V International Symposium on Schistosomiasis

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Why the International Schistosomiasis Symposia?

Zilton A Andrade

Opening Address

We are here assembled for the V International Symposium on Schistosomiasis. We are people interested on a particular subject, who came from different areas of Brazil and from abroad. About one year ago China, another country where the disease is also endemic, organized its I International Symposium on Schistosomiasis. Several similar symposia have been organized in Egypt, the last one quite recently.

Since the direct aim of such Symposia is not to establish public health policies, nor to draw the lines for a control program to government agencies, we might as well wonder from where comes the motivation for such meetings.

Schistosomiasis is a parasitic disease that presents a well known transmission cycle. Its epidemiological cycle contains weak points which could be easily blocked if public health authorities in endemic countries would be willing to concentrated efforts on prophylaxis. Schistosomiasis is a disease that can be cured with highly specific and effective drugs, administered by mouth in one single dose, practically without contraindications. Even in its advanced stage, with extensive hepatic fibrosis and severe destruction of the intrahepatic portal vein system, drug treatment can benefit the patient. Medical resources to deal with this disease are therefore available. Schistosomiasis now ranks with intestinal helminthiasis as the most easily curable parasitic diseases. The situation of schistosomiasis in Brazil now is highly illustrative of the fact that medical resources alone are not sufficient to control endemic diseases which are rooted in socio-economical problems.

Why are we now and again involved in an international symposium on schistosomiasis?

Perhaps for the same reason that some national and foreign agencies are giving financial support to studies on schistosomiasis. The WHO TDR Programme includes schistosomiasis among its six priorities. For several years the Rockefeller Foundation's "Great Neglected Diseases" Program maintained schistosomiasis as a main target for research. The Edna-Clark Foundation gave great stimulus to the studies leading toward a vaccine against schistosomiasis. Similar studies are constantly being supported by the American NIH, the Brazilian CNPq and FINEP, etc. Why such everlasting interest over a parasitic disease that has already disappeared from several endemic areas of the world regardless of official medical measures, but simply by the advent of socio-economic improvement?

If we ask such question at blank point to the people gathered in this room tonight, the main answer probably would be: because there are numerous people still infected with schistosomes. That is a good reason, indeed. However, we do not re-

ally know how many are they. The estimated WHO figure of 200 million is frequently repeated. But even if we assume that it is correct, we do not understand what it really means. We do not know how many of those infected people will present health problems. We are far from knowing which is the real impact that this parasitic disease cause in different countries, as compared for example to the losses caused by unemployment, by wastage, by pollution, by social inequalities, etc.

Why again the insistence with the International Symposium?

To find the correct answer, we should analyze what have occurred in our previous meetings. Simply, an exchange of scientific information. The involved individuals are stimulated by the existence of a parasitic disease presenting considerable potential for scientific research. There are good experimental models and several basic and applied problems to be investigated. Several of them seem simple at the surface but many are complex and involve basic aspects of medicine and biology. They function as potent attractive for researchers. The challenge is accepted not by sheer dilettantism. The scientists as well as the health planners know that the solution of the problems connected with schistosomiasis will lead to scientific progress in general and in particular to the improvement of laboratories located in underdeveloped areas, and, last but not least, to better means to control or even eradicate schistosomiasis. This challenge is thus the main reason for and explains the success and persistence of the International Symposia on Schistosomiasis.

The Symposia are also international because there are similar problems presented by the disease in different geographic areas and there are research interests shared by scientists living in nonendemic areas of the world as well. The existence of basic research problems attract colleagues from the best equipped laboratories located in places where schistosomiasis does not occur. The exchange with them is mutually advantageous.

