The Six Diseases of WHO

Schistosomiasis: some advances

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In man schistosomiasis is caused by three main trematode species, *Schistosoma mansoni*, *S haematobium*, and *S japonicum*. Other species that infect man are *S intercalatum*, *S mattheei*, and *S mekongi*, and various mammalian and avian schistosomes that do not complete their life cycles in the human host but may cause cercarial dermatitis or "swimmer's itch." Some 200 million people are probably infected with schistosomiasis and 500-600 millions exposed to the risk of infection. The disease has a widespread distribution in Africa and the Middle East (*S haematobium* and *S mansoni*) and in the Western hemisphere (Brazil, Venezuela, Surinam, and certain Caribbean islands) for *S mansoni*. In the Far East, China, the Philippines, and Indonesia are endemic areas of *S japonicum*, and limited foci have also been recorded in the Mekong and now in Malaya (*S mekongi* and *S japonicum* respectively).

Schistosomiasis is predominantly an infection of rural and agricultural communities, with some periurban distribution in many countries. Usually, poor quality housing, substandard hygienic practices, and a complete absence of sanitary facilities exist in these places. Children are an important reservoir source of infection as they contaminate fresh water through indiscriminate urination, while pollution of water with faeces as the result of inadequate sewage disposal is a critical factor in maintaining transmission of *S mansoni* and *S japonicum*. Schistosomiasis is an occupational hazard for fishermen, peasant farmers, and agricultural workers in developing countries, but other activities may also result in water contact and transmission, including domestic, recreational, and religious practices.

In the past decade many programmes for developing water resources have been established in endemic areas with a pronounced concomitant increase in prevalence and intensity of schistosomiasis. The creation of man-made lakes and the introduction of new irrigation schemes or the extension of existing ones in endemic areas, or in ones close to existing transmission foci, are important factors in the spread of the infection.

The basic life-cycle is complex entailing an alternation of generations with the sexual generation of adult schistosomes in the definitive vertebrate host and an asexual multiplicative stage in a molluscan host. The pathology of infection in man may be profoundly influenced by different patterns of exposure to cercariae, partly because of differences in immunological responses.

The adult worms may live for 20-30 years, but the mean duration of life span is probably much shorter (three to eight years). Each worm pair, according to the species of schistosome, produces 300 to more than 3000 eggs a day. As is the case with most helminths, the schistosomes do not multiply in the definitive host, and in terms of host-parasite populations this means that the infection process produces, or tends to produce, an overdispersed distribution of parasites within the host population, in which most individuals carry few parasites and a small proportion are heavily infected.[1 2] In schistosomiasis, even if the proportion of those with infections of high intensity is low, morbidity may be appreciable.[3]

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Pathology

Three disease syndromes are associated with schistosome infection: dermatitis, which results from cercarial penetration of the skin and is due to hypersensitivity reactions of both the immediate and delayed types; Katayama fever or acute schistosomiasis, which occurs in intense initial infection and usually coincides with the onset of egg laying by the worms, being considered to be a form of serum sickness or immune complex disease; and chronic schistosomiasis, in which lesions in different organs are dependent on the main egg-laying sites of the adult worms. The major parasite factor responsible for the occurrence of chronic disease is the egg. The host granulomatous response to the eggs, which, at least in *S mansoni* and *S haematobium*, is a form of delayed hypersensitivity, plays an essential part in the pathogenesis of the various schistosome syndromes. The development of large granulomas around the eggs causes the destruction of tissue, which heals with consequent scarring, and the development of important pathological changes is related to the intensity of infection, but also the intensity of host response. *S mansoni* and *S japonicum* are found in the portal and mesenteric vessels and disease mainly affects the gut and liver. *S haematobium* is found in the vesical plexus and disease affects the urinary tracts, genital tract, and lower bowel. The lungs may be affected when large numbers of eggs reach the organ through collateral circulation, and the central nervous system, when worm pairs are in situ.[3 4]

Epidemiology

Epidemiological, pathological, and quantitative necropsy studies have established that egg output accurately reflects intensity of infection (worm burden), being measured in the field either as eggs per gramme of faeces (*S mansoni*, *S japonicum*) or eggs per unit volume of urine (*S haematobium*). Egg output appears to be independent of the age of the host or the schistosomes, and is closely related to the number of worm pairs that the host carries. Hatchability of eggs may decrease, however, with the age of the host. Age-intensity curves are similar to age-prevalence curves but fall more sharply with age. The two indices prevalence and intensity are related and, generally, populations with high prevalence of infection tend to have high intensity.[5]

There appears to be a direct linear relationship between

intensity of infection and clinical disease. The linear relationship of hepatosplenic disease to intensity has been derived for *S mansoni* from data obtained in Puerto Rico, Brazil, and St Lucia.[6] This correlation is, however, less positive for similar data obtained in Kenya and in other African areas, and further studies are necessary.

