Schistosomiasis: progress and problems

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INTRODUCTION

Schistosomiasis, also commonly known as bilharziasis, is one of the most significant parasitic diseases of humans. A report of World Health Organization in 1996 estimated that over 200 million people were infested worldwide, mainly in rural agricultural and periurban areas. Of these, 20 million suffer severe consequences from the disease and 120 million are symptomatic. Symptoms range from fever, headache and lethargy, to severe sequelae including ascites, hepatosplenomegaly and even death. More than 600 million people in the tropics are at risk for developing schistosomiasis. Schistosomiasis is the major public health problem in rural Egypt, with almost six million Egyptians are infested.

Schistosomiasis is caused by digenetic trematodes belonging to phylum platyhelminthes, super family schistosomatoida, genus schistosoma. It is usually attributed to three species, subdivided into intestinal Schistosoma mansoni and Schistosoma japonicum or urinary Schistosoma hematobium types, according to the site preferred by the adult worms. In Egypt, the two species of bilharziasis are Schistosoma mansoni and hematobium whose intermediate hosts are fresh s nails, Biomphalaria alexandra, and Bulinus truncatus respectively.

In humans, these blood flukes reside in the mesenteric and vesical venules. They have a life span of many years and daily produce large numbers of eggs, which must traverse the gut and bladder tissues on their way to the lumens of the excretory organs. Many of the eggs remain in the host tissues, inducing immunologically mediated granulomatous inflammation and fibrosis. Heavy worm burdens may produce hepatosplenic disease in schistosomiasis.

mansonii and japonica and urinary tract disease in schistosomiasis hematobium. Because both the schistosomes and the eggs utilize host metabolites, and because the host responses to the parasite are affected by its nutritional status, malnutrition may strongly affect both the parasite and the complex host-parasite relationship.

HISTORICAL REVIEW

Egyptians have had a long history of symptoms caused by schistosomiasis, notably hematuria, which appeared classically in young boys and was once deemed to be a sign of puberty. It was in Egypt in 1851 that Theodore Bilharz discovered, in autopsy material that the causative agent of hematuria was Schistosoma. In 1903, Manson observed lateral spined eggs in the feces of a patient who had no hematuria. He suggested that more than one species of the worm was involved in the vesical and intestinal forms of the disease on grounds of dissimilar geographical distribution of both types of infestation.

In 1907, Sambon verified Manson's suggestion and named the worm that produced lateral spined eggs and caused intestinal infestation as Schistosoma mansoni.

In 1915, Leiper discovered the two genera of snails in Egypt (Bulinus and Biomphalaria) that transmitted the two species S. hematobium and S. mansoni, respectively.

In 1937, Scott reported on the prevalence of schistosomiasis in 100 Egyptian Villages. At that time, S. hematobium infestations were common, while S. mansoni infestations were rare in the Nile delta. Since 1977 this pattern of schistosomiasis in Egypt changed as the prevalence of S. mansoni infestation increased and of S. hematobium decreased. This change has important public health implications, because the hepatosplenic schistosomiasis caused by S. mansoni is more difficult to trace and is associated with more morbidity and mortality than the urinary schistosomiasis caused by S. hematobium.

LIFE CYCLE OF SCHISTOSOMA-PARASITE

The three species of schistosomes that commonly affect human (S. hematobium, S. mansoni and S. japonicum) have similar life cycles and develop by a succession of stages: the egg, miracidium, first stage sporocyst, second stage sporocyst, cercariae, schistosomule and adult.
All the species of schistosomes are contracted in the same way: by direct contact with infested surface water containing free-living forms of the parasite known as cercariae, which can penetrate the skin. Schistosome cercariae consist of a tail, used for motility in the water, and a head region, which is used for attachment to host skin, and glands containing proteolytic enzymes to facilitate penetration of the skin.

