# CONTENTS

**EDITORIAL**

**ORIGINAL ARTICLES**

- The impact of the country development in the expansion of schistosomiasis — S. de CAMARGO
- Impact of development on the spread of schistosomiasis in Egypt — M. SAIF & A. GABER
- Current results in the clinical therapy of schistosomiasis mansoni — N. KATZ
- Clinical development of oxamniquine in Egypt — M. SAIF & A. GABER
- Oxamniquine (Vansil) in the treatment of schistosomiasis in Rhodesia — V. de CLARKE
- Observations on the treatment of mansoni schistosomiasis with oxamniquine: Efficacy in children and in persistent salmonellosis; resistance of a strain of Schistosoma mansoni; hepatic toxicity and neurological side effects — R. de J. PEDRO, L. C. de S. DIAS, V. AMATO NETO & S. A. de CARVALHO
- The liver after oxamniquine treatment of schistosomiasis — Z. A. ANDRADE, H. A. dos SANTOS & J. A. GRIMAUD
- Evaluation of the treatment of severe forms of schistosomiasis mansoni with oxamniquine — A. COUTINHO & A. L. C. DOMINGUEZ
- A fifteen-month study on the efficacy of a single 15 mg/kg dose of oxamniquine (Vansil) in Schistosoma mansoni in an endemic area — J. P. NOZAIS
- Serum levels and efficacy of oxamniquine in patients with schistosomiasis mansoni following administration of a therapeutic dose — L. C. da SILVA, H. SETTE JR., C. CHRISTO, P. C. SETTE & B. KAYE
- Attempt to control the schistosomiasis transmission by oxamniquine, in an hyperendemic locality — A. PRATA, J. C. BINA, A. C. BARRETO & M. das G. ALECRIM
- Goals of applied chemotherapeutic research in schistosomiasis — A. DAVIS
- Schistosomiasis control in Peri-Peri (Minas Gerais, Brazil) by repeated clinical treatment and molluscicidal application — N. KATZ, H. S. ROCHA & J. P. PEREIRA
- Oxamniquine in the treatment of schistosomiasis in a population in an area with low endemicity — J. C. BINA & A. PRATA
- The role of chemotherapy in the special program for control of schistosomiasis — S. de CAMARGO
- Serum enzymatic changes in patients with schistosomiasis treated with oxamniquine or by-stand — Comparative study — A. SÀEZ-ALQUEZAR, N. OHITSUKI, H. SETTE JR., A. C. MAG-NANELLI, S. BAIA & L. C. da SILVA

**OXAMNIIQUINE SYMPOSIUM** — Summary of Round-Table discussions

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**ADDRESS**

Instituto de Medicina Tropical de Sã O Paulo
Avenida Dr. Enéas C. Aguirre
P.O. Box 2921 — S Paul — Brasil

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**SUBSCRIPTIONS**

<table>
<thead>
<tr>
<th>Country</th>
<th>One year (6 numbers)</th>
<th>Two years</th>
<th>Three years</th>
<th>Single number</th>
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<td>US$ 150.00</td>
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Many clinicians and researchers on tropical pathology have met in October 1978, in the city of Rio de Janeiro, in a Symposium with the purpose to evaluate the activity of a schistosomicidal drug named oxamnique (6-hydroxymethyl-2-isopropylaminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline) very efficient in the treatment of several forms of schistosomiasis.

The early studies of RICHARDS & FOSTER (1969) followed by other researchers, have made possible the use of this drug in human beings, with the observation of its therapeutic activity and eventual collateral effects. In 1973 the REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO has published a special supplement, in Portuguese and English, informing to the medical field the obtained data from several countries where schistosomiasis spreads endemically, mainly that caused by Schistosoma mansoni.

Concerning this helminthiasis, there is no doubt that we have passed from a therapeutic nihilism to a pharmacological conquest of real efficacy, in spite of little pharmacological effects, as there is no anodyne drug in therapeutics.

The important to be excelled is the proper utilization of the drug, trying the ideal therapeutic dose for each case, with all care to try an eventual whole control of this endemy. According to Professor A. PRATA, it is necessary to know who must be treated, with the preferred purpose of reducing the transmission of the disease without prejudice of other able measures of sanitary order to prevent the appearing of new cases or eventual re-infections, by deficiency of treatment.

The present supplement brings new and valuable contributions to the study of oxamnique, with a more safe estimation of its results. New trials have been performed, with estimation of the behavior of the drug in mild and serious cases of the infection. New therapeutical schemes in endemic areas with high risk were proposed by some researchers. We do not intend, by no means, to eradicate schistosomiasis from our country only by an efficient and managed treatment. Other known measures must be adopted through a health policy that attempts for the serious medical and sanitary problems. They reach large parcel of our population that many times is corroded by hunger and stigmatized by thirst.

As responsible Director and Editor of the REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO I praise the edition of this special number on oxamnique, with the certainty that the published observations could better orientate specialists and sanitary authorities, in the treatment and control of such serious endemy.

PROF. CARLOS DA SILVA LACAZ

Director of the Instituto de Medicina Tropical de São Paulo. Director and Editor of the Revista do Instituto de Medicina Tropical de São Paulo
THE IMPACT OF THE COUNTRY DEVELOPMENT IN THE EXPANSION OF SCHISTOSOMIASIS

Solon de CAMARGO

When we study the problem of schistosomiasis in Brazil, we may consider that its start and continuation in the country were due to the needs of development, mostly agrarian to supply the world with goods, such as sugar, of high cost and great demand.

With the knowledge of the adaptability of the lands in the Northeast to sugar cultivation, all the efforts were directed there and the sugar mills multiplied. The scarce manpower of the amerindian was not sufficient. Cheaper and more efficient was the importation of the African worker and we must remember that the slave trade from Africa to the Caribbean and Hispanic America was in operation before the discovery of Brazil, which then became a new route to the South Atlantic for this dirty traffic. This corruption was even greater as, on arrival, the accommodations and food for the workers was barely sufficient and sanitation was practically non-existent. The traffic of slaves started a few decades after the discovery of Brazil and the historical data available record a total of 18,000,000 slaves arriving in Brazil up to 1888. We must consider that the total population of the country in the census of 1872 was of 10,112,061.

We can postulate that the slaves were coming from areas where schistosomiasis, both mansoni and haematobium were endemic and we can imagine the parasite load dropped onto the soil with the excreta of the infected ones. Certain conditions, however, lessened the danger: 1) There was in Brazil no snail intermediary host for S. haematobium; 2) Not all the Brazilian areas had ecological conditions for the union of snails and miracidia; 3) Some time was required for the Schistosoma mansoni, coming from several region of Africa, probably with different strains, to adapt to the snails found in Brazil.

At the present time, three species of snails are able to transmit schistosomiasis in Brazil and we list them below according to their epidemiological importance:

1) Biomphalaria glabrata — SAY — 1918
   It is the best host which we consider to be constantly associated with schistosomiasis;

2) Biomphalaria straminea — DUNKER — 1948
   It is less susceptible and not as good a vector as B. glabrata but is very prolific and is found in almost all areas of the country, except in the South;

3) Biomphalaria tenagophila — ORBIGNY — 1835
   It is the species of the South of the country and until recently was considered not to be a vector, but today is already considered responsible for transmission in the states of Espirito Santo, Rio de Janeiro and Sao Paulo.

In this manner, conditions prevailed which permitted schistosomiasis to install itself in Brazil but not all regions had the introduction of the parasite follow as a corollary of transmission.

The Northeast of the country, however, with Salvador and Recife as the principal ports of entry of slaves had, in the humid soil of the sugar plantation, the ideal conditions for transmission. With the presence of B. glabrata and B. straminea after a certain period of adaptation of the parasite in the intermediary host, transmission was established. In that time, the population did not move very much, because of lack of transportation and the contaminated area of the Northeast remained almost without change for several centuries. The sugar cane cycle, which kept the worker tied to the land was leading to the permanence of
the endemic, brought on by the bad living conditions in the houses where men would defecate near the snails which were abundant in the streams. Therefore, we can consider the existence of the schistosomiasis endemic from the extreme Northeast of Rio Grande do Norte in the town of Teuros down to the region of "Recôncavo" in Bahia, Salvador.

The development of the country, mainly in the post-war era 1914-1918 began to change and the roads, even unpaved, began to be built and the population moved about when opportunities appeared.

In 1930, schistosomiasis was present in the states of Ceará and Maranhão, and in 1940, Alencar mentioned the finding in Redenção — CE.

Belo Horizonte, the capital planned for the state of Minas Gerais and built in the beginning of this century had in 1937, with the building of the Pampulha dam, created conditions for the proliferation of snails, in the case the B. glabrata. The introduction of the disease was favoured by the poor housing, environmental conditions which resulted from polluted streams coursing to the dam, and with the existence of numerous clay-pits dug by the brick factories which would become breeding places of epidemiological importance.

In 1950, the existence of schistosomiasis in Espírito Santo was mentioned as probably coming from Minas Gerais and Rio de Janeiro.

In São Paulo, initially there was a controversy as to the time, 1950, B. tenagophila was considered unable to be a vector. The laboratory studies, confirmed with field studies, showed that there was no question of adaptability of strains of schistosoma and of snails and the valley of the Paraíba do Sul river was infected.

Still in São Paulo, the plains near the city of Santos were found by SANTOS, in 1932, infected in the district of Jabaquaras and, in 1950, MOURA found another district infected; ANTUNES, in 1952, discovered foci in São Vicente, Cubatão, Itapuna and Marapé, and in the same year, L. REY found the interior near the city of Ourinhos also infected.

The attraction of the "TERRA ROXA", the fertile soil of Paraná, in a short time brought the disease with the development of big plantations of coffee and grain. In Paraná Biomphalaria glabrata is found most often in the extreme Northeast of the state, of "NORTE VE-LHO" (Old North) and in the "NORTE PIO-NEIRO" (Pioneer North). In those zones, and in the cities of Jacarezinho and Jacuizinho, Coutinho & Pessoa described the first foci in 1949, and later in the area to Praiaçu.

The creation of the capital city in the state of Goiás, Goiânia, brought also the burden of schistosomiasis, but it was a small focus and possibly because of the high chemical-biological contamination of the streams the infection disappeared.

In the North Region, the state of Pará has three localized foci:

1) Quatipuru Basin — flooded area with cultivation of mallow for utilization of fibers;
2) Periphery of the city of Belém — it is a focus of infection similar to those of almost all other capitals, where the slum areas of the periphery have the propensity for contamination which create conditions for continuation of the infection; 3) The focus in Fordlandia, created by the immigration of people of the Northeast to work the rubber plantations of Hevea that the Ford company had established in the area.

This focus practically disappeared with the discontinuation of the development of the plantation. The botanical studies made did not take into consideration that the planting of the trees close together would facilitate the propagation of phytopLAGues that destroyed the plantation and made its development un-economical. The local population moved to a neighboring cattle raising area, where good conditions for the transmission of schistosomiasis did not exist and, according to the last report, the focus disappeared.

The latest information we have with reference to the spread of schistosomiasis is:

1) A focus near Caçeres, Mato Grosso in an area now under development for agriculture and cattle raising. The disease found in one family who moved to a more favorable place. The focus sees now to be ending.
2) The focus near the city of Picos — Planí
The studies showed that this focus was initiated by migrants traveling the "TRAN.
SAMAZÔNICA" road who would camp beneath the bridge over the Guaribas river. In this way, they contaminated the Guaribas river where B. straminea is abundant and the transmission began. Up to the present, 17,248 stool examinations have been made with 860 cases found and 2,053 persons treated (among positives and relatives). Molluscicide control was done in the river with good results.

3) In the Distrito Federal (Federal Government area of Brazil)

As it is well known, Brasília was constructed mostly by the "candangos" (name given to the northeastern unskilled manpower), who carried with them a great amount of S. mansoni.

The effect of this "baggage" has already been felt in the Rio Preto basin, northeastern boundary with Goiás, and also near the satellite town Planaltina.

We believe that the foregoing gives information on the expansion of schistosomiasis in Brazil. We must attribute this to the fine work done.

Possibly, the "Transamazônica" road, except the occurrence in Picos, will not have a great effect because of ecological conditions in the area crossed by the road.

There is correlation between the development done by government of private organizations and the human emigration from the endemic areas with the accompanying conditions of poor sanitations and basic health services to create conditions propitious to the meeting — MIRACIDIUM — SNAIL — CERCARIAE — MAN.

One point that must be mentioned is the damming of rivers for irrigation or hydroelectric plants. It is necessary that when those big dams are planned the matter of Health be taken into consideration. In those dam sites where this was not done, and we have examples in a few dams in the Northeast, where the disease was already there before the work started, it is much more difficult to solve the problem. Where the precautions were taken, such as stool examination and malacological counts of the areas to be flooded, and where all the persons entering the area were examined in order to treat all positives, and with continuing surveillance then we have the successful elements to avoid endemic schistosomiasis.

Naturally, some areas are at bigger risk than others.

Itaipú Dam, in the Paraná river, now under construction is situated in an area where the malacological surveys showed the presence of B. tenagophila and B. peregrina. One of the snails is a dangerous vector and the other, to now, has never been found to be a field vector.

At this dam site, the health organizations examine and stool test all who come to work or to live in the area. In this part of the state of Paraná there is no transmission of schistosomiasis. We hope vigilance will be permanent, thereby assuring safety.

Reading back of what we wrote, particularly when we refer to the number of Africans who arrived in Brazil, we must remember that Salvador and Recife were the main ports of entry. Other regions, however, may have had their independent doors of entry and there is the possibility of finding conditions suitable for proliferation even if not as well developed as in the Northeast.

The state of Minas Gerais had the cycle of gold mining and many blacks who were working in the sugar cane industry in Rio de Janeiro went to the gold mines and it is possible that schistosomiasis was installed there by the people from Rio. However they also could have come from the Northeast.

The focus in the Santos Lowlands (state of São Paulo) is another one where there was a possible direct importation, perhaps slower because the ecological conditions are no as favorable as in the Northeast.

In summary, we see that schistosomiasis followed man to all locales when he went in search of new work in new areas.

The greater of lesser prevalence depended on the ecological conditions of snails, the adaptability of the schistosoma to the snail, and the exposure of man to the cercariae.
IMPACT OF DEVELOPMENT ON THE SPREAD OF SCHISTOSOMIASIS IN EGYPT

M. SAIF and A. GABER

When one speaks of the impact of development on schistosomiasis in Egypt many aspects must be considered including the impact of agriculture, industry, socioeconomic conditions and educational facilities in addition to the diagnostic, investigative, therapeutic and control measures for the disease itself. All these aspects are intermingled and one cannot present specific data which is based on solid statistically analyzed documented observations. Therefore, these comments are mostly generalizations that are, or will be, the subject of future study, which is deemed necessary for the benefit of worldwide knowledge concerning this disease which affects more than 200 million people worldwide.

S. haematobium infection is widespread in Egypt together with the country-wide distribution of the snail, Bulinus truncatus. However, S. mansoni infection is restricted to the Northern Nile Delta region in association with Biomphalaria alexandrina. Biomphalaria alexandrina was detected in Giza Governorate south of Cairo concomitant with S. mansoni infection in humans, and were sporadically detected thereafter in Upper Egypt (Southern) Governorates. There is no evidence of spread of human S. mansoni infection in Upper Egypt south of Cairo, except in the nearby Giza Governorate. Until recently most of Upper Egypt was cultivated through the basin irrigation system while the Nile Delta region was totally irrigated through the perennial irrigation system. The result was a high prevalence rate of both S. haematobium and S. mansoni infection in the Nile Delta region and the low prevalence rate of S. haematobium infection in Governorates of Upper Egypt.

The construction of the High Dam south of Aswan resulted in the formation of the Nasser Lake, one of the largest man-made lakes in the world, extening in length approximately 500 kilometers, of which 350 kilometers are situated in Egypt and 150 kilometers extend to Northern Sudan. The aftermath of this was the change of the irrigation system in most of Upper Egypt Governorates from the basin to the perennial irrigation system together with the increase in quantity or arable land through land reclamation. This resulted in a significant increase in the prevalence rate of S. haematobium infection. Another significant aspect was the observation of a demonstrable rise in the prevalence rate of S. mansoni infection in the Nile Delta region, in Lower Egypt. The reason for the increase is the subject of study now. A recent observation in Upper Egypt after the construction of the High Dam was the increase of the population of Biomphalaria alexandrina in the water courses of all Governorates of Upper Egypt. But so far none of these snails have been found to be infected and no cases of S. mansoni infection have been detected in this area. However, there is the possibility of having patients from the Delta region infected with S. mansoni moving to these areas, where non-infected Biomphalaria alexandrina exist. This movement might introduce the infection in such localities, but the risk is low inasmuch as the trend in migration is from Upper Egypt to Lower Egypt and to urban communities instead of the reverse.

The Middle Egypt Schistosomiasis Control Project has already started, and is expected to extend to the rest of Upper Egypt to Aswan. The project includes the killing of snails with niclosamide and treatment of positive bilharzial cases (haematobium) with metrifonate, the drug of choice for the treatment of S. haematobium infections. These methods may sup-
press the increasing spread of *S. haematobium* infection which ensued in Upper Egypt as a result of the construction of the High Dam, the resultant changes in the irrigation system, and the added reclaimed lands for agriculture. The reason for the increase in prevalence of *Biomphalaria alexandrina* snails is subject to study at the present time.

It is to be stressed that farm laborers are the most important sector of the population to be exposed to infection with schistosomiasis due to their continuous and inevitable contact with water. In most of the arable and, manual cultivation still prevails and mechanization is limited. The impact of the large scale mechanization of cultivation in the future on the prevalence rate of schistosomiasis cannot be determined.

Large scale fishing in Lake Nasser resulted in the movement of a larger number of adult males from the Southern Governorates to Aswan and it was deemed necessary to treat the positives before they were given permission to enter the Lake area. Treatment was carried out in the past with a single injection of bycanthone (3 mg/kg) but now niradazole is given for three days (25 mg/kg daily) while we await the availability of a better single dose compound. Metrifonate was found to be impractical to use because of the long duration of treatment (three doses with two week intervals between doses). Fishermen cannot remain away from work in the Lake area that long a time.

Interestingly, in the last few years in the Delta Region, in certain areas the prevalence rate of *S. haematobium* infection has been reduced while that related to *S. mansoni* infection has been significantly increased; however, the intensity of infection in terms of ova counts is, in general, low. To be studied is whether this observation is due to the reduction of silt in the water or to changes in water velocity or anything else as a consequence of the construction of the High Dam. Of possible significance is the fact that presently tartar emetic is used in the Delta Region for the treatment of both infections, but metrifonate is being considered for the treatment of *S. haematobium* in the Delta Region in the near future.

Land drainage by tiles is being introduced in some Governorates in both Upper Egypt and the Delta Region, but its influence on the prevalence rate of schistosomiasis cannot as yet be predicted. However, preliminary data from areas in which tile drainage began show that it has no material effect because the main drains are still open and are used for swimming by children and adolescents.

The prevalence rate of bilharziasis was reduced by the provision of potable water and sewage disposal facilities, especially in the suburbs of towns and cities. However, of importance is the higher economic level of the inhabitants of these towns — mostly government employees, traders, workers in factories, employees in other organization and students. Moreover, the high educational level of the population of these communities makes them keen to seek treatment should they become infected.

In towns and cities, apart from emigrants from rural areas who have untreated or inadequately treated infection, occasional cases are found among the children of well-to-do families. These occur because of the indiscriminate or illegal use of canal water for the irrigation of private gardens, the wading or swimming in shallow waters, the use of boating or canoeing clubs and vacationing in the outskirts of towns and cities. In villages with a population of more than 1,000 inhabitants, public water supplies and various types of private latrines are provided. Some homes in these villages are provided with pumps for water, but sewage disposal systems are usually defective. Therefore the people do their washing in the nearby water courses. Development of private toilets is a problem in some villages, despite the fact that the government will construct them free of charge for those who ask and cannot afford them.

The introduction of industrialization in the rural areas remarkably reduced the prevalence rate of schistosomiasis in adults due to their move from agriculture to industry. But the problem is with children. Schools at various levels are found in most of the rural areas but children, after leaving school, play in the fields and nearby water channels.

Development can materially affect the prevalence rate of schistosomiasis when it is supplemented by practical measures to provide potable water, sewage disposal and measures to prevent the traditional contact of man to
water. Adequate control measures through the use of chemotherapy and molluscicides are being carried out on a large scale. But this is not enough in the absence of practical well organized health education programs for both adults and children and provision of facilities to utilize what they have been taught. Also the expense of molluscicides is increasing and to be considered are their possible adverse effects on the terrestrial environment.

Egypt was the first country in the world to apply molluscicides in the control of schistosomiasis. This was done in the Dakhla oasis in 1927 (copper sulphate), and a countrywide snail control was started in 1940 using methods which have changed according to the situation:

1) Focal control in which molluscicides are applied only to sites where infected snails were found.

2) Radius control, whereby snail-infested streams are treated if located within a radius of 500 meters from the periphery of inhabited places, regardless of whether bilharzial infection is discovered in the snails or not.

3) Area control, in which molluscicide is applied to a whole circumscribed area.

The last method was found to be effective in isolated areas such as the Dakhla oasis in 1952, but in open areas in the Nile valley repeated blanketing together with chemotherapy was found necessary, e.g., Warrak-ElArab 10 km northwest of Cairo, in 1953 (pentachlorophenate), WHO/UNICEF/Egyptian Government project (Egypt 49) in 1962 to 1971. The Fayoum Project 1969 to the present (niclosamide and niridazole, the recently metrifonate) and in negotiation a plan to cover Middle Egypt and future extension to the whole Upper Egypt (niclosamide and metrifonate).

The above shows that the impact of development has resulted in changes of the pattern of distribution of bilharziasis in Egypt in terms of increase or decrease of prevalence according to area and to degree of development. Therefore, we are depending at present on the large scale control of the disease by use of molluscicides and chemotherapy, while we await the discovery of a better approach.

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CURRENT RESULTS IN THE CLINICAL THERAPY OF SCHISTOSOMIASIS MANSONI (*)

Naftale KATZ

In the last two decades a significant advance in the therapy of clinical schistosomiasis mansoni has been made. Three new antischistosomal agents are now in the market, namely, niridazole, hyancathone and oxamnilquine; two others are in clinical trials, amoscanate and praziquantel.

In this presentation, a critical review will be made concerning the more important facts observed in the clinical studies with the five compounds. The experimental aspects will be considered only when indispensable for a better judgment of the drugs.


NIRIDAZOLE

A nitrothiazole derivative, niridazole (1-(5-nitro-2-thiazolyl-2-imidazolidone) was synthesized at CIBA laboratories by WILHEIM & SCHMIDT (1966) 106.

Clinical trials done in Brazil, Africa, Philippines, Japan and Britain, showed that S. haematobium is more susceptible to the drug than S. mansoni, and S. japonicum the most resistant of the three 22,65,91. The primary side effects after niridazole administration were nausea, vomiting, anorexia, headache, myalgia, and weight loss. The most serious were those associated with the neuropsychiatric disorders, e.g. convulsions and hallucinations 22, 65,91.

The schedule suggested by most researchers for treatment of S. mansoni infections is 25 mg/kg/day, divided into two equal doses, administered for seven consecutive days. This treatment results in approximately 60% to 70% of cure in children and 80 to 90% in adults 22, 48,65,82. In Brazil, PRATA et al. (1966) 82 reported that to obtain higher cure rates it is better to prolong the period of administration instead of increasing the daily dosage, and CUNHA (1966) 28 preferred a schedule of 15 mg/kg/day for 15 consecutive days.

Similar to other antischistosomal agents, trials in different regions of the world show different cure rates. For example, in Puerto Rico, fifteen S. mansoni patients have been treated with 25 mg/kg/day for seven days and no cure at all was observed 84.

Other observations are: 1) neuropsychiatric disturbances are more frequent in patients with the hepatosplenic form than in those with intestinal form 25,36,38; 2) attempts to minimize the neuropsychiatric side effects by concomitant administration of antihistamine, barbiturate, benzodiazepine or phenobarbitaline, were not completely successful 1,46,52,71,108,112; 3) niridazole produces an increase of the glucose levels of treated patients 18,67; 4) the drug can trigger hemolysis in patients whose red blood cells are deficient in enzymatic glucose-6-phosphate dehydrogenase 69; 5) alterations of electrocardiographic tracings are common and involve depression or inversion of the T wave and sometimes myocardial ischemia 6,7,29,46; 6) alterations of the electroencephalogram appear in the form of paroxysmal discharges, indicating that the drug has an epileptogenic effect 6,7; 7) a temporary depression of spermatogenesis was noted in clinical and laboratory studies 82,88; 8) "in vitro" and "in vivo" tests demonstrated the mutagenic activi-

(*) This review has been supported, in part, by the Conselho de Desenvolvimento Científico e Tecnológico, Brasil de Desenvolvimento Científico e Tecnológico, Brasil.
ty of niridazole \(^{23,70,94}\); 9) in mice and hamsters niridazole is a potent neoplastic agent \(^{44,104}\), and 10) at least 6 drug-related deaths occurred in approximately 200,000 patients treated with niridazole \(^{107}\).

In summary, the problems observed with niridazole administration in schistosomiasis mansoni patients and in laboratory studies suggest that the drug should be avoided for clinical use.

**HYCANThONE**

A hydroxymethyl analog of Miracl D, hycanthone was obtained by the microbiological oxidation of the parent compound by ROSI et al.\(^{50}\) in Sterling-Winthrop Laboratories. Hycanthone is more active in *S. mansoni* than in *S. haematobium* human infection and inactive against *S. japonicum* \(^{106,110}\). The schedule of treatment varied considerably, according to different research groups. Dosages from 1.5 to 3.5 mg/kg of body weight given as single intramuscular injections have been employed.

Soon after its appearance, hycanthone was applauded as the “final solution” for the clinical treatment of schistosomiasis. Unfortunately, the increased experience shows that this drug, although used in single-dose, is far from the ideal.

The problems faced with hycanthone's usage are toxicity, mutagenicity, teratogenicity, carcinogenicity and strain resistance.

The toxicity of hycanthone is specifically directed to the liver, sometimes it produces only an elevation of plasma transaminase levels, sometimes it induces jaundice, and in some patients it causes a severe adverse reaction resulting in death. Forty severe adverse reactions of various kinds have been reported. They include 20 fatalities, 17 associated with hepatic necroses \(^{107}\). From those fatalities, some clear contraindications have emerged although others can only be presumed. The contraindications are past or present liver pathology, respiratory tract infection, concomitant use of other drugs (phenothiazines derivatives, male and female hormones) and debilitating diseases (lupus erythematosus disseminatus, chronic osteomyelitis, etc.).

It must be emphasized that a true frequency of severe side effects from hycanthone usage is not available.

Mutagenic effects associated with hycanthone were first reported by HARTMAN et al. (1971) \(^{41}\) on *Salmonella* and Escherichia coli T\(_{4}\) bacteriophage. Further studies showed that hycanthone produced chromosomal aberrations in lymphoma cell cultures \(^{21}\), in leukocyte cultures \(^{86}\), interference in cellular differentiation during the embryonic stage of chick and arachnidan eggs \(^{75}\), mitosis blockade, chromosomal breaks and anaphases with chromosomal bridge in *Allium cepa* root tips \(^{73,87}\), mutagenic effects on *Neurospora crassa* \(^{77}\) and on *Saccharomyces cerevisiae* \(^{43}\).

However, no mutations were observed in 16,196 offspring of male mice intraperitoneally injected with 150 mg/kg of hycanthone, which indicated that the test for gene mutation induction using specific locus methods was negative \(^{82,93}\). Again, no mutagenic effects were observed in *Habrobracon serinopae* females \(^{86}\), nor were chromosomal aberrations seen in the whole spermatogenic cycle of treated mice \(^{87}\), and no significant effect of hycanthone was found on the frequency of blood cells having chromosomal abnormalities in 13 Brazilian patients treated with 2.5 mg/kg body weight \(^{56}\).

Teratogenic effects of hycanthone were observed by MOORE (1972) \(^{74}\) in 49.6% of the litter fetuses (exencephalia, hydrocephalia, rib fusion and branching) and 44.6% fetus mortality when animals were treated with 50 mg/kg. Similar results were reported by SIEBER & ADAMSON \(^{85}\) in mice and rabbits.

The most controversial point is the carcinogenic activity of hycanthone. HAASE et al. (1973) \(^{40}\) show that hycanthone administered to infected mice produces a higher incidence of hepatomas as compared with uninfected hycanthone-treated mice and/or uninfected, untreated control animals. When YARINSKY et al. (1974) \(^{110}\) repeated this experiment, the frequency of liver tumors in the three groups of mice was the same. However, an important difference existed between the two trials concerning time of follow-up. In HAASE et al. (1973) experimental tumors started to appear after 17 months, whereas in the studies of YARINSKY et al. (1974) the 17th month was the last observation month. A small number of survivors were examined at that time \(^{34}\). More recently, HAASE & BUEDING (1976) \(^{39}\) confirmed the carcinogenic effects of hycan-
thione in mice with doses as high as 60 mg/kg, i.m. or as small as a single 3 mg/kg dose.