As a matter of fact, the control of schistosomiasis or even its eradication does not depend anymore on new strictly medical advances, but on public health political priorities aimed at the harmonious socio-economical improvement of the population, with full employment and a better quality of life for the population as a whole. However, the challenge of this parasitic infection continues in other fields and this has to do with us. During a WHO meeting in Nairobi, Kenya, I jokingly said that schistosomiasis was doing more for immunology than *vice-versa*. We were then at a moment where the advancements with experimental *in vivo* and *in vitro* research with schistosomules had brought new data to antibody-mediated immunity, which involved complement activity and the role of several effector-cells, such as macrophages, cytotoxic T-lymphocytes, eosinophils, neutrophils, mast-cells and even platelets. Accumulated data were so impressive that studies on schistosomiasis became the main leading movement toward the development of the new field of immunopathology of parasitic disease. Indeed, such studies everywhere stimulated the investigations about the function and significance of the eosinophil leukocytes, a subject which continues up to the present.

During a long time the granuloma of tuberculosis was considered the prototype of all granulomas. Nowadays, knowledge on schistosomal periovular granuloma is the most advanced of all. Schistosomal periovular granuloma is the best studied, the best known and represents the basic example for the understanding of the general pathology of this peculiar type of inflammation. Although, different host reactivity in early and late infection has been recongnized since a long time ago in studies on tuberculosis, it was the schistosomal periovular granuloma that allowed for the sound investigation on the phenomenon now called immunological modulation. The *in vivo* and *in vitro* models of granulomas formed around the eggs of *Schistosoma mansoni* turned possible the dissection of the several factors involved in the origin and evolution of periovular granulomas, and in its immunological modulation. With the new advances on the role of T-helper-cell subpopulations and their citokines, the adhesion molecules and the biology of the extracellular matrix, the unitary lesion of schistosomiasis (granuloma) keeps on giving model and stimuli to new advances of importance for general pathology, medicine and biology.

Another great impact to medical science, in my opinion still not sufficiently appreciated by researchers from other areas, concerns the observation on extracellular matrix degradation which follows the curative treatment of schistosomiasis in man and in experimental animals. Although this subject had been extensively studied in physiology and pathology of connective tissues, especially in rheumatic diseases, in post-partum uterus involution, in tumor metastasis, etc., the matrix degradation in these instances was considered as a focal and limited phenomenon. Dense cicatricial fibrosis was a different matter, and was considered irreversible.

Now, with ultrasonography facilitating the observations on post-chemotherapy hepatic fibrosis involution in hepatosplenic patients submitted to mass treatment in the field, previous clinical and pathological findings on extracellular matrix degradation were confirmed and extended. Similar degradation of fibrosis is currently being docu-

mented in the liver of patients with visceral leishmaniasis, and in the murine heart in experimental Chagas' disease.

Another aspect that may have a significance beyond our expectation, refers to the type of matrix degradation seen in advanced schistosomiasis. In general, more is known about matrix formation than about its degradation. Data on the latter concerning the participation of several proteases and metallo-proteases, with interference of excitatory and inhibitory factors originated from studies made in animal models presenting what we may call "acute" matrix degradation, in which the involution of fibrosis occurs from 1-2 up to 28-30 days. In chronic schistosomiasis extracellular matrix degradation is partial and occurs in 2 to 4 years after treatment in man or in 4 to 6 months in the mouse. This is a type that we may call "chronic" degradation. Are "acute" and "chronic" matrix degradation the same? We do not know. We should remember that hepatic post-chemotherapy fibrosis degradation in schistosomiasis is accompanied by a complex set of vascular re-arrangements, leading to the return of portal pressure toward normal, with disappearance of esophageal varices, diminution of splenomegaly and so on. These are aspects that may have considerable practical and conceptual importance.