During penetration of the skin, the tail is shed and several other major changes accompany transformation into a new form called the schistosomulum. After penetration of the wall of a nearby vein, schistosomula are carried in the host blood flow, eventually reaching the liver where they grow and reach sexual maturity. The mature male and female worms pair, and then, depending on species, migrate to the vessels of the bowel or bladder where egg production occurs. Many eggs pass through the intestinal or bladder wall and are excreted in the feces or urine. The schistosome lifecycle is completed when the eggs hatch, releasing free-swimming miracidia, which in turn, reinfect freshwater snails.

Rather than being excreted, however, some of the eggs may lodge in the tissues of the host. It is the presence of these retained eggs, rather than the worms themselves, that causes the pathology of schistosomiasis. In intestinal schistosomiasis, eggs lodged in the mucosa or submucosa of the gut cause granulomatous reactions, which may extend into the gut lumen as pseudopapillomas, resulting in colonic obstruction and blood loss. Eggs lodged in the liver result in portal fibrosis, leading to portal hypertension, splenomegaly, ascites, esophageal and gastric varices. Exsanguination from bleeding esophageal varices is the major cause of death[10].

DEVELOPMENT OF SCHISTOSOMA

In vitro cultivation methods can provide useful insights into the biology, nutrition and immunology of schistosomes. Among the key issues in parasite cultivation is the degree to which cultured organisms resemble their counter parts reared in normal hosts[11].

Trials to cultivate S. mansoni from cercariae have led to production of nonviable eggs by worm pairs grown entirely in vitro[11].

In 1974, Tiba et al.[12] showed that artificially prepared schistosomules can develop to maturity when injected into mice shortly after preparation. Basch et al.[13] demonstrated that 2 hour and 13 day old schistosomules grown in vitro from S. mansoni cercariae can complete normal development successfully after implantation into mouse mesenteric veins.

Clemens et al.[14] also studied the rate development of S. mansoni schistosomules in vitro, as determined by developmental milestones and thymidine incorporation into DNA.

An alternative approach, the study of egg production by pairs of mature worms maintained in vitro, has not been productive. In general, egg laying has been observed for only a few days after adult worms were transferred from the host to cultures and ceased after the 10th day[15].

In 1986, Wu et al.[16] demonstrated that the portal serum from various mammalian sources have components that stimulated S. mansoni oviposition in vitro.

In 1993, Hobbs et al.[17] established protocols for the initiation and maintenance of cultures from juvenile worms of S. mansoni. These cultures exhibited properties characteristic of the organism from which they originated and could be maintained for as long as 6 month in vitro.

The work of Taylor et al.[18] and Taylor[19] showed that in single-sex infestations, schistosomes migrated to the portal-mesentric venous system, indicating that each sex is capable of locating the preferred site independent of the other sex. Blood draining to the portal vein is derived from the gastrointestinal tract. Therefore, it is different from the peripheral blood in many respects[20]. The site preference of S. mansoni could be dependent on a constituent of portal blood that is not present in the periphery. This might take the form of a substance that the parasite recognizes or requires to develop.

It has been shown that egg production can be stimulated by portal serum components added to culture media, but not by serum from peripheral blood[21]. This occurred regardless of whether the host is a natural or not. More recently, immature schistosomes in culture have been shown to have enhanced cellular proliferation when portal serum was added to the medium. This effect could not be reproduced by serum obtained from the vena cava. Furthermore, when the serum was fractionated, the size of the stimulatory substances was estimated to be larger than would be expected for simple nutrients absorbed from the gut[22].

In experimental animals, granuloma formation has been shown to be induced and elicited by soluble egg antigens (SEA) secreted by the miracidia within eggs[23]. Over the years, several laboratories have isolated antigenic fractions from crude egg homogenates. A number of partially purified glycoproteins have been shown to possess serological, dermal, lymphocyte-stimulating, hepatotoxic, and granuloma inductive properties[24]. However, the relative importance of the various fractions as granulomatogenic agents remains unexplored. More recently, the differential
responsiveness of acute-versus chronic-infestation murine lymphocytes to a panel of SEA-derived fractions has been demonstrated. A 38-kDa fraction was found to be egg stage specific, to elicit strong lymph hokine production in vitro, and to induce granuloma formation in vivo during the acute stage of murine schistosomiasis[25].