Most infected individuals in a population harbour few parasites but a small proportion are heavily infected and are thus responsible for excreting the bulk of eggs and causing most of the contamination in the environment. In one case, for example, 6% of a population was found to excrete 50% of the eggs.[7] Such data may be of direct relevance in the development of control strategies such as "targeted" or "selective treatment" of the heavily infected.[8 10] Such an approach may be highly effective in preventing disease in high-risk groups, but its value in controlling transmission is uncertain.

Progress in control

Compared with some other communicable infections, progress in controlling schistosomiasis during the past 25 years has been relatively slow. This is attributable, in part, to the inadequacy of control measures for large-scale use and, in part, to the failure to appreciate the public health importance of schistosomiasis earlier, and therefore to accord it appropriate priority in public health programmes. It is vitally important to establish the relative importance of schistosomiasis to other health problems, and such analyses are essential to public health planning and to the rational allocation of resources for this purpose. While it has been recognised for some time that certain parasitic diseases may constitute a serious economic burden in developing countries, the attempts made so far to measure their economic significance, and the economic benefits that might accrue from their control, have been generally inadequate and of doubtful practical use for planning purposes.[11]

The economic assessment approach may not be applicable to all aspects of public health where other relevant factors may be considered, but its value in support of decision making must be appreciated. While some consider that this is attempting to measure the immeasurable, others are equally convinced that sufficient evidence of disease and social consequences caused by schistosomiasis exist in many areas to warrant the implementation of control measures and justify the requisite resources to support them.[12]

Recent advances

In epidemiological measurements the development and refinement of quantitative egg counting techniques have advanced, including the introduction of quality control procedures.[13 14] Quantitative techniques to examine stools now include modifications of the Kato method—that is, the quick Kato method and the Kato/Katz method—and nucleopore filtration of urine specimens has been developed.[15] There have also been developments in immunodiagnosis, and radioimmunoassay and enzyme-linked immunosorbent assay (ELISA) are promising.[16 17] Both tests require standardisation, however, and their further evaluation is needed. The use of new or improved techniques are giving more precision in epidemiological measurements, and recent studies have clarified the meaning and interpretation of epidemiological indices and of their implications in control programmes. Thus changes in prevalence and intensity of infection may be useful in assessing the effects of intervention in control programmes; it is, however, necessary to distinguish between such changes in a cohort (same individuals) and changes in an index group (different individuals).[18]

There is continuing interest in the development of epidemiological models of schistosome transmission and their relevance to control strategy.[10 19] Future progress will depend, however, on greater use of recorded data, and consideration of seasonal variation of transmission, immune phenomena and differences in the epidemiological characteristics of endemic circumstances.

During the 1960s the use of molluscicides provided the only reliable approach to control of schistosomiasis. During the present decade, however, integrated methods directed against different links in the life cycle are most likely to achieve rapid control, but the composition of any control programme must necessarily vary in the emphasis placed on one or more different approaches according to local conditions, the goal of the control effort, available resources, and a feasible strategy. There are occasions, however, where funds are limited and where a large measure of worthwhile benefit, such, for example, as "disease prevention," could be obtained by applying a single control approach through "selective" or "targeted chemotherapy," but this must be determined in relation to local considerations.

There is ample evidence that area-wide molluscicide is now successfully controlling snails in major control programmes—for example, in Egypt and China—and that control of transmission based on the essential focality of transmission in many areas (St Lucia, Ghana, Yemen, and Saudi Arabia) is also being successfully prosecuted by killing snails and surveillance. More adequate strategies and delivery systems are, however, desirable to optimise the cost-effectiveness of molluscicide but it is considered that this approach will play a vital and continuing part in the integrated control of schistosomiasis.

The recent advances in epidemiological knowledge and techniques already discussed, together with the advent of new safe highly efficacious schistosomicides, however, must be regarded as the most important events in the development of new schistosomiasis control strategies. These new drugs have appreciably increased the prospects for using population based chemotherapy in controlling transmission and for more direct disease prevention. They include:

Metriphonate (*Bilarcil*), which although only effective against *S haematobium* is very cheap and of low toxicity; the studies of Davis and Bailey[20] confirmed that the optimum individual dose was 7·5-10 mg/kg and a widely used schedule of 7·5 mg/kg, given in three oral doses at intervals of 14 days, has become the standard treatment regimen; cholinergic symptoms may be expected during treatment, but tolerance has been extremely good, and such symptoms, if they occur, are mild and disappear spontaneously in a few hours; high cure rates and substantial reductions in egg output have been reported in selective population chemotherapy programmes; the drug is extensively used in Egypt and elsewhere.

Oxamniquine (*Mansil*, *Vansil*), which is highly effective against *S mansoni* only, being administered as a single oral dose with few side effects has been used clinically in the treatment of acute, subacute, chronic, and complicated cases of *S mansoni* infection with excellent results; in the Western hemisphere, a single oral dose of 15 mg/kg bodyweight in adults produces high cure rates, but in children under 30 kg in weight the optimum regimen is a total dose of 20 mg/kg given in two divided doses of 10 mg/kg at a four to six hour interval; in Africa total doses of 40 and 60 mg/kg administered over two or three days have been found necessary to obtain good therapeutic response; even if parasitological cure is not achieved, egg output is appreciably reduced by 80-90%; the drug is very suitable for population-based chemotherapy and is being widely used in S America.