The study of schistosomiasis may go well beyond its frontiers, providing for a great deal of interdisciplinary collaboration. Unfortunately, some of such subjects have provoked a fleeting interest, giving the impression that its potential has been exhausted. Ramon y Cajal said that there are not such thing as exhausted questions, but only exhausted individuals. The potential for some multidisciplinary studies on schistosomiasis do remain, as we shall see below. One example is represented by renal involvement in hepatosplenic schistosomiasis. The concept of glomerulonephritis mediated by immune-complexes appeared before it was possible to demonstrate the presence of antigen in the renal glomeruli. Renal involvement in quartan malaria allowed the demonstration of malarial antigen in the lesions. Soon afterwards, the presence of schistosomal antigen (s) was documented in the kidneys of both man and experimental animals. In subjects living in endemic areas the presence and intensity of proteinuria showed positive correlation with hepatosplenic schistosomiasis, even in those presenting normal renal function. One study made in Sudan failed to show any correlation between hepatosplenic schistosomiasis and renal disease. However, I would like to remark that schistosomal glomerulopathy has been subjected to, let us say, the "Koch' s postulate" test. In Brazil, schistosomal glomerulopathy affects 15 to 20% of hepatosplenic patients, as seen in clinical and pathological studies made in several medical centers. Several histological types may appear, but all are known to be associated with the nephrotic syndrome, the main clinical manifestation of the condition. Morphological evidences of pre-clinical forms of renal involvement have been demonstrated in biopsy material taken during splenectomy in young people. The presence of antibodies and antigens have been shown by immuno-histology. The full glomerular lesion has been reproduced in monkeys and rabbits, especially when they are infected with *S. japonicum*. However, there is much more needing investigation. The clinical significance of renal involvement, its geographic variations and the influence of co-factors are among them. Let us hope that research on the relationship between schistosomiasis and renal disease be soon resumed.

Another challenge is represented by the pathogenesis of the hepatosplenic form of schistosomiasis. There is no clear explanation why some infected people develop systematized periportal fibrosis, the so-called "pipestem" fibrosis of the liver, as Symmers called it 91 years ago. In hyperendemic areas the proportion of hepatosplenic patients may reach 4-12%, which means that a large majority of heavily infected people living under the same environmental conditions fail to develop severe disease. Hepatosplenic patients present heavy worm load, but with mild to moderate worm burden will develop the severe form of the disease. On the other hand, only a fraction of heavily infected people will evolve to hepatosplenic schistosomiasis. The role of the spleen has been emphasized in some studies, but "pipestem" fibrosis of the liver can occur in the absence of splenomegaly. These cases are now more frequently seen, probably due to the use of ultrasonography. There are interesting data pointing to a modulatory defect due to an abnormal response in the generation of anti-idiotypic antibodies, but some of our recent results to be presented in this Symposium failed to give support to such possibility. But, it is not only the pathogenesis of the advanced forms of schistosomiasis that have excited the efforts and ingenuity of the scientists. Their association with viral and bacterial infections sometimes reveals peculiar characteristics. Problems related to viral hepatitis and septicemic salmonelosis are examples known by all of you. Further studies are needed to clarify host-parasite relationship in such situations.

The goal of an effective and practical vaccine against schistosomes has appeared to us intermittently as very near or too far distant. Much effort and money have been expended on it. Although a large body of collateral data on basic knowledge have been produced, it is my opinion that the goal of a vaccine remains elusive. The question is to know

whether we really need a vaccine. This question is a sensitive one, but we have not so far attempted to rationally answer it. Of course, the obtaining of such vaccine will be a breakthrough that will stimulate the whole field of anti-parasitic research.

Up to this point I have mentioned some facts about schistosomiasis research that have stimulated investigators in several parts of the world. The motivation they have to accept the challenge and to come to the meetings to report to and to learn from colleagues, is the same that moves men and women of science since Galilei.

In the fields, hospitals and medical clinics there are intense activities to minimize the defficiencies of our public health assistance and to lessen patient suffering. Many individuals in these institutions go beyond their routine and accumulate valuable experience to help the fight against schistosomiasis. Applied research has always been a significant part of our Symposia.

Let us hope this Symposium will keep the same high standard of the previous ones. To achieve this there has been much dedication from the Organizing Committee, its President, the Fundação Oswaldo Cruz support and the enthusiastic response of the Brazilian and foreign investigators.

Tomorrow we will initiate our scientific activities. Let the scientific progress appear in a cordial and stimulating environment, so all of us will be looking forward to new advances and to the continuation of this activities in the next Symposium. Things being so, the V International Symposium on Schistosomiasis would certainly reach its main objectives.