

BRAZILIAN CONTRIBUTIONS TO EPIDEMIOLOGICAL ASPECTS OF SCHISTOSOMIASIS MANSONI

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A review of epidemiological aspects of endemic areas for schistosomiasis, especially in Brazil, will be presented. These studies, performed by several authors from different states of the country, have been very useful in indicating the relative efficacy of control measures. For example quoting only one aspect, specific treatment was demonstrated by Brazilian researchers to be the most important individual tool for morbidity control. More recently the study of risk factors in endemic areas has been seen to be a very important approach when transmission control is the final goal.

Key words: schistosomiasis mansonii – epidemiology – Brazilian contributors

I would first like to thank the organizing committee of the 3rd International Symposium on Schistosomiasis and the 3rd National Meeting on Schistosomiasis, and in particular Dr Amaury Coutinho, for the invitation to give this opening address. The opportunity to make the acquaintance again of friends amongst both Brazilian and foreign researchers, of these beautiful beaches and "arrecifes" which keep the sea so calm and which I hope we will have time to enjoy at the end of the week, of the typically rich food and lastly of a very Brazilian atmosphere, which reminds us of the epic struggle of the Pernambuco people in defense of the national territory, is more than enough to make me grateful for this honoured invitation.

It is perhaps the conjunction of all these factors that made me choose, for the theme of this presentation, a historical summary of Brazilian discoveries in the field of schistosomiasis, especially in the area of epidemiology. This is an excellent opportunity since it allows colleagues, especially the younger ones and those from other countries, to learn a little more, of what has been discovered and developed in this country.

Brazilian researches are not cited in the literature, as a whole, in proportion to the quality and quantity of their production. Perhaps because of a number of reasons, amongst which we can cite, publication on Portuguese and the lack of indexation of many of our journals.

The involvement of national researchers in the field of schistosomiasis dates from 1908 when Pirajá da Silva had a decisive role in the characterization of the species *Schistosoma mansonii* which at the time was the subject of great dispute between English and German researchers (Pirajá da Silva, 1908; Falcão, 1957, 1959). It was his work that showed that in Brazil the worms and the laterally spined eggs were of a single species, clearly different to the situation in Africa, reinforcing the arguments of Manson and Sambon.

Following this researcher from Bahia is Adolpho Lutz who, in 1919, published in the *Memórias do Instituto Oswaldo Cruz* a magnificent paper entitled "The schistosome and schistosomiasis according observations made in Brazil" where the morphology and physiology of the parasite, mechanisms and techniques of infection, as well as malacology are studied. It is also in this work that Lutz described the method of spontaneous sedimentation in water for the diagnosis of schistosomiasis by means of fecal examination. This method was redescribed in 1934 by Hoffman, Pons and Janer and came to be known by the name of these authors. It is only thanks to the paper of Coura (1973) that this historical truth was re-established. In 1943, Geth Jansen undertook the first work involving large scale treatment in Brazil with the view of controlling the disease. Previously, Maciel (1929) had treated a large number of sailors in the naval health service but it is in Catende, in the State of Pernambuco, that Jansen undertook the first

effort at control and who followed the level of infection in the human and snail populations. The control measures undertaken in the first two years consisted of 27 applications of molluscicide in the principal water sources at three monthly intervals, treatment of approximately 2,000 people with tartar emetic and other antimonial derivatives, construction of public latrines and tanks for washing clothes as well as sand filters in the community water reservoirs. Of the 1,252 houses in the urban area, 33.7% did not have latrines. After the programme this percentage fell to 13.4%. After two years of the programme, the results showed a percentage reduction in snails in various water sources in addition, the prevalence of schistosomiasis in the population of Catende which was 53% fell to 12% in the 800 inhabitants examined (Jansen, 1946).