The drug also induces malignant transformations of Rauscher virus-infected rat embryocells 42.

The *S. mansoni* strain resistance in animals was demonstrated by ROGERS & BULDING (1971)89. YARINSKY repeated these experiments using *S. mansoni* from the same origin and from another source. He confirmed the resistance of one strain, but not the second 109.

Further experiments show that resistance to hycanthone, to oxamniquine and to two chloronidazole analogs of hycanthone, was maternally transferred and remained stable for several generations. Resistance was also observed when immature schistosomes within mice (28 days infection) were exposed to the drug. In this way, four out of five strains of *S. mansoni* became resistant 45. Using the same methodology, it was impossible to induce resistance to the L.E. strain or to a Puerto Rican strain of *S. mansoni* 3,108. However, for the first time, KATZ et al. (1973)58 reported resistance in mice to *S. mansoni* strain isolated from two patients who had been treated twice with hycanthone and once with niridazole, and who had not been cured by this triple treatment. Other research groups confirmed this observation 17,30. Recently, in our laboratory eight strains, isolated from treated and untreated patients, with a different response to hycanthone and to other known antischistosomal agents, were observed 8.

The discussion concerning the meaning of the results found in "in vitro" and "in vivo" tests with hycanthone and its mutagenic or carcinogenic activity is still controversial as relates to the contraindication to use of the drug in clinical therapy. An important study to answer this specific question and for general information could be the analysis of results of part of 1,500,000 patients already treated with hycanthone all over the world since 1971.

Experimental studies with some analogs of hycanthone show that is possible to reduce the mutagenic activity without decreasing antiischistosomal potency. Unfortunately, from these experiments, no new drugs emerged as candidate antischistosomal agents for clinical trials. At present, every drug to be used in clinical therapy of schistosomiasis must be screened for mutagenic and carcinogenic activity. Despite the increased cost and time of the trials, there is no doubt that this will give more confidence in the safety of the drug. This was a very good "side effect" which resulted from hycanthone usage.

**OXAMNIQUINE**

A mirasan derivative, oxamniquine is the 3-hydroxymethyl-2-isopropyl-aminomethyl-7-nitro-1,2,3,4-tetrahydroquinaline described by RICHARDS & FOSTER (1969)86 at Pfizer Laboratories.

This drug when orally administered at the dose level of 15 mg/kg for adults and 20 mg/kg for children in the clinical trials in Brazil demonstrated a cure rate of 80 to 90% and 85 to 90%, respectively 54,61,97. In trials performed in some African countries, oxamniquine is being given in dosages three times higher with lower parasitological cure rates 19,32. Different from all other antischistosomal agents in current use, oxamniquine gives similar cure rate in patients with acute or chronic phases of schistosomiasis 56,57.

The most common side effects observed after oxamniquine administration were dizziness, nausea, headache and drowsiness. These symptoms appeared one or two hours after the drug administration and persisted, in most cases, less than one day. In some trials, irritability, excitability, hallucination or convulsion have been reported 12,24,51,47,54,61,62. Laboratory tests in a few patients revealed an elevation of plasma transaminase levels, leukopenia, hematuria and proteinuria.

Discreet alterations of electroencephalographic and electrocardiographic tracings have also been observed.

In Brazil, the Ministry of Health is conducting a program of schistosomiasis control in the northeastern part of the country. As one facet of this program, treatment has been given to about 1,000,000 people. No fatal case or severe side effects have been observed 13.

Low mutagenicity activity of oxamniquine has been detected in the frameshift mutant of some *Salmonella typhimurium* strains 41, but negative results were found in the cytogenetic,
host-mediated or dominant-lethal tests. More recently, fairly high mutagenic effect was observed in host-mediated assay with two strains of S. typhimurium.

It is interesting to note that when the host's intestinal bacterial flora is reduced by antibacterial agents, administration of oxamniquine did not produce any mutagenic effects in the urine or in the host-mediated assay and antischistosomal effect remains unchanged.

No carcinogenicity effect with this drug has been detected. Partial or total strain resistance has been demonstrated in S. mansoni isolated from patients who were treated previously with hycanthone and niridazole or with hycanthone and oxamniquine. Recently, two patients were treated orally with the drug on three different occasions without cure. Experimental studies of the schistosomula in mice did not reveal resistance of the strains isolated from those patients. The fourth clinical treatment with oxamniquine given by intramuscular route produced the parasitological cure. This fact probably indicates that the failure of treatment is not only dependent of S. mansoni strain sensitivity, but also on the pharmacokinetics or metabolism of the drug in a particular human host.

Summing up, oxamniquine appears to be a safe and effective compound, that can be used for large scale treatment, especially in countries where S. mansoni strains are sensitive to the drug. Nevertheless, the value of large scale or mass treatment, as a tool for the control of schistosomiasis in endemic area, is a subject beyond the scope of this paper.

AMOSCANATE

This new-anthelmintic, synthesized at GIBA-GEIGY laboratories is the 4-isothiocyanato-4-nitrodiphenylamine (C 9333; GO/CGP 4540).

Experimental studies show that amoscanate has a broad anthelmintic spectrum: hookworm, several species of filariae and the three primary human schistosome parasites, S. mansoni, S. haematobium and S. japonicum (STRIEBEL, 1976; BUEDING et al., 1976).

Preliminary clinical trials performed by McMahan (1977) in Tanzania on patients harboring S. haematobium infections showed poor schistosomicidal activity. Amoscanate was administered at dose levels of 10 to 115 mg/kg. With the higher doses a decrease of oviposition was observed, but the toxic effects produced prevented further dosage increases. With doses up to 100 mg/kg, patients developed staggering gait, chest pain, palpitations and dizziness.

In our studies, therapeutic activity of amoscanate has been demonstrated in mice and hamsters experimentally infected with S. mansoni.

Preliminary clinical trials have been done in patients with S. mansoni infections. Ten patients have been treated with single oral doses of 30 mg/kg and another 10 patients with 50 mg/kg. The side effects observed were drowsiness, headache, gliddiness and malaise, of mild and moderate intensity.

Only one out of ten patients treated with 30 mg/kg and three out of nine patients with 50 mg/kg have been considered as cured.

Since there is evidence that cure rates in experimental animals can be increased when amoscanate is administered in smaller sized particles, a new formulation must be produced for further clinical trials.

PRAZIQUANTEL

This broad-spectrum antischistosomal agent developed from joint research conducted by E. MERCK and BAYER AG, is the 2-(cyclhexylicarbonil)-1,2,3,6,7,11b-hexahydro-4-H-pyrazine (2,1-a)-isoquinolin-4-one. Experimental trials showed that praziquantel is very active against S. mansoni, S. haematobium and S. japonicum infections in mice, hamsters, Macaca, in several species of monkeys, and different species of cestodes.

The first clinical trial in S. mansoni infection has been made in Brazil. This trial was divided into three stages. In stage I, double-blind trials for patients tolerance and efficacy were conducted at three different dose levels (total doses of 20 mg/kg, 40 mg/kg and 60 mg/kg) in 28 patients treated with praziquantel and 27 treated with placebo. In stage II, trials were done to assess the therapeutic efficacy of praziquantel at a total dose of 60 mg/kg divided into three oral doses in 30 patients, and in stage III, a single oral dose of 50 mg/kg in 31 patients.
The most common side effects observed were nausea, abdominal pain, headache, dizziness and drowsiness; other rare but serious side effects were palpitations, pruritus, urticaria, vomiting, ketosis and lightheadedness. This symptomatology was generally mild or moderate, and lasted for 24 to 48 hours. There was a direct correlation between increased dosage and increased frequency of side effects. In fact, total doses of 50 to 60 mg/kg seems to be the upper limit of drug tolerance.

In a few patients abnormalities were noted in liver function tests, but in general laboratory tests showed little change. Although the alterations were suggestive of subclinical hepatotoxicity, they were not actually proven to be drug-related. In fact, the alterations were more frequently observed in patients given lower doses of praziquantel than in those given higher doses. Paired electrocardiograms did not show abnormalities of clinical significance, but the alterations found in the electroencephalograms indicate that further evaluation is necessary.

The parasitological follow-up demonstrated that over 90% of patients treated with praziquantel with total doses of 50 to 60 mg/kg at 6 and 12 months remained cured.

Further clinical trials by several research groups are in progress in Brazil, and Africa for S. haematobium, and in the Philippines for S. japonicum. Recently, we treated 115 patients divided into three groups, according to dosage: Group I, 39 patients treated with single oral dose of 30 mg/kg; Group II, 39 patients with 40 mg/kg, and Group III, 37 patients treated with a total dose of 50 mg/kg, divided into two doses, administered with a six-hour interval.

The side effects observed were similar to those already described, the most common being abdominal distress, headache, diarrhea, and giddiness. The parasitological follow-up done in 64 patients, up to six months after treatment shows percentages of cure of about 41%, 68% and 58% respectively for groups I, II and III.

The difference in the cure rates between the first and second trials probably can be accounted for by the age groups. In the first trials only adults were treated, whereas in the second, most of the patients were children.

Further clinical trials must be performed with praziquantel to reach a final conclusion as to its standing as a schistosomicidal drug for routine treatment.

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**DISCUSSION ON DR. KATZ’S PAPER — CURRENT RESULTS IN THE CLINICAL THERAPY OF S. mansoni**

Dr. M. SCHULTZ (U.S.A.)

I would like to congratulate Dr. Katz on his presentation. I was particularly interested in his comments that praziquantel gave cure rates of 40 to 60%. We know that cure rates are not the best way of judging a drug; it is the percentage of egg reduction that is really important. Do you have the figures available for the percentage egg reduction in this trial?

Dr. N. KATZ

The question of whether to look for complete cure or only egg reduction is not only important in clinical trials but also in considering control of schistosomiasis. In the clinical trial we are discussing, egg reduction was approximately 90%. I believe that we should strive for cure and not be satisfied with egg reduction, as there is no evidence that reducing the number of eggs will cure the patients’ symptoms or be successful in controlling the disease. I know that in some African countries low doses of hyacinthane are being recommended to achieve egg reduction rather than cure. This was the case 30 years ago when we had the antimonials and suppressive management was all that could be achieved, but now with several good drugs that are well tolerated we should attempt to cure our patients.

Dr. A. DAVIS (GENEVA)

I think that you have to be very careful in defining your terms as control of schistosomiasis is actually two things. One is disease control using drugs, and the other is transmission control using a combination of drugs and molluscicides. Both disease control and transmission control go toward the control of schistosomiasis. I will be talking about this in greater detail tomorrow, but there is a dangerous simplicity in the assumption that a 90, 95, or 99% reduction in egg output is necessarily a good thing. There are many ecological situations in the world where even one or two eggs can still maintain a transmission cycle of schistosomiasis. I tend to agree with Dr. Katz that in the past when we had fairly toxic and subcurative drugs, we strove for so-called suppression, but now we are getting to a stage where we have a variety of drugs and we should strive for optimal effects. These are maximal cure rates, minimal side effects and lowest costs. Only in this way are we liable to control schistosomiasis both in terms of disease and transmission.

PROF. PRATA

This is an important point, and it is certainly easier to obtain egg reduction than com-
plete cure with drugs that are currently available. In the evaluation of a drug the important thing is negativity. In many parts of the world, results are reported as egg reduction; but usually in Brazil we look for the percentage of cases who are negative after at least five or six stool examinations performed over a period of four to six months following treatment. This is my definition of cure, and I think that is general agreement within this country.

Dr. J. CHIRIBOGA (SAN JUAN)

I agree that we should look for complete cure to avoid transmission, and as Dr. Davis said each situation is different and it depends on the local ecological factors. For example schistosomiasis can be easily controlled in six thousand people working on a sugar plantation as it is simple to treat everyone and control their environment. In other places in the world the situation is different. When discussing schistosomiasis control, there are three factors to consider. One is cure of the disease, the second is what can be done with the snails, and the third is what can be done with the people at an educational and socio-economic level.

PROF. PRATA

Dr. Katz mentioned another important point that reduction in the number of eggs is important in preventing severe forms of the disease. We now have sufficient proof that the intensity of infection in terms of worm load correlates with the severity of the disease in terms of severe forms and hepatosplenic disease. We do not have any proof that reduction in eggs improves other symptoms in the patient. The other important point is that there is no proof that reduction in the number of eggs is useful in the general control of the disease. We need more information.

Dr. Z. ANDRADE (SALVADOR)

I want to stress the point that if you have a drug that cures 100% of patients this is excellent, and every effort should be made in the direction of improving drugs to obtain 100% cure. We should not obscure the fact that by treating a patient and not obtaining a complete cure, we are giving benefit to the patient by reducing his worm burden. If by doing this we can avoid the development of severe forms of the disease, it is important. The common hepato-intestinal form is a mild disease and most patients are asymptomatic. The few symptoms that they have can also be found in people without schistosomiasis. Schistosomiasis is important because it causes hepatosplenic disease, and this causes death. If we can prevent the development of this form of disease by giving drugs, we are performing a service. I do not mean that we should not look toward drugs that would eradicate or cure 100% of infections and help us control schistosomiasis, but this is a complex task an involves many other aspects besides chemotherapy.
CLINICAL DEVELOPMENT OF OXAMNUINIQUE IN EGYPT

M. SAIF and A. GABER

Recently interest has been focused on the search for nonantimonial drugs for the treatment of schistosomiasis and oxamnique, a tetrahydroquinoline derivative obtained by hydroxymethylation of 2-aminomethyltetrahydroquinoline has been introduced for the treatment of Schistosoma mansoni infection. It is 6-hydroxymethyl-2-isopropylaminomethyl-7-nitro 1,2,3,4-tetrahydroquinoline.

Pharmacodynamic studies showed that oxamnique is well absorbed after oral administration and is metabolized into inactive acidic metabolites which are largely excreted in the urine.

The single oral dose (50 mg/kg body weight) of oxamnique has a potent schistosomical action against both mature and immature S. mansoni forms in mice and hamsters as well as in South American monkeys (Cebus sp.), East African monkeys (Cercopitheus sp.) and baboons (Papio sp.). Male S. mansoni worms were shown to be more susceptible than females. Effective control of the infection was achieved by the action against males, for in their absence, egg laying by residual females ceased. Even when large number of the males survived, egg laying was not resumed for at least six month after treatment.

Our experience with oxamnique in the Institute for Research for Tropical Medicine in Cairo started early in 1970 when we undertook a pilot study of the intramuscular formulation of oxamnique.

We started at a dose of 1/5 the predicted therapeutic dose. Thus, we started at 1.0 mg/kg body weight, and raised the dose progressively in subsequent treatment groups by 1.0 mg/kg up to a dose of 10.0 mg/kg. Although we investigated all cases parasitologically to obtain information on dose response, the basic purpose of the experiment was to determine the safety of the drug because in Egypt, schistosomiasis is treated on a large scale basis and the use of safe drugs is a primary requirement. Clinically most of the patients in both the S. haematobium and S. mansoni groups had no obvious gross pathology. A fair proportion had hepatomegaly, hepatosplenomegaly or splenomegaly and a variety of concomitant diseases. Previous chemotherapy had usually been tartar emetic.

PLAN OF THE EXPERIMENT

We were initially interested particularly in patients with pure S. haematobium infection, and we excluded most of those with incidental S. mansoni infection. Patients were admitted to the Institute for Research for Tropical Medicine in Cairo. Pre-treatment tests included urinary ova counts on three consecutive days pre-treatment using Bell's technique and miracidial hatching tests, full haematological studies, investigation of a number of biochemical parameters (SGPT, SGOT, serum bilirubin, alkaline phosphatase and glucose 6-phosphate dehydrogenase), urinalysis and electrocardiography. All these studies were repeated 7, 14, 21 and 28 days after treatment. Chest X-ray was done only once pre-treatment. Oxamnique was given as a single intramuscular dose in the buttock, and daily clinical follow-up occurred during the entire hospitalization period which lasted for at least four weeks.

RESULTS

Regarding side effects, we found very few patients reporting systemic side effects, those reported were mainly temporary salorrhoea and feelings of generalized "heat". In respect to toxic effects, although in the clinical patient material in the study this was most difficult to interpret, there were no demonstra-
ble nor any significant trends of abnormality in the various hematological and biochemical parameters investigated.

**S. haematobium**

While there was a nil effect with the first two doses, i.e. 1.0 and 2.0 mg/kg body weight, there was a progressive increase in reduction of egg output between doses 3.0 and 4.0 mg/kg, (mean reduction was 33.0% and 81.2% respectively). In doses given subsequently there was a diminishing effect to 7.0 mg/kg and around a 50% reduction at 8.0 mg/kg. From 3.0 mg/kg onwards, we experienced increasing trouble with pain, tenderness, and induration at the inoculation site. The decreased efficacy seen after 4.0 mg/kg was possibly because of induration at the inoculation site which perhaps “locked up” the compound in some way, and prevented absorption (subsequently, an American study showed biochemical evidence of this). This local induration was transient and did not require any specific treatment. However, when the largest dose, 8.0 mg/kg, was split and given by simultaneous separate inoculations which avoided to some extent the swelling and induration, we were unable to prove the postulate of focal trapping of the drug.

Apart from a fall or rise in egg output, no patient was cured. Two patients with extremely low egg counts in fact did reach zero, but one reverted to a low positive again on longer term follow-up, and the other can be discounted because he had a count of only one egg pre-treatment.

With the intramuscular formulation, 8.0 mg/kg is really the highest tolerable dose in a single injection. Thus the intramuscular picture did not look too good, because although we did achieve inconsistent mean falls in egg count over the first four weeks post-treatment, with all the doses employed; miracidial hatching tests were undertaken in all cases and all were positive (except for the patient with one egg pre-treatment), which indicated the continued presence of viable eggs.

**S. mansoni**

In the meantime, oxamniquine was investigated in experimental schistosomal infesta-

tions in baboons and there was evidence from this screen that the compound might be more effective against *S. mansoni* than *S. haematobium*.

Thus we investigated the use of oxamniquine in *S. mansoni* patients, using small groups only, at dose of 8.0, 10.0 and 2 x 4.0 mg/kg. It was found that four weeks after treatment, there was a significant reduction in ova counts but none of the patients attained negativity. The side effects were as aforementioned.

The intramuscular route, therefore, was considered not promising and was abandoned. We then shifted to another pilot study using the compound in the form of capsule and suspension for oral administration.

**S. haematobium**

The following dosage schedule was used in four groups of five patients each suffering from *S. haematobium* infection:

1) 20.0 mg/kg body weight single dose for one day;
2) 15.0 mg/kg body weight twice daily for two days;
3) 12.5 mg/kg body weight single dose for two days;
4) 12.5 mg/kg body weight twice daily for one day.

Results again proved oxamniquine therapy not to be effective in *S. haematobium* infection and it was concluded that oxamniquine is of no practical value in patients with urinary schistosomiasis.

Efforts were then concentrated on a controlled pilot study of treatment of *S. mansoni* infection using the oral formulations of oxamniquine.

A preliminary dose response study was carried out which revealed that the optimal dosage of *S. mansoni* cases in Egypt is a total of 69.0 mg/kg body weight given over 2-3 successive days. This schedule combines permissible safety with maximal efficacy.

Two groups of patients suffering from *S. mansoni* infection were studied: the first comprised 10 male patients and the second 23 patients (20 males and 3 females), ages 18-70 years and weight range 38-70 kg. All were suf-
ferring from active intestinal bilharziasis and
were excreting viable S. mansoni ova in the
stools. Concomitant viable S. haematobium ova
were also seen in three patients.

All patients were hospitalized for at least
five weeks. Eggs in one gram of stools were
counted by a modification of Bell's technique
and the results were expressed as number of
eggs/gram of stool. One gram of stool was
repeatedly washed (five times) with form glyc-
erin solution, then following the final wash,
the sediment was filtered and stained with
ninhydrin. The egg count was done for three
consecutive days before treatment and mira-
cidal hatching test was performed before
treatment to test for the viability of eggs.
These procedures were repeated after therapy
at weekly intervals for a follow up period of
at least four weeks. After discharge from the
hospital, follow up of some cases was discon-
continued for a longer period of time.

Two weeks before starting oxamnique
therapy, intestinal helminths were treated by
use of suitable anthelmintics. All the patients
were chosen on the condition that they had
not been previously treated for bilharziasis
for at least six months prior to their entry
into the present study.

Liver function tests (serum bilirubin,
SGOT, SGPT and serum alkaline phosphatas-
e) kidney function tests (endogenous creatini-
ne clearance, BUN and complete urinalysis),
haemograms, platelet counts and EKG trac-
ings were done once before treatment, were
repeated one the day after completion of ther-
apy, and then once weekly during the period
of hospitalization.

Dosage schedule: The two groups recei-
ved oxamnique orally in a total dose of 60
mg/kg body weight, which was split in the
first group to 15 mg/kg body weight twice dai-
ly for two days, while in the second group
the drug was given in a single daily dose of
20 mg/kg body weight for three consecutive
days. Oral administration of the drug was
under direct supervision and side effects we-
re recorded after direct questioning of each
patient.

Thorough clinical examinations were ma-
de on each patient. Some who were suffering
from concomitant organic diseases, such as
rheumatic heart disease, chronic asthmatic
bronchitis, nephrotic syndrome, ascites, anaem-
ia and multiple nutritional deficiencies we-
re included in the study to see if there was
any possible contraindication-to using the
drug in complicated cases. We found in the
previous experiments on S. haematobium that
complicated cases tolerated the drug well. He-
patomegaly and/or splenomegaly were obser-
ved in 26 patients (78.7%) from both groups.

RESULTS

The criteria of cure adopted in this stu-
dy were based on a complete disappearance of
eggs (100% egg reduction) and absence of via-
bile eggs by miracidial hatching test.

The range of pre-treatment egg count per
one gram of stool was 78 — 3078 with an ave-
rage of 770 in Group I and 13 — 1578 with
an average of 492 in Group II. Four weeks
after oxamnique therapy, cure was recor-
ded in nine out of ten patients (90%) in Group
I and in 17 out of 23 patients (73.9%) in Group
II. In the patients who failed, egg reduction
was 97.0% in one patient from Group I and
93.9% (average) in six patients from Group II
(Table I).

Toleration was generally good, but light
headiness and drowsiness were reported by
80% of the patients in Group I. Mild trans-
ient diarrhea was reported by five patients
(15.2%) in the two groups.

There was no obvious effect on hepatic
and renal functions and the blood picture. EKG
tracings showed no abnormal changes.

CLOSED COMMUNITY STUDY

After the safety and efficacy of oral
oxamnique was determined in the treatment of
S. mansoni infection as shown by the re-
results of the aforementioned controlled pilot
study, we arranged for a closed community
controlled study. Though the main aim was
to assess the response to the total dose of 60
mg/kg given over three consecutive days, a
small group of patients was given a trial to-
tal dose of 40 mg/kg over two consecutive
days. The reason for this was to reassess the
efficacy of the relatively smaller dose on
TABLE I
Pilot study
Results of schistosomiasis mansoni therapy with oxamnique

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Cases</th>
<th>Dose mg</th>
<th>Pre-treatment Ova Count</th>
<th>4 Weeks Post Treatment</th>
<th>% Reduction in Egg Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10</td>
<td>15 mg bid x 2 days</td>
<td>R.: 78-30%</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>23</td>
<td>20 mg/ day x 3 days</td>
<td>Av.: 779</td>
<td>R.: 13-1579</td>
<td>17</td>
</tr>
</tbody>
</table>

R = Range
Av = Average

A larger number of patients than that studied previously.

Three hundred and seventy three male patients in the age range of 20-22 years, all of them newly recruited trainees for police service in Tura Prison near Cairo, were the subject of this study. Their body weights ranged between 62 and 75 kg and all of them suffered from S. mansoni infection. They were clinically examined and other intestinal parasites were treated one week before the administration of oxamnique. Three hundred nine patients were given a dose of 20 mg/kg body weight daily for three days (total of 60 mg/kg body weight) while 64 patients were treated with the same daily dose for only two days, i.e., a total of 40 mg/kg body weight. The drug was given two hours after breakfast. Ova counts were done using Bell's technique. Follow up was made biweekly for three months after the administration of the drug.

Blood counts were made before, immediately after, and one week and one month after the administration of the drug. The mean egg count/gm of stool was 284±95.

RESULTS

Two hundred thirty of the 309 patients treated (74.4%) with the total dose of 60 mg/kg body weight were found negative while 33 out of the 64 patients given the total dose of 40 mg/kg body weight were negative (51.6%). The criteria of cure adopted were based on complete disappearance of eggs (100% egg reduction, and absence of viable eggs by miracidial hatching test. In both groups a very remarkable and significant reduction of egg counts in non-cured cases was found to occur and ranged from 91-99% (Table II).

Liver function tests (serum bilirubin, SGOT, SGPT, serum alkaline phosphatase), kidney function tests (endogenous creatinine clearance, BUN, and complete urinalysis), hemogram and platelet counts showed no conspicuous changes. Also no post-treatment changes could be detected in the EKG tracings.

No obvious side effects or toxic reactions were reported other than transient diarrhea in a small number of the patients. The side effect did not require any adjuvant treatment and disappeared within two days. Some of the patients in the first group complained of same vague sense of light headedness on the third day post-treatment.

After the assessment of the efficacy, tolerance and safety of oxamnique in a closed community study, arrangements were made to carry out a larger scale field trial. Inasmuch as it is well known that areas of S. mansoni infection in Egypt usually include a large number of patients suffering from both S. mansoni and S. haematobium, it was decided to carry out a further pilot study on mixed infections using metrifonate and oxamnique concomitantly. The aim of this study was mainly to ensure safety and tolerance of both compounds when given together and to exclude the possibility of drug interaction.

Thirty two other patients, also newly recruited soldiers, were found to suffer from mi-
TABLE II
Closed community trial
Results three months after oxamniquine therapy

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Total dose mg/kg</th>
<th>Pre-treatment Ova Count</th>
<th>After 3 Months</th>
<th>% Reduction in Ova Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>60</td>
<td></td>
<td>230 79</td>
<td>(74.4%)</td>
</tr>
<tr>
<td>60</td>
<td>40</td>
<td>246 ± 95</td>
<td>33 31</td>
<td>(51.5%)</td>
</tr>
</tbody>
</table>

ixed infection, i.e., S. haematobium in urine and S. mansoni in stools. All procedures carried out on the previous mansoni group were done here in addition to ova counting in the midday urine sample. Average ova count/gram of stool was 227 (13-593) and count/10 ml urine was 507 (35-787).

All patients were treated with metrifonate in the single oral dose of 10 mg/kg body weight every two weeks for a total of three doses. Fourteen of them were given oxamniquine in the total dose of 60 mg/kg body weight and 10 patients were given the total dose of 40 mg/kg body weight. The first dose of metrifonate was administered simultaneously with the second dose of oxamniquine, two hours after breakfast. Eleven of the 14 patients of the 60 mg/kg body weight subgroup were found negative three months after treatment for both S. haematobium and S. mansoni (78.6%) while 12 out of the 18 patients of the 40 mg/kg body weight subgroup were cured of S. haematobium (66.7%) and only eight were cured of S. mansoni (44.4%) (Table III).

No significant side effects or any evidence of intolerance were observed in any of the patients thus treated.

TABLE III
Closed community study
Results three months after combined oral oxamniquine and metrifonate (*) therapy in mixed infections

<table>
<thead>
<tr>
<th>No. of Patients Treated</th>
<th>Oxamniquine Total Dose mg</th>
<th>No. of Patients Cured</th>
<th>No. of Failure Cases</th>
<th>% Cure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>60</td>
<td>11 S.H.</td>
<td>3 S.H.</td>
<td>78.6</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
<td>12 S.H.</td>
<td>6 S.H.</td>
<td>66.7</td>
</tr>
</tbody>
</table>

(*) Mefronate dose in this group was 10 mg/kg b.w. every two weeks for three doses
S.H. = S. haematobium
S.M. = S. mansoni

LARGE SCALE FIELD STUDY

A village in the Nile Delta region, about 35 kilometers northeast of Cairo, was chosen for the large scale field study with oxamniquine, with the understanding that no molluscicide measures were being done in the nearby water courses. This study was considered to be an acid test for the assessment of oxamniquine alone as both a therapy and a control measure. This village (Sindewa) has a population of about 5,000. Preliminary screening of the inhabitants in 1976 showed a prevalence rate of 56.0% of S. mansoni infection. Nine hundred fifty six patients suffering from S. mansoni infection were included in this study and 129 patients were excluded (pregnant females or defaulters during pretreatment
examinations). The age and sex distribution is shown in Table No. IV.

**Table IV**

<table>
<thead>
<tr>
<th>Field study — Sindewa village Cases treated — Age distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
</tr>
<tr>
<td>&lt; 5</td>
</tr>
<tr>
<td>5 — 12</td>
</tr>
<tr>
<td>13 — 19</td>
</tr>
<tr>
<td>20 — 29</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

Males: 492 Females: 464

All the patients were clinically examined and stool ova counts were done using the modified Bell's technique.