THE IMMUNE RESPONSE IN SCHISTOSOMIASIS

The immunology of schistosomiasis is largely dependent on the biological characteristics of the parasite itself. After skin penetration, schistosomula undergo a complex migratory life cycle in the vertebrate host before they settle, in the case of S. mansoni, in the blood vessels of the portal and mesenteric system. In this intravascular situation, the adult worms release a large amount of excretory or secretory material, which elicits a strong antibody response. Antigens may be found in the serum and various body fluids in the form of free antigens, and more generally as immune complexes[1]. This continuous release of soluble antigens has important implications in the regulation of the immune response, both in terms of antigenic competition and as direct factors of immunosuppression or tolerance. The major role of antibodies in protective immunity is to induce cytotoxic destruction of schistosomula targets, and antibody-cell mediated cytotoxicity appears to be the main mechanism for destruction of parasites both in rat and human schistosomiasis[26].

The persistence of the trematodes in an immunologically hostile environment has been attributed to their ability to acquire or synthesize, during their maturation, surface antigenic determinants (host antigens) to which the animal is unresponsive[27]. The worm tegument, which undergoes a continuous and rapid turnover, acquires numerous host molecules ranging from various serum proteins or glycolipid to major histocompatibility antigens. This phenomenon has been considered as an essential escape mechanism[28-30].

It has been assumed from epidemiological studies in endemic areas that age-dependent immunity may develop against infestation, or against reinfection after treatment, with S. mansoni[31] or S. hematobium infestation[32]. Using a mathematical model, it has also been shown that predicted patterns of variation in age-related changes in the intensity and prevalence of S. hematobium infestation are consistent with the epidemiological effects of acquired immunity[33]. At present, however, there is no effective vaccine against schistosomiasis or any other human parasitic disease. In order to develop such vaccines, it is obviously important to elucidate mechanisms involved in protective immunity at the cellular and molecular levels because of the complex life cycle and stages of parasites which occur in the human body.

CLINICAL MANIFESTATIONS

Clinical manifestations reflect developmental stages of the parasites and host responses to toxic or antigenic substances derived from the parasite and eggs.

During the early stage of infestation, the patient may present with signs caused by cercarial penetration of the skin (cercarial dermatitis), followed by bronch pulmonary manifestations attributed to the passage of schistosomules through the lungs. Approximately five weeks after infestation, more dramatic symptoms, often known as Katayama Disease consist of malaise, weight loss, gastrointestinal symptoms, eosinophilia and fever. They are caused by the initial deposition of eggs by female worms[34].

In the case of S. japonicum and S. mansoni, female worms lay eggs in the mesenteric branches of the portal vein along the intestinal wall and although a relatively large part of the eggs are carried into the liver and other organs by the blood flow, the remainder of them may stay in the small venules until the embryo contain developed to miracidia within 10 days. Antigenic substances excreted from miracidia diffuse out through submicroscopic pores in the egg shell, and elicit an acute inflammation in the surrounding tissues, resulting in the rupture of the vascular wall and escape of the eggs from the venules through the intestinal submucosa and mucosa into the intestinal lumen. The inflammation causes recurrent daily fever, abdominal pain and enlarged tender liver and spleen, and discharge of eggs into the intestinal canal is accompanied by dysentery or diarrhea[35]. Blood chemistry may reveal a transient elevation of glutamic pyruvic transaminase, glutamic oxaloacetic transaminase and alkaline phosphatase 5-6 weeks after infestation. Eosinophilia may be observed in most of the patients with or without increase of leukocyte counts. Serum level of IgE may increase as observed in other helminth infestations[36].