In 1953, Hoel Sette underwent a contest for the position of Professor of Clinical Therapy in the Faculty of Medicine of the University of Recife having as his approved thesis "The treatment of schistosomiasis mansoni in the light of hepatic pathology – a clinical study". In this work, undertaken in 1951, the survey of the population of Catende is presented. During the period from 1943 to 1947, 3539 people were treated, initially by Geth Jansen and Nicolino Limonge and afterwards by other physicians. Sette examined 796 treated patients and 100 non-treated patients. In these two groups the frequency of splenomegaly was 1.7 and 9.0% respectively. Based on the information provided by the illustrious Brazilian researcher Madureira Pará (1948), who compared the results of histological examination of liver fragments obtained by biopsy, from 1937 to 1941 and from 1942 to 1951, that is before and after the control campaign, Sette showed that the number of cases with "cirrhosis" was 32.6 and 11% respectively. Sette (1953) makes the following conclusion: "it is confirmed, therefore, that there is a higher incidence of cases of hepatosplenic syndrome in non-treated than treated individuals". We will return to this subject later.

In 1949, Amilcar Vianna Martins, in Belo Horizonte, published his thesis showing the value of fecal examination by spontaneous sedimentation in water for the diagnosis of schistosomiasis. Up until then, the direct method or that of flotation was used according to the technique of Willis (1921), which uses an aqueous solution saturated with sodium chlo-

ride. Since the material to be examined is obtained at the surface, and since the *S. mansoni* egg is denser than the solution and sinks rapidly, cases of diagnosis of this parasitism were rare. After Martins' studies, the method of sedimentation was introduced into the Public Health Services and the parasitological diagnosis of schistosomiasis by means of fecal examination was begun to be correctly undertaken. It is this method that was going to permit Pellon and Teixeira, in 1948 and 1949, to undertake for the first time in Brazil, a national survey resulting in the classic paper: "Geographic distribution of schistosomiasis mansoni in Brazil", published by the Division of Hygiene Organization in 1950. This investigation was undertaken in 11 states of the Federation and 400,000 children from 7 to 14 years of age were examined, in whom a prevalence of 10% was obtained.

At this point it is important to stress the great contribution made by Samuel Barnsley Pessoa to the epidemiology of schistosomiasis in Brazil. At the beginning of the 1950s Pessoa began studies which were to result in very important contributions. In fact, in 1953 Pessoa and Barros called attention to the fact that the prevalence of schistosomiasis alone is not representative and that it is necessary that those infected should be classified according to the "form of the disease". They presented a clinico-epidemiological classification which came to be used henceforth, with few modifications, by Brazilian researchers. Pessoa and Barros proposed classification into five types which are: Type 0, toxemic; Type I, intestinal; Type II, hepato-intestinal; Type III, hepatosplenic (compensated phase of cirrhosis); Type IV, hepatosplenic (decompensated phase of cirrhosis) and stated that the frequency of types III and IV is indicative of a higher level of transmission of the helminth and a higher worm burden in the population. Pessoa studied the infection of populations in Paraíba with the help of Silva (1955), in the State of Sergipe with the help of Barros, in Alagoas with the help of Amorim (1957a, b) in Bahia with the help of Coutinho (1949), and also subsequently in Paraná.

Referring to these important pieces of work, we come across a lot of information which can be summarized thus: schistosomiasis is of recent introduction, it came with the slaves in the 17th and principally the 18th centuries. Being newly arrived, it has not yet become

stabilized and has an expansionist tendency in our country. The non-white groups have a tendency towards a higher percentage of more serious clinical forms (Pessoa, 1956). This last statement is in disagreement with the papers of Cardoso (1953), Prata & Schroeder (1967) and Tavares Neto (1987), but agree with the data of Brener & Mourão (1956). Thus, since it is a controversial subject it requires further investigation.

Pessoa calls attention to the necessity of epidemiological surveys where the clinical forms are examined for later evaluation after the introduction of control measures. He further details the importance of what he calls quantitative measurement of the disease on prevalence, measurement of transmission, that is the density of snails in breeding places and the number of infected snails and a new concept which is the amount of transmission of schistosomiasis in a restricted locality which can be evaluated by the percentage of children (between 3 and 10) who exhibit infection in the locality. For this measurement he proposes that only indigenous children should be considered, that is, those born and raised in the locality and who have never been away (Pessoa and Amorim, 1957a, b). Other valuable statements he makes concern the importance of snail foci near to habitation, the appearance of serious forms related to type of work, etc.

