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REINFECTION AFTER TREATMENT OF SCHISTOSOMIASIS: ENVIRONMENT OR "PREDISPOSITION"?

Kurt KLOETZEL (1)

SUMMARY

Although very efficient for the control of morbidity due to **S. mansoni** in individual patients, chemotherapy has not proven successful in the management of transmission within hyperendemic areas when used alone, even if repeated at short intervals. Consequently, a great deal of effort has been expended toward immunologic investigation and development of a specific vaccine.

Based upon a study of a group of children (5-14 years) from the state of Alagoas, the author demonstrates that the outcome one year after chemotherapy depends essentially on the "risk rating" of the area of domicile. A regression analysis did not reveal significant correlation to neither age, sex or initial egg counts. Although the study was not designed to reveal individual variations in the immune status, it is postulated that putative differences in genetic make-up are irrelevant in terms of large-scale intervention.

Since morbidity due to **S. mansoni** has substantially declined during the last two or three decades, a control policy based on vaccination can only be justified if high levels of protective immunity can be attained. At any rate, such a vaccine will have to be administered in early childhood (preferably below the age of three). It can also be demonstrated that immunization in adolescence or adulthood serves no purpose whatsoever.

The author is convinced that environmental intervention, usually dismissed as unrealistic in terms of the developing countries, is not only feasible, if done on a selective basis, but prioritary.

KEY WORDS: Schistosomiasis mansoni; control; Brazil.

INTRODUCTION

There seems to be a general consensus that mass chemotherapy for schistosomiasis mansoni, even when these campaigns are carried out repeatedly and at short intervals, has by and large proven unsuccessful, with the possible exception of a few small, well-circumscribed and hardly representative areas.

Environmental intervention, on the other hand, has in most cases been given little thought, under the preconceived notion that control of the foci of transmission would require investments lying beyond the means of the developing nations.

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(1) Faculdade de Medicina, Universidade Federal de Pelotas (Caixa Postal 464, CEP 96100 Pelotas, RS, Brazil).

Thus it is only natural that a great deal of attention has lately be focused upon the immunology of schistosomiasis as well as development of a specific vaccine. However, since such an enterprise likewise demands substantial investments in time, money and personell, it is only fair once again to inquire: Is a vaccine really necessary?

In the animal model, there are many indications in favour of an acquired protective immunity. There is also some evidence that vaccination may protect against infection by **S. mansoni**, although incompletely[8, 27].

As far as the human species is concerned, findings are not as clear-cut. Some sort of age-dependent protective immunity has often been postulated[5, 8, 11, 16, 29, 32], with the exception of a paper by ONGOM & BRADLEY[26], who reported sustained high egg outputs until old age in a population of Uganda. (Since this area is also endemic for malaria, it may be worthwhile to investigate a possible causal relationship).

While it has proven difficult to determine whether the decrease in the intensity of infection starting in adolescence indicates acquired resistance to further infection or is mostly a consequence of behavioral changes (i.e., less exposure), the latter hypothesis seems unlikely owing to the unusually abrupt inflection of the curve relating age to egg output (such as reported in[14, 22, 25]). Whe have also shown that this sudden and spontaneous drop in egg counts is concomitant, in cases of very intense infection, with the onset of splenomegaly, a finding which certainly offers further opportunities for immunologic investigation[15]. In addition, a well-designed study by WILKINS and his group[33], allowing for differences in the intensity of exposure to **S. haematobium**, clearly revealed significative differences in the rate of reinfection of children beyond 10 years of age.

A study by KLOETZEL & SILVA[20], however, carried out in a group of Portuguese immigrants first exposed to schistosomiasis in adulthood, suggests that duration of exposure rather than age may be the factor determining resistance to reinfection.

As a corollary to the widely-accepted postulate of a time-dependent acquired immunity, a number of authors have voiced their fears that drug treatment might counteract or even abolish this type of immunity[6, 10, 31].

Be it as it may, an acquired resistance toward infection which takes 10-15 years of exposure to be effective cannot offer much hope. By that time the bulk of the egg output (thus the risk to the environment) has already taken place and, if individual conditions should happen to predispose to severe morbidity, this is already irreversible.