Concomitant parasitic infections were treated before the start of oxamnique therapy, as follows:

- **Ascaris, Ancylostoma, Oxyuris, Trichostongylus:**
  - Pyrantel pamoate 10 mg/kg b.w. single oral dose
- **Taenia saginata:** Niclosamide single dose of 4 tablets
- **Amoebiasis:** Tinidazole oral tablets.

Eight hundred fifteen patients were treated with the dose of 20 mg/kg daily for three consecutive days, 72 cases were treated with the same daily dose for two consecutive days and 69 cases were treated with a single dose of 23 mg/kg. The results of follow up 1, 3, 7 and 18 months after treatment are shown in Table V.
Assessment of the chemotherapeutic activity of oxamniquine on a one and three months basis reveals the best efficacy was found for the three days course (Table V) and favorable results for the two days course. But the overall results at seven and 18 months were lower. The lowering of these results comes from the impact of reinfection on the younger age group (5-12 and 13-19) who usually are very difficult to keep away from water as they have no other place to play (Table VI).

Also a considerable number of farm laborers (14-18%) could not return for follow up because they were engaged in cotton harvesting at the time and had been negative during the first two follow-ups. The two days course appears to give better long-term follow-up results but one cannot be definite inasmuch as the number thus treated is rather smaller than that given the three days course of therapy.

The side effects were minimal and did not require specific treatment.

### Table V

Field study — Sindewa village. Overall results of oxamniquine therapy

<table>
<thead>
<tr>
<th>Dose</th>
<th>No. of Cases</th>
<th>1 Month</th>
<th>3 Months</th>
<th>7 Months</th>
<th>18 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Neg.</td>
<td>Total</td>
<td>Neg.</td>
<td>Total</td>
</tr>
<tr>
<td>20 mg/kg x 3 days</td>
<td>815</td>
<td>771</td>
<td>(97.0%)</td>
<td>766</td>
<td>658</td>
</tr>
<tr>
<td>20 mg/kg x 2 days</td>
<td>72</td>
<td>66</td>
<td>51</td>
<td>69</td>
<td>56</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>69</td>
<td>63</td>
<td>32</td>
<td>67</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>956</td>
<td>900</td>
<td>754</td>
<td>902</td>
<td>737</td>
</tr>
</tbody>
</table>

(*) Young age group (5-12 and 13-19) + defaulters

### Table VI

Field study — Sindewa village

Results according to age group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose Follow Up</th>
<th>20 mg/kg x 3 days</th>
<th>20 mg/kg x 2 days</th>
<th>20 mg/kg x 1 day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 M.</td>
<td>3 M.</td>
<td>7 M.</td>
<td>18 M.</td>
</tr>
<tr>
<td>&lt;5</td>
<td>T.</td>
<td>10</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>N.</td>
<td>9</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>90</td>
<td>90</td>
<td>66.7</td>
</tr>
<tr>
<td>5-12</td>
<td>T.</td>
<td>241</td>
<td>238</td>
<td>207(*)</td>
</tr>
<tr>
<td></td>
<td>N.</td>
<td>198</td>
<td>194</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>82.2</td>
<td>81.5</td>
<td>50.7</td>
</tr>
<tr>
<td>13-19</td>
<td>T.</td>
<td>146</td>
<td>146</td>
<td>119(*)</td>
</tr>
<tr>
<td></td>
<td>N.</td>
<td>122</td>
<td>118</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>83.6</td>
<td>80.8</td>
<td>57.1</td>
</tr>
<tr>
<td>20-29</td>
<td>T.</td>
<td>87</td>
<td>85</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>N.</td>
<td>75</td>
<td>74</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>83.2</td>
<td>87.2</td>
<td>71.8</td>
</tr>
<tr>
<td>30-</td>
<td>T.</td>
<td>289</td>
<td>287</td>
<td>249</td>
</tr>
<tr>
<td></td>
<td>N.</td>
<td>267</td>
<td>263</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>92.4</td>
<td>91.2</td>
<td>71.8</td>
</tr>
</tbody>
</table>

T.: Total Number of Cases
N.: Negative Cases
(*) Defaulters (14% — 18%)
TABLE VII

<table>
<thead>
<tr>
<th>Dose</th>
<th>No. of ova per gm</th>
<th>Pretreatment</th>
<th>Months after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>20 mg/kg x 3 days (315 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 — 50</td>
<td></td>
<td>747</td>
<td>97</td>
</tr>
<tr>
<td>51 — 100</td>
<td></td>
<td>56</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 100</td>
<td></td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg x 2 days (72 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 — 50</td>
<td></td>
<td>67</td>
<td>14</td>
</tr>
<tr>
<td>51 — 100</td>
<td></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg/kg x 1 day (69 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 — 50</td>
<td></td>
<td>68</td>
<td>31</td>
</tr>
<tr>
<td>51 — 100</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt; 100</td>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

As regards ova counts/gm pretreatment and during follow up, they are shown in Table VII. Higher negative rates in females than in males are recorded. This is expected because the female is less exposed to infection and reinfection than the males (Table VIII).

TABLE VIII

Field study — Sindewa village. Results according to sex distribution

<table>
<thead>
<tr>
<th>Dose</th>
<th>After 1 month</th>
<th>After 2 months</th>
<th>After 7 months</th>
<th>After 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>20 mg/kg x 3 D.</td>
<td>409</td>
<td>362</td>
<td>406</td>
<td>360</td>
</tr>
<tr>
<td>T</td>
<td>354</td>
<td>317</td>
<td>348</td>
<td>310</td>
</tr>
<tr>
<td>N</td>
<td>86.6</td>
<td>87.5</td>
<td>86.7</td>
<td>86.1</td>
</tr>
<tr>
<td>%</td>
<td>72.7</td>
<td>81.8</td>
<td>74.3</td>
<td>82.2</td>
</tr>
<tr>
<td>20 mg/kg x 2 D.</td>
<td>33</td>
<td>33</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>N</td>
<td>24</td>
<td>27</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>%</td>
<td>72.7</td>
<td>81.8</td>
<td>74.3</td>
<td>82.2</td>
</tr>
<tr>
<td>20 mg/kg x 1 D.</td>
<td>16</td>
<td>16</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>N</td>
<td>16</td>
<td>16</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>%</td>
<td>44.4</td>
<td>59.3</td>
<td>34.2</td>
<td>34.5</td>
</tr>
</tbody>
</table>
| T = Total | M = Male | F = Female
| N = Negative |

Worth mentioning are 55 patients who were found to have mixed infections; 49 of them were treated with both metrifonate (10 mg/kg once every two weeks for three doses) and oxamniquine (20 mg/kg daily for three consecutive days). Table IX shows the three months cure rate for S. mansoni to be 83.7% and for S. haematobium to be 95.9%. No side effects or any evidence of intolerance were observed in this group. There were no significant changes in the blood picture or platelet counts done in 30 patients immediately before the combined therapy, and repeated on post-treatment days 3, 10 and 30 thereafter. The cure rate of S. haematobium in this group is higher than that obtained in the preliminary mixed infection study mentioned previously. The use of a new lot of metrifonate in this field study may explain the difference. The batch used in the former study was near the expiry date.
TABLE IX
Field study
Combined metrifonate and oxamniquine therapy in mixed infections

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Sex</th>
<th>No. Followed up</th>
<th>Results after 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>S. mansoni</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neg.</td>
</tr>
<tr>
<td>55</td>
<td>43</td>
<td>12</td>
<td>49</td>
</tr>
</tbody>
</table>

M = Male
F = Female

All the data obtained from these studies show that oxamniquine can safely and effectively be given for large scale chemotherapy of S. mansoni infection without any significant side effects or toxic reactions. Though the three day course of 20 mg/kg daily is better from the chemotherapeutic point of view, the same daily dose for only two days gives favorable results. The concomitant use of metrifonate and oxamniquine in mixed S. mansoni and S. haematobium infections is useful for treating these patients safely and effectively.

TABLE X
Field study — Sndewa village
Details of cases died after oxamniquine therapy

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Code No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Date of oxamniquine therapy</th>
<th>Date of death</th>
<th>Cause of death</th>
<th>Relation to oxamniquine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td>60</td>
<td>M</td>
<td>Jan. 15, 16, 17, 1977</td>
<td>Feb. 16, 1977</td>
<td>Cardiac disease</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>539</td>
<td>68</td>
<td>F</td>
<td>Feb. 5, 6, 7, 1977</td>
<td>Apr. 16, 1977</td>
<td>Cardiac disease</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>495</td>
<td>30</td>
<td>F</td>
<td>Feb. 5, 6, 7, 1977</td>
<td>Apr. 21, 1977</td>
<td>Meningitis (in Fever Hosp.)</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>735</td>
<td>45</td>
<td>M</td>
<td>March 15, 16, 17, 1977</td>
<td>June 5, 1977</td>
<td>Coronary cardiac disease</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>743</td>
<td>65</td>
<td>M</td>
<td>March 15, 16, 17, 1977</td>
<td>Aug. 25, 1977</td>
<td>Cardiac disease</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>577</td>
<td>60</td>
<td>M</td>
<td>Feb. 8, 9, 10, 1977</td>
<td>Jan. 1, 1978</td>
<td>Cardiac disease</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>412</td>
<td>50</td>
<td>M</td>
<td>Jan. 29, 30, 31, 1977</td>
<td>Feb. 6, 1978</td>
<td>PUE (in Fever Hosp.)</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>322</td>
<td>35</td>
<td>F</td>
<td>Jan. 25, 26, 27, 1977</td>
<td>March 9, 1978</td>
<td>Obstructed labour</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>609</td>
<td>60</td>
<td>F</td>
<td>March 12, 13, 14, 1977</td>
<td>Apr. 24, 1978</td>
<td>Cardiac disease</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>79</td>
<td>55</td>
<td>M</td>
<td>Jan. 11, 12, 13, 1977</td>
<td>May 12, 1978</td>
<td>Cardiac disease</td>
<td>None</td>
</tr>
</tbody>
</table>

M = Male
F = Female

RECAPITULATION
OXAMNIIQUE STUDIES IN EGYPT

** Institute of Research for Tropical Medicine

— Pilot Studies

• Intramuscular Formulation
  — S. haematobium
  — S. mansoni

• Oral Formulation
  — S. haematobium
  — S. mansoni

— Closed Community Controlled Study
  — S. mansoni

— Combined Mefriofate and Oxamniquine in Mixed Infection
— Large Scale Field Study
  — S. mansoni
REFERENCES


** Other Studies in Egypt

Namru-3:
Oxamniquine in Complicated Intestinal Schistosomiasis
Faculty of Medicine, Alexandria University
Oxamniquine in — Schistosomal Colonic Polyposis — Intestinal Bilharziasis
Faculty of Medicine, Al-Azhar University
Oxamniquine in Intestinal Schistosomiasis
Oxamniquine in Egyptian Children
OXAMNIQUE (VANSIL) IN THE TREATMENT OF SCHISTOSOMIASIS IN RHODESIA

V. de CLARKE (1)

Rhodesia has one of the most progressive and intensive programmes of water conservation and irrigation in Africa, and because of this it has one of the most serious problems of schistosomiasis. Both Schistosoma haematobium and S. mansoni are common throughout the country, but whereas the former is still the most widespread, it is the latter, S. mansoni, which is spreading most rapidly and with the spread not only the prevalence, but also the intensity of the infection are increasing. Severe sequelae to infections, previously rare or even unheard of, are now commonplace and Manson's schistosomiasis must now rank with malaria as the two most important tropical diseases in Rhodesia. However, malaria can be readily controlled in most communities, but the control of schistosomiasis, remains difficult and costly and it must be restricted in its application; thus the treatment of the individual case, as opposed to community protection, becomes of great importance.

Great strides have been made in the chemotherapy of schistosomiasis in the past two decades particularly with the introduction of niridazole, hyancanthone and metrifonate. All three are particularly efficient in the treatment of S. haematobium infections, but the treatment of S. mansoni remained difficult until the release of the oral formulation of oxamniquine.

RICHARDS & FOSTER (1969) reported on the investigation of a series of synthesized compounds originally derived from hyancanthone and one of these, later to be called oxamniquine, was shown to have strong schistosomicidal activity in vivo in animals when administered by either the parenteral or the oral route. After preliminary safety trials in man an inter-muscular formulation of this drug was released for controlled trials in Africa and in Brazil. The results of these first clinical trials were for the most part very encouraging with workers in Brazil (e.g. PRATA et al., 1973; COUTINHO et al., 1973; KATZ et al., 1973; DA SILVA et al., 1973) all reporting near perfect results, and most workers in Africa (e.g. REES et al., 1973; EYAKUSE, 1973) reporting similarly high therapeutic effects. Only CLARKE et al. (1973) from Rhodesia reported poor results with no radical cures, although most subjects showed a significant decrease in egg production. However, although the use of inter-muscular formulation has been proven in routine use in Brazil, its efficacy in Africa was not confirmed and the oral formulation has been accepted as being considerably more effective than the parenteral formulation under African conditions. Neither formulation has any significant effect on S. haematobium infections.

CLARKE et al. (1976) undertook detailed, controlled dose finding trials of the oral formulation in the treatment of S. mansoni infections and they eventually recommended a total dose of 69 mg/kg to be given in four equal doses of 15 mg/kg, morning and evening over two days. In their original trials, they reported radical cure in over 80% of the 57 people treated, and a marked egg reduction in a further 10% giving a total of over 90% of S. mansoni cases which benefited significantly from treatment. Following reports from East Africa of satisfactory therapeutic results using total doses of only 30 or 45 mg/kg further trials were undertaken at these dose levels. However, under conditions existing in Central Africa these doses appear to be inadequate; effective therapy was not achieved below the total dose of 60 mg/kg. These initial results have been confirmed by the subsequent treatment of several hundreds of patients infected with S. mansoni.

(1) Blair Research Laboratory. P. O. Box 8105, Causeway, Salisbury, Rhodesia
The trials of CLARKE et al. (1976, op. cit.) and subsequent treatments done by them have shown that at the recommended dose level of 60 mg/kg, there is an important relationship between therapeutic efficacy and the age, size or weight of the subject. In small children the therapeutic effect of this dosage is lower than it is in older and heavier persons. For this reason, and because the drug is so well tolerated by children, it is recommended that the principles of CATZEL (1963), later applied to the treatment of S. mansoni with oxamniquine by AXTON & GARNETT (1976), be used generally. Under this system, the dose is related to surface area of the body, rather than to the weight, and levels of up to 1.6 g/m² give satisfactory and safe treatment.

In the trials mentioned oxamniquine proved to be of low toxicity and very safe for use with all categories of patients. In the several hundred people treated from the Blair Research Laboratories there have been no cases of serious side effect or toxicity from the drug. There was the one case previously reported (CLARKE et al., 1976) where a nine year old girl showed abnormalities in liver function after treatment with the total dose of 30 mg/kg, but not necessarily as a result of this treatment. They state "a nine year old girl had no biochemical tests done on the blood before treatment because the sample was spoiled. Three days after treatment a raised bilirubin concentration was detected and intensive investigations were initiated. Although the child felt well, she was admitted to hospital for a further series of biochemical and haematological tests, and a liver biopsy was performed. The report of the pathologist who examined the biopsy specimen stated that the appearance was that of recovering hepatitis. During her 10 day stay in hospital, biochemical tests showed raised blood urea, transaminases, total bilirubin and alkaline phosphatase, but these all subsided to near normal values by the time of her discharge and all were fully normal two weeks after her discharge. Except for vomiting after the liver biopsy the child did not feel ill and neither she nor her parents understood the need for hospitalisation. No other serious side effects have been noted and even minor transient side effects are uncommon. Dizziness, varying from very mild to moderate, has been reported by approximately one in ten of the treated cases and there have also been infrequent reports of nausea and headache. It would appear from observation that these mild side effects can be further limited by administering the doses immediately after meals. In most of the trials in Rhodesia detailed haematological and biochemical testing have been undertaken both before and after treatment of most cases. Seven of the haematological parameters tested showed statistically significant changes after treatment, but in all cases they were considered to be too slight to have real clinical significance (CLARKE, 1977).

The safety of oxamniquine was further demonstrated by AXTON & GARNETT (1976). On the strength of the reports of the safety of oxamniquine they decided to use this drug for the treatment of a group of 57 children of whom 29 had significant liver enlargement. Alternative treatment with niridazole or hydantoine was considered to be too dangerous in the presence of the liver enlargement. They applied the principles of CATZEL (1963, op. cit.) who showed that it was more realistic to select a paediatric dose based on surface area of the body rather than on the weight of the child. AXTON & GARNETT treated the 57 children at a dosage of 800 mg/m² body surface per day in two divided doses for two days. On this system the approximate equivalent dose for a 70 kg adult would be 40 mg/kg per day for two days, though for a 20 kg child it would be 60 mg/kg per day for two days (i.e., double the dose recommended by Clarke and his co-workers). Although AXTON & GARNETT experienced some difficulty in retaining contact with the children long enough to undertake parasitological evaluation of the efficacy of the higher dose regime, the safety data were immediately available and they confirmed that even at this level oxamniquine causes few side effects and those which do occur are mild and transient.

Since the above reports were made two other trial series on patients infected with S. mansoni had been conducted and these demonstrate additional advantages of oxamniquine over previously used drugs.

The first of these trials concerned the treatment of sufferers of Katayama Fever — the
early, acute phase of an intense schistosome infection, usually of *S. mansoni*.

CLARKE et al. (1970) reported on a severe outbreak of Katayama Fever in Rhodesia in 1969 and eventually they themselves undertook detailed investigations of 40 such cases, all of whom were subsequently treated with either niridazole or hyancathone. However, the results of these treatments were poor and the majority of sufferers were subjected to several courses of each of these drugs without significant effect on the parasite loads. In addition to these cases there were a number of others where heavy *S. mansoni* infections persisted despite repeated treatment with available drugs. Since then over 120 of these patients with persistent *S. mansoni* infections have been treated with oxamniquine with results which are consistent with results of the trials discussed above.

The second of these trial series concerned the treatment of the Katayama syndrome itself during the acute phase. It had been demonstrated (JEWSBURY, 1973) that oxamniquine was active against developing schistosomula in animals, and therefore it was assumed it could be used for the treatment of katayama fever. However, there was concern lest the degradation products of the killed immature worms would actually exacerbate the allergic state. It was thus decided (CLARKE & GELFAND, unpublished results) to treat katayama patients with the normal dose of oxamniquine, whilst suppressing the allergic state by concomitant steroid therapy. Although a number of presumed cases have been thus treated, there have only been six where the diagnosis was emphatic, and where satisfactory follow-up examinations have been possible. In all cases, the two day course of oxamniquine: at the accepted dose level has been accompanied by a course of prednisolone (5 mg twice daily for three days, then 5 mg twice daily for two days, then once daily for two days) and the results have been dramatic. Within six hours the patients have recovered except for residual weakness from the pyrexia, and there have been no relapses. Of the six patients, five failed to pass any schistosome eggs in several months of follow-up examinations, but the sixth, who had subsequent exposure, later passed large numbers of *S. mansoni* eggs.

Oxamniquine has proved itself to be the drug of choice for the treatment of *S. mansoni* infections and its value is enhanced by indications of its usefulness in the treatment of katayama fever due to heavy infections of *S. mansoni*.

ACKNOWLEDGEMENTS

I wish to thank the Secretary for Health, Dr. E. Burnett Smith, for permission to deliver this paper.

REFERENCES


DISCUSSION on Dr. V. CLARKE’S PAPER — OXAMNQUINE, VANSIL, IN THE TREATMENT OF SCHISTOSOMIASIS IN RHODESIA

Dr. A. DAVIS (GENEVA)

How was the diagnosis of Katayama fever made?
Dr. V. CLARKE (SALISBURY)

It is difficult to diagnose and, now, virtually impossible to confirm that patients actually had Katayama fever. The diagnosis is based on a history of probable or possible exposure, a sudden onset of acute fever occurring in the early evenings, unusually severe sweating during and immediately after the fever, dramatic loss in weight, and, of course, a marked eosinophilia, often as high as 80% with a corresponding rise in total white cells. It is common for the patient to develop a transient urticarial rash and a dry, hacking expirational cough. The liver is usually slightly enlarged and tender.

Dr. DAVIS

I think it is a very difficult diagnosis to make, and one is inclined to get it confused with leptospirosis, the various forms of typhus, and various other tropical pyrexias. I am always suspicious about Katayama fever as the group of symptoms are related to hypersensitivity in all of its forms. There is nothing to put your finger on, as even the immunological tests can show cross reactions. There is really no proof of the diagnosis unless you have a control group who later passes eggs. It is mainly a diagnosis based on history and in-depth immunological evidence.

Dr. Z. ANDRADE (SALVADOR)

I would rather not use Katayama fever as a designated diagnosis but call it acute schistosomiasis. Recently we have had two patients with a severe manifestation. One died and at autopsy we were able to make the diagnosis of schistosomiasis by finding several worms and granuloma in the tissues. The second patient was treated and recovered dramatically. The point that should be stressed is that treatment during acute toxemic schistosomiasis can benefit the patient.

Prof. PRATA

We have also treated patients with acute forms of schistosomiasis with good effect. In Brazil we only have S. mansoni and Katayama fever has rarely been described with S. mansoni infestations.

Dr. DAVIS

We are arguing about words. It is really the acute preliminary phase of schistosomiasis, when the schistosomulum is maturing into a schistosome, the phase that leads to symptoms. I prefer the term acute preliminary schistosomiasis or acute schistosomiasis rather than Katayama syndrome, which is a catch-all for any sort of pyrexial symptoms associated with a history of exposure to schistosomiasis.

Prof. PRATA

There is preliminary evidence that in acute schistosomiasis there may be high levels of immune complexes in the serum, and results of any treatment incorporating corticosteroids should be carefully interpreted. The dramatic results seen in acute schistosomiasis may be due purely to steroids. To fully answer this question, one would need a control group treated with antischistosomal therapy and no steroids.

Dr. CLARKE

I accept that the immediate reduction in fever and symptoms is actually the result of the steroid therapy and to some extent would confirm the diagnosis. However the prevention of the maturation of the schistosome infection is the result of the oxamniquine therapy. If both have been effective and no maturation occurs, the confirmation of diagnosis is present. It is our experience that serology can be misleading in Katayama fever.
OBSERVATIONS ON THE TREATMENT OF MANSONI SCHISTOSOMIASIS WITH OXAMNUQUINE: EFFICACY IN CHILDREN AND IN PERSISTENT SALMONELLOSIS; RESISTANCE OF A STRAIN OF SCHISTOSOMA MANSONI; HEPATIC TOXICITY AND NEUROLOGICAL SIDE EFFECTS

Rogério de Jesus PEDRO (1), Luiz Candido de Sousa DIAS (1) Vicente AMATO NETO (2) and Silvino Alves de CARVALHO (3)

In this presentation we will consider the newer aspects of treatment of Schistosomiasis mansoni in order to further evaluate oxamnique in the treatment of this disease. Therefore, in the time allowed, we will not speak about the widely known characteristics of the drug, but will present our findings on five aspects of the current use of oxamnique.

I. Effectiveness of oxamnique in the treatment of S. mansoni infection in children.

II. Resistance of a human strain of S. mansoni to lycanthone and oxamnique.

III. Histopathological changes in the liver during treatment with oxamnique.

IV. Neurological side effects of oxamnique.

V. Treatment of persistent salmonella infections with oxamnique.

I. TREATMENT OF CHILDREN INFECTED WITH Schistosoma mansoni WITH A SINGLE DOSE OF OXAMNUQUINE

We have previously published our data on the efficacy, and safety of oxamnique in the treatment of adults therefore we have concentrated our most recent efforts on the treatment of children. In children, the efficacy of oxamnique in the treatment of Schistosoma mansoni infections is quite different from that seen in adults.

Oxamnique given orally in doses of 10 mg/kg of body weight reportedly produced parasitological cure in 82.2% of adults but in only 40.0% in children ages 4 to 14 years. The diminished cure rate in children has also been seen with other schistosomicidal agents, therefore we conducted a study to treat children with oxamnique and the results presented here are those we obtained in that study.

Three hundred and ninety-one children, ages 1 to 14 years, of both sexes, who demonstrated viable eggs of Schistosoma mansoni in their stools, were treated with a single oral dose of oxamnique. The patients were separated into four groups and received one of the following dosages: either 11 to 15 mg/kg of body weight of oxamnique, or 16 to 20 mg/kg, or 21 to 25 mg/kg, or 26 to 33 mg/kg of oxamnique. All patients had chronic schistosomiasis of various clinical forms but none of them had the advanced stage.

The therapeutic efficacy of oxamnique was evaluated by repeat stool examinations according to the technique of Hoffman, Pons and Janer and qualitatively by the Kato method. Cure of the disease was based on the recording of negative stool examination monthly for 6 months, or when a negative stool examination was obtained with four monthly stool specimens obtained consecutively the second month after treatment.

Forty percent of the children treated showed no side effects. However, in the remainder, side effects noted were in order of decreasing frequency: dizziness, drowsiness, abdominal pain, and vomiting. The side effects observed were mild and of short duration. There was no significant difference between the number and severity of the side effects

(1) Universidade Estadual de Campinas (Disciplina de Doenças Transmissíveis e Departamento de Parásitologia), Campinas, São Paulo, Brasil
(2) Universidade de São Paulo (Clínica de Doenças Infecciosas e Parasitárias), São Paulo, São Paulo, Brasil
recorded for each of the four dosage regimens of oxamniquine.

To this point in time, 225 children have completed the parasitological follow-up (see Table I). The treatment schedule of 21 to 25 mg/kg achieved the best parasitological cure (92.5%) without a significant increase in incidence and severity of side effects over that seen with the lower doses. We therefore recommend that oxamniquine be used in dosages larger than 21 mg/kg body weight in children.

**Table I**

<table>
<thead>
<tr>
<th>Single Dose mg/kg</th>
<th>Number of Patients Followed up</th>
<th>Patients with Negative Faeces Examinations(∗)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>11 to 15</td>
<td>20</td>
<td>11 55.0</td>
</tr>
<tr>
<td>16 to 20</td>
<td>118</td>
<td>98 74.9</td>
</tr>
<tr>
<td>21 to 25</td>
<td>50</td>
<td>74 93.5</td>
</tr>
<tr>
<td>26 to 33</td>
<td>7</td>
<td>86.7</td>
</tr>
</tbody>
</table>

(∗) Stool examinations performed according to Hoffman’s technique and Kato’s method, during a period of 4 or 6 months (1 exam per month)

II. HYCANTHONE AND OXAMNIQUINE RESISTANCE TO A HUMAN STRAIN OF SCHISTOSOMA MANSONI

In January 1975, in spite of treatment with hycanthone at a dosage of 2.5 mg/kg body weight i.m., we isolated viable eggs from the feces of a patient infected with *S. mansoni*. A second attempt at treatment in November 1976 using oxamniquine at a dosage of 14.0 mg/kg body weight orally, we had no better success than the preceding treatment because the feces still contained viable eggs.

In the laboratory, the eggs from a patient were incubated and the miracidia were passed to *Biomphalaria glabrata* snails and the resulting cercariae were put into contact with albino mice by the tail immersion technique. The mice weighing approximately 18 grams each were infected with 100 cercariae each (M A P parental generation). Thereafter many snails were infected with the miracidia which resulted from the viable eggs excreted by the mice. The same procedure was used to infect another 36 mice which gave rise to the first generation of worms (M A P F₁).

Evaluation of the activity of the drugs Hycanthone 80 mg/kg and oxamniquine 100 mg/kg, was undertaken in two lots of 12 animals each. A third lot of 12 animals was kept untreated for control purposes. Mice were sacrificed 10 days after treatment and schistosomes in the liver and mesenteric vessels were recovered by perfusion and examined through use of a dissecting microscope. For oogram studies, preparations from intestinal fragments were made. Changes in the oogram were considered indicative of antischistosomal activity when one or more of the developing stages of immature eggs was absent. A similar study was carried out with the BH strain of *S. mansoni* which is now routinely used in our laboratory.

The control group (M A P F₁) gave rise to a second generation of schistosomes (M A P F₂), which using the above procedure, were studied in parallel with the BH strain to test the antischistosomal activity of niridazole at 100 mg/kg given orally each day for 5 consecutive days. Autopsies were carried out 15 days after beginning the treatment.

Comparative studies of M A P F₁ and M A P F₂ progeny and BH strains have shown a marked difference in their sensitivity to the schistosomacides (Table II). The BH strain was sensitive to hycanthone, oxamniquine and niridazole, but M A P F₁ and M A P F₂ were resistant to hycanthone and oxamniquine. However, the oogram pattern of niridazole treated animals (M A P F₁) was indicative of drug sensitivity although the hepatic shift was approximately 49.5%.