At this moment we ought to record our remembrance and our respect for this great researcher and great citizen Samuel Pessoa, founder of the Brazilian School of Parasitology.

It is also in the 1950s, that important contributions were made to the understanding of clinical aspects, therapy and pathology of schistosomiasis and in this respect Caio Benjamin Dias (1949, 1952), José Rodrigues da Silva (1949, 1955), João Alves Meira (1951), Ruy João Marques (1951) and Luigi Bogliolo (1958, 1959), amongst others, should be cited.

An outstanding figure in Brazilian research, Wladimir Lobato Paraense, started, in the 1950s, some fundamental pieces of work that imposed "order" on the systematics of the snails, intermediate hosts of schistosomiasis, as well as resolving various problems which until then had been causing innumerable disagreements during the scientific conferences held at the time (Paraense, 1961, 1966, 1975).

In fact, there was a discussion, at times heated, between a group of investigators who succeeded in infecting the snails found in São Paulo and another which stated that these snails were refractory. Lobato Paraense, with characteristic calmness and depth of thought, making use of simple methods and a lot of creativity, infected the snails with miracidia from the same locality demonstrating that the two groups were right. In fact, snails and miracidia from the same area are found to be adapted so that the life cycle is maintained, while snails and miracidia of different regions are not always compatible (Paraense & Correa, 1963). More recently, Paraense (1966) described two new species of snail, one from the Amazon region, which was named *Biomphalaria amazonica* and another from the southeast of the country, *B. occidentalis*. These new discoveries have important implications for epidemiology: firstly to demonstrate the possibility of the spread of schistosomiasis to the Amazon region, since *B. amazonica* is susceptible to miracidia from human cases in Minas Gerais and the Northeast, which constitute the principal source migration of infected individuals migration to that region, and secondly, because *B. occidentalis* is refractory to infection. This latter fact, helps us to understand the geographical distribution of the disease in São Paulo and other regions and indeed opens up interesting possibilities for biological control.

Creator and director of the International Center for Malacology, localized in the Fundação Oswaldo Cruz in Rio de Janeiro, Dr Lobato Paraense honors and dignifies Brazilian science.

In 1956, Brener and Mourão undertook a clinico-epidemiological investigation in five localities in Minas Gerais, demonstrating different prevalences and different frequencies of serious forms. After 10 years, the same patients resident in three of these localities were reexamined by Katz and Brener (1965).

In 1957, the most important work on rectal biopsy in Brazil appeared, undertaken by Aluizio Roza Prata and which was the subject of his thesis for the Professorship of Tropical and Infectious Diseases at the Faculty of Medicine of the Federal University of Bahia. In this work, the basis and applications of rectal biopsy in the diagnosis and evaluation of therapy was so scientifically an exhaustively put forward that it practically left no space for

later contributions. Despite the unimportance of the technique of rectal biopsy in epidemiological studies, this work cannot be left unmentioned because of the quality and excellence that it possesses.

In the second half of the 1950s up until the beginning of the following decade, José Pellegrino was to standardize the immunological reactions (intradermal reaction, complement fixation, circunoval test, immunofluorescence, etc.) demonstrating their value for epidemiological surveys (Pellegrino, 1959, 1963, 1968; Pellegrino & Andrade, 1962).

Without doubt, José Pellegrino, who died prematurely at the age of 54, is one of the most creative and respected Brazilian scientists. Pellegrino left more than 350 published papers as well as innumerable followers and ideas that are only now, more than 14 years after his death, beginning to be fully appreciated.