While acquired immunity appears to be a phenomenon which can be generalized, there is also some evidence toward individual differences in immuno-competence. Thus STURROCK et al[31], for instance, reported that reinfections were significantly less in children presenting detectable cytotoxic anti-schistosomular antibody and eosinophil counts above 400/mm^3. BUTTERWORTH et al[5] as well were able to show that some 30% of children do not attain high egg counts despite intense exposure to **S. mansoni**, a phenomenon which likewise seemed to be age-dependent. Although both susceptible and resistant children have elevated levels of antibodies with defined effector function, the presence of blocking antibodies[12] "may prevent the expression of immunity"[6]. Yet more recently. DESSEIN et al[9] demonstrated in children individual differences in respect to IgG reactivity toward a larval surface antigen. It thus appears that immunity in schistosomiasis has to be looked at as multifactorial.

These findings as well as their own studies have led BENSTED et al[2] to speak of a individual "predisposition" toward the acquisition of schistosomiasis, although the term is used rather sweepingly and includes "ecological, nutritional, genetic, social or behavioural factors, acting either in isolation or combination".

The hypothesis that the intensity of schistosome infection as well as the morbidity pattern might be dependant upon the genetic make-up was first raised in connection with the high incidence of such cases within certain families[13, 17, 25]. However, after it was recognized that **perido-**

miciliary foci were in fact responsible for most of the transmission in Northeast Brazil[19, 21, 28], it is only natural that this suggestion has to be revised.

However, evidence of a relationship between hepatosplenic schistosomiasis and certain histocompatibility antigens lend credence to the hypothesis that genetic factors may determine if not the level of acquired immunity at least the morbidity pattern[32].

It is quite evident that much ground remains to be covered by basic research before immunoprophylaxis of schistosomiasis can attain its maturity. Still, notwithstanding the incompleteness of our knowledge regarding immune mechanisms, at the present time it is our task to examine the relevance, if any, of a vaccine for large-scale control of schistosomiasis in the poorer countries, a setting which does not make allowances for individual predisposition but requires that realistic solutions designed for general use be adopted.

This is the issue to which the author will adress himself. It is obviously understood that the findings of the present paper refer specifically to schistosomiasis mansoni, as seen in Northeast Brazil.

MATERIAL AND METHODS

The concepts developed in this paper are the result of experience gained since 1956 in 12 areas endemic for schistosomiasis mansoni in 4 Brazilian states. The numerical data, however, refer specifically to the towns of Viçosa and Branquinha, both situated in the **zona da mata**, the humid coastal area of the state of Alagoas. Viçosa has a population of around 15.000 and was described elsewhere[17, 19] while Branquinha has an estimated 5.200. Although distant from each other only 21 miles, they occupy distinct watersheds.

All stool examinations were done by the same laboratory staff, using the Kato-Katz technique. While most of our past work has dealed with schoolchildren (7-14 years), in Branquinha we exceptionally examined a population of 5-14 years and, more recently, extended the range so as to comprise individuals of 14-18 years. We estimate that around 92% of the individuals in these age groups were reached. (Since no consistent differences were found in these and other surveys, results for both sexes are pooled).

Both counties participated in the programme for mass chemotherapy developed by the Brazilian public health authorities (PECE). Thus, since 1979 Viçosa was submitted to 3 such control campaigns, while the population of Branquinha was treated on 4 occasions. A non-participation rate estimated as 40% in the former and 35% in the latter town obviously jeopardized the success of these campaigns although the great majority of the population received oxamniquine at least once.

In addition, during the course of these studies we administered yet another course of treatment within the selected age group (non-participation rate of 11% in Branquinha), compliance with treatment being closely monitored. The adopted dosage of oxamniquine was 25 mgs/Kg.

The concept of "risk rating" introduced in this paper (Tables 3 and 4) is a function of the arithmetic mean of the egg counts within that area of the city. In Figs. 1 and 2 it is translated into density of shading.

RESULTS

In the course of the 1987 survey 719 children of Branquinha were examined. Of a total of 392 positive for **S. mansoni** (54.5%), 350 could be treated. Owing to unusually heavy floods and ensuing social instability, only 248 were again examined in 1988 (Group A, Table 1).

Of the 327 negative children (which obviously were not given drug treatment), 230 were likewise examined after one year (Group B, Table 1).

In addition, the 1988 survey included yet another 235 children, seen for the first time (group C, Table 1).

TABLE 1
Branquinha: age-related data in three groups of children.