III. HISTOPATHOLOGICAL ASPECTS OF THE LIVER DURING TREATMENT OF SCHISTOSOMA MANSONI INFECTIONS WITH OXAMNIQUINE

We studied twenty-two liver biopsies from eleven patients with schistosomiasis, each patient had a biopsy taken before and another three days after treatment with oxamniquine. By this method each patient served as his own control. All biopsy specimens were studied with an optical microscope and six were addi-
TABLE II

Antischistosomal activities of hyacanthone, oxamniquine and niridazole in mice experimentally infected with two strains of Schistosoma mansoni

<table>
<thead>
<tr>
<th>Strain of S. mansoni</th>
<th>Drug(*)</th>
<th>Number of animals</th>
<th>Animals dead</th>
<th>Mean worm burden</th>
<th>Distribution of schistosomes %</th>
<th>% of mice with oogram changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liver</td>
<td>Mesenteric vessels</td>
</tr>
<tr>
<td>MAP (P1)</td>
<td>Hycanthone</td>
<td>12</td>
<td>2</td>
<td>16.3</td>
<td>6.1</td>
<td>93.9</td>
</tr>
<tr>
<td></td>
<td>Oxamniquine</td>
<td>12</td>
<td>2</td>
<td>12.5</td>
<td>13.7</td>
<td>86.3</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>12</td>
<td>0</td>
<td>19.4</td>
<td>5.3</td>
<td>94.2</td>
</tr>
<tr>
<td>BH</td>
<td>Hycanthone</td>
<td>12</td>
<td>0</td>
<td>6.1</td>
<td>86.1</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Oxamniquine</td>
<td>12</td>
<td>1</td>
<td>7.8</td>
<td>100.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>12</td>
<td>1</td>
<td>20.1</td>
<td>20.2</td>
<td>79.3</td>
</tr>
<tr>
<td>MAP (P2)</td>
<td>Hycanthone</td>
<td>12</td>
<td>2</td>
<td>37.9</td>
<td>19.9</td>
<td>80.1</td>
</tr>
<tr>
<td></td>
<td>Oxamniquine</td>
<td>12</td>
<td>3</td>
<td>45.4</td>
<td>26.0</td>
<td>74.0</td>
</tr>
<tr>
<td></td>
<td>Niridazole</td>
<td>12</td>
<td>1</td>
<td>11.0</td>
<td>40.5</td>
<td>59.5</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>12</td>
<td>0</td>
<td>33.4</td>
<td>34.7</td>
<td>75.3</td>
</tr>
<tr>
<td>BH</td>
<td>Hycanthone</td>
<td>12</td>
<td>2</td>
<td>28.2</td>
<td>100.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Oxamniquine</td>
<td>12</td>
<td>1</td>
<td>23.3</td>
<td>100.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Niridazole</td>
<td>12</td>
<td>2</td>
<td>7.1</td>
<td>100.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>12</td>
<td>3</td>
<td>30.3</td>
<td>24.4</td>
<td>75.6</td>
</tr>
</tbody>
</table>

(*) Schedule of treatment: mg/kg/day and routes
- Hycanthone 80 x 1 i.m.
- Oxamniquine 100 x 1 p.o.
- Niridazole 100 x 5 p.o.

We conclude from our studies that the use of oxamniquine did not produce any degenerative or inflammatory alteration of the liver. The alterations of the smooth endoplasmic reticulum were present before and after treatment and therefore cannot be attributed to the drug.

IV. NEUROLOGICAL SIDE EFFECTS OF OXAMNIQUINE

In this study, one hundred and eighty-one children and adults were treated with oxamniquine and were observed for any signs of neurological side effects. Oxamniquine was given as a single oral dose, with adults being treated with 12.5 to 15.0 mg/kg of body weight. One group of children, ages 11 to 15, received the same dosage as adults and the other group of children in this age range received 16 to 20 mg/kg of oxamniquine. Children 5 to 10 years old received 16 to 20 mg/kg
of body weight. The side effects attributable to the nervous system were drowsiness (50.0%), dizziness (41.0%) and a reversible amnesia (2.2%), an alteration in behavior (1.7%), and convulsion (1.1%). Electroencephalographic studies were made in twenty patients before treatment. In three of these patients an alteration in the EEG was noted at 90 and 120 minutes following treatment. These patients had had no previous history of convulsions and did not report any symptomatology associated with an anterior cerebral dysrhythmia. Two patients, ages 17 and 28 years, who were not included in the electroencephalographic study group, exhibited a grand mal seizure with durations of time of 5 and 15 minutes. One of them had an encephalographic study made thereafter and it was reported that the patient suffered a possible basal dysrhythmia.

V. TREATMENT OF PERSISTENT SALMONELLOSIS WITH OXAMNQUINE

It has been recognized that an association of schistosomiasis with salmonellosis exists in some patients. With this in mind we attempted to determine the effectiveness of treatment with oxamniquine in these patients. Eight patients with concomitant mansoni schistosomiasis and salmonellosis were identified. The fever in seven patients had lasted for six or seven months; however, one patient had fever of only eight days duration. Salmonellosis was identified in two patients through the Widal reaction and in the others by identification of Salmonella species or Salmonella typhi, or S. cholerae-suis.

The patients were all given oxamniquine in a single oral dose of 12.5 to 17.0 mg/kg body weight. In all the fever became undetectable after five to fifteen days with a reduction in liver and spleen enlargement. Thereafter examination of the stool revealed the absence of viable S. mansoni eggs.

DISCUSSION ON DR. AMATO NETO’S PAPER—PRESENT STATUS OF OUR STUDIES OF OXAMNQUINE IN THE TREATMENT OF SCHISTOSOMIASIS

Prof. PRATA

Dr. Amato Neto, I would like to clarify the point that patients with schistosomiasis and salmonella infections were treated with oral oxamniquine alone and it cured both infections.

Dr. AMATO NETO

Yes, with oral oxamniquine alone.

Prof. PRATA

We have also had some experience in treating patients with concomitant schistosomiasis and salmonella infections with oxamniquine. When intramuscular oxamniquine was used alone, the results were dramatic, but when oral oxamniquine was used the fever was more prolonged. In the past we observed that when hycanthone or ambilhar were used in these patients it was not necessary to give chloramphenicol as well.

Dr. A. GABER (Egypt)

In Egypt we treat patients with schistosomiasis and chronic salmonellosis with antischistosomal drugs and chloramphenicol.

Prof. PRATA

Do you have any information on the response of these patients to antischistosomal drugs alone? Initially we used to treat these patients with combined therapy but with experience have found that ambilhar, hycanthone, and now oxamniquine, are sufficient.

Dr. J. CHIRIBOGA (San Juan)

The parasite is a good culture medium for salmonella; and in animals and man it
has been shown that, after antischistosomal treatment when the worms migrate to the liver, abscesses can form around the worm remnants.

Prof. PRATA

I do not agree. People who have treated patients with antischistosomal drugs have shown cure of salmonellosis, not abscesses.

Dr. N. KATZ (Belo Horizonte)

We are discussing a lot of different things. Initially it is not only salmonella but other bacteria that can use the schistosome as a reservoir. Nirdazole also has activity against salmonella, and the patients are cured. Perhaps some microabscesses do occur after the worms shift to the liver and are later absorbed. We have not seen any clinical findings of abscess formation.

Dr. L. CAETANO (São Paulo)

Could Dr. Amato Neto explain in more detail the problem of resistance to the different antischistosomal drugs.

Dr. AMATO NETO

By passing strains of S. mansoni through mice, treating with different drugs, and sacrificing the mice ten days after treatment, we can observe the distribution of the remaining worms. By this method we have been able to show cross resistance between oxamnique, hycanthone and nirdazole. These findings are different to other studies that have been reported where cross resistance between hycanthone and oxamnique have been demonstrated but not against nirdazole.
THE LIVER AFTER OXAMNIQUINE TREATMENT OF SCHISTOSOMIASIS

Zillon A. ANDRADE (1), Helio Araujo dos SANTOS (2) and Jean Alexis GRIMAUD (3)

SUMMARY

Oxamniquine given by intramuscular injection (7.5 mg/kg b.w.) to 14 patients with mild schistosomiasis and two with the hepatosplenic form of the disease, did not cause either functional or ultrastructural hepatic alterations 48 hours after administration. In this regard, oxamniquine appears to differ markedly from hyanthone.

INTRODUCTION

In our previous study on hepatotoxicity due to hyanthone we examined 14 liver biopsy specimens from patients with schistosomiasis taken before and 48 hours following the drug administration. A selective diffuse vacuolization of the endoplasmatic reticulum of the hepatocytes was seen in the second, but not in the first, biopsy material in every case. That change was not accompanied by any significant alteration in the serum levels of transaminases, alkaline phosphate or bilirubins. However mild, that damage to the hepatic endoplasmatic reticulum reflected a toxic potential of the drug, which in rare cases was observed to produce more severe of even fatal lesions in the liver.

When oxamniquine began to be used in large scale in Brazil, we decided to investigate its hepatotoxic potential by employing the same methodology we had applied to hyanthone. Although clinical studies have not indicated any serious functional hepatic alterations in schistosomiasis patients treated with oxamniquine, we could not exclude the possibility of minimal ultrastructural changes in the liver cell.

MATERIALS AND METHODS

Sixteen patients with viable Schistosoma mansoni eggs in the stools were informed concerning the procedures of this research and agreed to participate. All cases were of the mild or hepatointestinal form of the disease, except two who had the compensated hepatosplenic form. There were 10 females and 6 males, and their ages varied from 17 to 35 years (see Table 1). The patients had come to the hospital for various reasons, but at the time of treatment with oxamniquine they were seen to be in good general condition and to have no evident associated disease. A liver biopsy was taken with a Menghini needle 48 hours after treatment with oxamniquine. The drug had been administered by intramuscular injection in the dose of 7.5 mg per kilogram of body weight. Six patients had two liver biopsies taken, one just before treatment and the other 48 hours afterward. Side effects reported such as dizziness and nausea were few in number, mild and transient.

The hepatic biopsy material was divided into two parts: one part was fixed in neutral formalin, paraffin embedded, and sections stained with H & E, PAS, and Gomori's reticulum method for light microscope examination. The other part was minced into small fragments, fixed on 2% osmio acid in cacodylate buffer (pH 7.4), embedded in Epon 812 and cut by a Rechert OMU2 ultramicrotome. Sections were contrasted by means of uranyl-acetate and lead citrate and examined in a Philips EM 300 electron microscope, at 60 Kv.

(1) Dept. of Pathology, University of Bahia Faculty of Medicine, Salvador, BA, Brazil
(2) Dept. of Medicine, Univ. of Bahia Faculty of Medicine, Salvador, BA, Brazil
(3) Electron Microscopy Center, Pasteur Institute, Lyon, France
RESULTS

The levels of serum transaminases, bilirubin and alkaline phosphatase as determined immediately before and 48 hours after oxamniquine treatment appear in Table I.

Light microscope examination did not show any change which could be attributable to a toxic damage to the liver cells. Under the electron microscope no sign of cytotoxicity was detected, in any case. Lipopigments were present at the biliary poles of the liver cells, but with no modification of the canalicul network. There was an abundant deposit of glycogen and a few droplets of fat in the liver cell cytoplasm (Figs. 1 and 2). Both rough and smooth endoplasmic reticulum showed no alteration. There were a few lymphocytes and polymorphonuclears within the vascular spaces.

COMMENTS

Both functional and morphological data obtained in the schistosomiasis patients treated with oxamniquine failed to show any evidence of toxic effect to the liver cells, within the first 48 hours following drug administration. Thus, oxamniquine differs from hyacanthone in this regard may be considered as a drug which does not exhibit a direct hepatotoxic action.

The present findings are in agreement with those obtained by TREVISAN et al. with similar methodology. Of course, some toxic reactions may appear in the liver parenchyma later on, due to the death and disintegration of dead worms, but that aspect of the problem was not considered in the present investigation. Similarly, the results here presented do not exclude the possibility of toxic reactions to other organs, that could be related to oxamniquine administration.

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Age</th>
<th>Sex</th>
<th>GOT (u.u.) B.</th>
<th>(u.u.) A.</th>
<th>GPT (u.u.) B.</th>
<th>(u.u.) A.</th>
<th>Alk.Ph. (B.L.u.u.) A.</th>
<th>Total Bilirubin (B. A.)</th>
<th>Type Schisto</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>12</td>
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<td>2.1</td>
<td>0.3</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>F</td>
<td>—</td>
<td>30</td>
<td>7</td>
<td>10</td>
<td>1.7</td>
<td>1.8</td>
<td>0.3</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>F</td>
<td>18</td>
<td>18</td>
<td>14</td>
<td>11</td>
<td>2.7</td>
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<td>8</td>
<td>28</td>
<td>F</td>
<td>—</td>
<td>13</td>
<td>21</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>9</td>
<td>19</td>
<td>F</td>
<td>23</td>
<td>18</td>
<td>26</td>
<td>24</td>
<td>2.6</td>
<td>5.0</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>M</td>
<td>19</td>
<td>19</td>
<td>35</td>
<td>30</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td>11(**)</td>
<td>20</td>
<td>M</td>
<td>15</td>
<td>25</td>
<td>23</td>
<td>20</td>
<td>2.7</td>
<td>3.5</td>
<td>0.2</td>
</tr>
<tr>
<td>12(**)</td>
<td>20</td>
<td>M</td>
<td>18</td>
<td>25</td>
<td>16</td>
<td>23</td>
<td>2.7</td>
<td>2.2</td>
<td>0.2</td>
</tr>
<tr>
<td>13(**)</td>
<td>17</td>
<td>F</td>
<td>25</td>
<td>25</td>
<td>16</td>
<td>23</td>
<td>—</td>
<td>4.0</td>
<td>—</td>
</tr>
<tr>
<td>14(**)</td>
<td>29</td>
<td>F</td>
<td>12</td>
<td>18</td>
<td>10</td>
<td>23</td>
<td>1.3</td>
<td>2.9</td>
<td>0.7</td>
</tr>
<tr>
<td>15(**)</td>
<td>26</td>
<td>F</td>
<td>32</td>
<td>26</td>
<td>26</td>
<td>27</td>
<td>4.5</td>
<td>9.0</td>
<td>—</td>
</tr>
<tr>
<td>16(**)</td>
<td>45</td>
<td>F</td>
<td>25</td>
<td>17</td>
<td>26</td>
<td>20</td>
<td>1.7</td>
<td>3.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

(*) Bessey-Lorens u.u.
(**) Two hepatic biopsies: before and after treatment
(***) Hepatosplenic form
Fig. 1 — Several normal hepatocytes are to be seen around a sinusoidal lumen. Liver biopsy taken 48 hours after oxamniquine administration. 3,500 X

Fig. 2 — Normal hepatocyte showing many mitochondria, alpha-glycogen particles and a few lysosomes. From a patient with mild schistosomiasis treated with oxamniquine 48 hours previously. 8,000 X
REFERENCES


DISCUSSION ON DR. Z. ANDRADE’S PAPER

— PATHOLOGICAL CHANGES ASSOCIATED WITH SCHISTOSOMICIDAL THERAPY

Dr. J. CHIRIBOGA (San Juan)

I would like to ask Dr. Andrade about his methods for determining the size of granulomas in the liver and how they change with time.

Dr. ANDRADE

To evaluate the granuloma size in schistosomiasis, all that is needed is to get a complete egg in the section; you can then assume that you are in the middle of a granuloma.

Dr. Warren has described a method for lung where 100 granuloma are measured and an average is taken.

Dr. CHIRIBOGA

This is true in the case of the lung, but in my experience the liver is more difficult.

Dr. ANDRADE

The only difference is that in the liver both old and new granuloma are seen, so you need a much larger section. We find at least 50 granuloma that can be measured, then compare a treated and a control group. The diminution in size of the granuloma is impressive following treatment. In a new infection the first granuloma to form are very large and destructive, but by 20 or 25 weeks they are smaller and without necrosis. There is proliferation with macrophages and fibroblasts and you can see that the egg is well preserved with internal structures of the miracidium being seen. This is a protective reaction by the host. Usually there is a correlation between reinfection and the type of granuloma formed.

Dr. J. COURA (Rio de Janeiro)

I would like to make a comment about the persistence of worms in the liver and their correlation to reinfection in man. In endemic areas we see very few reinfections in the first six months after treatment but then the incidence rises.
EVALUATION OF THE TREATMENT OF SEVERE FORMS OF SCHISTOSOMIASIS MANSONI WITH OXAMNIQUINE (*)

Amaury COUTINHO (1) and Ana Lucia C. DOMINGUEZ (2)

In recent years specific chemotherapy has been widely used in mild forms of schistosomiasis mansoni, and today there is an almost unanimous agreement on the advantages and benefits of such treatment, especially when a better tolerated drug, as oxamniquine is available.

In previous publications, we have reported good results obtained in clinical trials with oxamniquine in its different formulations: injectable-1.M.1, oral-capsules2,3, and oral-syrup 4.

However, the specific treatment of severe forms of the disease, particularly the hepatosplenic form, is a problem because of the advanced state of the structural and pathophysiologic alterations, reflected in hepatic and cardiopulmonary changes, and/or because of the greater number and severity of the reactions to the treatment which has based on use of poorly tolerated drugs: antimonials 5, ariidazole 6, and hyancithone 7,8. The purpose of this study was to evaluate oxamniquine therapy in severe forms of schistosomiasis and to determine its value in these advanced cases.

METHODS AND RESULTS

All schistosomiasis patients were treated at the “Hospital das Clínicas, Univ. Federal de Pernambuco”, and almost all as inpatients due to the severity of their disease. The study included 92 patients (27 males and 65 females) ages 9-55 years. Oral oxamniquine, as capsules, was administered in a usual dosage of 12.5 - 15.0 mg/kg body weight for adults and 15.0 - 20.0 mg/kg body weight for children. Table I gives the diagnoses of the patients according to the clinical form and the complications present. We attempted to analyze side effects of the drug, the reactions provoked by the treatment per se (death of worms) and the late benefits, six months or more after treatment. The results attained for each clinical sub-group will be evaluated separately.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS compensated form</td>
<td>40</td>
</tr>
<tr>
<td>Transitional type (DHS — GHS)</td>
<td>12</td>
</tr>
<tr>
<td>HS decompensated form</td>
<td>3</td>
</tr>
<tr>
<td>HS + Hypertensive cardio-pulmonary form</td>
<td>6</td>
</tr>
<tr>
<td>HS + Cynotic form</td>
<td>3</td>
</tr>
<tr>
<td>HS + Schistosomal nephropathy</td>
<td>8</td>
</tr>
<tr>
<td>HS + Chronic salmonellosis</td>
<td>6</td>
</tr>
<tr>
<td>HS (or HI) + Chronic viral hepatitis</td>
<td>13</td>
</tr>
<tr>
<td>Severe intestinal polyposis</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>92</strong></td>
</tr>
</tbody>
</table>

HS: hepatosplenic
HI: hepatointestinal
DHS: decompensated hepatosplenic
CHS: compensated hepatosplenic

COMPENSATED HEPATOSPLenic (CHS) FORM

The treatment of this clinical form has been reported in earlier research2,3 and recent publications 4. We now report on 40 cases treated. As regards side effects to the drug, there has been no significant difference seen in this group as compared to groups treated with the mild forms of the disease. The most common side effect continues to be dizziness, and no other sign or symptom was seen more frequently in the treatment of this clinical form (CHS).

(*) Study carried out with the aid of the “Conselho de Desenvolvimento Científico e Tecnológico (CNPq).”

(1) Full Professor of Clinical Medicine, UFPE
(2) Assistant Professor, Dept. of Clinical Medicine, UFPE

41
In relation to the hepatic function, few alterations were observed in the tests performed. We show, in Figs. 1 and 2, and Table II, the absence of individual changes in the transaminases before and three and ten days after drug administrations.

![Graph](image1)

**Fig. 1** — Distribution of glutamic oxalacetic transaminase in 19 hepatosplenic patients, before and after oral oxamnique

![Graph](image2)

**Fig. 2** — Distribution of glutamic pyruvic transaminase in 19 hepatosplenic patients, before and after oral oxamnique

Slight rises in transaminases values were observed in only one patient (Table III) three and ten days after drug administration. However, after some weeks, changes were observed more often (2nd, 3rd and 4th patients). This response probably represents the effects of the treatment (not drug related) by virtue of the abrupt death of numerous parasites. We have also attributed to this effect the post-treatment increase of serum alkaline phosphatase and gammaglobulin in some patients and the small reduction of plasma albumin which occurred less frequently (Fig. 3).
TABLE II

Mean values of transaminases in compensated hepatosplenic patients before and after oxamniquine

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>Before</th>
<th>3rd Day</th>
<th>10th Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>17</td>
<td>41.7</td>
<td>39.9</td>
<td>33.7</td>
</tr>
<tr>
<td>Oral</td>
<td>19</td>
<td>57.2</td>
<td>50.6</td>
<td>48.5</td>
</tr>
</tbody>
</table>

SGPT

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>Before</th>
<th>3rd Day</th>
<th>10th Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>17</td>
<td>23.0</td>
<td>23.2</td>
<td>25.0</td>
</tr>
<tr>
<td>Oral</td>
<td>19</td>
<td>33.1</td>
<td>30.6</td>
<td>31.8</td>
</tr>
</tbody>
</table>

In addition to these hepatic changes, there was a moderate increase in eosinophils and circulating antibodies which is a response to the liberation of a large quantity of worm antigenic material (Fig. 4). Sometimes these responses were associated with moderate clinical manifestation of hypersensitivity (pruritus, urticaria, etc.).

Fig. 3 — Evolution of plasma albumin and gammaglobulin in patients treated with oxamniquine

TABLE III

Slight changes of transaminases in four hepatosplenic patients after oxamniquine

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Test</th>
<th>Before</th>
<th>3rd Day</th>
<th>10th Day</th>
<th>30th Day</th>
<th>5th Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SGOT</td>
<td>43</td>
<td>50</td>
<td>51</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>SGPT</td>
<td>35</td>
<td>87</td>
<td>81</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>SGOT</td>
<td>35</td>
<td>17</td>
<td>31</td>
<td>57</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>SGPT</td>
<td>11</td>
<td>7</td>
<td>14</td>
<td>69</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>SGOT</td>
<td>17</td>
<td>16</td>
<td>27</td>
<td>46</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>SGPT</td>
<td>25</td>
<td>19</td>
<td>24</td>
<td>52</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>SGOT</td>
<td>123</td>
<td>104</td>
<td>—</td>
<td>218</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>SGPT</td>
<td>66</td>
<td>60</td>
<td>—</td>
<td>104</td>
<td>51</td>
</tr>
</tbody>
</table>

However, it is most important to emphasize in the majority of treated patients the progressive long-term return *to normal* of the biochemical (Fig. 3), hematological, and immunological alterations observed either before treatment (due to the death of worms in situ). The improvements in laboratory test results are often accompanied by apparent clinical improvement of general and digestive tract symptoms or by such solid evidence as, for example, the reduction in about 50% of the cases of the hepatomegaly and splenomegaly. However, these reductions did not continue to complete regression (Table IV).
**TABLE IV**

Evolution of the hepatomegaly and splenomegaly in schistosomal patients treated with oxamniquine

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>No. of Patients</th>
<th>No.</th>
<th>Charge</th>
<th>Increase</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>17</td>
<td>7</td>
<td>41.1</td>
<td>2</td>
<td>11.7</td>
</tr>
<tr>
<td>Oral</td>
<td>18</td>
<td>5</td>
<td>27.7</td>
<td>2</td>
<td>11.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>35</strong></td>
<td><strong>12</strong></td>
<td><strong>34.3</strong></td>
<td><strong>4</strong></td>
<td><strong>11.4</strong></td>
</tr>
</tbody>
</table>

| Splenomegaly            |                 |      |        |          |           |           |
|-------------------------|-----------------|------|--------|----------|-----------|
| IM                      | 14(*)           | 4    | 28.5   | 0        | 0         | 10        | 71.4     |
| Oral                    | 14(*)           | 8    | 57.1   | 1        | 7.1       | 5         | 35.7     |
| **Total**               | **28**          | **12** | **43.3** | **1**    | **3.5**   | **15**    | **53.6** |

(*) Three of the IM group and four of the oral group had splenectomy before treatment.

**TRANSITIONAL AND DECOMPENSATED HEPATOSPLENIC (DHS) FORMS**

After one year or more of successful experience with the use of oxamniquine in the compensated HS form, we began to use it carefully in more advanced or complicated forms. The cases called transitional are those HS patients in a poor nutritional and generally debilitated state, with some symptoms of hepatic dysfunction, principally mild or moderate reversible ascites, abnormalities in the liver function tests, and hepatic histology showing some alterations of the parenchyma, greater portal and intralobular inflammatory activity and formation of septa.

These patients, after treatment by rest and nutritional care, generally shown clinical and functional hepatic improvement, and change from the decompensated to the compensated phase. After this improvement, we gave spe-
cific treatment with oxamniquine in 12 cases. In a few patients, inasmuch as an adequate clinical compensation had not been attained with rest and nutritional therapy, we used oxamniquine in the decompensated phase.

Tolerance to the drug was, in general, satisfactory in this group, with no worsening in the clinical laboratory picture that might be directly ascribed to the treatment. In some patients, the improvement initiated with the general treatment was progressive on a long-term basis, as can be seen from the laboratory test results shown in Table V.

<table>
<thead>
<tr>
<th>Period</th>
<th>SGOT</th>
<th>SGPT</th>
<th>AP</th>
<th>ALB</th>
<th>gamma GLOB</th>
<th>BSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>54</td>
<td>30</td>
<td>19.4</td>
<td>2.52</td>
<td>5.03</td>
<td>9.4</td>
</tr>
<tr>
<td>day</td>
<td>3rd day</td>
<td>66</td>
<td>51</td>
<td>2.67</td>
<td>4.66</td>
<td></td>
</tr>
<tr>
<td>10th day</td>
<td>95</td>
<td>35</td>
<td>19.5</td>
<td>2.46</td>
<td>4.53</td>
<td></td>
</tr>
<tr>
<td>60th day</td>
<td>26</td>
<td>27</td>
<td>16.9</td>
<td>3.53</td>
<td>3.53</td>
<td>4.4</td>
</tr>
<tr>
<td>90th day</td>
<td>27</td>
<td>20</td>
<td>16.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

But in other patients the hepatic disease remained unchanged or changed irregularly, with improvements noted during the patients’ hospital stay and progressive worsening on their return to the poor nutritional care and environmental home conditions. However, in none of the patients did the specific therapy with oxamniquine contribute, in any way, to aggravation of the histologic, pathophysiologic and clinical condition of the disease itself.

CARDIOPULMONARY FORMS

In the hypertensive forms (schistosomal pulmonary arterial hypertension) which is generally associated with the HS form, the immediate and late results of the specific treatment depend on the stage of the cardiopulmonary process and on the grade of pulmonary vascular resistance. Through previous experience with other antischistosomal drugs, in treating the most severe cases of pulmonary hypertension, we used a corticosteroid (preferably prednisone) in the dose of 30.0 - 40.0 mg/day started one week prior to oxamniquine therapy and continuing the corticosteroid in decreasing doses for two additional weeks after oxamniquine. By this, we sought to avoid - and have attained the objective - the immediate generally severe exacerbation of the clinical picture and EKG abnormalities in the form of acute cor pulmonale which has been seen frequently before the use of prednisone. On the long-term basis, in the less advanced cases, the clinical results have been relatively satisfactory, with improvement of the symptomatology, chiefly dyspnea on effort and incapacity to work. However, as regards laboratory data, X-rays, EKG, and hemodynamics, the improvements are slight or almost nil, principally in patients with more advanced pulmonary hypertension. However, the disease has not been aggravated by the treatment. It appears to us that oxamniquine when used in a relatively early stage of the disease has the possibility of reversing or retarding the evolution of this severe form, with a favorable clinical response. In the cyanotic form, although oxamniquine was well tolerated, improvement of the cyanosis or laboratory parameters was not observed in the few patients treated. However, the small number of patients and the short time of observation are not sufficient to draw a conclusion on the efficacy of the drug in this condition.

SCHISTOSOMAL KIDNEY DISEASE

The patients here described are from the Nephrology Unit, H.C. (Dr. João Absalão and associates) who kindly placed at our disposal the essential data for the present review. There are data from eight patients, all of them HS form with kidney disease: four with the urinary form (proteinuria, hematuria, cylindruria), three with the nephrotic syndrome and one with arterial hypertension.
Relative to therapy with oxamnique, tolerance to the drug was satisfactory. However, short-term laboratory results showed that three patients had an apparent urinary alteration, with increase of proteinuria and hematuria in one case; of proteinuria or hematuria in two other patients. The changes were transient, lasting from days to a few weeks, and are probably related to the death of worms and circulation of parasitic antigens. In two patients there was progressive long-term improvement of proteinuria. However, there is need for a greater number of treated patients and a longer observation period in order to arrive at conclusions as to the beneficial effects of the drug in this group of patients. The more advanced cases with nephrotic syndrome or arterial hypertension have not shown, during the observation period, any change in the evolution of their disease. Here too, there is need for a larger data base to draw a definite conclusion.