Chronic schistosomiasis is characterized by a series of chronic inflammatory lesions produced in and around blood vessels by the eggs or their product[37]. The chronic manifestations in S. japonicum and S. mansoni infestations is characterized by hepatosplenomegaly, although development of polyps or mucosal proliferation of the intestine may also be observed in most cases. Egg granulomas are replaced by fibrotic tissues, which are prominent in the periportal areas and lead to the development of pipestem fibrosis[38].

Hepatosplenic schistosomiasis refers to the
major complication of chronic infestation with *S. mansoni* and *S. japonicum*. Hepatosplenic schistosomiasis is usually, but not invariably, associated with enlargement of the liver and spleen, and reversible hepatosplenomegaly may occur in early infestations not com plicacy by the development of portal hypertension[39].

The liver is invariably involved in intestinal schistosomiasis, but the extent of such involvement depends on many factors including intensity of infestation and duration of infestation which are mainly responsible for the changes produced. The liver gradually decreases in size, but increases in hardness as fibrosis is gradually extended into the paranchyma, resulting eventually in liver cirrhosis in severe cases. The enlarged spleen may reach the level of the umbilicus or even at times expand to fill most of the abdomen[35].

End stage hepatosplenic schistosomiasis may be complicated by features of hepato cellular failure, ascites often being the most obvious clinical sign. While this may all result from severe schistosomiasis, the possibility of other coexistent liver disease must be considered. In Nairobi, two of 25 patients cons idered to have schistosomal portal hypertension also had histological evidence of cirrhosis[39].

The portal hypertension of schistosomiasis is presinusoidal and presumably relat ed to the portal zone reaction[40]. In advanced schistosomiasis, hepatic arterial hypertension contributes to increased sinusoidal pressure[41]. Retrograde flow develops in the portal vein. Hepatic blood flow is not significantly reduced.

At the stage when hemorrhage occurs from varices, the granulomatous reaction may have subsided and the picture is predominantly that of fibrosis[42]. Portal hypertension is considered present when the portal vein pressure is raised to 5 mmHg above inferior vena caval pressure, when the intrasplenic pressure is above 15 mmHg, or when the portal vein pressure measured directly at surgery is above 30 mmHg[43]. While portal hypertension is a prer equisite for the development of a collateral circulation, in cirrhosis the risk of bleed ing cannot be directly correlated with the exact portal vein pressure, although hemo rrhage is unlikely in cases where the portal vein pressure is less than 10 mm Hg above inferior venal caval pressure[44].

Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodule formation[45]. It has followed hepato-cellular necrosis. Although the causes are many, the end result is the same.

Fibrosis is not synonymous with cirrhosis. Fibrosis may be in zone 3 in heart failure, or in zone 1 in bile duct obstruction and congenital hepatic fibrosis or interlobular in granulomatous liver disease, but without a true cirrhosis[42].

Urinary schistosomiasis is caused by *S. hematobium* and affects the genito-urinary system. The stage of oviposition is manifested by genito-urinary trouble such as cystitis, dysuria with terminal hematuria, dull suprapubic pain, sperm a torrhea and hemospermia. Spontaneous recovery is rare and the condition may be complicated by the bladder ulcer, calculi, polyps, fistulae, hydroureters or hydronephrosis or carcinomatous changes of the bladder[46].

The association of bladder cancer with *S. hematobium* has been discussed in the context of the involvement of urinary tract infestations by species of nitrate-reducing bacteria. The urine of patients infected with *S. hematobium* contained higher levels of nitrosamines, in association with nitrate-reducing bacteria, than the urine of either Egyptian or German controls, and this may result in the endogenous formation of carcinogenic N-nitrosocompounds in the urine[47].