Praziquantel (*Biltricide*), which is highly effective against all human schistosome species, is unquestionably a major advance in the chemotherapy of the disease; it is highly effective when given in a single oral dose of 40 mg/kg bodyweight for *S haematobium*; for *S mansoni* in a single dose of 40 mg/kg or 2×20 mg/kg at an interval of four hours in one day; and for *S japonicum* the present recommended regimen is 2×30 mg/kg at an interval of four hours in one day or 3×20 mg/kg in one day; the available evidence shows that patients with advanced disease from infection with *S japonicum* or *S mansoni* with ascites or portal hypertension tolerate the drug very well, which offers an optimistic outlook for the future treatment of advanced cases.[21 22]

Other available methods of control reduce transmission

without any direct effects on the human worm load, but chemotherapy reduces egg output and thus reduces transmission. Further, by killing worms in the treated individual the risk of morbidity and mortality due to disease is reduced, and the patient is enabled to recover from reversible lesions. Chemotherapy, therefore, achieves "primary" and "secondary" control of schistosomiasis. The goal of primary or transmission control should be to reduce the egg output, of as large a proportion of the infected population as possible, to zero within the limits of drug toxicity, cost, and possible effects on immunity. As the intensity of infection rises, the severity of schistosomiasis increases, but many patients with low rates of egg excretion show severe lesions. It is therefore considered desirable to treat all infected individuals to achieve maximum secondary or disease control. Where operational constraints exist, however, priority should be given to the heavily infected or high-risk groups, such as school children, with targeted treatments.[18]

Clearly much more information is required about the relative merits of different treatment regimens such as "mass treatment" (treatment of an entire community); "selective population chemotherapy" (based on examination of the community, followed by treatment of infected individuals); or "targeted chemotherapy" (treatment of high-risk groups only, after diagnosis); what will be the effect on transmission of treating only "high-risk" groups of the population; and what are the effects of treatment on acquired immunity, and should this be considered in formulating treatment policy? More investigations are required into the most appropriate timing of chemotherapy to stop transmission in relation to the bionomics of local snail intermediate hosts, and of the desired frequency of chemotherapy campaigns in relation to local transmission dynamics. The development of schistosome resistance to any individual compounds, and cross-resistance to others, must also be monitored and surveillance of long-term drug effects must be made if periodic campaigns are to be used in a future long-term maintenance strategy.

Clearly chemotherapy will be a major component of control programmes over the next decade, both as a single measure and integrated with control of the snails by molluscicides. Complementary control of habitats by environmental changes and engineering, requiring medium to long-term planning and execution (together with improved water supplies, sanitation, and health education) must, however, also play an important part in consolidating many long-term maintenance strategies.

Vaccines

The development of safe and effective vaccines preventing infection and disease would provide the most effective approach to control. A vaccine is, however, not currently available, although one consisting of highly irradiated cercariae may be the first practical vaccine and has the potential of being available within a decade.[23] Cercariae attenuated with high doses of irradiation have conferred substantial resistance in animals with few undesirable effects, and such vaccines can be cryopreserved. There is also much basic research effort going into unravelling the complex immune mechanisms concerned in immunity to schistosomes, and this may eventually lead to the development of inactivated vaccines containing highly purified antigens.

In addition to the "conventional" types of vaccines, which are intended to limit the numbers of schistosomes developing from cercarial challenge infections, another type of "vaccine" is also under consideration—the "antipathology" vaccine.[24] This approach aims at reducing the harmful delayed hypersensitivity responses to egg antigens by injection of purified egg antigens.

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Is it safe to refreeze deep-frozen food that has been thawed?

It is one of the precepts of good food handling practice *not* to refreeze deep frozen foods that have thawed. There is usually some loss of food quality when frozen foods are refrozen after thawing, but the principle reason for this advice concerns microbiological safety.[1] While freezing usually results in a substantial loss in the numbers of bacteria in the vegetative stage it has little effect on spores.[2] Deep-frozen foods are, therefore, not sterile. If they are allowed to reach temperatures above 0°C and thaw out there is the possibility of bacterial growth, which would make the food unsafe to eat. The general rule is subject to some exceptions—fruit products may be refrozen as may packaged flesh foods and vegetables if the packing is undamaged and some ice is still present.[3] If, however, there are any doubts about the integrity of the package or the presence of ice the material should be discarded. If a food does not contain pathogenic organisms it would, in principle, be safe to refreeze after thawing but in normal use this information is not available, and the general rule that deep-frozen food should not be refrozen once thawed is sound.—D A T SOUTHGATE, nutritionist, Norwich.

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