Age (years)	Prevalence rate in 1988 (%) Group A* (n = 248)	Group B** (n = 230)	Group C (n = 235)	Mean and median egg counts (eggs/g)*** Group A Before	After	Group B	Group C
5	53	35	39	307 (14)	706 (34)	89 (- -)	146 (- -)
6	56	26	38	166 (7)	84 (4)	425 (- -)	372 (- -)
7	55	33	55	139 (7)	206 (11)	82 (- -)	197 (10)
8	50	31	57	204 (9)	269 (12)	89 (- -)	113 (6)
9	63	59	55	413 (24)	226 (13)	365 (20)	230 (11)
10	74	57	56	125 (8)	192 (13)	194 (10)	490 (23)
11	58	47	80	451 (24)	65 (3)	94 (- -)	540 (39)
12	67	56	67	182 (11)	266 (16)	94 (5)	535 (33)
13	38	56	53	146 (- -)	257 (- -)	127 (6)	413 (20)
14	40	50	55	125 (- -)	60 (- -)	48 (2)	1181 (59)
15			51				247 (11)
16			46				113 (- -)
17			49				127 (- -)
18			40				62 (- -)

* Positive in 1987.
** Negative in 1987.
*** Median in brackets. Mean in terms of positives only.

Differences between the groups are non-significant, with the exception of the mean and median egg counts of Group C ($p < 0.005$).

Overall findings for 1987 and 1988, comprising all individuals seen at that time, are depicted in Figs. 1 and 2.

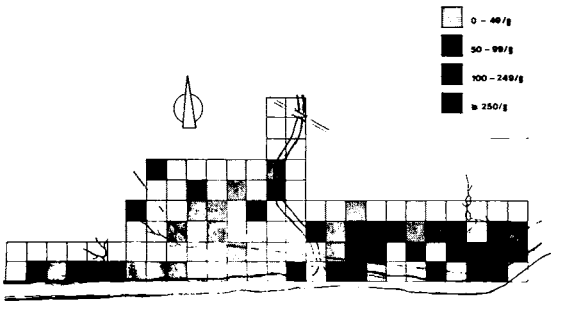

Fig. 1 — Branquinha, 1987: the intensity of shading (corresponding to a "risk rating" of I to IV) is a function of the arithmetic mean of the egg counts of all 5-14 year olds residing in that part of town.

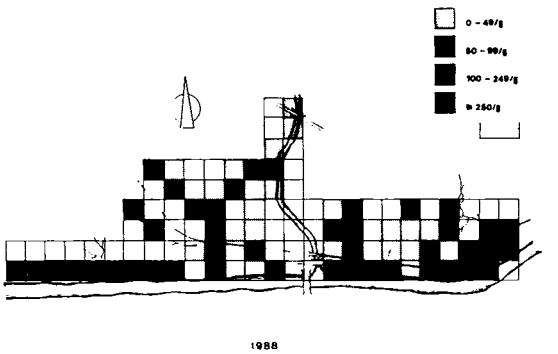

Fig. 2 — Branquinha in 1988, one year after chemotherapy in that age group.

Table 2 lists the effects of chemotherapy in two distinct age groups.

TABLE 2
Branquinha: effects of chemotherapy in two age groups (Group A)

Age (years)	Number of children	Egg counts Decreased	Equal	Increase of < 250 g	> 250 g
5 - 9	113	73 (65%)	6 (6%)	22 (19%)	12 (10%)
10 - 14	135	90 (67%)	9 (7%)	23 (17%)	12 (9%)

Table 3 lists the effects of chemotherapy in Group A in relation to the risk rating of the area of domicile.

TABLE 3
Group A: Effects of chemotherapy as related to risk rating of area of domicile.

Risk rating*	Number of children	Prevalence (%) (1)	Mean egg counts** (eggs/g) (2)	Egg counts < 250/g (%) (3)	Median (eggs/g) (4)
I	46	42	185	9	—
II	73	60	187	15	9
III	94	59	242	18	11
IV	35	76	322	21	23

* For 1987: I = 0-49/g; II = 50-99/g; III = 100-249/g; IV = > 250/g.
** All counts.

A Chi-square analysis results in the following significance levels:
For (1) — $p < 0.001$ (3) — $p > 0.05$
(2) — $p < 0.01$ (4) — $p < 0.001$

The results of the regression analysis is given in Table 4.

TABLE 4
Group A: correlation matrix.