SCHISTOSOMIASIS PLUS CHRONIC SALMONELLOSIS

Our experience is restricted to six patients with the HS form complicated by an infection with enterobacteria (salmonellae), who were initially treated for salmonella septicemia with chloramphenicol and ampicillin. Immediately thereafter they were treated with oxamnique, and had favorable short-term and long-term clinical and laboratory test results.

However, in three of the patients we had to repeat oxamnique in larger dosages (15.0 - 17.0 mg/kg) some months later inasmuch as they were still excreting eggs in the stools, although in a very small number. We also repeated the antibiotic therapy in one patient because of the recurrence of fever related to the enteric infection.

SCHISTOSOMIASIS PLUS VIRAL HEPATITIS

In recent years, we have observed a relationship between HS schistosomiasis and chronic viral hepatitis with an exacerbation of the laboratory and clinical picture of both liver diseases. The HS form becomes worse, tending toward hepatic decompensation and the hepatitis also becomes worse progressive to a chronic hepatitis, or active chronic hepatitis or post-necrotic cirrhosis with the persistence of the AgHbs virus in the blood.

Until recently, before oxamnique was available, there was a formal contraindication to the use of specific treatment for schistosomiasis in patients with evident or suspected viral hepatitis because of severe aggravation of the liver disease which led on occasions to massive hepatic necrosis and death of the patient. In the absence of hepatotoxicity shown in the studies of oxamnique, and its being well tolerated in the severe cases of schistosomal liver disease and other forms of schistosomal disease, we decided to use in patients with schistosomiasis and viral hepatitis. The result of 13 patients treated so far are summarized in Table VI, where we recorded the histologic diagnosis of the hepatitis, the presence of absence of the AgHbs in the blood, the clinical form of schistosomiasis, the combined use with prednisone and the patients response to specific therapy.

<table>
<thead>
<tr>
<th>Table VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 cases of schistosomiasis + viral hepatitis treated with oxamnique clinical form</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Hepatitis</th>
<th>AgHbs</th>
<th>Schistosomiasis</th>
<th>No. of Cases</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Absence of hepatitis lesion</td>
<td>+</td>
<td>CHS</td>
<td>1</td>
<td>Favorable</td>
</tr>
<tr>
<td>B</td>
<td>Persistent chronic hepatitis</td>
<td>+</td>
<td>HI</td>
<td>1</td>
<td>Favorable</td>
</tr>
<tr>
<td>C</td>
<td>Active chronic hepatitis</td>
<td>-</td>
<td>CHS</td>
<td>4</td>
<td>3 — Favorable</td>
</tr>
<tr>
<td>D</td>
<td>ACH — Cirrhosis</td>
<td>-</td>
<td>HI</td>
<td>2</td>
<td>Irregular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>CHS</td>
<td>1 (+Pred)</td>
<td>Favorable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>DHS</td>
<td>2 (+Pred)</td>
<td>1 — Irregular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>3 (+Pred)</td>
<td>2 — Death</td>
</tr>
</tbody>
</table>
Firstly, the treatment with oxamniquine was well tolerated with no side effects different or more severe from those reported usually. However, the antischistosomal therapy has not modified the persistent AgHBs present in eight patients; they continue with this condition.

In a general way, the use of oxamniquine appears to have not modified the usual clinical picture of the patients with chronic viral hepatitis plus schistosomiasis. In the patients with persistent chronic hepatitis, the change was favorable, as is usual in this form of hepatitis, with no aggravation of the schistosomal or viral liver disease, despite persistence of AgHBs in two patients. Table VII shows an example of a favorable response in a patient with HS schistosomiasis, complicated with persistent chronic hepatitis and treated with oxamniquine. (It should be noted that the chemotherapy was administered when the patient still showed hyperbilirubinemia and slight raised transaminases; it did not cause any further increase in those values).

<table>
<thead>
<tr>
<th>Test/Date</th>
<th>Splenectomy Transfusion Nov. 73</th>
<th>Ox. 15mg/kg 8/9/75</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25/6/73 ↓ 29/1/74 21/6/75 11/6/75 ↓ 24/9/75 7/10/75 6/8/75</td>
<td></td>
</tr>
<tr>
<td>SGOT</td>
<td>27 310 135 101 138 123 46</td>
<td></td>
</tr>
<tr>
<td>SGPT</td>
<td>12 169 114 63 69 63 25</td>
<td></td>
</tr>
<tr>
<td>Alk' ph.</td>
<td>8.4 9.2 — 7.5 11.7 10.9 —</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.7 10.6 6.2 3.6 2.9 1.5 1.5</td>
<td></td>
</tr>
<tr>
<td>Alb.</td>
<td>2.6 3.3 2.6 3.7 3.4 3.4 3.3</td>
<td></td>
</tr>
<tr>
<td>Gamma Glob.</td>
<td>3.8 2.9 2.7 4.1 2.8 2.6 1.8</td>
<td></td>
</tr>
<tr>
<td>Ag HBs</td>
<td>— neg. — neg. — —</td>
<td></td>
</tr>
<tr>
<td>No. eggs (Kato)</td>
<td>— — 820 300 — neg. neg.</td>
<td></td>
</tr>
</tbody>
</table>

In the patients with active chronic hepatitis, with or without extension to cirrhosis, the response was relatively favorable after treatment with oxamniquine, but only when the patients were given prednisone, simultaneously and regularly (one of them also received Imunan).

In the patients who used immunosuppressive agents irregularly (generally because of cost; they returned to their homes and were not able to return to the hospital) or with more serious liver disease, the response was unpredictable, with periods of improvement and exacerbation, and two instances of death in the cirrhosis group.

**SEVERE INTESTINAL POLYPOSIS**

A patient with severe intestinal polyposis, who we had the opportunity to see with Dr. Ruy Pereira and Dr. Suzana T. Almeida, presented interesting features that deserve brief comment. He was a young man, 18 years of age, from Limoeiro, PE, who had had, for many years, a serious diarrhea with fever and a debilitated general state. When he was eleven he had been hospitalized repeatedly in the Pediatric Clinic, where the following diagnoses were made: HS schistosomiasis, chronic salmonellosis and extensive intestinal polyposis chiefly at the sigmoid level (biopsy indicated schistosomal granuloma). However, the attending
physician at the clinic had not given specific treatment for schistosomiasis for fear of side effects and because of the precarious state of the patient's health. They simply treated him for salmonellosis and suggested splenectomy and worm filtration by extracorporeal circulation (this filtration was not done for technical reasons). In the course of time, the diarrhea and the nutritional state became worse and hereafter a state of cachexia. The patient was hospitalized in the Medical Clinic in such poor condition that the risk of therapy was evident. He was first given supportive treatment, anabolics and parenteral nutrition for 24 days. During this period, along with a clinical picture of partial intestinal obstruction, palpation of the flank and left iliac fossa revealed that the descending colon and sigmoid were enlarged. Radiologic and endoscopic examinations of the large bowel showed extensive blockage with polyloid formations extending as far as the transverse colon. After moderate improvement with the previously described therapy, we decided to administer oxamnique in the dosage of 20 mg/kg body weight in two doses. We took the precaution of administering prednisone, 40 mg/kg for 7 days prior to the oxamnique and continued with prednisone, in decreasing doses, for two weeks after the oxamnique.

Tolerance was good and the immediate results were favorable, with reduction of the diarrhea and progressive improvement of his general state of health. At a return visit eight months later, the progress of the patient was gratifying. He had appreciable improvement of his clinical state and a weight increase of about 20 kg. All symptoms had disappeared, including the colic, induration, and the slight splenomegaly. The radiologic and endoscopic examinations showed marked reduction in the size of the polyloid formations.

COMMENTS AND CONCLUSIONS

In the present study, we have attempted to solve the problem of the specific treatment of severe forms of schistosomiasis mansoni, through evaluation of therapy with oxamnique.

The problem is of paramount importance in the hyperendemic regions of the disease such as the Brazilian Northeast, where severe cases are frequent, as well as in other regions of the country where severe cases of the disease occur occasionally. We will comment upon our results from three standpoints: drug tolerability, immediate and sometimes unfavorable responses to treatment itself, and the possible long-term benefits of the treatment.

The introduction of a drug better tolerated by the patient and the convenience of a single oral dosage, as is true of oxamnique, opened new horizons for the treatment of schistosomiasis.

After extensive study of oxamnique by the Brazilian medical profession, study which showed no evidence of toxic effect on the liver, heart, kidneys and blood cells (with only slight and transient activity on the central nervous system in a few patients), oxamnique has positioned itself as the current drug of choice for the treatment of this parasitic disease which is of so great socio-economic importance in our country. It has gained recognition to the point of its now being used in large scale in the Special Program of Schistosomiasis (PECE) of the Ministry of Health of Brazil.

In the present study of the treatment of advanced forms of the disease, where one would almost expect an increased number and severity of side effects, we report the good tolerance and almost complete absence of severe adverse effects due to oxamnique. Another aspect of the question to be dealt with is the possible deleterious effects of the treatment per se (not drug-related) which results from the abrupt death, in situ, of numerous parasites. These transitory effects do exist and are shown, in general, by laboratory data, such as increase of eosinophils, circulating antibodies, gammaglobulin, proteinuria, hematuria, and sometimes by clinical manifestations that may have importance, principally when seen in the severe forms of the disease.

Since more pronounced histological and pathophysiological changes occur in these severe cases, it is logical for one aware of the biology and localization of the parasite to be concerned with a more serious organic repercussion to the specific chemotherapy. We have seen this response in some patients, particularly in those with the severe hypertensive cardiopulmonary form, when one stimulates by treatment an overload on the pulmonary
vascular resistance which results in acute Cor pulmonale.

However, with the use of prednisone, prior to, simultaneously with the specific therapy (oxamniquine or other drug), and after, we have been able for some time to prevent or lessen the temporary exacerbation of the pathophysiological and clinical manifestations of the disease or the appearance of severe manifestation of hypersensitivity. We have adopted this mode of therapy with satisfactory results, in all the patients with evident severe disease, and chiefly when there might be the possibility of a hypersensitivity reaction to the treatment: chronic cases of pulmonary arterial hypertension, of the polypoid form or in badly debilitated patients with the acute forms of the disease.

The third and last question is related to the long-term claimed benefits of the treatment. Unfortunately, due to the age and probable irreversibility of the anatomic and pathophysiological changes common to these severe and complicated forms, late benefits are often limited or nil. We have observed this, for instance, in the decompensated hepatic forms, in the nephritic syndrome, in the severe pulmonary hypertension, and schistosomiasis complicated by active hepatitis and/or hepatic cirrhosis. From animal experimentation, we are aware of reports on the irreversibility of the lesions after the specific treatment in animals with old infections. However, in the case of hepatic, cardiopulmonary or other disease states, less advanced or without significant complications, it is possible to have clinical improvement and partial reversibility of the pathophysiological changes in some of the structural lesions. This is the response of the HS form patients, some patients with the transitional type, patients with the incipient cardiovascular form, and patients with associated chronic salmonellosis or persistent chronic hepatitis. Hence, the importance of treating, in these patients, the etiologic agent as soon as practicable and using other medical/surgical therapy as needed for each patient. In this way, it may be possible to reverse the alterations and to arrest the extension of the process, and thereby avoid progression to irreversibility, which is seen in some unfortunate patients described here and still observed in our population.

The condition is often brought about by delay to seek medical care on the part of the patient, because of their well-known precarious socioeconimic condition and also, it must be said, because of the unfamiliarity of some physicians with the treatment methods. In this connection, we want to call attention to the severe cases of HI or incipient HS form, with or without polypoid form, who can be treated specifically with good results. This was the result, for example, of the patient with the polypoid form described herein, who had an excellent therapeutic response and who should have been treated much earlier, to avoid the state of the disease he reached. We are aware of two equivalent events which occurred in other medical centers of the country. One of these events took place in Salvador, Bahia, where a very sick child (intense diarrhea and general debilitation and dehydration) with S. mansoni eggs in the stools, was not given specific therapy and died in a few days. The necropsy revealed intense schistosomal infection, almost millitary in character. Sometime later, a sister of this child was admitted to the hospital with quite a similar picture. The patient was treated with oxamniquine and had total recovery.

The other event took place in Brasilia (Hospital Distrital do Sobradinho). A young man, 14 years old, with HS syndrome, had intense diarrhea, general debilitation and ascites. Because S. mansoni eggs were found in the stools he was treated, after some days of hospitalization, with oxamniquine. The day following therapy the patient became worse, had irreversible shock and died. Necropsy revealed, apart from a schistosomal hepatosplenomegaly, a tumor formation of schistosomal etiology localized in the subserosa of the descending colon and sigmoid and projecting toward the abdominal cavity. An unusual finding was a great conglomerate of adult schistosomes partially occluding the portal vein. It is fair, in this case, to suggest the possibility that the shock and death of the patient could have been prevented had the treatment been combined with a corticosteroid, as has been mentioned previously. The partial occlusion of the portal vein by the conglomerate of worms did not appear to us to have been influential in causing death because of the rapid evolution from treatment to death, and the hepatic findings at necropsy.
It is interesting to observe, in passing, a relatively increased incidence of cases of the tumorous form, including the polypoid, and of severe intestinal and hepatointestinal forms, all classified clinically as subacute. This is indicative of a superinfestation and a decrease in the immunological resistance of the host.

It is also of interest to recognize the existence in the literature of broncho-pulmonary reactions and others which occurred after the use of oxamniquine and are probably related to a hypersensitivity response to the death of numerous worms.

From the result of our study and the discussion which followed, we suggest the following provisional conclusions: 1) Due to the good tolerance of oxamniquine in the majority of the patients treated, and the lack of hepatotoxic, cardiotoxic and nephrotoxic effects, the drug may be used in severe forms of schistosomiasis mansoni; 2) Oxamniquine may then be used in the less advanced Hs form, alone or associated with the cardiopulmonary form, schistosomal nephropathy, infection by enterobacteria, chronic viral hepatitis and other complications; 3) Therapy with oxamniquine must be given carefully at the earliest possible time to patients with the severe intestinal schistosomiasis, tumorous forms of the disease, including polypoid formations and, if possible, with the use of a corticosteroid, as described; 4) Evidence of transient exacerbation of the clinical and/or laboratory picture may, sometimes, be observed, particularly in patients with the hypertensive cardiopulmonary form. This exacerbation, whether drug-related or due to changes resulting from the treatment itself, may be prevented or corrected by the use of a corticosteroid (prednisolone); 5) Fairly good long-term clinical and laboratory results may be observed in patients with less advanced disease, with regression of the symptoms and partial improvement of the laboratory parameters; 6) In the patients with disease of greater severity or with complications, the beneficial effects are minimal or nil; 7) There is no evidence that the specific therapy with oxamniquine has contributed, in any way, to an exacerbation of the histologic, pathophysiologic or clinical condition arising from the disease itself; 8) It is not possible to avoid the occasional and unpredictable occurrence of hypersensitivity reactions, sometimes severe, which may accompany treatment, especially when a corticosteroid is not used simultaneously — a method of treatment emphatically recommended by the authors of this study.

REFERENCES


DISCUSSION ON DR. A. COUTINHO’S AND DR. DOMINGUES’ PAPER — EVALUATION OF THE TREATMENT OF SEVERE FORM OF SCHISTOSOMIASIS MANSONI BY OXAMNIQUEINE

Prof. PRATA

Do we have information on the evolution of hepatosplenic disease following treatment?

Dr. COUTINHO

There is great variation but regression can usually be seen after six months.

Dr. L. CAETANO (São Paulo)

This is very impressive, and I have observed an improvement in hepatosplenomegaly following treatment but only in patients without portal hypertension. When the patient has portal hypertension we do not see any significant improvement, so the patients who show the greatest improvement are children and young adults with hepatosplenic disease and moderate worm loads.
A FIFTEEN-MONTH STUDY ON THE EFFICACY OF A SINGLE 15 MG/KG DOSE OF OXAMNQUINE (VANSIL*) IN SCHISTOSOMA MANSONI IN AN ENDEMIC AREA

J. P. NOZAIS

Oxamnique (Vansil*) is a derivative of 2 aminomethyl tetrahydroquinoline. When administered by the oral route, it is quickly absorbed and blood levels are obtained in 0.5 to 3 hours. It is rapidly metabolized with the elimination of inactive metabolites in the urine along with small amounts of unchanged drug. In animal models, oxamnique causes a migration of adult worms to the liver; male worms are more susceptible and are killed with the loss of egg laying by the female within three days. Oxamnique is specific for S. mansoni and does not show clinically useful efficacy against S. haematobium infestations.

The optimal dose of oxamnique in humans varied depending on the particular strain of S. mansoni. In South America a single oral dose of 15 mg/kg will cure 90% of patients. In East Africa, Kenya a single dose of 15 mg/kg dose leads to a negative findings in 80-90%, whereas in Egypt, Uganda and the Sudan, up to four times this dose is required giving a total dose of 60 mg/kg.

PATIENTS AND METHODS

Patients

The study population consisted of 142 school children aged 6 to 14 years living in an endemic bilharzial area in the Ivory Coast. The general health of the children was good, although 31% were found to have splenomegaly. Polyparasitism was common, and 80% were found to have S. haematobium, 70% Necator americanus, 40% Ascaris lumbricoides, and 11% Strongyloides stercoralis and/or Trichuris trichura. The mean S. mansoni egg load was 350 eggs per gram of stool, with 48 children having less than 100 eggs per gram, 44 having between 101 and 300 eggs per gram, and 37 between 301 and 1200 eggs per gram.

Methods

A double-blind study was carried out using 94 children. S. mansoni egg counts were performed using Kato's Method. A fluorescent antibody assay, using as antigen frozen sections from adult S. mansoni worms, was performed at the same time as parasitological examinations at the first, second, third, fourth, twelfth, and fifteenth month after treatment.

All children had full clinical examinations and serological tests performed prior to treatment. Oxamnique was then administered in a single oral morning dose of 15-20 mg/kg, and patients were seen the following day and after ten days to determine when their side effects had occurred. At the end of 15 months children were reexamined and a serological examination performed, and a second course of treatment of 15-20 mg/kg of oxamnique was given. Prior to the second course of treatment, stool examinations were carried out on another 100 children living in the same village in order to establish the prevalence of schistosomiasis at that time.

RESULTS

Parasitological Results

After the first and second month, 19 of the 142 children remained positive for S. mansoni ova, giving an initial treatment failure rate of 13%. These children had severe infestation with a pretreatment egg count of 400
per gram stool and over half had splenomegaly.

At the end of the third month, 11 of the 123 children who showed an early cure developed a positive Kato smear for S. mansoni, giving a reinfection rate of 9%. Thus at this time 30 of the original 142 children (21%) were positive, but their egg excretion was only 5% of pretreatment levels (Table I).

<table>
<thead>
<tr>
<th></th>
<th>Total Number of Eggs Prior to Treatment (Mean)</th>
<th>Total Number of Eggs After Treatment (Mean)</th>
<th>Number of Children Examined</th>
<th>Total % of Reinfested Children</th>
<th>Total % with S. mansoni (Reinfested plus not cured)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third Month</td>
<td>49,275 (347)</td>
<td>2,600 (18)</td>
<td>142</td>
<td>9%</td>
<td>21%</td>
</tr>
<tr>
<td>Fourth Month</td>
<td>14,200 (1416)</td>
<td>1,400 (36)</td>
<td>39</td>
<td>19%</td>
<td>25.5%</td>
</tr>
<tr>
<td>Twelfth Month</td>
<td>24,700 (353)</td>
<td>3,900 (50)</td>
<td>70</td>
<td>26%</td>
<td>40%</td>
</tr>
<tr>
<td>Fifteenth Month</td>
<td>31,000 (408)</td>
<td>6,500 (86)</td>
<td>76</td>
<td>31%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Thirty-nine patients were examined at the end of the fourth month. Three of these children had not shown an initial cure; and of the remaining 38 children, 7 became reinfested. Thus a total of 25.5% of children were not cured or were reinfested after four months. The egg excretion in this group remained at only 10% of pretreatment levels.

Seventy patients were examined twelve months after treatment. Of this group 15 children (26%) had become reinfested between three and twelve months, and 13 had not shown an initial cure, giving an overall infestation rate of 40%. Egg excretion was only one sixth of pretreatment levels.

After fifteen months 76 children were re-examined; 31% had become reinfested and 12 (15%) had not shown an initial cure, giving an overall infestation rate of 42%. Egg excretion was 20% of pretreatment levels. Following this examination the children were retreated with oxamniquine.

At the time of the fifteen-month follow-up examination, stool examinations were performed on 100 children from the same village. These children had not been included in the original study. Thirty-eight percent were found to be positive for S. mansoni ova, with an average load of 260 ova per gram of stool compared to 85 ova per gram in the treated group.

**SEROLOGICAL RESULTS**

Prior to treatment the average fluorescent antibody titre was 1:80, with 91% of children having an antibody titre equal to or above 1:20. Results of the serological tests are given in Fig. 1. There was an initial rapid rise in antibody levels following treatment, reaching a peak at three months in children who were not cured or became reinfested, and at two months in children who were cured and remained cured throughout the study.

After twelve months antibody levels had dropped to below pretreatment levels and remained the same between twelve and fifteen months after treatment.

Antibody levels performed fifteen days after the second course of treatment showed an increase in levels, both in infested and parasitologically cured patients.

**SIDE EFFECTS**

Approximately one-half of the children experienced side effects. However, when side effects are compared in the double blind placebo controlled segment of the study, only diz-

Fig. 1 — Curves of average fluorescent antibody titre

Fig. 2 — Comparison of the antibody response following treatment with oxamniquine at three different dose levels
ziness was more common in the oxamniquine treated group (Table II). All side effects were regarded as mild and transient, and no child was required to miss school because of side effects.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Oxamniquine Treated Group</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimness</td>
<td>52%</td>
<td>14%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26%</td>
<td>22%</td>
</tr>
<tr>
<td>Headaches</td>
<td>21%</td>
<td>26%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Serological studies had been performed in previous clinical trials using oxamniquine at doses of 60 mg/kg and 30 mg/kg in the Ivory Coast. There was a rapid rise in antibody titres reaching a peak after one month and returning to pretreatment titres after 70 days in the 60 mg/kg group and 135 days in the 30 mg/kg group. Results with the 15 mg/kg dose were significantly different with peak levels being delayed to two to three months and return to pretreatment levels to eight months. It is postulated that by using lower doses the prolonged antibody response is due to a maintenance of antigenic stimulation by living female worms that remain in the mesenteric vessels. This hypothesis is confirmed by the low rate of reinfection seen over twelve months following treatment, and the rate in antibody levels seen in parasitologically cured patients following a second course of therapy. This rise in antibody levels suggests that non-egg laying worms are present and are destroyed by retreatment thereby releasing antigens which cause the antibody response.

As the maturation of S. mansoni from exposure to egg laying takes approximately six weeks, we assume that a positive parasitological test within the first two months indicates persistence of the infestation, and a positive finding after three months indicates reinfection.

In long-term follow-up over one year it was found that the incidence of S. mansoni infestation in treated and nontreated children exposed to the same endemic environment was similar. However, the intensity of infestation as judged by ova output was less in treated children.

**CONCLUSIONS**

Oxamniquine in a single dose of 15 mg/kg cured 87% of children with S. mansoni infestation in the Ivory Coast. The treatment of only 33% of the school population in an endemic environment brought about a decline in the overall incidence of S. mansoni in the school age population over 15 months.

Following treatment there is a prolonged antibody response due to persistent antigenic stimulation from a unisexual infestation.

The use of a single dose of 15 mg/kg of oxamniquine can be recommended in the treatment of Schistosomiasis mansoni in West Africa and a significant decline in prevalence, or perhaps eradication, can be obtained when using two successive courses of treatment at eight to twelve month intervals.

**REFERENCES**


DISCUSSION ON DR. J. NOZAIS’ PAPER — A FIFTEEN MONTH STUDY ON THE EFFICACY OF A SINGLE 15 mg/kg DOSE OF VANSIL IN MANSON’S SCHISTOSOMIASIS IN AN ENDEMIC AREA

Dr. N. KATZ (Belo Horizonte)

I would like to congratulate Dr. Nozais on his presentation, but I believe that some of his conclusions are optimistic. You have stated that control or even eradication can be obtained by giving two courses of treatment eight or twelve months apart. Our data suggests that you cannot eradicate or control the disease with such a dosage regime in an area of high transmission. The other conclusion that I would challenge is that the reinfection percentage fifteen months after treatment was identical to the percentage of schistosomiasis among children at the same school who were not treated. In our findings when we have reinfection after treatment, there is a low egg count. We assume that after treatment some worms remain in the body and through an immunological response protect against reinfection to some degree.

Prof. A. PRATA

I believe that reinfection is connected to immunity or the continuing presence of worms in the body. My view is that therapy increases immunity and consequent resistance against reinfection. We do not see reinfection immediately after treatment; it takes some time. When we enter a study area, we determine the normal curve of infection for that area and find a peak incidence of say the 15-year age group. When we treat we see that this peak is moved to the left, i.e. to a younger age group. The age group with the peak incidence thus gives you a representation of the degree of resistance of that population.

In a hyperendemic area, you may find the peak incidence in the 15–18 or 20-year age groups. The older people in a hyperendemic area develop a natural resistance to schistosomiasis. With treatment the peak incidence is moved to the left, to a younger age group. It should also be remembered that after treatment it is the younger age groups that become reinfected, with little reinfection being seen in the older age groups. My point is that with treatment you anticipate the natural resistance to the disease.

Dr. NOZAIS

I agree that the term eradication is too ambitious; to develop further data I plan to treat a village with a 100% disease incidence three times at intervals of eight months. Af-
ter 24 months, the prevalence will be determined and compared to that prior to treatment.

Dr. S. CAMARGO (Brasilia)

In our experience it is easier to treat the older age groups and to keep them negative. The younger age groups are more difficult to treat and are more easily reinfected. We have also seen marked regional differences in disease incidence with some areas having a peak incidence of infestation at about 25 years, possibly because of ecological and working conditions.

Dr. KATZ

I would like to ask Professor Prata what were the reinfection rates in the group of patients he followed for six years.

Prof. A. PRATA

The reinfection rate increases with time, I do not know the exact percentage but after six years it was almost the same as prior to treatment.

Dr. KATZ

This is a contradiction to the statement that immunity increases after treatment because if you have the same reinfection rate you have no immunity or only partial immunity.

Dr. PRATA

Immunity only lasts for a period of time and after that it is possible to become reinfected and acquire the disease.

Dr. KATZ

With schistosomiasis we must also consider the disease transmission because reinfection also required contact with water and cercariae. In some communities we only have seasonal transmission, so you need infected snails and water contact at this time. So we have two problems-immunological and epidemiological, both must be considered.

Prof. A. PRATA

In this study we only treated young patients with the objective of seeing if it was possible to prevent severe forms of the disease. However, these patients did not acquire the same intensity of infection even after six years.
Oxamniquine has been shown in Brazil to be a very effective drug for the treatment of schistosomiasis mansoni. However, 15% of adult patients and 25% of children do not obtain cure after a single oral dose of 15 and 20 mg/kg of body weight, respectively. Cure rate is higher (90 to 95%) after intramuscular administration of the drug (7.5 mg/kg b. wt.) 7.

Different rates of absorption and excretion of the drug could account for the above mentioned differences in efficacy.

The purpose of the study was to determine the relationship between the apparent systemic availability of oxamniquine (area under the curve of serum concentrations versus time) and its efficacy, following oral and intramuscular administration.

MATERIAL AND METHODS

PATIENTS

All patients included in the study had visible Schistosoma mansoni eggs in stools and exhibited the hepatointestinal form of the disease. The spleen was barely palpable in some children. We have studied 46 patients who were grouped as follows:

**Group A** — 13 adults were given a single intramuscular dose of oxamniquine (7.5 mg/kg);

**Group B** — 17 adults were given a single oral dose of 15 mg/kg (capsules);

**Group C** — 5 children were given a single oral dose of 15 mg/kg (capsules);

**Group D** — 11 children were given a single oral dose of either 15 mg/kg (4 children) or 20 mg/kg (7 children) syrup.

METHODS

All patients fasted on the day of the drug administration, prior to and for at least four hours following the dose.

BLOOD

For Group A, blood samples were obtained from each patient before and 1, 3, 5, 7, 9, 24, 48, 72 and 96 hours after drug administration. Serum was extracted and stored at -20°C prior to drug analysis. For the other groups, blood samples were obtained from each patient before and 0.5, 1.5, 3, 5, 7, 9 and 24 hours after the drug administration. Serum was treated as in Group A.

Transport of frozen samples from São Paulo (Brazil) for assay at Pfizer Central Research in Sandwich was made by airfreight in insulated boxes.

ASSAY FOR OXAMNIQUINE

Serum levels of oxamniquine were determined by a specific gas chromatographic method. The drug was extracted from basified serum converted into its trimethylsilyl derivative and assayed using a 63 Ni electron capture detector.

ASSESSMENT OF EFFICACY

The efficacy of the drug was assessed by determining whether eggs of S. mansoni were absent from the faces at several monthly examinations after the treatment. Egg counts were done by the Kato-Katz technique. Parasitological cure was considered to be achieved when negative stool examinations were observed at least six months after treatment.

