

SCHISTOSOMIASIS: PAST, PRESENT AND FUTURE

KENNETH S. WARREN

Health Sciences Division The Rockefeller Foundation, 1133 Avenue of the Americas, New York, NY 10036, USA

On this occasion, combining an international symposium on schistosomiasis with the first Brazilian national meeting on the greatest of all helminth diseases, I would like to emphasize the international nature of the problem. Invited speakers at this meeting are from Israel, USA, Venezuela, England, Denmark, France, Egypt, Kenya, Switzerland and China as well as Brazil. In my own career in schistosomiasis, which now spans three decades, I have worked at length on schistosomiasis in the USA, England, Brazil, St. Lucia, Kenya, Egypt, the Philippines and China. Schistosomiasis is endemic throughout most of Africa, and many countries of the Middle East, the Caribbean, Latin America and Asia. It is variously estimated to infect between 100 and 200 million people, and is believed to be the most important of the helminth infections of man. Approximately thirty years ago, at the height of the malaria eradication campaign, Asa Chandler in his Introduction to Parasitology (John Wiley & Sons, New York, 1961) claimed that "Schistosomiasis is today the most important human disease caused by animal parasites". He added, "In spite of intensive research there's still no easy means of control, and the extension of irrigation projects and concentration of human populations are increasing its distribution and intensity". These statements contain an important lesson. We can never be complacent no matter how good our tools for controlling parasites and vectors appear to be. Schistosomiasis has again become number 2, because malaria has forged ahead through the combined resistance of the parasites to antimalarial drugs and the mosquito vectors to insecticides. Thus, the world must continue its pitched battle against these scourges of mankind.

The international nature of this research effort is exemplified by the scientists gathered here who are dedicated to increasing our understanding of these complex organisms and devising new, better and more specific weapons to treat, prevent and control them. Historically, it should be noted that schistosomiasis was discovered by a German pathologist working at

an Egyptian hospital. The life cycles of the three major schistosome species infecting man were elucidated by Japanese and English scientists. An exhaustive computerized bibliography of schistosomiasis which covered the first 110 years, from its discovery in 1852 through 1962, included approximately 10,000 papers in 27 different languages. A follow-up bibliography covering an additional 12 years revealed the further output of about 5,700 papers. Since then the number of papers has continued to increase at an accelerating rate.

While there have been some advances in our knowledge of the parasites themselves in the last 30 years, the great efforts of the past on all stages of the life cycle have provided us with an enormous fund of knowledge. In the last two decades, major advances have occurred in the areas of pathogenesis, clinical status, immunology, diagnosis, treatment, ecology and epidemiology, all leading to more cost-effective strategies for the control of schistosomiasis.

Pathogenesis

Beginning with the discoveries of Bilharz in 1852, the pathogenesis of the chronic forms of schistosomiasis effecting the urinary tract, liver, intestines, lungs and central nervous system has been ascribed to the schistosome eggs lodged in the host tissues. In the 1950s, however, scientists in Latin America and Africa suggested that eggs were not the principal cause of hepatosplenic disease and implicated dead worms or toxins produced by living worms. Exponents of the dead worm theory even suggested that anti-schistosomal treatment would exacerbate the disease. In the 1960s a series of studies on a murine model of hepatosplenic disease revealed that eggs were clearly the primary cause. It was later shown that eggs alone did not block liver blood flow and that the host granulomatous response to them was an essential pathogenetic factor. Studies of the granuloma both *in vivo* and *in vitro* revealed that this inflammatory response was an immunological reaction of the delayed hypersensitivity or cell-mediated type.

This led to the concept that schistosomiasis is essentially an immunological disease. The immuno-modulation of granuloma formation was then demonstrated in chronic infection and was later associated with amelioration of hepatosplenic disease.

The dynamic nature of the pathogenesis of schistosomiasis was revealed showing that the development of disease is related to the number of eggs produced by the worms and the rate of their destruction in the tissues of the host, the induction of granulomatous hypersensitivity and the rate of its suppression or modulation, and the balance between the rate of collagen synthesis and degradation. Studies of these reactions in the tissues of experimental animals and man then elucidated the unique pathophysiology of hepatosplenic disease in which total liver blood flow remains normal in the presence of portal venous obstruction and hypertension. This was shown to be due to neovascular formation in the fibrous tissue resulting in the arterialization of the liver. The dynamic processes involved in the development of hepatosplenic disease also suggested that it might ameliorate following treatment when egg production ceases, inflammation recedes, and collagen degradation exceeds production. This explains recent observations in both Brazil and Kenya of the decline of hepatosplenomegaly following treatment of patients with advanced disease.

Clinical Disease

The epitome of chronic schistosomiasis *mansoni* is hepatosplenic disease with liver enlargement, portal hypertension, splenomegaly and esophageal varices, the etiology of which is described above. Pure uncomplicated cases have normal liver function tests and do not display the clinical signs and symptoms of hepatocellular dysfunction seen in cirrhosis of the liver.