Somebody, such as I, who had the honor and pleasure of being taught by and to have closely interacted with such an illustrious scientist knows very well the fertility of his intellectual production. Innumerable times we discussed in the laboratory of the Centro de Pesquisas "René Rachou" in Belo Horizonte, where for years Pellegrino undertook his work in leishmaniasis, Chagas' disease and schistosomiasis, the methodology to be developed in order to answer a certain scientific question, however without success. Pellegrino would go home to think and wake up during the night with the solution to the problem. He would call in the early hours of the morning designing the experiment and calling for an early start in the laboratory to test his idea which would invariably be right.

To Pellegrino, great research, teacher of researchers, inspirer of new talents, faithful friend who raised the name of Brazilian science in the field of endemic tropical diseases, our thanks, respect and remembrance.

Since 1951, Frederico Simões Barbosa, in the Institute "Aggeu Magalhães" in Recife, had come to study schistosomiasis and in particular the snail from a number of different angles: its biology, behaviour, infection, control, etc (Barbosa, 1956, 1978; Barbosa & Coelho, 1956; Barbosa et al., 1958, 1971). Many pieces of most important information concerning the

intermediate host were published in more than 50 papers over a period of 10 years. In these, Barbosa initiated important field studies with the view of achieving a better understanding of schistosomiasis in Pernambuco and the application of control methods. Barbosa allied a solid basic training with a humanistic political vision in which he sees social consequences as the principal reason for development.

As Barbosa said very well (1978), the majority of studies emphasize specific biological factors which has led to a compartmentalization which does not favor overall understanding. From this perspective, it is not a matter of introducing studies on economic and social factors as though they were yet more factors to put together with others, it is a matter of seeing the real conditions in which the the life cycle of schistosomiasis is established and its impact on human life. This type of approach was to take more than 10 years to be understood and applied.

But let us return to 1965 when Rodrigues da Silva, then director of the National Institute of Rural Endemic Diseases (INERu), section of research of the Department of Rural Endemic Diseases of the Ministry of Health (DNERu), invited various researchers, some who were already working on the natural history of schistosomiasis and others who were new to the area, who in four states, Rio de Janeiro under his own coordination; Bahia, Aluízo Prata; Pernambuco, Frederico Simões Barbosa and Minas Gerais, Ernest Paulini and later Naftale Katz, were to start pilot projects in order to understand better how to control schistosomiasis in endemic areas. Already at this time, this was beginning to be appreciated by Brazilian researches and in 1978, Barbosa was to put together the following position: "Brazil is currently the country with the highest level of scientific and technical level where schistosomiasis still constitutes a health problem. We constitute a scientific community of the highest value and have already effectively answered diverse problems concerning the control or eradication of various endemic diseases. Nevertheless, we continue to battle with many of these diseases, amongst which is schistosomiasis. It is encumbant upon us Brazilians to respond to this challenge. The problem is ours and it is for us to find the solution". These premises stimulated studies in endemic areas leading to significant advances in the understanding of the epidemiology of

schistosomiasis in the 1960s and 1970s and which continue to the present day. The creation, at the beginning of the 1970s, of the Integrated Plan of Research in Endemic Diseases by the National Research Council (CNPq) which financed work in the area of schistosomiasis should also be highlighted.

There exist two important facts that should be mentioned in order to understand this movement in the direction of epidemiological studies and field work as well as changes in approach to control. The World Health Organization (WHO) had come to favor the use of molluscicides as the method of control of schistosomiasis for several years. In 1967, an evaluation of the project Egypt-49 was published where, for seven years, the method of using molluscicide (niclosamide) for control was applied. The evaluating group, led by Gilles, has the important involvement of Barbosa, who at this time was working for the WHO in Geneva (Gilles et al., 1973). The clear demonstration that the application of molluscicide for a number of years did not alter either the prevalence or the incidence of the disease started to reduce the credibility of this method of control. But it was not to be discredited so rapidly since in 1978, during the meeting of the "Expert Committee of the WHO", the use of molluscicides is highly recommended (WHO, 1980). The second fact is that during the 1970s for the first time the possibility appeared of using a schistosomicidal drug, with relative safety and in a single dose, for large scale treatment. Initially, hycanthon was used which unfortunately had to be abandoned because of the deaths that it produced, and subsequently oxamniquine which was shown and is being shown to be well tolerated and therapeutically effective in more than 14 million treatments already undertaken in Brazil.