The involvement of gynecological organs may be observed in *S. hematobium* infestation. As a disease entity, female genital schistosomiasis has been neglected, despite the fact that vaginal schistosomiasis was reported from Egypt as early as in 1899. It has generally been considered that the presence of *S. hematobium* eggs is not as common in female genital organs as in male genital organs, although in the female lesions are found in the vulva, vagina, cervix and less commonly the ovaries, fallopian tubes or uterus[48]. However, *S. hematobium* may migrate through the network of female pelvic vasculature during puberty and especially during pregnancy make ectopic localization of the parasites possible[49]. Because sexually transmitted disease increase the probability of HIV transmission, presumably through lesions in the genital mucosa, female genital schistosomiasis may be an important risk factor for tran smission of HIV[50].

**PATHOGENESIS AND PATHOLOGY**

The pathological changes in schistosome infestations are caused mainly by the de position of the eggs into various tissues and organs where granulomas or pseudo tubercles are formed around them. In primary infestations, the granuloma is composed of aggregations of mononuclear phagocytes, neutrophiles, lymphocytes, plasma cells and fibroblasts. Giant cells are also frequently observed in the granulomas. Granulomas may vary in size and cellular components with the immune status of the host in experimental infestations in immunized animals, a dominant cellular infiltration of eosinophils and lymphocytes is observed around the
eggs and the egg granuloma is smaller\cite{35}.

Granuloma formation around schistosome eggs has been considered to be the result of delayed-type hypersensitivity reactions mediated through a T cell mediated immune response to soluble egg antigens\cite{51}. However, recent studies have demonstrated that there exist at least 2 subsets of T helper cells with a CD4 phenotype, termed Th1 and Th2 cells, which can be distinguished from each other by their cytokine production\cite{52}. The cytokines derived from Th1 cells, such as IL (IL)-2, interferon or tumor necrosis factor (TNF), may be responsible for activation of macrophages and cell-mediated immunity, whereas IL-4 or IL-5, the cytokine produced by Th2 cells, stimulates IgE production or eosinophilia, respectively\cite{53}.

**DIAGNOSTIC TESTS**

Decisions on individual and community treatment, estimations on prognosis and assessment of morbidity, evaluation of chemotherapy and control measures all depend on the results from diagnostic tests. Selection and application of methods should, therefore, correspond to the type of information sought by the clinician or the epidemiologist\cite{54}.

Specific diagnosis of schistosomiasis can be made by detection of the characteristic eggs in the stools or urine under microscopic examination.

In *S. mansoni*, where eggs are excreted in feces, simple concentration and sedimentation of fecal specimens are reliable. Many concentration techniques have been described\cite{55}. These involve removal of fat, fecal debris and mucus and require more sophisticated laboratory facilities. They find their optimum use in the detection of “light” infestations where few eggs are excreted or, in some cases, eggs are excreted intermittently.

Currently, the cellophane thick fecal smear, the Kato technique\cite{56}, or one of its numerous modifications\cite{57,58} have become standard diagnostic tools in epidemiological studies. They are simple microscopic methods which examine about 50 mg of stool and are quantitative thus permitting comparisons on data.

Infestation with all human schistosome species are efficiently diagnosed through microscopic examination of minute biopsies of the rectal mucosa. Snips are taken from suspicious lesions or if absent, from the plica transversalis recti. Even in infestation with *S. hematobium*, eggs are frequently detectable in rectal snips\cite{59,60}. Since rectoscopy is an invasive technique, its application is limited to the hospital or the experienced gastroenterologist\cite{61} has, therefore, advocated rectal swabs with for patients in areas that lack these resources.

It is rarely necessary to resort to liver biopsy for diagnosing infestation with intestinal schistosomes, but where this has been done, the examination of hepatic tissue in crush preparations is more efficient than sectioning of the material. The probability of aspirating tissue that contains egg granulomas is rather low in conventional and even ultrasound-guided fine needle liver puncture\cite{62}.