In addition, a variety of other signs and symptoms have been described in patients with chronic schistosomiasis. Chief among these are fatigue, inability to work, and symptoms related to intestinal involvement including diarrhea, dysentery and abdominal pain. It is interesting to note, therefore, that studies at the village level in Uganda, St. Lucia, Brazil, Kenya, Liberia, Ethiopia, the Philippines and China have revealed that chronic schistosomiasis *mansoni* and *japonica* are much more

benign than originally believed. All of these studies were done with quantitative measures of intensity of infection. In spite of high egg counts in many of the areas studied, there was little evidence of fatigue, diarrhea, dysentery and abdominal pain, these being seen largely in the small proportion of patients with heavy infections, many of whom also displayed hepatomegaly and splenomegaly. Recent hospital-based studies in London of patients with schistosomiasis have also revealed the remarkable lack of generalized and abdominal symptomatology.

Immunology

The immunology of schistosomiasis covers the areas of immunodiagnosis, immunopathogenesis and immunity, including the development of vaccines. Thirty years ago, research was dominated by studies of immunodiagnosis, involving both serological and intradermal tests. Investigations a decade later began to question the sensitivity and specificity of these methods and they are little used at present. Simple quantitative methods of parasitological diagnosis have superseded them and will be discussed below. Immunodiagnosis is still alive, however, and methods are being developed involving purified antigens, monoclonal antibodies, rapid test systems that can be used in the field, immunoblotting and nucleic acid hybridization. In the last few decades the immunopathology of schistosomiasis has been intensively studied as described above. Not only have the mechanisms of induction and suppression been elucidated, but the egg antigens responsible for these reactions have been isolated. For the future, it is possible that an anti-immunopathology vaccine will be developed which will induce the responses that modulate granuloma formation and thereby prevent the development of severe disease.

The presence of immunity or specific acquired resistance to schistosomiasis has long been accepted by the community of workers in this field. One of the most striking expressions of this belief was published in 1963, "Clinical data from human infections give almost irrefutable evidence of man's acquired immunity. The fact that man lives at all under conditions of constant reexposure such as those experienced by the Egyptian fellaheen and the rice farmers of the Orient who have been in almost daily contact with cercaria-containing water since

childhood, truly indicates an acquired resistance to infection". In spite of this impression, however, there was little direct evidence for immunity in either man or experimental animals. Human exposure experiments performed in the Belgian Congo, Ghana and Rhodesia suffered from severe design flaws. Furthermore, carefully designed passive transfer studies of both humoral and cellular immunity in St. Lucia have provided negative results. Recently, ecologically controlled projects in both Kenya and Brazil have provided evidence of some degree of resistance to infection after prolonged exposure.

For many years, studies of immunity in experimental animals were also equivocal. While immunity was observed in non-permissive hosts such as the rat and rhesus monkey (both of which show self-cure phenomena), it was only within the last decade that immunity has been consistently and unequivocally demonstrated in permissive murine hosts by methods such as passive transfer. The advent of techniques of killing of schistosomula *in vitro* by cells and serum has revealed many putative mechanisms by which human and experimental animal hosts attack the parasites. The cells involved include eosinophils, neutrophils, macrophages and platelets and the humoral factors include IgG, IgM, IgE and complement.

Immunologists working on schistosomiasis now believe that the development of vaccines is not only possible but is inevitable. Not only has passive transfer of serum from chronically infected animals been shown to be protective but monoclonal antibodies also are effective. These have been used to identify and isolate antigens which induce active immunity. The variety and types of immunity inducing antigens identified by at least 10 different laboratories in France, Germany, Switzerland, England, USA and Brazil is indeed remarkable. They include not only surface antigens, but enzymes such as hemoglobinase and glutathione S-transferase, and structural proteins such as paramyosin. These antigens can now be produced in large amounts by genetic engineering via schistosome cDNA and genomic libraries and the identification of putative antigens by monoclonal and polyclonal antibodies and by nucleic acid hybridization. Protection has been produced not only by antigens, but by anti-idiotypic antibodies. Antigens with homology to proteins in snails and the keyhole limpet

have been shown to be protective. While levels of protection hover around 50%, it is expected that "cocktails" of different antigens, and the induction of cell-mediated immunity with antigens and adjuvants and non-specific immunity with immunostimulants, will provide a much higher degree of resistance to reinfection.

Diagnosis

A crucial factor in the diagnosis of schistosomiasis is the determination of the intensity of infection. This is essential not only for determining the treatment of individuals, but for devising strategies for preventing disease in populations and monitoring control systems. The development of simple and rapid quantitative parasitological egg counting methods such as the Kato and Peters techniques, respectively for fecal and urine examination, has been a major breakthrough. It is worthy of note that while these methods may not detect exceedingly low levels of infection, such infections are unlikely to be associated with disease (with the rare exception of central nervous system involvement) or with significant transmission of infection.