Dependent variable	Correlations				
	Sex	Age	Risk factor	Eggs 1*	Eggs 2**
Sex	1.0000	-.0607	.2099****	.1424	.0628
Age	-.0607	1.0000	-.0506	.0461	-.0446
Risk	.2099****	-.0506	1.0000	.2196****	.1496***
Eggs 1*	.1424	.0461	.2196****	1.0000	.1153
Eggs 2**	.0628	-.0446	.1496***	.1153	1.0000

* Egg counts before treatment; ** Egg counts after treatment (outcome); *** $p < 0.01$; **** $p < 0.001$.

Finally, Table 5 compares the data for the two "zones" of the city of Viçosa presenting the extremes in socio-economic conditions. (For full data see KLOETZEL & SCHUSTER[19]).

DISCUSSION

Although repeated chemotherapy of schistosomiasis has ocasionally been reported to be effective in the control of transmission of schistosomiasis mansoni[30], it seems to be the general experience that under hyperendemic conditions-and as the sole tool of intervention-results are invariably discouraging. A concrete example of the difficulties to be met with in the management of transmission within entire populations is provided by a comparison of Figs. 1 and 2: one year after drug treatment the overall pattern in Branquinha has remained essentially the same.

While results for the three groups have been pooled in these illustrations, Table 1 affords a better insight. One can see how swiftly Group

TABLE 5
Viçosa: age-related findings in two zones of the city (KLOETZEL & SCHUSTER[19])

Age (years)	Prevalence Zone C (n = 269)	Rate (%) Zone G (n = 374)	Mean egg counts (eggs/g)* Zone C	Zone G	Median Zone C	Zone G
7	17	61	77	276	—	15
8	12	62	65	650	—	33
9	16	75	48	509	—	29
10	14	67	151	324	—	17
11	22	66	350	583	—	32
12	29	76	302	545	—	30
13	14	69	139	377	—	20
14	19	74	250	626	—	38

* In terms of positives only

A reverts to the original situation, and the infection rate for Group B, individuals who if not negative for **S. mansoni** in 1987 at least must have had very low egg counts, likewise proved to be substantial.

Although we employed oxamniquine throughout our recent studies[18, 19, 21], identical results are certain to occur with other drugs. The hypothesis of an acquired resistance of the parasite toward oxamniquine can be summarily dismissed: otherwise how would one explain the wide differences in prevalence rate and intensity of infection within a same city, such as shown by Table 5?

The author cannot present personal data supporting or invalidating the hypothesis of a particular susceptibility or resistance toward infection by **S. mansoni.** As regards acquired resistance, everything leads to the conclusion that this factor cannot play a significant role in epidemiology, being at the most secondary to ecologic and behavioral conditions.

Our Table 2 is in disagreement with the paper by WILKINS et al[33] in that no significant age-related differences could be found, at least up to the age of 14. In this connection, it might be pertinent to recall MOTT's[24] suggestion that "epidemiological data support the presence of natural imunity to **S. haematobium** infection more than to **S. mansoni** infection" thus a vaccine would be more effective against the former species.

In the case of schistosomiasis mansoni, acquired immunity starts to play a role in the 15-19 age group, a period in which egg counts decline abruptly and the prevalence rate also decreases, although to a lesser degree. This has been shown on numerous occasions and can also be seen in Table 1. This phenomenon can probably be likened to a natural vaccination.

At any rate, by late adolescence eventual morbidity is already manifest[14, 15] and, owing to changes in habit as well as the drop in egg counts, this group ceases to play a significant role in transmission. Clearly, intervention-whether preventive or curative-has to be done at a much earlier date.

It is thus evident that a putative vaccine has to be used during the first years of life. BUTTERWORTH & HAGAN[6] preconize it be employed before blocking antibodies can develop and maintain that even partial protection would be acceptable, since it would prevent severe morbidity.

This view is highly debatable, at least in the case of Brazil. In this country the incidence of hepatosplenic schistosomiasis has been steadily declining for two decades or so, and at the present time is to be found very rarely in younger

individuals[1, 19, 23]. We are thus faced not with the task of controling **morbidity** as such but **transmission.**

Strangely enough, at the present time morbidity is not as closely linked to intensity of infection as it used to be and, although a proportion of the children rapidly regain egg counts in the thousands, the clinical pattern still remains benign. While in one of our early surveys 43% of the 10-14 years old with egg counts > 500/g presented a grossly enlarged spleen[14], a recent survey in 3 cities of Alagoas revealed a rate of only 13%, and in every case but one the spleen had a soft consistency and did not exceed 2 cm below the costal border.