Moreover, diagnosis of peripheral fibrosis is made with similar efficiency by means of ultrasonography and, therefore, does not require biopsies with histological sectioning\cite{63}. Except when carcinoma of the bladder is considered as differential diagnosis, cystoscopy and bladder biopsy seem wholly unjustified. In contrast, filtration of several 24 h urine samples is commonly available in hospital and frequently leads to the detection of ova in urine\cite{64}. Furthermore, Burki *et al*\cite{65} have demonstrated that ultrasonography compares favorably with cystoscopy and pyelography to detect specific pathology.

Indirect methods for the diagnosis depend on clinical symptoms and signs, and biochemical or immunological analyses. Especially for urinary schistosomiasis, hematuria is a suggestive sign and microhematuria or proteinuria may correlate well with the intensity of infestation in endemic areas\cite{66}.

In intestinal schistosomiasis, the repeated presence of blood in stool is indicative of high intensity of infestation\cite{67}.

Immunodiagnosis may be useful for demonstration of active or chronic schistosomiasis. A unique immunological method for the diagnosis of schistosomiasis is the circumoval precipitin (COP) test in which precipitate is formed around the eggs containing live miracidia after incubation in the serum of infected individiuals\cite{68}.

The enzyme linked immunosorbent assays (ELISA) is also widely used in diagnosis. Furthermore, ELISAs for the detection of circulating anodic antigen (CAA) and circulating cathodic antigen (CCA) in serum and urine have been developed and applied as an epidemiologic tool in a recent, intense focus of *S. mansoni* in Senegal\cite{69}. CAA and CCA in serum and CCA in urine were found in 94%, 83% and 95%, respectively, of the population of which 91% were positive on stool examination. Circulating antigens were also detectable in sera and urine of most egg-negative individuals. The sensitivities of the urine CCA and serum CAA ELISA were substantially higher than that of a single egg count and increased with egg output. The CAA and CCA levels correlated well with egg counts and with each other. The age related evolution of antigen levels followed a similar pattern to egg counts, providing supplementary evidence for a genuine reduction of worm burden in adults in spite of the supposed
absence of acquired immunity in this recently exposed community\textsuperscript{[70]}

**TREATMENT OF SCHISTOSOMIASIS**

There have been great advances in chemotherapy of schistosomiasis during the past 2 decades. Compared to antimonials, which were the only available chemotherapeutic agents for schistosomiasis from the 1920s to the 1960s, new drugs are more consistently effective, less toxic and applicable to oral rather than parenteral administration, thereby making field trials of mass chemotherapy feasible\textsuperscript{[38]}. The major antischistosomal drugs that have been or still are in use against infestation with schistosomes are metrifonate, oxamnique and praziquantel and all three are included in the World Health Organization list of essential drugs\textsuperscript{[70]}

The classification of antischistosomal drugs can now be simplified into two categories\textsuperscript{[71]}:

1-The one drug effective against all species of schistosomes infecting man (praziquantel).

2-The other drugs effective against one species of schistosomes \textit{i.e.} the monospecific drugs: oxamnique, effective only against \textit{S. mansoni} and metrifonate, used in \textit{S. hematobium} infestations.

Praziquantel is the newest and most effective drug for treating schistosomiasis occurring in man\textsuperscript{[72]}. It is effective orally in a single dose (40 mg·kg\textsuperscript{-1}) yielding 70% to 95% cure rates against all species of schistosomes infecting man. With few significant side effects and no adverse reactions on liver, renal, hematopoietic or other body functions, praziquantel is undoubtedly the most advanced in antihelminthic chemotherapy of recent decades.