(1) Instituto de Medicina Tropical de São Paulo, São Paulo, Brazil

(2) Pfizer Central Research, Sandwich, England

58
RESULTS

Group A (13 adults)

All patients who received the drug by the intramuscular route (7.5 mg/kg) experienced pain at the injection site, even when the drug was formulated as a fine particle suspension (first 5 patients).

Maximal serum concentrations of the drug varied from less than (20 ng/ml to 250 ng/ml) (Table I), and were observed 3 to 7 hours after the administration (Fig. 1).

<table>
<thead>
<tr>
<th>Table I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum concentrations of Oxamnique (ng/ml) in adults (Group A) with S. mansoni, following a single intramuscular dose of Oxamnique (7.5 mg/kg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Patient No.</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>7</th>
<th>9</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>51</td>
<td>22</td>
<td>20</td>
<td>30</td>
<td>30</td>
<td>20</td>
<td>Cured</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>170</td>
<td>180</td>
<td>190</td>
<td>250</td>
<td>190</td>
<td>94</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>Not cured</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>41</td>
<td>55</td>
<td>60</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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</tr>
<tr>
<td>4</td>
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<td>160</td>
<td>120</td>
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<td>85</td>
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<td>20</td>
<td>ND</td>
<td>Cured</td>
</tr>
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<td>5</td>
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<td>23</td>
<td>71</td>
<td>84</td>
<td>110</td>
<td>85</td>
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(*) Negative stool examination at the fourth month
ND = non detectable

The serum concentration versus time profile (see Fig. 1) was prolonged; drug was detected in sera from 7 out of 13 patients 96 hours after the dose.

Parasitological cure at six months was observed in 8 patients and negative stool examinations at the fourth month in 2 patients; follow-up was lost in two patients (cases No. 6 and 13). The only non-cured patient (case No. 2) showed the highest blood levels within the first 24 hours. Egg count of the fecal sample showed 24 eggs per gram at the third month post-treatment. Hatching test was not performed. A rectal biopsy one month later was negative. The patient did not return for further evaluation.

Group B (17 adults)

Following oral administration (capsules) to adults, maximal serum concentrations were reached after 1.5 to 3 hours (Fig. 1). The maximal serum level ranged from 70 to 2595 ng/ml. Oxamnique was fairly rapidly eliminated from serum, because the drug was detected in only three out of the 14 adults 24 hours after the ingestion (Table II).

![Graph](image)

**Fig. 1** — Mean serum concentrations of oxamniquine in patients with S. mansoni after a single dose of either 15-30 mg/kg p.o. or 7.5 mg/kg i.m.

**TABLE II**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>0.5</th>
<th>1.5</th>
<th>3</th>
<th>5</th>
<th>7</th>
<th>9</th>
<th>24</th>
<th>Follow-up</th>
</tr>
</thead>
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<tr>
<td>Patient No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>1</td>
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<td>40</td>
<td>1150</td>
<td>560</td>
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<td>1080</td>
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</tr>
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<td>12</td>
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<td>ND</td>
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</tr>
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</table>

(*) Negative stool examination at the fourth month
ND = non detectable
NS = no sample
Parasitological cure was observed in nine patients and negative stool examinations at the fourth month in three patients; follow-up was lost in three patients (cases No. 10, 14 and 17). Patient No. 3 and 7 were not cured. The first one vomited after ingestion of the drug and showed the lowest serum concentration of oxamniquine in Group B (Table II). In patient No. 7, high serum concentrations were observed up to 9 hours after administration.

Illustrative patterns of blood levels from these patients and from two other cured patients are shown on Fig. 2. Of interest is the fact that patient No. 7 had twice previously received the same treatment regimen and continued to have viable eggs in the stools (Fig. 3).

Some degree of resistance of this strain of S. mansoni to oxamniquine was demonstrated experimentally and will be published separately.

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**Fig. 2** — Serum concentrations of oxamniquine, 4 adult patients after a single dose of 15 mg/kg bw.

**Fig. 3** — Resistance of S. mansoni to oxamniquine in a patient (V.A.A. 20 y.) with the hepatointestinal form.
Group C (5 children)

Following oral administration (capsules) to children, maximal serum concentrations ranging from 89 to 1500 ng/ml were seen after 1.5 to 3 hours (Fig. 1 and Table III). Oxamniquine was not detected 24 hours after administration.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>0.5</th>
<th>1.5</th>
<th>3</th>
<th>5</th>
<th>7</th>
<th>9</th>
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<td>&lt;20</td>
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</table>

(*) Negative stool examination at the fourth month
ND = non detectable
NS = no sample

Parasitological follow-up was carried out in only two patients who were shown to be cured.

Group D (11 children)

Following oral administration (syrup) to 11 children, maximal serum concentration ranging from 120 to 928 ng/ml were reached 0.5 to 1.5 hours after the dosage of 15 to 20 mg/kg b.wt. (Fig. 1 and Table III). Oxamniquine was detected in only three patients 24 hours after the treatment.

Parasitological cure was observed in six patients and negative stool examinations at the fourth month in two patients; one was not cured (No. 2) and two others (No. 4 and 11) did not return for follow-up evaluation. The non-cured patient showed the lowest serum concentration of the group (Table III).

DISCUSSION

Serum concentrations of oxamniquine varied widely among the groups and within the groups. However, a characteristic trend was observed after intramuscular (IM) and oral administration of the drug. In group A (7.5 mg/kg IM), low serum levels were recorded (Fig. 1), with maximum concentrations varying between less than 20 to 250 ng/ml (Table I), 3 to 7 hours after the injection. However, in 7 out of 13 patients, the drug was detected 96 hours after administration. This demonstrates that the drug is slowly released into the circulation after intramuscular injection.

The persistence of oxamniquine serum levels presumably results in absorption of lethal quantities of drug by the parasites. Of importance is the fact that all 10 patients followed may be considered as cured. The only
non-cured patient (No. 2) had a very low egg count (24 eggs/g of faeces) in the third month post-treatment and a negative rectal biopsy one month later. Unfortunately the patient did not return for further stool examinations.

The efficacy of oxamniquine after intramuscular administration is already well established, with cure rates varying from 90 to 95% 3. However, the pain at the injection site, precludes the general use of the drug by this route.

Following oral administration of 15 mg/kg b.w.t. of the drug formulated in capsules, adults (17 patients) showed high serum levels of oxamniquine with the maximal concentrations varying from 70 to 2595 ng/ml (Table II), which were seen at 1.5 to 3 hours after the administration (Fig. 1); detectable amounts of oxamniquine were found in only three patients after 24 hours.

Parasitological cure or negative stool examinations at the fourth month were observed in twelve of the fourteen patients evaluated. One non-cured patient (No. 3) vomited after the drug administration and showed the lowest serum concentration in Group B. In this patient parasites presumably did not absorb lethal amounts of drug. Re-treatment was given seven months later with the same schedule and the patient was completely cured after a 10-month follow-up. The other patient (No. 7) had been previously treated twice before with the same schedule and seems, therefore, to belong to the “resistant group”. Such resistance of S. mansoni to chemotherapy was demonstrated with hymanthone, the resistance being transmitted to mice 1,4. As far as oxamniquine is concerned, drug resistance was shown in mice 3, and clinically suggested in some of our patients, but experimental transmission has not been established 9.

Children seem to have shorter periods of high blood levels (Fig. 1), not only after capsule administration (Group C), but especially after syrup (Group D). As expected, the nine children who received the syrup preparation showed a rapid absorption of drug, with maximum concentrations (120 to 920 ng/ml) seen after 0.5 to 1.5 hours (Table III). Oxamniquine levels were detected in only three patients 24 hours after the administration. Here again, the non-cured patient showed the lowest blood levels in the group.

The shorter period of high blood levels in children, especially after syrup administration, may explain somewhat lower cure rate in these patients. In summary, our data suggest that cure rates are associated with high serum levels of oxamniquine or, preferably, with the presence of the drug in the blood for long periods of time. Lower serum levels of drug may also reduce the incidence of dizziness, as none was reported following intramuscular administration. This symptom is rather after oral therapy 7. It is possible that a better therapeutic response by oral route may be achieved with the same dose of oxamniquine by modifying the oral drug serum level profile to make it similar to that found after intramuscular administration, i.e., by increasing the persistence of drug in the serum, even though this leads to a reduction in the height of the serum levels. This could be achieved by giving two oral doses of 7.50 or 100 mg/kg with an 8 hour-interval between doses 5 or alternatively by giving a single dose with food, which should slow down the absorption rate. As a matter of fact, oxamniquine given after breakfast produces significantly less side effects than that given before breakfast 7. Possible differences in cure rate have not been established. Another possibility would be the reformulation of oxamniquine so that the drug would be more slowly released in the gastrointestinal tract.

CONCLUSIONS

 Intramuscular administration of oxamniquine produced the most prolonged blood levels whereas the syrup produced the most rapidly attained blood level. Capsules given to adults by oral route produced the highest blood levels, with a persistence in the serum slightly longer than that produced by syrup. Cure rate seems to follow serum concentration patterns — higher after intramuscular administration and lower after syrup.

REFERENCES


ATTEMPT TO CONTROL THE SCHISTOSOMIASIS TRANSMISSION BY OXAMNIOQUINE, IN AN HYPERENDEMIC LOCALITY

Aluizio PRATA (1), J. C. BINA (2), Air C. BARRETO (1) and Maria das Graças ALEGREIM (1)

SUMMARY

Our study was an attempt to control schistosomiasis only with repeated treatments in a population of initially 395 persons who lived in a hyperendemic area. The medication used was oxamniquine in an oral single dose of 12.5 — 15.0 mg/kg body weight to adults and 20.0 mg/kg to children. We made 8,491 examinations of feces from which we discovered positive results in 821 persons over a four year period. There was an extensive mobility of the population with many arrivals and departures of inhabitants. The original 314 treatments were followed by an additional 504. The cure rate was 85.5%, after evaluation of five examinations of feces in eight months, but decreased to 31% following 25 examinations in four years. We repeated treatment in 178 patients; twice in 80, three times in 44, four times in 18, five times in seven and six in two, seven in one, and eight in another, and reduced the initial prevalence of schistosomiasis from 71.2% to 3.9%. In the last six months the reduced prevalence has remained almost stationary. The age group of 5-19 years is the group which is most often reinfected. After the initial treatment we recorded a reduction in the number of eggs per gram of feces from a mean of 638 in the general population to 85 in the remaining positives.

INTRODUCTION

The campaigns of voluntary mass treatment of schistosomiasis with antimonials had their beginning in Egypt in 1922. Later the treatment became compulsory, at least in some provinces. Mass treatment was later attempted in other countries, Sudan and Rhodesia.

In Brazil, the large scale use of the antimonials as therapy for schistosomiasis, was started by MACIEL, and treatment of a smaller population was initiated by JANSSEN. In 1954 the Ministry of Health began to use antimonials in the campaign against schistosomiasis, and treated more than 100,000 patients. Recently, PRATA reviewed the Brazilian experience of mass treatment and concluded that it could reduce the prevalence of schistosomiasis, even in endemic areas, but its value in the control of the disease was not yet known. He suggested the possibility of mass treatment for schistosomiasis as was done for malaria.

The availability of drugs for use in a single dose, principally oxamniquine, has opened wide the opportunities for the treatment of schistosomiasis. Well-controlled studies made by BINA have confirmed Kloetzl studies that treatment could prevent the hepatosplenic form of the disease.

In recent years, the Ministry of Health has increased its activities of its anti-schistosomiasis program and is expected to treat millions of persons.

Study carried out with the support of the Ministry of Health
(1) Universidade de Brasília
(2) Universidade da Bahia
All investigators with experience in the treatment of schistosomiasis in endemic areas have reported a marked decrease in the prevalence rate which was then followed by progressive reinfestation. As an example, we cite the study done by BINA & PRATA \(^3\) in 597 persons in Canabrava (Bahia), where the schistosomiasis prevalence was 46.3%.

After 14 months after treatment, it was 25.5%, at which time 61% of the patients with positive stool examinations were treated again. A 38-months evaluation after the initial treatment showed a prevalence rate of 19%.

Later data showed that this percentage had risen to 31.7% four years later. In the attempt to control schistosomiasis only by specific treatment, we decided to concentrate on one locality, to identify the positive cases and repeat the treatment over a long period of time. The present report is our experience over four years of study.

**MATERIALS AND METHODS**

The area where we attempted to control schistosomiasis only by specific treatment is called Fazenda Nova Esperança and is located about 80 km northeast of Jacobina (Bahia). The dwellings there surround a lagoon, which is the only source of water supply for the residents and animals. The lagoon, nearly 50 meters in diameter, is shallow, perennial, and has neither inflow or outflow.

The census in 1972 gave the population as 395 persons, 197 males and 198 females. There were 51 whites, four blacks, 323 mulattos and 17 whose color was not recorded. The distribution by age group was as follows:

<table>
<thead>
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<th>Years</th>
<th>No. of Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 — 4</td>
<td>73 (18.5%)</td>
</tr>
<tr>
<td>5 — 9</td>
<td>63 (15.9%)</td>
</tr>
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<td>10 — 14</td>
<td>49 (12.4%)</td>
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<td>15 — 19</td>
<td>37 (9.8%)</td>
</tr>
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<td>20 — 24</td>
<td>32 (8.1%)</td>
</tr>
<tr>
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<td>32 (8.1%)</td>
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<tr>
<td>30 — 39</td>
<td>37 (9.4%)</td>
</tr>
<tr>
<td>40 — 49</td>
<td>24 (6.1%)</td>
</tr>
<tr>
<td>50 — 59</td>
<td>25 (6.3%)</td>
</tr>
<tr>
<td>More than 59</td>
<td>16 (4.0%)</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>18 (4.8%)</td>
</tr>
</tbody>
</table>

In November 1972, we began physical examination of the population, skin testing with antigens of adult worms, and stool examinations, qualitative by Kato's technique \(^5\) and quantitative by Stoll's technique \(^12\).

In January 1975, we first treated the population with oxamniquine, in capsules given orally as a single dose, in the dosage of 12.5 — 15.0 mg/kg body weight. Children were given 20.0 mg/kg in the form of syrup. At that time, there were 63 persons weighing from 10 to 19 kg, 49 from 20 to 29 kg, 28 from 30 to 39 kg, 38 from 40 to 49 kg, 65 from 50 to 59 kg, 36 from 60 to 69 kg, eight from 70 to 79 kg, one over 80 kg and 107 whose weight has not been recorded.

From July to August 1975, we made four stool examinations, and from December 1975 to December 1978 we repeated stool examinations monthly for a total of 23 examinations (exceptions were February, October, December 1976; January, April, May, July, October, December 1977; and January, April, November 1978). The technique used was Kato's quantitative, modified by KATZ \(^6\).

From October 1975, we repeated the treatment of the patients with oxamniquine whenever one of the 25 examinations revealed S. mansoni eggs in the stools.

After May 1976, we included in the program all the newly arrived persons to Nova Esperança. In December 1978, the number of individuals in the total program had reached 821; however, many of them had moved from the town.

We had avoided treating pregnant women but, on the supposition that some might have been treated inadvertently, in January 1978 we reviewed all the births and abortions which had occurred in Nova Esperança, by questioning 98 women who had given birth. The births were determined through baptism certificates and the dates were associated with the dates of treatment.

Our work routine in Fazenda Nova Esperança consisted of a monthly visit by one or two technicians for 4-6 days for collection of stool samples for examination. Generally, the repeat treatment was given one day of the following month. The persons who were absent or not able to attend for examination of
treatment in one month would await the next month.

The schistosomiasis vector in the area is the *Biophthalmaria glabrata*, which according to information from the local people, was introduced in the lagoon after 1964. To evaluate the potential for schistosomiasis transmission, we determined the degree and the rate of infection of the snails which were collected in the months of February, April and October 1973, September 1974, May, July and October 1975, and March 1976.

The snails samples were collected by means of four scoopsfuls of water from each of the 45 stations on the margin of the lagoon. We also exposed mice to infection in the months of December 1977, February and October 1973, June and August 1974, May and October 1975. The mice, in metal cages, were partially immersed in the lagoon for one hour between noon and 1:00 p.m. for three consecutive days.

**RESULTS**

**Prior to Treatment** — The physical examination of 376 persons revealed 18 patients with the hepatosplenic form of the schistosomiasis (spleen at least at the costal margin), nine patients with nodular liver and 352 with the common form (intestinal or hepato-intestinal). There were also 20 patients with arterial hypertension, two with pulmonary hypertension, two paraplegies, one each with aortic insufficiency, hyperthyroidism, or schizophrenia. Historically, of importance were episodes of hematemesis reported as having occurred in 15 persons, living or dead. The stool examinations in 323 persons revealed positive results in 270 (71.21%), distributed, according to the age groups, as follows:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 — 4</td>
<td>15 (22.8%)</td>
<td>44</td>
</tr>
<tr>
<td>5 — 9</td>
<td>37 (5.5%)</td>
<td>12</td>
</tr>
<tr>
<td>10 — 14</td>
<td>37 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>15 — 19</td>
<td>24 (66%)</td>
<td>1</td>
</tr>
<tr>
<td>20 — 24</td>
<td>26 (93.3%)</td>
<td>3</td>
</tr>
<tr>
<td>25 — 29</td>
<td>22 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>30 — 39</td>
<td>27 (69%)</td>
<td>3</td>
</tr>
<tr>
<td>40 — 48</td>
<td>17 (73.9%)</td>
<td>6</td>
</tr>
<tr>
<td>50 — 59</td>
<td>13 (54.5%)</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 59</td>
<td>8 (53.3%)</td>
<td>7</td>
</tr>
<tr>
<td>not mentioned</td>
<td>5 (33.3%)</td>
<td>8</td>
</tr>
</tbody>
</table>

Ova counts in 251 persons showed a mean of 638 eggs per gram of feces, with the following distribution according to age:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>0</th>
<th>100-400</th>
<th>Eggs per gram of feces</th>
<th>500-400</th>
<th>1000-2000</th>
<th>&gt;2000</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 — 4</td>
<td>11</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>827</td>
<td></td>
</tr>
<tr>
<td>5 — 9</td>
<td>5</td>
<td>20</td>
<td>8</td>
<td>5</td>
<td>9</td>
<td>685</td>
<td></td>
</tr>
<tr>
<td>10 — 14</td>
<td>3</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>9</td>
<td>1.217</td>
<td></td>
</tr>
<tr>
<td>15 — 19</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>1.020</td>
<td></td>
</tr>
<tr>
<td>20 — 24</td>
<td>2</td>
<td>16</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>682</td>
<td></td>
</tr>
<tr>
<td>25 — 29</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>666</td>
<td></td>
</tr>
<tr>
<td>30 — 39</td>
<td>7</td>
<td>17</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>202</td>
<td></td>
</tr>
<tr>
<td>40 — 49</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>294</td>
<td></td>
</tr>
<tr>
<td>50 — 59</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>323</td>
<td></td>
</tr>
<tr>
<td>&gt; 59</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>not known</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>566</td>
<td></td>
</tr>
</tbody>
</table>

| Total       | 50 (19.9%) | 111 (44.2%) | 45 (17.9%) | 21 (8.4%) | 24 (9.6%) |

In 260 skin tests for the diagnosis of schistosomiasis, 60 (23%) were negative, with the following distribution by age groups: 42 in the 0-4 years, eight in the 5-9 years, and ten in
the remaining groups. If one considers the repeated stool examinations and the skin tests together, we find that in only 55 (18.8%) of the 327 persons were negative by both tests.

In 29 (15.8%) of these 55 patients, we did additional skin tests and more than one stool examinations; and in the remaining 26, only one of the examinations. The age distribution of the 29 negative cases mentioned above was as follows: one was 55 years old, one 5 years, five 4 years, four 3 years, eleven 2 years and six were under 2 years.

**Initial Treatment** — Of the 395 inhabitants of Nova Esperança, 224 were treated in January 1975. The remaining 111 were not treated for one or more of the following reasons: pregnancy (13 cases); under age of 4 years (15); incapacitated (2); cachexia (1); amaurosis (1); four had died and 75 were out of town or did not attend the session.

Among the patients treated there were 11 with the hepatosplenic form, 6 with proeminent nodular liver, 1 with pulmonary hypertension, 11 with arterial hypertension plus one of the following diagnoses: Parotiditis; alcoholism; chronic tuberculosis; schizophrenia, aortic insufficiency and hyperthyroidism.

The side effects and the toxic reactions reported were: dizziness (51%), drowsiness (23%), vomiting (6%), nausea (5%), headache (4%), abdominal pain (2%) and myalgias (0.8%). In May, four months later, we returned to the area and treated 30 patients, including those who had returned home or whose pregnancy has terminated. In this way, we reached a total of 314 patients treated (80.3% of the initial population, excluding the four deaths).

On the 314 treated, 236 had positive stools; ten had only positive skin test; 22 had either negative stools or negative skin test, or both, and in 48 no examinations had been made. Justification for the treatment of these 66 cases negative for *S. mansoni* in the stools is that, in view of the high prevalence of schistosomiasis they would certainly have been found to be positive had the stool examinations been done repeatedly.

Of the five parasitologic examinations programmed for the July-August 1975 period, 95 patients had all done, 47 had none, and 172 had from one to four examinations. Of the 267 who had at least one examination, 38 (14.2%) were found to be positive. The number rose to 203 (58%) after the 25th stool examination, from among the 294 patients (out of the initial 395) remaining in the program.

Of the 40 patients ages 0-4 years who had had negative stool examinations (because of this needed not to be treated) but who continued in the area, 18 became infected later and were treated, whereas 22 always remained negative. The age distribution of these 22 patients in December 1978 was: six were 6 years old; three 7 years; seven 8 years; three 9 years and three 10 years; 11 were males and 11 females. In addition, there was a 55 year old male patient who always had negative stools.

**Change in Population** — In the four years of follow-up, there was a great movement of people in and out of the Fazenda Nova Esperança (Table I). There were 18 deaths, 426 persons had arrived at the locality to reside for at least some time, and 273 had moved away. The temporary absences, for weeks or months, were very frequent. This explains the 30% failure rate in obtaining monthly examinations and the delay in treating many positive patients, whose treatment had to be programmed repeatedly (Table I).

**Identification of Positive Cases** — Excluding those made before the initial treatment, 6,087 stool examinations were done of which 613 were positive for *S. mansoni* eggs (Table I). Of these patients, two died, fifteen moved to another locality and 92 had positive stools in the repeat examinations. Thus in the area, we identified 534 patients who had to be treated: 194 for the first time and 340 for repeat treatment.

**Later Treatment** — In addition to the 314 treatments given at the time of initial treatment, another 504 treatments were given: 173 for the first time and 331 repeated. The great majority of those treated for the first time were newcomers to the area. Of the 331 repeat treatments, 178 were repeated only once, 80 twice, 44 three times, 18 four times, seven five times, two six times, one seven times and one eight times. In relation to age (Table II), 70.8% of the repeated treatments were given
to the 5-19 year old group, who constituted 36.8% of the general population. No patient over age nineteen repeated treatment more than three times. The analysis of the age of the 91 patients who remained negative after 25 stool examinations (out of the 294 patients who stayed in the program) shows that 74% were over 19 years (Table III).

### Table I

<table>
<thead>
<tr>
<th>Date</th>
<th>Inhabitants</th>
<th>Stool Examinations</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Moves</td>
<td>New</td>
</tr>
<tr>
<td>Dec/72</td>
<td>305</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan/May/73</td>
<td>4</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Oct/75</td>
<td>363</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec/76</td>
<td>182</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Jan/76</td>
<td>170</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>March</td>
<td>190</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>April</td>
<td>189</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>May</td>
<td>4</td>
<td>79</td>
<td>435</td>
</tr>
<tr>
<td>June</td>
<td>1</td>
<td>11</td>
<td>442</td>
</tr>
<tr>
<td>July</td>
<td>4</td>
<td>19</td>
<td>460</td>
</tr>
<tr>
<td>August</td>
<td>6</td>
<td>15</td>
<td>470</td>
</tr>
<tr>
<td>September</td>
<td>6</td>
<td></td>
<td>464</td>
</tr>
<tr>
<td>October</td>
<td>4</td>
<td></td>
<td>458</td>
</tr>
<tr>
<td>November</td>
<td>19</td>
<td>11</td>
<td>485</td>
</tr>
<tr>
<td>February</td>
<td>2</td>
<td>11</td>
<td>32</td>
</tr>
<tr>
<td>March</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>June</td>
<td>2</td>
<td>24</td>
<td>46</td>
</tr>
<tr>
<td>August</td>
<td>25</td>
<td>15</td>
<td>494</td>
</tr>
<tr>
<td>September</td>
<td>29</td>
<td>48</td>
<td>513</td>
</tr>
<tr>
<td>November</td>
<td>22</td>
<td>14</td>
<td>498</td>
</tr>
<tr>
<td>February 73</td>
<td>1</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>March</td>
<td>1</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>April</td>
<td>3</td>
<td>15</td>
<td>493</td>
</tr>
<tr>
<td>May</td>
<td>14</td>
<td>4</td>
<td>494</td>
</tr>
<tr>
<td>June</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>July</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>August</td>
<td>29</td>
<td>497</td>
<td>348</td>
</tr>
<tr>
<td>September</td>
<td>11</td>
<td>508</td>
<td>311</td>
</tr>
<tr>
<td>October</td>
<td>5</td>
<td>513</td>
<td>344</td>
</tr>
<tr>
<td>December</td>
<td>10</td>
<td>534</td>
<td>359</td>
</tr>
</tbody>
</table>

Total: 16 273 426 5491 833 518

(*) The examinations were repeated in some patients

### Table II

<table>
<thead>
<tr>
<th>Initial Age (years)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Total No. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 -- 4</td>
<td>2</td>
<td>2 (0.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 -- 9</td>
<td>43</td>
<td>19</td>
<td>8</td>
<td>2</td>
<td>72 (23.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 -- 14</td>
<td>42</td>
<td>39</td>
<td>20</td>
<td>11</td>
<td>14</td>
<td>108 (32.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 -- 19</td>
<td>33</td>
<td>13</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>53 (16.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 -- 24</td>
<td>13</td>
<td>6</td>
<td>2</td>
<td>36 (7.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 -- 29</td>
<td>13</td>
<td>3</td>
<td>4</td>
<td>19 (5.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 -- 39</td>
<td>16</td>
<td>7</td>
<td>3</td>
<td>26 (7.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 -- 49</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>14 (4.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 -- 59</td>
<td>5</td>
<td>5 (1.5)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 59</td>
<td>4</td>
<td>4 (1.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not mentioned</td>
<td>2</td>
<td>2 (0.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total: 178 80 44 16 7 2 1 1 331

### Table III

<table>
<thead>
<tr>
<th>Initial Age (years)</th>
<th>No.</th>
<th>Patients %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 -- 4</td>
<td>9 (23.9)</td>
<td></td>
</tr>
<tr>
<td>5 -- 9</td>
<td>6 (21.5)</td>
<td></td>
</tr>
<tr>
<td>10 -- 14</td>
<td>6 (21.5)</td>
<td></td>
</tr>
<tr>
<td>15 -- 19</td>
<td>3 (23.0)</td>
<td></td>
</tr>
<tr>
<td>20 -- 24</td>
<td>13 (43.3)</td>
<td></td>
</tr>
<tr>
<td>25 -- 29</td>
<td>13 (43.3)</td>
<td></td>
</tr>
<tr>
<td>30 -- 39</td>
<td>16 (47.1)</td>
<td></td>
</tr>
<tr>
<td>40 -- 49</td>
<td>12 (36.9)</td>
<td></td>
</tr>
<tr>
<td>50 -- 59</td>
<td>5 (15.6)</td>
<td></td>
</tr>
<tr>
<td>&gt; 59</td>
<td>5 (15.6)</td>
<td></td>
</tr>
</tbody>
</table>

Total: 91
After the initial treatment there was evident reduction in the number of eggs per gram of feces (Table IV). The mean number of eggs per gram of feces was 55 in 178 patients after the initial treatment, 35 in 80 patients after the second treatment, 65 in 44 patients after the third treatment, 52 in 18 patients after the fourth treatment and 46 in seven patients after the fifth treatment.

**Table IV**

<table>
<thead>
<tr>
<th>Eggs per gram of feces after each treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(no.)</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>23 — 69</td>
</tr>
<tr>
<td>92 — 239</td>
</tr>
<tr>
<td>253 — 483</td>
</tr>
<tr>
<td>506 — 989</td>
</tr>
<tr>
<td>&gt; 989</td>
</tr>
<tr>
<td>not mentioned</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

**Treatment of Pregnant Women** — Among the 98 women of childbearing age, we confirmed that six had taken oxamniquine, inadvertently, during pregnancy. Two in the first month of pregnancy, two in the second month and two in the fourth month. One of those who took the drug in the fourth month aborted three months later. One of the children, whose mother was treated in the second month, died at four months of age, after coughing episodes. Of the four living children, three were 2 years old and one, 1 year. All were given a careful physical examinations and, except for the absence of testes in the scrotal pouch in two of them, which seemed normal to us, nothing unusual was detected.