Here it is worth pointing out the important participation of the group of Brazilian researchers who contributed greatly to the development of new drugs, allowing those that worked well to be introduced onto the Brazilian market and preventing others from being sold either because of lack of therapeutic effect or toxicity. This group, which was never formally formed but which existed in practice, has had a great importance in the development and evaluation of schistosomicidal agents and even at the risk of omitting some individuals we cannot leave uncited the names of Aluizio Prata, Amaury Coutinho, Carlos Alberto Argento,

José Rodrigues Coura, Luiz Caetano de Silva, Naftale Katz and Roberto Sena Rocha.

The technique of fecal examination known as Kato-Katz, described in 1972, has to be considered as another important factor in facilitating epidemiological studies and which has currently come to be widely used in this country and abroad (Katz et al., 1972). Because of the quantitative information that it provides, it is absolutely indispensable in epidemiological studies and the evaluation of control methods (WHO, 1985).

Let us now return to the contribution which I consider to be a highlight of Brazilian work. I want to call attention to the daring, intuition and creativity of our colleague Kurt Kloetzel. To show how Kloetzel thinks I would like to cite the introduction to his thesis presented at the Faculty of Medicine of the University of São Paulo in 1962: "to study epidemiology is more or less the same as observing the Martian canals and trying to infer their nature.... will anyone dispute the value of studying the Martian canals? Well then, our vanity suggest to us that schistosomiasis mansoni is of more immediate importance than astronomical observations" (Kloetzel, 1962).

The perception and perspective, together with the intuition that only the gifted possess, allowed Kloetzel to make several important recommendations: (I) the importance of quantitative methods in epidemiological studies and control; (II) the value of chemotherapy (though at that time an antimonial derivative had been used) for the lowering of prevalence or parasite burden and finally his most important recommendation; (III) that children resident in an endemic area, with high numbers of eggs, should be treated with the view of preventing the appearance of hepatosplenic forms even though the children were at high risk of reinfection (Kloetzel, 1967). These data obtained in Gameleira - Pernambuco have a considerable weight in the medical literature and undoubtedly influenced José Carlos Bina when, in Caatinga do Moura in Bahia under the supervision of Aluizio Prata, he prepared his thesis. The data obtained by Bina (1977) constitute an unambiguous confirmation of the effect of specific chemotherapy in the prevention of hepatosplenomegaly. Other Brazilian investigators have confirmed this fact which has become the consensus of opinion in the literature of those with experience in this field.

In November of 1984, in a meeting of the "Expert Committee of the WHO" which included three Brazilian scientists, this fact finally became officially accepted and the WHO aimed its recommendation at the control of morbidity with the objective of avoiding or reducing the appearance of hepatosplenic forms. Without doubt the presence of Dr Kenneth Mott, Head of Schistosomiasis and other Helminthic Infections Section of the Parasitic Diseases Program of the WHO who studied and worked for many years in Bahia, also influenced this decision. This concept consigned to history, the memorable and provocative disputes almost a "Battle of the Guararapes" with which the School of Pathology of Recife led by Coutinho & Coelho (1940) challenged the data of Dias, Rodrigues da Silva, Sette, Bogliolo and others. The Pathology School of Recife did not, in fact, accept clinical treatment with the argument that this was more harmful than beneficial and indeed caused the hepatosplenic form. From this dispute came the famous phrase of Coutinho (1954) that "the liver is the cemetery of dead worms".

I would now like to try to briefly review the innumerable data from epidemiological and control studies obtained by the groups of researches led by Aluizio Prata, Frederico Simões Barbosa, José Rodrigues Coura (who since 1973 has undertaken important investigation in Minas Gerais, Sergipe and Paraíba which have come to be known as the "Geographical Pathology of Schistosomiasis in Brazil"), Kurt Kloetzel and our own group. I would also like to cite as contributors to these understandings two excellent professionals from our group, Roberto Sena Rocha and Maria Fernanda Furtado de Lima e Costa, as well as José Carlos Bina, Sebastião Loureiro and Mauricio Barreto from Bahia.