Treatment

The first major antischistosomal drug was tartar emetic discovered in the Anglo-Egyptian Sudan in 1916. It is only in the last 20 years that this lethal drug, which requires multiple intravenous injections, has been rendered obsolete. It has been said that perhaps more people have been killed by tartar emetic and similar antimonial compounds than by schistosomiasis itself. Since then we have used an intensely mutagenic compound and another which suppresses cell-mediated immunity for weeks. In the last decade we have attained the age of miracle drugs for trematode infections, particularly praziquantel. These compounds have revolutionized both the treatment and control of this great parasitic disease. A concern for the development of resistance to antischistosomal drugs, and the lessons we've learned from malaria suggest that we must continue to search for more and better compounds.

A new era for pharmacology has been ushered in by the development of molecular biology. Thus, key parasite enzymes can be cloned and sequenced. The three dimensional structure of these molecules can then be

determined by x-ray crystallography, nuclear magnetic resonance spectroscopy and computer simulation. Then drugs conforming to the structure of the enzyme combining sites can be designed. One such possibility was suggested by the investigations presented by an Israeli scientist at this meeting. She has isolated *S. mansoni* acetylcholinesterase, cloned and sequenced it, and demonstrated that antibodies raised against this antigen will kill schistosomes. But it should also be recognized that one of the best and cheapest drugs now available for schistosomiasis is an anticholinesterase, metrifonate. One enigma has been the fact that this drug is effective only for *S. haematobium*. Knowledge of the tertiary structure of the enzymes for *S. mansoni*, *S. japonicum* and *S. haematobium* should enable the design of better drugs for all of these organisms.

Ecology, Epidemiology, Control

These three areas are presented as one because they are intimately interrelated. A major conceptual breakthrough was a mathematical simulation by an English parasitologist in 1971 describing the negative binomial distribution of helminth parasites in host populations. This concept, which reveals that for organisms which do not multiply in the definitive host, i. e. man, only a very small proportion of infected individuals harbor heavy worm burdens. Field studies quickly confirmed this distribution in schistosomiasis and revealed that only those with heavy infections develop hepatosplenic disease. These observations then led to the development of a key strategy for the control of schistosomiasis which has been called targeted mass treatment or selective population chemotherapy which will be described below. It is worthy of note that similar observations in the Rockefeller Foundation's global campaigns to control hookworm in the early 1920s resulted in the development of chemotherapeutic control measures directed largely toward heavily infected school children.

A major integrated analysis of the ecology of schistosomiasis was carried out on the island of St. Lucia in the 1960s and 70s. This, in conjunction with studies from all over the world, have clearly suggested that individuals in highly endemic areas are not constantly exposed to large numbers of infectious organisms. In terms of the life cycle of schistosomiasis,

under most conditions only a very small percentage of snails (usually less than 1%) are infected. Cercariae are produced only at certain times of the day, and under natural conditions remain highly infectious for only a few hours. Furthermore, they are widely dispersed in large volumes of water. *S. mansoni* cercariae take approximately 10 minutes to penetrate the skin and if drying occurs before then, they are killed. There is a good correlation between degree of water exposure and intensity of infection. Studies not only in St. Lucia, but in Ghana and Kenya have shown that, in general, children have the highest degree of water exposure and intensity of infection. Finally, in the last two decades, investigations of migrant populations and those in areas where control measures have been instituted have reduced the mean life span from 20 to 30 years to less than 5 years, indicating a relatively rapid turnover of the parasites in the host. All of these studies suggest, therefore, the targeting of control efforts toward the small proportion of highly infected individuals. Aside from occupational exposure, these individuals are usually school-aged children.

The St. Lucia study, which lasted for 16 years, went on to examine three different means of controlling schistosomiasis—molluscicides, water supplies and sanitation, and treatment. The end results clearly showed that treatment was by far the most effective and least costly means of controlling schistosomiasis. In spite of these results, which were confirmed elsewhere, the World Health Organization (WHO) maintained a highly costly multi-disciplinary approach to the control of schistosomiasis for many years. In the last decade this strategy was adopted by the Brazilian government in its massive attempt to control schistosomiasis at a cost of \$250 million. Recently, WHO has changed to a strategy of morbidity control dependent largely on chemotherapy.

The concept of control of schistosomal disease rather than infection brings together virtually all of the ideas presented in this paper. Thus, the pathogenesis of schistosomiasis, though complex and involving a variety of host responses, requires the presence of heavy infections. The modulation of immunopathology as well as the presence of partial resistance to reinfection support the effects of chemotherapy in limiting both the intensity of

reinfection and the degree of host-mediated inflammation. The study of clinical disease in field populations reveals that there is little morbidity of any kind except in those with heavy infections. New methods of parasitological diagnosis enable the rapid determination of those with heavy infection. New "miracle" drugs allow treatment with a single oral dose with negligible side effects. Molecular biology should facilitate the design of even better drugs as well as effective vaccines. The studies of ecologists and epidemiologists have suggested a negative binomial distribution of infection

and disease. They have also shown a slow rate of infection and reinfection in populations which is related to the degree of water contact, and a relatively rapid turnover of worms. All of these investigations have resulted in a new cost-effective strategy for control of morbidity. The effectiveness of this strategy has been confirmed in field studies in Africa and in Brazil where it has been shown that treatment not only results in amelioration of hepatosplenic disease thereby constituting good therapeutic medicine, but also prevents its development thereby constituting excellent prophylaxis.