Wilson *et al.*, 2008). With the advent of transcriptomic, proteomic and glycomic analysis techniques it has been possible to define a subset of proteins and glycoproteins expressed at or released from the parasite–host interface (Wilson, 2012; Yang *et al.*, 2019). However, many problems remain to be solved before a truly effective vaccine becomes a reality. These include the need to identify multiple targets and evaluate their relative contributions to protection. The formulation of those antigens in adjuvants that will elicit the desired high-intensity response, which must persist with minimal boosting from infection, is also a challenge.

Conclusions

Our understanding of schistosomiasis has advanced enormously in 100 years since Cawston's paper, so much that in 2012 the World Health Assembly endorsed measures to eliminate the disease. Indeed, the roadmap of the WHO in the same year talked optimistically about elimination in some regions by 2020. However, workers running large control programmes in the field have questioned whether current targets for elimination are realistic (Fenwick and Jourdan, 2016; Secor and Colley, 2018).

- The propensity for introgressive hybridization between the large number of animal and human schistosome species, is a future concern for schistosome adaptability.
- The goal of routine detection of a single worm pair for the diagnosis of both urinary and intestinal schistosomiaisis remains distant, leaving a diagnostic deficit to be filled.
- The introduction of praziquantel proved a game-changer but the development of resistance seems inevitable. Given the lead time for new drugs, the institution of a clinical pipeline for human trials seems prudent to avoid the collapse of control measures if/when praziquantel resistance emerges.
- Mass treatment programmes have led to the almost complete elimination of the severe pathologies, but for schistosomiasis mansoni with limited drug coverage, hepatosplenic cases are still detected, while for schistosomiasis haematobia both female and male urogenital sequelae are under appreciated.
- Work with animal models has shown that immunity to this persistent blood parasite can be acquired. However, translating that knowledge into a highly protective vaccine has proved elusive and the current focus on single 'magic bullet' antigens seems unlikely to yield the desired product. More ingenious approaches are needed.

Is it feasible to move from controlling schistosomiasis and its associated morbidities to an all-out programme for eradication, as some researchers are now advocating (Rollinson *et al.*, 2013)? In this respect we are in a similar situation to malariologists in 1955 when the Global Malaria Eradication Programme was established (Li *et al.*, 2019). It had initial successes but notably, the African subcontinent was excluded. The programme was revitalized in 2000, with more comprehensive definitions of objectives and of the interventions/surveillance systems needed to achieve and then verify the absence of transmission, before certification that a country was disease-free. A similar organizational structure is needed for schistosomiaisis and the last word in this context must go to the thought-provoking article by Secor and Colley

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(2018). They suggest that we do not yet know how to bring about a cessation of transmission, or equally important to verify that it has been accomplished. It seems very unlikely that it can be achieved by annual mass drug treatment programmes alone. These need to go hand in hand with topics not covered here: snail control; health education; sanitation. The eradication of schistosomiasis japonica in Japan shows that it can be done, even for a zoonotic parasite. However, it took 73 years from the identification of *S. japonicum* in 1904 to the last infected human detected in 1977 and many different measures plus economic development played a significant part in that success story.

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