**Infection Rate in Snails and Mice** — The *Biomphalaria glabrata* population remained stable during the observation period (Table V). Their infection rate by the *S. mansoni* cercariae was very high initially, but began to decline even before the treatment of the human population. Positive snails were not found in the last two collections.

**Table V**

<table>
<thead>
<tr>
<th>Year</th>
<th>Month</th>
<th>Snails Collected</th>
<th>Positive</th>
<th>Mice Exposed</th>
<th>Mice Infected</th>
<th>Mean of worms per Mouse exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1972</td>
<td>Dec</td>
<td>32</td>
<td>7 (22%)</td>
<td>32</td>
<td>15 (48%)</td>
<td>10</td>
</tr>
<tr>
<td>1973</td>
<td>Feb</td>
<td>14</td>
<td>5 (36%)</td>
<td>62</td>
<td>18 (29%)</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>April</td>
<td>51</td>
<td>7 (14%)</td>
<td>45</td>
<td>9 (20%)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>June</td>
<td>45</td>
<td>4 (11%)</td>
<td>35</td>
<td>4 (11%)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Aug</td>
<td>24</td>
<td>3 (7%)</td>
<td>62</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sept</td>
<td>42</td>
<td>3 (7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975</td>
<td>May</td>
<td>108</td>
<td>4 (4%)</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>July</td>
<td>71</td>
<td>2 (3%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oct</td>
<td>65</td>
<td>0</td>
<td>34</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>March</td>
<td>115</td>
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The infection rate of the exposed mice and the number of worms per animal, also decreased before the treatment of the human population.

**Comments**

After trying for four years to control schistosomiasis by specific treatment in the hyperendemic locality of Nova Esperança, we have succeeded in reducing the prevalence of *S. mansoni* eggs in stool examinations from 71.2% to 3.9%. This reduced prevalence has maintained itself practically unchanged for the last six months. At present, we are working more aggressively in order to reduce it further. In this attempt, the two great obstacles encountered are the mobility of the population and the pregnancies. The latter obligates us to postpone treatment even when the
Patient continues excreting eggs. The migration of the population interferes in various ways: new patients arrive and treatment of the identified cases is delayed which facilitates reinfection of treated patients. After treatment, the patients, even when not cured, eliminate fewer eggs in the stools. By our calculations, the mean number of eggs per gram of feces in the population, before the initial treatment, was 63. After the initial treatment it dropped to 85 among the patients with positive stools. Before treatment there was 36% of stools with more than 500 eggs per gram of feces and after the treatment this fell to 1.4%. As already mentioned, of the 40 children who were under five years of age and without schistosomiasis at the beginning of the study, 22 (55%) have never become infected although they continued to live in Nova Esperança. Judging from the initial prevalence, the possibility of the children becoming infected in the absence of treatment, would have been 75.5% for the 19 ages 5-9 years and 100% for the three 10 years old. All these data show that the transmission of schistosomiasis diminished greatly in Nova Esperança. This decrease was documented by the diminished infection rates of snails and mice, notwithstanding the small number of determinations made. It is interesting to note that the transmission of schistosomiasis began to decrease even before we began treatment. We attribute this fact to our presence in the area which contributed to a better knowledge of the transmission mechanisms of the disease. However, we believe that the transmission of schistosomiasis still occurs in the lagoon because it was certainly there that some of the residents of Nova Esperança became reinfected.

Another point worthy of mention refers to the percentage of cure and the reinfection rate of the population. Of the 365 initial inhabitants we kept 295 in the study for the whole period. We were, therefore, able to see from stool examinations that we had a "cure" percentage of 85.8% after eight months. In the 4-year follow-up it fell to 31%, probably due to reinfection. We confirmed in Nova Esperança (Tables II and III) what BINA & PRATA 3 had found in Canabrava concerning the relationship between age and reinfection. The individuals in the age bracket 5-19 years are those in whom reinfection occurs most frequently. In Nova Esperança this occurred in 70.3% of that age group and in Canabrava in 73.6%. The population of the age group accounted for only 38.8% and 38.2% respectively of the total population.

Before they had persistently negative stools, many patients had to have repeated treatments. However, only 3.8% of the patients needed more than four treatments. If it were not for the problem of having to administer the drug to many persons who do not require it, we certainly would have obtained the same result and would avoided the need of 8,087 stool examinations if we simply had programmed four treatments for everybody. This aspect will have to be considered in control programs, along with the cost of the program, intolerance to the drug, and the risk of development of an organism possibly resistant to the drug.

The patients accepted the repeated treatments well and tolerance to the drug was satisfactory. In the women who received oxamnique in their first months of pregnancy, we did not see any harmful event related to the use of the drug. However, the number of patients is small and our method is not to use the drug in pregnant women.

The required nine treatments in one patient, eight treatments in another and seven treatments in two patients is interpreted by us as due to reinfection, although we cannot exclude with assurance the possibility of a resistant organism or inadequate absorption of the drug.

The transmission of schistosomiasis was reduced but it has continued to persist in the location studied.

ACKNOWLEDGEMENTS

The wish to thank Pfizer Quimica Ltda. for their assistance in carrying out this work.

REFERENCES


GOALS OF APPLIED CHEMOTHERAPEUTIC RESEARCH IN SCHISTOSOMIASIS

A. DAVIS

SUMMARY

The conventional parasitological techniques of measuring success in the chemotherapy, which involve repeated excretal examinations by a wide variety of parasitological methods which may or may not be concentration techniques, are cumbersome to use, not inexpensive and are of limited sensitivity. One worthwhile goal is to stimulate further studies on the utility of the newer immunological techniques whether they be applied to detection of antibody or antigen. The advances in “ELISA” methodology and radioimmunoassay give hope that antigen purification and modifications of appropriate technology may, in the future, give us much more sensitive and specific monitoring devices than those currently used. In this brief scan of applied chemotherapeutic research goals it seems clear that there is no shortage of opportunity for many different types of personnel, physicians, epidemiologists, biologists, malacologists, immunologists or public health administrators. This augurs well for future activities in both research and control of schistosomiasis.

INTRODUCTION

Transmission of schistosomiasis is characterized by the extreme variability of the different ecological settings in which it occurs and also by a complexity of epidemiological variables seldom found in other parasitic or communicable infections.

Therefore it is neither wise nor advisable to extrapolate data and results of control measures obtained in one situation to another and this should be obvious from a review of the various ecological backgrounds (savannah belts, secondary forest zones, island sites, man-made foci such as lakes or irrigation systems, perturban bands or oases etc.). Yet, despite this seemingly clear proposition, it is common for rather simplistic concepts and rules of action to be applied to widely heterogeneous habitats.

The correct approach to control in any individual epidemiological situation must be based on accurate diagnosis. The diagnosis must delineate the human demographic, behavioural and parasitological collections of variables, the biological characteristics of the intermediate snail hosts and the ecological factors relating to water and land characteristics, use and management. Quite clearly these are not simple investigative procedures and in practice the collection of all these data is attempted but rarely. Perhaps this is one reason why outstanding successes in the control of schistosomiasis have been infrequent. But another reason is, apart from the lack of suitable control tools, our knowledge of the properties of the available tools and of the best way in which to use them is sub-optimal. This lies at the heart of applied or operational research, particularly when applied to chemotherapy.

The advances in schistosomiasis research of the last twenty years have affected chemotherapy more than any other field and, with the advent of more effective and less toxic drugs, chemotherapy is playing and will continue to play an increasing role in control. Yet
chemotherapy by itself will rarely if ever be entirely satisfactory in control and the first goal of applied chemotherapeutic research therefore is to learn to use the available drugs optimally, that is, with maximal success in both disease control and transmission control, with minimal incidence of side effects and at smallest monetary cost.

This is by no means the easy exercise that it sounds and the reasons are not hard to find. They lie in the different populations inhabiting the many varieties of transmission foci, their customs, cooperation and motivation, their heterogeneity in drug tolerance, their genetic constitution, genetic variations in drug metabolism and their nutritional status in addition to the different durations and intensities of schistosomiasis infection and a wide spectrum of concurrent complicating pathological conditions. Add to these the specific pharmacokinetic variables of bioavailability and excretion rates found with any drug, strain differences in parasite response to a given compound and the restricted specificity of the therapeutic effect of some schistosomicides e.g. the monospecificity of oxamniquine against *Schistosoma mansoni* or metrifonate against *S. haematobium*, then the variety of responses to one single schistosomicide in different geographic areas, and indeed at different locations within one geographic area is not surprising.

The different goals of applied chemotherapeutic research can be summarised under the headings: 1) Research to answer specific chemotherapeutic questions; 2) Research into optimal delivery systems; 3) Research into the less immediate effects to chemotherapy on disease or transmission control.

Numerous specific questions arise in the first category of research and usually need to be answered with reference to the various chemotherapeutic agents available in heterogeneous epidemiological situation characterised by different transmission dynamics.

For example: what are the effects of different doses of available drugs on the achievement of conventional “cure rates” or on the reduction of viable egg output? Which dose variations of an acceptable regime can produce broadly comparable results at a lower cost? What is the incidence of side effects, both immediate and remote, at different dose levels, and what is the local “optimal dose” giving the maximal therapeutic response with the minimal incidence of adverse reactions?

What are the differences in dose régimes required to produce comparable “cure rates” in children and adults and what effect will this have on control campaigns when it is widely known that children constitute the majority of the target population; handle drugs differently to adults and usually have the highest worm loads and greatest eggs outputs. When discussing success rates in chemotherapy we should not neglect the therapeutic failures and, as pointed out previously, it is of great importance to concentrate investigations on the therapeutic failures after conventional schistosomical treatment in order to identify those pretreatment attributes frequently associated with the failure of treatment (DAVIS, 1972). If these attributes are undetected or, when known, if not circumvented by appropriate action, then transmission may continue.

Are there epidemiological groups of patients who are at a particular high risk of a disproportionate incidence of adverse effects, perhaps due to advanced structural or functional pathological changes, enzyme deficiencies, or genetic abnormalities of red cell or haemoglobin and is there a simple way to identify such people who may, in the field, largely determine the success or failure of population coverage in chemotherapy?

Numerous other questions may be asked and answered by applied chemotherapeutic research, and the success of control by chemotherapy can frequently depend on asking the right question and then designing an appropriate experiment in order to provide an answer with a specified degree of probability.

The second category of research, into optimal delivery systems, is of value both to clinicians and to public health administrators who are interested in maximal returns, in a population sense, for minimal outlay. Since the use of chemotherapy in control involves repeated treatment, this type of activity deals with time sequences of dose schedules and the different incidences of side effects on varying chemotherapeutic schedules. Research on optimal delivery systems, while of intrinsic value in the short term, is also of profound importance in answering questions on the third category of chemotherapeutic research, the effects of chemotherapy, given in optimal
schedules, on the remoter sequelae of disease control and transmission control.

There are many questions to be answered here; e.g. what are the effects of optimal chemotherapy on the disappearance of existing hepatosplenomegaly or the incidence of hepatosplenomegaly in patients with intestinal disease only; what are the effects, of different schedules of chemotherapy on reinfection rates and thus its influence on transmission control. Intimately related to the human parasitological responses to drugs are the effects of chemotherapy on the excreta contamination factor, which can be measured by a "clean snail" technique and on snail infection rates and the question whether such biological measurements can be used as a measure of the efficacy of chemotherapy in the biological sense of acting as a transmission control agent.

Further questions arise which may be difficult to fit into any one categorical classification and in fact often overlap into different categories. We do not yet know the relative effects on either disease or transmission control, of mass chemotherapy (in which every member of a population is treated whether infected or not), of selective population chemotherapy (which is the treatment of all those members of a community shown to be infected with schistosomiasis) or of targeted chemotherapy (the treatment of some particular section of a population e.g. those heavy infections with egg excretion of over 500 eggs per gram of stool or those of a particular age group). Nor do we know much of the influence of regular chemotherapy on the prophylaxis of schistosomiasis in those uninfected yet constantly exposed populations.

JEWESBURY et al. (1977) have shown recently that metrifonate was an effective prophylactic when given regularly against S. haematobium but I am not aware of parallel studies in S. mansoni or S. japonicum infections.

The question of resistance to schistosomicides is of major importance and its implications spread into all fields of chemotherapeutic research. The diagnosis of resistance must only be suspected after the most searching investigations to exclude other possible explanations, such as pharmaceutical inactivity of drug due to adverse storage or transport conditions, lack of populations compliant when drugs are self-administered, decreased bioavailability metabolic abnormality, or continued frequent exposure to heavy reinfections etc. Furthermore the diagnosis must always be confirmed by passage of eggs from suspected cases through the appropriate snail and experimental animal host with a subsequent demonstration of diminished or absent parasitological response to a dose the drug known to produce high cure rates in other strains of the same parasite in the same experimental model. Clearly, these complex procedures can rarely be performed in field control programmes but the potential importance of resistance underlines the importance of a close association between the purely laboratory side of chemotherapeutic research and field practice.

Finally we should include, as a goal of applied chemotherapeutic research, the search for improved methods of monitoring chemotherapeutic success.

DISCUSSION ON DR. DAVIS' PAPER — GOALS OF APPLIED CHEMOTHERAPEUTIC RESEARCH IN SCHISTOSOMIASIS

Prof. PRATA

Dr. Davis has given us a very good summary on the whole problem of schistosomiasis control. He has also highlighted the need for more information on the use of chemotherapy.

Dr. Z. ANDRADE (Salvador)

I would like to emphasize one point from Dr. Davis' paper and that is the importance of economical development on the control of parasitic diseases. We all know that malaria was eradicated in the United States and Europe before insecticides and antimalarial drugs were available. Factors related to economical development, such as the well-being of the population, interest in hygienic measures, etc., will help the way parasitic disease can be conquered. So in the fight against schistosomiasis, economical development, complex as it is, will be important. At times medical progress goes beyond economical or socioeconomic developments, but on other occasions medical progress can help the population while they are waiting for socioeconomic progress. In schistosomiasis we should use all of the weapons available, and as Dr. Davis said, chemotherapy is the first line.
Dr. DAVIS

I find myself in complete agreement with Dr. Andrade. If I did stress chemotherapy, and this is a chemotherapy meeting, I also said that chemotherapy alone will never totally control the disease. The control of schistosomiasis is a very complex matter; it involves economic advancement; it involves technology, which can be regarded as a damping-down operation, but you can only damp things down while you are building things up from the bottom. The socioeconomic factors have positive and negative aspects to them. One of the great difficulties we face is that with one arm of the organization we are attempting to control schistosomiasis, and with the other arm we are attempting to prevent new schistosomiasis coming in from ill-conceived development schemes such as irrigation, man-made lakes, and other water development resources. The harsh truth of the matter is that when this well-meaning money goes into the tropical belt, it invariably involves an increase in intermediate snail hosts and other vector hosts of other diseases. I just want to stress that Dr. Andrade is perfectly correct; chemotherapy is a prime tool, but we have to have the building blocks of socioeconomic development to achieve lasting success.

Prof. PRATA

I know of three examples where control of schistosomiasis was successful - Puerto Rico, Japan, and Venezuela. If possible I would like Dr. Davis to comment on these success.

Dr. DAVIS

Japan has been outstandingly successful due to an economic post-war explosion and massive technological aid. That is one success story. Israel was successful because they had a very highly motivated population and an excellent public health service; they also had the advantage that the intermediate snail host was living at the biomedical or biogéographical extreme of its characteristics and therefore it was easy to eradicate. Venezuela, by a campaign from the 1950s, has now gotten its prevalence down to somewhere between 1 and 3% in various samples, and it seems to have remained stable for the last two years. You are right when you say that there had been outstanding success, but there hasn't been eradication. Similarly, with China there had been outstanding success for rather different reasons — the reasons in China are a total population commitment to action and a political system which allowed the mobilization of hundreds of thousands of people. The Chinese have treated schistosomiasis as a disease of major public health importance, because in Japan the parasite lives high in the small intestine, and lays eggs at a greater rate than either mansoni or hematobium, the eggs embolize early, and you get extreme hepatosplenomegaly. In Old China with the use of human manure in fields, where snails were, there was a very intensive transmission cycle, and young farmers in their 20s died of hepatosplenomegaly, and ascites and varices. It became noticeable to the politicians that this was a grave public health problem in a country who depended on agriculture. Therefore they singled it out as one of the major diseases to attack, and attacked it with every available means; — repetitive chemotherapy, repetitive population surveys, and had an advantage because the snails are unlike the aquatic snails and can be attacked by physical means. In fact mollusciciding played less of an important part than did the physical methods of snail killing in China. In reclaiming land, you can actually drown the snails by burying them in mud. They also have a variety of techniques of adapting excretal disposal systems so that the schistosome eggs die. Excreta are held in sewage-like tanks for some weeks, and then can be used as sewage on the fields, retaining the night soil concept, without transmitting the disease, because the eggs are dead. I think there are special reasons why the Chinese succeeded, and although they have succeeded they have not succeeded in eradicating it yet; and I don't think that any knowledgeable person in China would deny that. They have reduced the physical extent of the disease to a level where it is no longer a major public health problem and can be dealt with by relatively low-grade personnel — barefoot doctors and highly competent teams who have minimal training but yet can get adequate population coverage to give drugs, to examine stools, etc. I might point out that their program has lasted a quarter of a century and is still going on. Schistosomiasis control is not a thing that you envisage in two, three, four, or five years' time; schistosomiasis control's scale is one of decades and may take 30, 40, or 50 years.
FIELD EXPERIENCES WITH ORAL OXAMNUQINE IN THE TREATMENT OF SCHISTOSOMIASIS MANSONI (*)

J. RODRIGUES COURÃ, Carlos Alberto ARGENTO, Maria José CONCEIÇAO, Ethelene Margareth LEWIS, Mozart Lima dos SANTOS and Paulo MAGALHÃES

SUMMARY

The Authors report a field experience with oral oxamniquine in the treatment of schistosomiasis mansoni in four areas of the State of Minas Gerais, involving a total population of 3,782 persons examined and a trial population of 1,789 patients.

The patients were treated with oral oxamniquine in the single dose of 12.5-20 mg/kg. They remained in the endemic area and were followed-up by physical examination and quantitative fecal examinations in the 2nd, 4th, 6th, 8th, 12th, 18th and 24th month after treatment.

The Authors conclude that treatment with oxamniquine in endemic areas temporarily reduces the schistosomiasis prevalence and the number of S. mansoni eggs in the population treated, that, however, become reinfected in a rate of 10-15% a year in the areas with initial prevalence of 40% or more of the population. It is also verified that although the large-scale chemotherapeutic treatment is incapable of controlling schistosomiasis in a determined endemic area, it seems to reduce the number of severe forms of the disease. On the other hand, it is demonstrated that treatment singly is not able to interrupt the infection cycle.

INTRODUCTION

Oxamniquine has been largely used in the treatment of schistosomiasis in Brazil, from the clinical trials with the intramuscular formulation conducted by many Authors and presented at the Symposium on Oxamniquine (injectable) — held in Rio de Janeiro and published in a special number of the Rev. Inst. Med. Trop. São Paulo, 15 (Supl. 1): in 1973 29 — to the mass treatment with the oral formulation, which has been used by the Ministry of Health in its Special Program of Schistosomiasis Control (PECE) 19,22,25 in some regions of the country.

Prior clinical trials, conducted in hospital and ambulatory settings, with the drug by both intramuscular 9,29 and oral route 11,14,20, showed high rates of parasitological cure and low toxicity. Although the intramuscular formulation has been abandoned due to the intense and prolonged pain at the injection site, the oral formulation, less effective than the previous one but of easier application and less side-effects, has been well accepted for the individual treatment of patients with schistosomiasis mansoni.

In 1974, after extensive experimentation in hospital setting, the authors started some field trials 6,10,23 with oral oxamniquine in order to evaluate the perspectives of the drug as a control weapon of the human infection

(*) Study conducted by the Department of Preventive Medicine, School of Medicine, Federal University of Rio de Janeiro (UFRJ), partially grant-aided by the CNPq (National Council of the Scientific and Technological Development) Rio de Janeiro, Brazil
in its natural transmission environment. This study had the following objectives: a) Assess the importance of the specific treatment alone in the schistosomiasis control; b) Determine the parasitological cure rates for the individuals treated with oxamnique in field conditions; c) Evaluate the grade of reinfecion for the treated persons remaining in the endemic area; d) Study the interference of the treatment in the evolution of the disease clinical form.

CASUISTICS AND METHODS

The experiences were undertaken in 4 areas: one in the Municipality of Galliêia (District of São Geraldo do Baixio); two in the Municipality of Itanhoti (local government seat, and settlement of Santa Luzia do Cara-neiro); and one in the Municipality of Padre Paralízo (Village), all in the State of Minas Gerais.

Experience in São Geraldo do Baixio
(Galliêia)

The Village of the Municipality of Galliêia is, in an eastward direction, 90 km distant from the town of Governador Valadares; and the District of São Geraldo do Baixio lies in a remote area (a valley set between mountain ranges), 30 km, in a northward direction, away from the Village of the Municipality of Galliêia. The population of São Geraldo do Baixio in the beginning of the study (December, 1974) was of 1,040 inhabitants. According to the methodology adopted, the urban area of the District of São Geraldo was fully mapped (Fig. 1), noting every street and respective houses and the streams around the settlement. After the population census, a parasitological feces examination was performed by the following methods: Lutz (Pons-Hoffman and Janer) and Kato's quantitative, modified by Katz, CHAVES & PELLEGRINO, with two slide-examinations for each method. The individuals with presence of S. mansoni viable eggs in the stools were summoned for treatment with oxamnique in a single dose of 12.5-15 mg/kg for adults and of 15-20 mg/kg for children under 14 years of age, in an attempt to treat the universe of the infected people. A team, comprising 3 physicians, 2 domiciliary visitors and 1 driver, stayed in the area for 3 days at the first treatment stage and at two other control stages, earnestly encouraging the population for treatment and retreatment of the positive cases.
The drug was administered by the medical team in person, in the form of capsules to those over 10 years of age and of syrup to those under 10 years. Control of the parasitological cure was performed in the 2nd, 4th, 8th, 18th and 24th month after treatment by the same methods used for the initial diagnosis. Five hundred and fifty-two (552) patients were treated and 32 were re-treated during the observation period.

At the same time, a survey of the transmission foci, for localization of the snail breeders and determination of their infection rates by S. mansoni cercariae, was made before the treatment of the population and throughout the reviews.

Experience in Itanhomí (Village)

The Village of the Municipality of Itanhomí was mapped, the houses were numbered and the streams surrounding the village, noted. Next, parasitological feces examinations were performed by the same techniques used in São Geraldo do Baixio, from a systematic sample of approximately 25% of the resident population (family unit of one out of every four houses) totaling 769 persons, 282 (36.6%) of whom were infected with S. mansoni. Treatment was done with a 12.5-15 mg/kg dose of oxamniquine for adults, and of 15-20 mg/kg for children. Cure control was carried out in the 2nd, 4th, 8th, 12th and 16th month after treatment by the same methods of the initial diagnosis. During this period, 194 of the treated patients were followed-up. The patients selected for treatment were examined clinically, classified according to the clinical form and re-examined at the time of the control by feces examination.

Experience in Santa Luzia do Carneiro (Itanhomí)

The settlement of Santa Luzia do Carneiro is a small locality 15 km away from the Village of the Municipality of Itanhomí, with a population of 284 inhabitants. After the mapping of the area and census of the population, parasitological feces examinations by the same techniques previously described were carried out in the 284 individuals present, aiming at treating all the individuals infected. Treatment was done with a 15 mg/kg dose of oxamniquine for adults and 20 mg/kg for children. Parasitological cure control was performed in the 6th and 12th months after treatment and the cases found positive in these controls were re-treated. Of the 111 patients, 103 were treated; during the follow-up period, 20 patients were re-treated after 6 months and 26, after one year.

Experience in Padre Paraízo (Village)

The Village of the Municipality of Padre Paraízo is located in the Rio-Bahia Highway, 100 km to the north of Teófilo Otoni, in the Northeast of the State of Minas Gerais. In this locality, parasitological feces examinations by the already mentioned techniques were made from a systematic sample of 25% of the population (family group of one out of every four houses), totaling 1,820 persons examined. As in the previous trials, the area was mapped, the dwelling houses were numbered, and stations for capture of snails were established along the river courses, at regular 100-meter intervals. Feces examinations were done in 1,783 subjects of the sample, 1,709 of whom were examined clinically. The cases positive for S. mansoni were classified according to the classification proposed by Pessoa and Barros, modified by BARBOSA; Type I = Schistosomiasis infection; Type II = Schistosomiasis disease, hepatointestinal form; and Type III = Schistosomiasis disease, hepatosplenic form. Patients were divided into 2 groups: Group A, which received the active drug (oxamniquine) in the dose of 15 mg/kg for adults and of 20 mg/kg for children under 15 years; and Group B, which received placebo (starch) in capsules similar to those of oxamniquine. According to this schedule, 436 patients were given the active drug and 427, placebo. Control of cure was performed through feces examination by the aforementioned methods and physical examination in the 4th, 8th and 12th month after treatment.

RESULTS

With a view to facilitate understanding, the results of each experience will be presented separately, and the conjoined results, under the Comments and Conclusions heading.
a) Experience in São Geraldo do Baixio (Galliléa)

Parasitological feces examinations were performed in 1,013 of the 1,040 inhabitants of the district, 504 (49.7%) of whom were found positive was S. mansoni viable eggs. Only 27 of the residents did not refer material for examination, the large majority for absence from the locality and just a few for refusal. At the first stage we were able to treat only 310 of the 504 persons infected because of contraindications to the drug, absentes and refusals, notwithstanding the permanence in the area of 3 physicians, 2 visitors and 1 driver, insisting during 3 days that the infected population present and free from contraindications were treated. At a second stage, one year later, 242 more patients were treated, totaling 552. At this same occasion, we treated 33 patients from 83 therapeutic failures or reinfections occurred in 295 patients controlled among the 310 treated in the first stage.

Control of cure by feces examinations using Lutz sedimentation method and Kato's quantitative, modified by Katz, CHAVES & PELLEGRINO, performed in the 2nd, 4th, 8th, 18th and 24th month after treatment, revealed the respective prevalence of S. mansoni viable eggs in the population treated: 8.8%; 13.2%; 22.3%; 28.1% and 30.2% (Fig. 2).

The pre-treatment S. mansoni eggs mean of 216 eggs per gram of feces, evaluated by Kato's modified method, was reduced to 86.6 in the 2nd month; 109 in the 4th month; 84.3 in the 8th month; 93.7 in the 18th month; and 159.8 eggs per gram of feces in the 24th month after treatment (Fig. 3).

Side-effects reported by the population treated were rare and mild, represented in some cases by dizziness cephalic and abdominal pain; it is possible that the lack of active questioning on complaints by the medical team has lessened the frequency and intensity of the complaints reported.

b) Experience in Itanhomi (Village)

Pre-treatment feces examinations, performed by Lutz and modified Kato's methods, in 789 persons from a systematic sample of 25% of the population resident in the Village of the Municipality of Itanhomi, revealed a 38.6% prevalence rate of S. mansoni infection in the population examined. Of the 282 patients infected, 194 were treated with oxamniquine and followed-up for 18 months.

Control of cure of the 194 patients followed-up through feces examinations in the 2nd, 4th, 8th, 12th and 18th month after treatment showed prevalence of S. mansoni viable eggs of 17%, 23%, 27%, 29% and 32%, respectively (Fig. 4).
The pre-treatment S. mansoni eggs mean of 80.5 per gram of feces was reduced to 57.4 eggs per gram at the end of the control period.

The main side-effects attributed to oxamniquine in the 194 patients treated were: dizziness in 42 patients (21.6%), cephalgia in 10 (5.1%), vomiting in 5 (2.5%), abdominal pain in 4 (2%) and convulsion in 2 (1%).

c) Experience in Santa Luzia do Carneiro (Itanhomi)

Feces examinations by the already referred methods were performed in 264 of the 284 inhabitants of the settlement of Santa Luzia do Carneiro. An infection prevalence rate of 42% was observed in the population examined. Of the 111 positive patients, 103 were treated;
of the remaining 8 were not treated for
contraindications (6 for pregnancy, 1 for heart
failure) and 1 for absence from the locality.

Control of cure made in the 6th and 12th
month after treatment revealed infection pre-
valence rates of 19.5% and 25%, respectively.

The pre-treatment S. mansoni eggs mean
was of 144 eggs per gram of feces. It was re-
duced to 48 in the controls performed in the
6th and 12th month after treatment.

The main side-effects were dizziness in 18
cases (17.5%), cephalgia in 9 (8.8%), vomit-
ing in 3 (2.9%), nausea in 2 (1.9%) abdomi-
nal pain in 2 (1.9%) and diplopia in 2 (1.9%).

d) Experience in Padre Paraíso (Village)

The examination performed by Lutz’ se-
dimentation method and Kato’s modified
method, in a sample of 1,709 residents in the
Village of the Municipality of Padre Paraíso,
showed a mean prevalence of S. mansoni in-
fection of 62.4% in the population studied. Of
the 1,067 patients with S. mansoni viable eggs
in the feces, 883 were randomly selected for
treatment, 438 with the substance A (active
substance = oxamnique) and 427 with the
substance P (placebo).