It has been forward that:

1 – there appears to be a direct correlation between prevalence, intensity of infection and frequency of hepatosplenic forms.

2 – The prevalence curve shows that the groups of youngest individuals accumulate infections up to 15 to 20 years of age which then stabilize for a few years and then have the tendency to decline with a "spontaneous cure" in many cases.

3 – Up until 10 years of age concomitant immunity, if it exists, is not sufficient to prevent reinfection, in the group with frequent

contact with infested water. Although in the majority of cases, adults appear to have resistance to reinfection.

4 – Six to 12 months after specific treatment, (with hycanthone, oxamniquine or praziquantel) there exists a profound fall in the number of cases eliminating *S. mansoni* eggs in the feces.

5 – Parasitological evaluation undertaken two years after treatment shows a rise in the number of cases of reinfection.

6 – Reinfection is directly related to initial prevalence or the "transmission force" of the schistosomiasis area.

7 – The degree of reinfection is three to five times greater in children than in adults.

8 – Following "cure", reinfection, in the majority of cases, occurs with a reduction in the number of eggs in the feces.

9 – In areas of medium and high endemicity, a single treatment diminishes prevalence.

10 – Treatment with a view to the control of morbidity can be repeated annually, or every two or more years. Shorter intervals of repetition do not appear to be advantageous.

11 – Specific treatment prevents (or greatly reduces) the appearance of new cases of the hepatosplenic form: those already existing as well as hepatointestinal forms have the tendency to regress to the intestinal form in the majority of cases.

12 – Mass treatment can only be applied when the prevalence is 60% or more. In other areas only those who are eliminating *S. mansoni* eggs in their feces should be treated.

13 – Special attention should be given to the age group of up to 20 years of age in control programs.

14 – Specific treatment alone, in areas of medium and high endemicity is not sufficient to control transmission. Other associated measures should be included such as basic sanitation, changes in the environment, health education and application of molluscicides.

In recent years the epidemiological understanding of populations resident in areas endemic for schistosomiasis has permitted immunological and genetic studies of great importance. In Brazil these studies were initially

undertaken by Daniel Colley, Giovanni Gazzinelli with our group and by Alain Dessein with the group of Prata. The data obtained to date will be presented in this congress.

It should be pointed out that the current tendency in epidemiological studies is towards the understanding of the risk factors responsible for infection and serious forms of the disease. In this field it is necessary to mention that at least three groups of researchers are undertaking such work in Belo Horizonte, Uberaba and Bahia.

I would like to mention that in this short time I have not presumed to try and mention all Brazilian work in the field of schistosomiasis and have thus been more selective than exhaustive.

Various subjects have not been mentioned including, for example, the problem of rodents and other animals implicated in the maintenance of the life cycle; I also did not have time to discuss the Special Control Program of the Ministry of Health, started in 1975 or the Second National Survey of prevalence undertaken between 1977 and 1979 by SUCAM. Lastly, I am sure that many other facts and authors which are important in the history of schistosomiasis in our country were not mentioned. For these omissions I ask your forgiveness. Nevertheless, this failure will be compensated, at least in part, since shortly my colleagues Omar dos Carvalho, Henrique Leonardo Guerra, Alaor Marques Júnior, Pedro Jurberg and I are going to publish, within the Integrated Program of Schistosomiasis of the FIOCRUZ, a biographical list with more than 3,000 papers on schistosomiasis published in our country in indexed and non-indexed journals to facilitate the research of our colleagues here and abroad.

To finish, I would like to make a quotation from the last century of an author who today is out of fashion but whose justice and depth of thought is undeniable. As Karl Marx said "He who doesn't know history is condemned to repeat it: the first time as a tragedy, the second as a farce".

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