The author is firmly convinced that the investment in vaccine research and production is justifiable only if one is secure that such a vaccine is capable of leading to a substantial degree of resistance towear schistosome infection. Otherwise other solutions will be prioritary, namely those that are not specifically targeted toward schistosomiasis but benefit the general living conditions of the population, including the control of other water-borne diseases.

One cannot ignore that the conditions of the environment are of paramount importance and the example presented by Table 5, which compares data from two of the zones of Viçosa, should suffice. Both populations have the same ethnic background, received identical attention on the part of national programme for the control of schistosomiasis (PECE), however the two zones differ widely in sanitary conditions. While Zone C is part of a fairly recent urban renewal project and is provided with domestic water supply and a sewer system, Zone G, its counterpart, by and large has maintained the same aspect which we first witnessed two decades ago. (Calculation demonstrates that, taking the 7-14 year group as a basis, Zone G is 9.6 as hazardous as Zone C).

Table 3 further illustrates how closely the reinfection rate after chemotherapy reflects the risk rating of the area of domicile which, as shown by the figures, remains essentially identical in the course of one year. These conclusions seem to be confirmed by the correlation matrix of Table 4. (The association between risk and sex is obviously fortuitous).

Warren's experience led him to similar conclusions: "Although it is probable that some degree of immunity occurs following prolonged and perhaps heavy exposure, it still appears that the ecologic relationship between man and parasite plays the crucial role in determining the prevalence and intensity of schistosomiasis in populations."[32].

The prominent role at present occupied by research and development of a vaccine against the schistosomes has a number of explanations, the most pertinent being the belief that environmental intervention appears to be hopeless in the case of developing countries. In fact, with the exception of a few very limited attempts, apparently designed for political purposes, no significant attention has been given to this area, since the control of transmission is still vizualized in terms of major investments in sanitary engineering as well as sweeping programmes of vector control in rivers, dams, lakes and swamps.

Should an endeavor of such magnitude be required, it would in effect be utopic. Fortunately, investments of this order are not necessary, at least in the areas studied by our group[18, 19, 21]. In Northeast Brazil, peridomiciliary transmission seems to be the rule and the responsible foci are always of small size and, once detected, easily erradicated through local efforts. Agencies responsible for sanitation have lately agreed with us that overflowing septic tanks play a significant role in maintaining transmission and it is clear that management of such foci does not require impossible efforts.

However, there are hundreds of such potential foci even in a small community, thus intervention of a selective nature is called for. This raises a major question: how can the important foci be detected without recourse to very substantial manpower?

This question has occupied us for some time, finally leading to the development of a sampling procedure based upon population clusters, which considerably simplified detection[18]. It was also shown that "empirical screening", i.e., de-

tection on grounds of suspicion, can be a very useful tool in the hands of experienced field personell.

Although our project is still in progress, we feel convinced that a substantial fraction of the transmission of schistosomiasis mansoni can be readily controled once a selective policy (both in regard to chemotherapy as well as to environmental intervention) is adopted. At the present moment such a policy appears to hold much better perspectives than those offered by reliance on mass immunization.

RESUMO

Reinfecção após tratamento na esquistossomose: fatores ambientais ou predisposição?

Embora a quimioterapia possa ser bastante eficiente no controle da morbidade a nível individual, quando usada como recurso único não tem sido bem sucedida no controle da transmissão da esquistossomose mansônica em regiões hiperendêmicas, mesmo que repetida a curtos intervalos. Daí os esforços dispendidos em pesquisas imunológicas e para o desenvolvimento da vacina específica.

Com base no estudo de crianças entre 5 e 14 anos do Estado de Alagoas, o autor procura demonstrar que os resultados registrados um ano após a quimioterapia estão intimamente ligados ao "índice de risco" da zona de domicílio. Uma análise de regressão não demonstrou correlações em nível significativo com idade, sexo ou contagem inicial de ovos. Embora o estudo não compreendesse variações individuais no estado imunitário, o autor sustenta que eventuais diferenças de ordem genética se tornarão irrelevantes quando se pretendem campanhas de caráter mais amplo.

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