The exact mode of action of praziquantel is unknown. Most evidence implicates the susceptibility of muscle and tegumental systems as important sites of action. Praziquantel’s effect on worms is very dramatic. Worms exposed to 1\textmu M praziquantel \textit{in vitro} show almost an instantaneous and sustained contraction with a half-maximal effect time of 12 sec. This contract ion results in paralysis of the parasite leading to the hepatic shift observed \textit{in vivo} which is 95% complete within 5min after a single oral dose for infested mice\textsuperscript{[73]}

The effect of praziquantel on worm muscle tension seems to result from the ability of the drug to increase the permeability of the worm muscle cells to calcium ions. Praziquantel also, causes severe destruction of the worm’s tegument\textsuperscript{[74]}

Recently, however, the possible existence of an \textit{S. mansoni} isolate tolerance to praziquantel has been reported from Senegal where the parasitologic cure rate 12 weeks after treatment was as low as 18%\textsuperscript{[75]}. The tolerance of the Senegalese isolate to praziquantel may be defined as tolerance, indicating an innate insusceptibility of a parasite to a drug to which it has never been previously exposed\textsuperscript{[76]}. In contrast, a genetically transmitted loss of susceptibility in a parasite population that was previously susceptible to a given schistosomicidal drug has been termed resistance\textsuperscript{[70]}. Indeed, in recent work carried out in Egypt, where praziquantel has been extensively used, it has been demonstrated that a small percentage (1%-2.4%) of villagers may harbor parasites which cannot be killed even after repeated administration of high doses of praziquantel\textsuperscript{[77]}. When isolates obtained from these uncured individuals were examined in the mouse model, the ED\textsubscript{50} values of the isolates were found to be 3 times higher than that of one reference control isolate\textsuperscript{[76]}. The reduced susceptibility of \textit{S. mansoni} to praziquantel in infected human populations has important implications for current schistosomiasis control programs.

Oxamnique is widely used in the treatment of infestation due to \textit{S. mansoni}. It is a well known, highly useful drug for the treatment of all forms of \textit{S. mansoni} infestation including many complicated syndromes\textsuperscript{[78]}

Recent studies showed that oxamnique irreversibly inhibits nucleic acids and protein synthesis in adult worms. Male were more susceptible than females to the drug and showed a higher degree of inhibition of protein synthesis\textsuperscript{[79]}

Metrifonate, an organophosphorus cholinesterase inhibitor, is used for the treatment of urinary schistosomiasis. Metrifonate, like other organophosphorus compounds, inactivates the enzyme that destroys acetylcholine. Because this action allows the chemical neurotransmitter to persist, cholinergic symptoms might be expected during treatment. These include fatigue, muscular weakness, abdominal colic, nausea, diarrhea and vomiting. All of these symptoms are a reflection of stimulation of cholinergic synapses in the autonomic nervous system, ganglionic sites in both parasympathetic and sympathetic divisions, the neuromuscular junction and several sites in the cardiovascular system\textsuperscript{[71]}

**CONCLUSION**

In conclusion, control of schistosomiasis is not an easy task. Even after successful treatment, reinfection easily takes place in most of endemic areas, unless transmission is cut off somewhere between the intermediate hosts and the final hosts in the life cycle of the parasites.

Much work has concerned the immunopathology of the disease, particularly granuloma formation. Although the granulomas contribute significantly to the pathology, they does
see to protect the host liver from the toxic secretion of the egg. Reduction in granuloma size, without affecting its protective function, would seem to be a desirable aim. A number of approaches are currently under investigation, including the use of live cercariae and schistosomules, and the use of more or less purified antigens.

A wide range of approaches are being taken towards the development of an effective vaccine for schistosomiasis. These range from basic research into schistosome biology through to human epidemiological and immunogenetic studies, construction of a variety of different types of vaccine including native or recombinant proteins, peptide constructs and nucleic acid vaccines, as well as vaccination trials utilizing these in experimental animals ranging from mice to water buffalo. Taken together, the breadth of research into schistosomiasis vaccine development is substantial. Hopefully, these efforts will result in a successful outcome.

Schistosomiasis can be treated with relative ease today since a number of good drugs, several of which are taken orally, have become available. The response to some of the drugs may differ markedly according to geographic location. The emergence of poorly susceptible (tolerant) strains is an area of concern, and that deserves further research to develop new agents for control of the disease.

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