Post-treatment control by feces examina-
tions performed in the 4th, 8th and 12th
month revealed the following prevalences: for
the Group A — 17.2%, 37.1% and 40.2%; and
for the control Group P — 31.7%, 89.9% and
79.3%, respectively.

The Group A pre-treatment S. mansoni
eggs mean of 391 eggs per gram of feces was
reduced to 69 in the 4th month, 22 in the 8th
month and 92 in the 12th month after treat-
ment with oxamnique. The Group P pre-
treatment mean of 388 eggs per gram of fe-
ces increased to 437, 460 and 437, respective-
ly, after the use of placebo.

From the standpoint of clinical evolution of
the patients treated with the active sub-
stance (oxamnique) and with placebo, the
following observations were made: twenty-
four (24) patients treated with oxamnique
(11.8%) among the patients re-examined after
12 months, changed from Type I to Type II
of the disease, while 26 (12.3%) treated with
placebo changed from Type I to Type II. On-
ly 1 patient treated with oxamnique changed
from Type II to Type III, while 3 patients
given placebo changed from Type II to Type
III. As to the regression of the clinical type,
it was observed that of the patients treated
with oxamnique, 41 (42.3%) changed from
Type II to Type I and 4 (25%) changed from
Type III to Type II 12 months after treatment,
while, at the same period, only 18 (21.7%) of
those treated with placebo changed from Type
II to Type I and none of them changed from
Type III to Type II.

COMMENTS AND CONCLUSIONS

The control of schistosomiasis mansoni by
chemotherapy has been attempted since the
pioneer experimentations with tartar emetic in
Egypt1.3.18 till the most recent studies with
drugs more effective and less toxic, such as
hyacinthone and oxamnique6.8.10.55.21.

The initial attempts have failed, on the
one hand for the high toxicity of the antimo-
inals and on the other hand for the exigen-
cy of multiple doses, leading to severe side-
effects and to the abandonment of more than
40-50% of the treatments initiated. These in-
conveniences led authors like MARTINS17 and
other to disapprove the mass treatment on
account of its inability to reduce the infection
prevalence. However, other Authors like Ayad
in Egypt3 and KLOETZEL18 in Brazil have
later demonstrated the reduction of the severe
forms with the large scale or selective treat-
ment with the antimonials.

Opportunist, this fact sums to have been
demonstrated first of all in Brazil in the stu-
dy undertaken by JANSEN19 in Catende,
reviewed later by SETTE34.

Still after the discovery and use of che-
motherapeutic agents by oral route, like Mira-
cil D and Anibihar, there remained the in-
conveniences of the multiple doses and per-
sistence of significant side-effects reducing
the possibilities for their use in mass treatment
or even in large-scale treatments.

With the advent of drugs more active, less
toxic and of easier single dose application,
like hyacinthone and oxamnique, new pros-
pects were opened up for the use of mass or
targesscale chemotherapy for control of schistosomiasis mansoni.

However, the impossibility of diagnosis for all the individuals with active infection in a determined area (for failure of the diagnostic method, temporary absence from the place and refusal to send the material for examination) as well as the impossibility of treating all the infected person (because of contraindications to the drug, absentees and refusals to treatment) and also for therapeutic failures (10-20% with the most active drugs) and constant reinfections, make the problem of schistosomiasis control by chemotherapy alone extremely vulnerable, as demonstrated by the present study and other prior studies already issued 4,6,10,15,26,27,28.

It seems beyond all doubt, however, that large scale chemotherapy with the new schistosomicides, such as hycanthone and oxamniquine, reduce temporarily the prevalence of the human infection and the emergence of severe forms of the disease, as demonstrated by BINA & PRATA6, PRATA23, BINA5, KATZ et al.15, COOK et al.7, MOTA et al.19, SANTOS23 and COURÁ et al.10, among others, which have demonstrated, on the other hand, a tendency to reinfections increasing with time, the more intense, the higher the endemicity of the area, demanding new treatments at 6-12 months intervals.

This fact, besides augmenting the maintenance cost, favors the selection of S. mansoni strains resistant to treatment with the drug in use and, certainly, the cross resistance with other drugs, with progressive reduction of cure rates 6,30.

Based on the experiences presented in the present study and in others already published, the Authors conclude: 1) that oxamniquine in single dose, by oral route, in field trials, reduces temporarily the schistosomiasis prevalence and the number of S. mansoni eggs in the feces of the population treated; 2) that the reinfections increase progressively after treatment, in an average of 10 to 15% per year, in the areas with initial prevalence rate of 40% or more of the population; 3) that the number of S. mansoni eggs per gram of feces suffers a drastic reduction after treat-

ment, with slow elevation in the first two years; 4) that the large-scale chemotherapeutic treatment of schistosomiasis in a determined area seems to reduce the number of severe forms of the disease; 5) that, although chemotherapy singly is not able to promote schistosomiasis control, the treatment used selectively in patients infected, principally children and young adults, may be considered an excellent ancillary means of control, along with the fundamental measures of basic sanitation, supply of treasyed water, sanitary education and improvement of the social, economic and cultural conditions of the population.

REFERENCES


DISCUSSION OF DR. COURRA’S PAPER — PERSPECTIVES OF THE THERAPY WITH OXAMNQUINE AS A MEASURE TO CONTROL SCHISTOSOMIASIS MANSONI

Prof. PRATA

Dr. Courra has emphasized an important point in the comparison of results of clinical examinations performed by different physicians. We have had similar experiences, and this makes it very difficult to interpret results of reduction in the size of the liver or spleen in these studies.
SCHISTOSOMIASIS CONTROL IN PERI-PERI (MINAS GERAIS, BRAZIL) BY REPEATED CLINICAL TREATMENT AND MOLLUSCIDE APPLICATION

Naftale KATZ, R. S. ROCHA and J. P. PEREIRA

SUMMARY

In Peri-Peri, an endemic area of schistosomiasis in the state of Minas Gerais, a schistosomiasis control project was attempted by treatment of infected individuals with oral oxamniquine at yearly intervals, and application of niclosamide to bodies of water where ever the snail vector was found. The initial prevalence of schistosomiasis based on a single stool examination by the quantitative Kato-Katz method was 43.7% in a population of approximately 650 inhabitants, (the arithmetical mean an median of the number of S. mansoni eggs were 592 and 208, respectively). Within the period of four years, 294 patients had received a single treatment of oxamniquine; 108 two treatments and 15 patients three treatments; and 24 applicators of molluscicide had been made. At that time, the prevalence had fallen to 13.9% and the arithmetical mean and median of the number of S. mansoni eggs were 183 and 60, respectively. Infected snails were found only at the beginning of the control period and in one of the following years. However non-infected B. glabrata were found in the pools, throughout the time of the project. The percentage cure was higher in adults than in children (85% and 72%) respectively, with no difference noted between those treated once or twice. However, there was a lower cure rate in adults after the third treatment; only one of the five adults treated three times was considered cured. At the time of the last clinical examination, there was a significant decrease in the frequency of the hepato-intestinal and/or hepatosplenic forms. The schistosomiasis prevalence in the 0-4 years age group at the beginning of the project was 13.9% and four years later, 0%. Tolerance to the drug was good, with the exception of one noteworthy instance: a patient who experienced a convolution and loss of consciousness. Despite the good results obtained in the control of schistosomiasis in this area, the authors warn of the danger of simply extrapolating these data to the control of this disease in vast territorial expanses. To do this, such factors as human migratory habits, high cost of chemotherapy and molluscicide applications for undetermined periods and the impossibility of treating all infected patients may handicap the program. Therefore, the authors point out that the application of these specific measures, without modification of socio-economic conditions, are not sufficient for the large scale control of schistosomiasis.

INTRODUCTION

Studies done in Brazil have demonstrated that the administration of schistosomicides to the population residing in areas of median and high endemicity produces a prompt and marked fall in the prevalence of schistosomiasis\(^1\),\(^2\),\(^3\),\(^4\),\(^5\),\(^6\),\(^7\),\(^8\),\(^9\),\(^10\),\(^11\),\(^12\),\(^13\).

The present study was done with the aid of the “Conselho de Desenvolvimento Científico Tecnológico (CNPq)” in the “Centro de Pesquisas René Rachou” — FIOCRUZ.

Requests for reprints: Dr. Naftale Katz, Caixa Postal, 1743 — 31.000 — Belo Horizonte, MG., Brazil
However, this measure alone is not sufficient to keep the prevalence at a low level, since if control of the transmission is not achieved, reinfections will occur. In fact, in the areas studied so far, two years after the treatment, 30-40% of the children and 5-10% of the adults had viable *S. mansoni* in the stools. 9,12.

Studies designed to control the transmission of schistosomiasis by a combination of molluscicide and clinical treatment have been carried out by JANSEN (1945) in Catende (Pernambuco), KATZ et al. (1970) in Badim (Minas Gerais), and more recently, in Santo Antonio dos Trempes (Pernambuco), in the Special Program of Schistosomiasis Control (PECE) of the Ministry of Health (CAMARGO, 1977). 3.

In Catende, the study included 27 applications of virgin lime of the pools and streams at three-month intervals, treatment of 1,990 patients with antimonials, and construction of basic sanitation facilities and health education for the public. The infection percentage of *Tropicorhitis centenometralis* (*Biomphalaria straminea*) were 0.0 to 18.5% depending on water site tested. After two years, this percentage varied from 0.0% to 7.9%. The prevalence of schistosomiasis in the population has also decreased significantly, from 53% to 12% (JANSEN, 1946). According to SETTE (1953), a total of 3,334 patients in this area were treated during years 1943 to 1947, and of the 427 patients reexamined in 1951, 60% continued to be negative for schistosomal infection. A marked reduction in the frequency of heptosplenomegaly was also observed in the patients treated, when compared with a non-treated group.

In Badim, a molluscicide (niclosamide) was applied three times with the view of keeping the area free from snails for 6 months. In two weeks, approximately 760 patients or 90% of the infected population were treated with hyacanthone. The percentage of cure was 95%, based on a parasitological evaluation carried out 6 months after treatment. Patients who were not cured after the first treatment were treated again 9 months later. Infected snails (*B. glabrata*) were found 4 months after the reappearance of snails in the streams and six months later, the percentage of the infection was similar to that found before the start of the molluscicide and clinical treatment (KATZ et al., 1970). Two years after treatment, 40% of the children and 9% of the cured patients were again infected.

In Santo Antonio dos Trempes, nearly all population was treated with oxamnique (547 out of 571 patients). One month after the treatment, only 0.6% of the treated population continued eliminating *S. mansoni* eggs whereas before the treatment the prevalence was 50.4%. In 76 newcomers to the area (non-treated), the percentage of positivity was 14.4%. Of the 5,500 snails (*B. straminea*) found in the area, none was infected. Niclosamide applications are being made periodically and clinical treatment given whenever patients are found positive for *S. mansoni* eggs in the stools. In the present paper, the results obtained during 4 years in Peri-Peri, an endemic area of schistosomiasis in Minas Gerais, where annual clinical treatment and application of molluscicide are discussed.

**MATERIALS AND METHODS**

Peri-Peri is a village in the Municipality of Campim Branco (MG), situated about 40 km from Belo Horizonte. It is crossed by a river (Ribeirão da Mata) which has two main tributaries the waters from which are used in agricultural irrigation ditches, domestic use, bathing, recreation, etc. Only a few homes are supplied with piped water and have not privy, the sewers falling directly into streams. Peri-Peri is characterized by the presence of small farms of 1-3 hectares where primarily grow garlic.

This activity plus a brick factory absorb the great part of the working male population. At the start of our study, the locality was mapped, all the houses were numbered and the inhabitants identified. The census has been made annually since April 1974 (Table I).

The prevalence of schistosomiasis as well as the arithmetical mean and median of the number of *S. mansoni* eggs was determined through a single parasitological examination of stools by the Kato-Katz method, using two preparations of each sample. For the treatment of patients, oral oxamnique was used in dosages of 12-20 mg/kg for adults and 13-25 mg/kg for children. For children (up to

**TABLE I**

<table>
<thead>
<tr>
<th>Date</th>
<th>Population of the area</th>
<th>No. of patients examined</th>
<th>No. of patients with S. mansoni (%)</th>
<th>No. of S. mansoni eggs per gram of feces</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arithmetical mean</td>
</tr>
<tr>
<td>April/74</td>
<td>653</td>
<td>591</td>
<td>258 (43.7)</td>
<td>592</td>
</tr>
<tr>
<td>October/74</td>
<td>1st treatment: 220 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>September/75</td>
<td>650</td>
<td>462</td>
<td>114 (24.7)</td>
<td>445</td>
</tr>
<tr>
<td>May/76</td>
<td>1st treatment: 52 patients 2nd treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>October/76</td>
<td>625</td>
<td>223</td>
<td>84 (28.7)</td>
<td>122</td>
</tr>
<tr>
<td>May/77</td>
<td>606</td>
<td>305</td>
<td>84 (21.3)</td>
<td>268</td>
</tr>
<tr>
<td>October/77</td>
<td>1st treatment: 22 patients 2nd treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>October/78</td>
<td>632</td>
<td>410</td>
<td>57 (13.9)</td>
<td>183</td>
</tr>
</tbody>
</table>

15 years) the dosage was administered in one dose or divided into two doses with an interval of 6-8 hours between doses. This variation of dosage was due to the different forms of oxamnique used capsules of 250 mg and syrup containing 50 mg per ml.

The drug was always given to outpatient, after the patient had had a general physical examination. The patients was advised to eat a light meal before drug administration and to return the next day for reexamination. Each physician treated an average of 70 patients per day.

Evaluation of cure 4-6 months after treatment, was based on three successive parasitological examinations of stool (2 preparations of each sample) by the Kato-Katz method 3.

In brief, the sequence used was: parasitological examination of stools of all the population, treatment of those eliminating S. mansoni eggs in the stools, repetition of the parasitological-stool examinations of the treated case 4-6 months after oxamnique administration, and repeat stool examination of all the population, yearly. This schedule was repeated four times, some patients were therefore treated for three times. Throughout duration of the project, malacological survey were made at all the water locations serving the locality at 2 to 3 months intervals, and molluscicide (niclosamide) was applied as necessary by dripping or with spraying pumps.

**RESULTS**

Table I summarizes the results obtained. At the beginning of the project (April, 1974) the population was 653, of whom 591 were examined. The prevalence of schistosomiasis was 43.7% with arithmetical mean and median of the number of S. mansoni eggs in stools of 592 and 268, respectively. At the time (October 1976) of the last stool parasitological examination performed in 410 patients (after treatment of 294 patients for one time, of 107 for two times, and 15 for three times), the prevalence was 13.9%, with arithmetical mean and median of the number of S. mansoni eggs of 183 and 60, respectively. Graph I shows the initial and final prevalence in the different age group. As can be seen in the 0-4 age group the initial prevalence was 13.9% and four years later, 0%. Side effects observed or reported by patients who were treated once (Table II) or twice (Table III) differed significantly in incidence and/or severity. There were fewer side effects reported after the second treatment and their severity was lessened. In general, the treatment was well tolerated, but it should be noted that one patient had a convulsion with loss of consciousness, lasting for some minutes, 15 minutes after the ingestion of oxamnique.
Graph I — Prevalence of schistosomiasis in different age groups, in the population of Peri-Peri (MG) in the years of 1974 and 1978

TABLE II
Side-effects observed or reported after the 1st treatment with oxamniquine (Peri-Peri, MG)

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Adults</th>
<th>Children</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Dizziness</td>
<td>35</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cephalalgia</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Convulsion</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

No. of patients with side-effects/treated: 47/138 (34%) 78/156 (50%) 125/294 (43%)

TABLE III
Side-effects observed or reported after the 2nd treatment with oxamniquine (Peri-Peri, MG)

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Adults</th>
<th>Children</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cephalalgia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No. of patients with side-effects/treated: 20/79 (25%) 10/28 (36%) 30/167 (18%)

The therapeutic cure rate of oxamniquine, which varied from 72 to 85%, was always greater in adults than in children, independent of their being treated once or twice. However, in those treated three times, only one of the five adults was considered cured (Table IV).
TABLE IV

Results obtained in the patients treated one, two or three times with oxamniquine (Peri-Peri, MG)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age Group</th>
<th>Treatment</th>
<th>Controlled</th>
<th>Cured (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.a</td>
<td>Adults</td>
<td>186</td>
<td>176</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>96</td>
<td>94</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>284</td>
<td>270</td>
<td>217</td>
</tr>
<tr>
<td>2.a</td>
<td>Adults</td>
<td>48</td>
<td>43</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>60</td>
<td>59</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>108</td>
<td>102</td>
<td>78</td>
</tr>
<tr>
<td>3.a</td>
<td>Adults</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>10</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>15</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>

In Table V, are shown the data from the patients with schistosomal infection detected at the first examination, who were treated one or more times, and the results of their last parasitological examination. There was marked decrease in the prevalence, arithmetical mean and median of the number of *S. mansoni* eggs in stools as well as a decrease in the percentage of patients with the hepatointestinal and hepatosplenic form of the disease. During all the project period there were no new cases of hepatosplenic form. Of the patients who were not infected initially, 19.2%, 6.3% and 6.7% began to excrete *S. mansoni* eggs, after one, two and three years, respectively (Table VI).

TABLE V

Comparative data in a population group before and after the introduction of the control measures (Peri-Peri, MG)

<table>
<thead>
<tr>
<th></th>
<th>1974</th>
<th>1978</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population examined</td>
<td>591</td>
<td>330</td>
</tr>
<tr>
<td>with <em>S. mansoni</em> eggs in the stools</td>
<td>258 (43.7%)</td>
<td>49 (14.8%)</td>
</tr>
<tr>
<td>Arithmetical mean</td>
<td>99</td>
<td>182</td>
</tr>
<tr>
<td>Median</td>
<td>208</td>
<td>60</td>
</tr>
<tr>
<td>Patients examined clinically</td>
<td>220</td>
<td>116</td>
</tr>
<tr>
<td>Intestinal form</td>
<td>66.5%</td>
<td>93.8%</td>
</tr>
<tr>
<td>Hepatointestinal form</td>
<td>28.5%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Hepatosplenic form</td>
<td>5.9%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

TABLE VI

Result of the parasitological stool examinations in patients previously “negative”, 1, 3 and 4 years after the start of the project (Peri-Peri, MG)

<table>
<thead>
<tr>
<th>Year</th>
<th>Adults</th>
<th>Children</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Examed with <em>S. mansoni</em> (%)</td>
<td>Examed with <em>S. mansoni</em> (%)</td>
<td>Examed with <em>S. mansoni</em> (%)</td>
</tr>
<tr>
<td>1975</td>
<td>99</td>
<td>9 (8.1)</td>
<td>88</td>
</tr>
<tr>
<td>1977</td>
<td>80</td>
<td>5 (6.2)</td>
<td>61</td>
</tr>
<tr>
<td>1978</td>
<td>78</td>
<td>6 (7.6)</td>
<td>55</td>
</tr>
</tbody>
</table>

TABLE VII

Malacological surveys and applications of molluscicide (Peri-Peri, MG)

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of surveys</th>
<th>No. of snails</th>
<th>Molluscicide (niclosamide)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Collected</td>
<td>Examined</td>
</tr>
<tr>
<td>1974</td>
<td>4</td>
<td>469</td>
<td>84</td>
</tr>
<tr>
<td>1975</td>
<td>5</td>
<td>125</td>
<td>106</td>
</tr>
<tr>
<td>1976</td>
<td>5</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>1977</td>
<td>8</td>
<td>788</td>
<td>221</td>
</tr>
<tr>
<td>1978</td>
<td>4</td>
<td>168</td>
<td>97</td>
</tr>
</tbody>
</table>

(+): 48 snails found in a dam
In the survey conducted in 1978, it was discovered that 82 new residents had moved to Peri-Peri. Of these, 55 were examined and 9.1% were found to be eliminating S. mansoni eggs.

The data from the malacological surveys and of the applications of molluscicide (grouped by year) can be seen in Table VII. After introduction of the repeated use of molluscicide, the number of the snails found was always lower than that found initially except in 1977, when 789 snails were found, 50 of which were infected. The majority of these snails and almost all of the infected ones (48) were in a small dam built in 1977, which had been examined later on.

**DISCUSSION**

The control of the transmission of schistosomiasis is a problem which, unfortunately has not been duly equationed yet. Several attempts for control have been made in Brazil, and in various parts of the world by using chemotherapy, molluscicide, basic sanitation and health education as isolated or combined measures.6,12

To avoid repeating what has already been exhaustively dealt with in previous reports, we may simply say that in the countries where schistosomiasis has been controlled or is being controlled, such as Japan, the People’s Republic of China, Venezuela, and Puerto Rico, the specific control measures have always been combined with socio-economic development.4,5

The socioeconomic achievements with primarily environmental sanitation, pure water supply and satisfactory sewage disposal system, improvement in agriculture either by irrigation systems or by changes in the methods of farming and land drainage, etc., are the achievements that will ultimately lead to control of the transmission of the disease. Sticking strictly to facts, the only manner of facing the problem lies in the political decision of the top-ranking members of the Government to solve it, providing it is understood that this endemia installs, expands or keeps itself as such due to the existing state of social organization, production, income distribution, etc., or, in other words, due to social, economic and political conditions and not only to strictly medical conditions.4

The results here presented were obtained from a small pilot study, which, although serving to demonstrate that specific measures — represented in this case by drug treatment and application of molluscicide — were sufficient for the control of schistosomiasis, in no way should serve as a model to be simply copied in instances where it is necessary to think of control in one or in various states of the country. In fact, also here, the whole is not just the sum of its parts.

In Peri-Peri, it was shown within the parameters of our study, that there is a drug, oxamniquine, which can be used in the field with good results because of its good tolerance, lack of toxicity, and therapeutic activity. The first treatment reduced the prevalence of schistosomiasis one half after one year and after the third treatment to a quarter of the original (from 43.9% in 1974 to 13.9% in 1978).

Molluscicide was applied to pools and streams throughout the project; this specific control measure has undoubtedly helped to maintain the low prevalence rate, and contributes to the control of the disease.

The examination of the children born after the introduction of the control measures, i.e. the 0-4 years age group, revealed no child eliminating S. mansoni eggs in the stools, whereas in the beginning of the project the prevalence was 13.9% in this age group. A marked clinical improvement measured by a pronounced diminution of the frequency of hepato-intestinal and hepatosplenic forms of schistosomiasis and a significant reduction in the number of S. mansoni eggs in the stools of patients still infected was also observed in the population.

In 1978, 82 persons had moved to the locality. In the newcomers examined, the prevalence of schistosomiasis was 9.1%. The figure points out the importance of internal migration in the dissemination of the parasitosis. Also the detection of newly positive cases in patients previously negative shows the importance of examining the population several times.

The excellent results obtained in this locality show, without any doubt, the possibility of reducing or even preventing the transmission of schistosomiasis in a given ende-
mio area. However, it poses some questions: 1) How does one control the newcomers in the community; 2) How does one treat those who, in spite of 2 or 3 treatments, still continue excreting eggs in the stools; 3) For how long should the clinical treatments and applications of molluscicide be continued.

The first question, for example, demonstrates that if we think of a campaign (as what is intended by the term of Brazil) for schistosomiasis control it would be impossible to detect these cases. Hence, the need for uniforming the control program in the general context of medical assistance to the community.

The second indicates the need of another schistosomicide drug and of further studies directed to the problem of resistance of the S. mansoni strains in the field. The third question is, no doubt, the most difficult and at present the answer would be "indefinitely".

Summing up, one may conclude that the control of schistosomiasis transmission in a small area is possible, but the extrapolation of these data to a large scale program is fraught with danger and should be carefully considered.

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DISCUSSION ON DR. ROCHA’S PAPER:
SCHISTOSOMIASIS CONTROL IN PERI-PERI (MINAS GERAIS, BRAZIL) BY REPEATED TREATMENT AND MOLLUSCIIDE APPLICATION

Dr. A. DAVIS (Geneva)

The last two papers have been excellent and nicely illustrate the problems caused by large-scale chemotherapy. I was impressed with Dr. Coura’s methodology, and it shows the importance of having a control group. One reason why people have become disappointed and disenchanted with population chemotherapy is that clinicians can achieve 80, 85, 90, or 92.5% cure rates in selected people. But in population chemotherapy, you never achieve anything like that because of refusals, contraindications to the drugs, absenteeism, and immigrants who were not there at the initial
survey. If in population terms you get a cure rate of 50%, you are doing well. If you get a cure rate of 50% with a drug, it will take eight annual treatments, assuming complete population coverage, to get the prevalence below 1%. Dr. Coura showed his reinfection rates, and at 18 months it was back to the original level. This to me is a clear indication for treatment at 6 monthly intervals. Once the graph starts to rise, then you should retreat. Both papers also pointed out the focality of infection; and I agree that it is difficult to control on a national basis, but by concentrating on isolated areas it should be possible. I would like to ask Dr. Katz whether he plotted out the time of reinvasion after mollusciciding and whether it varied over the course of four years.

Dr. KATZ

In Brazil we recently had an expert committee meeting, and I think that the conclusions would be interesting. The recommendations on the indications for chemotherapy as a tool for schistosomiasis control are — (a) infected people living outside an endemic area, (b) infected people in an area with no transmission but susceptible snails are present, and transmission could occur, and (c) large scale treatment of endemic areas after sanitation improvements. When the prevalence is over 60% the whole community may be treated. As an attempt to prevent severe forms in areas of medium or high transmission, target treatment of the 5-25 year age group should be given. As has been seen in other countries, the main factor in control is socioeconomic development. Only when schistosomiasis control is included in the general health service, with the full cooperation, participation and responsibility of the community, will underdeveloped countries have a chance in achieving success in its control.

Prof. PRATA

We have all observed and reported clinical regression of the severe forms of schistosomiasis. I would like to ask Dr. Andrade whether he has seen regression of Symmer's fibrosis at the microscopical level.

Dr. Z. ANDRADE (Salvador)

The large amount of fibrosis in the portal tract caused by heavy infections of Schistosoma mansoni can regress to a certain amount but probably does not disappear. Portal obstruction can be relieved by collateral circulation, and this can reduce portal pressure and diminish the size of the spleen. The clinician can see some improvement in the health of the patient if the treatment is effective and the lesions are not too far advanced. As pathologists we define hepatosplenic disease as portal obstruction, leading to portal hypertension and then to hepatosplenomegaly. In the field as clinicians you may see hepatomegaly and hepatosplenomegaly, which may be due to many disease processes; but if you are in an endemic area of schistosomiasis you will not be far from the truth in using
these as clinical criteria. Before defining hepatosplenic disease we should also look for other criteria of portal hypertension, such as bleeding varices, etc.

My final point is the use of the term "economical development". This is not merely the donation of large sums of money; but for success you must have the full participation of the community.
OXAMNIQUINE IN THE TREATMENT OF SCHISTOSOMIASIS IN A POPULATION IN AREA WITH LOW ENDEMICITY

J. C. BINA (1) and Aluizio PRATA (2)

SUMMARY

Oral oxamniquine in a single dose was administered to 313 patients with schistosomiasis who lived in a rural area of low endemicity. The schedules used were: 20 mg/kg body weight as syrup to patients up to 30 kg, and capsules in the dose of 12.5 — 15.0 mg/kg to those over 30 kg. Tolerance was good and the cure rate was 83.2%. In the late follow-up an increasing rate of reinfection was detected. The non-cured patients showed significant reduction in the number of S. mansoni eggs in the stools. This finding suggests that the drug may be used on a large scale as one of the measures for the control of Schistosomiasis mansoni.

INTRODUCTION

As various investigators had confirmed the high efficacy and good tolerance of oxamniquine in clinic and hospitalized patients, we began, in 1974, to use it in a rural area, firstly with the syrup form in the treatment of children. The usefulness of the 20 mg/kg dosage, in single doses or divided into two doses with a 4-6 hours interval between doses, has been demonstrated 4.5.6.7.8.9,10.11.12,13. We were aware of the ease of the treatment of patients in rural areas and in January 1975 treated nearly all patients of the village of Mirangaba, Bahia, who were excreting viable S. mansoni eggs in the stools.

The methodology and results of this study form the present report.

MATERIALS AND METHODS

The township of Mirangaba is situated about 500 km to the northeast of Salvador. The village of the township has a population of 1,212 persons who occupy 281 dwellings. The largest part of the population is engaged in agriculture in the “caatinga” and cultivate the soil without irrigation. The principal source of water is an artesian well. Minor sources are represented by water holes and a brook, whose waters are used by the residents and animals. In these waters, specimens of Biomphalaria glabrata, is the intermediate host encountered in this area. In recent years, the homes on the main streets began to be served with piped water.

The diagnosis of schistosomiasis was made by Lutz’ quantitative method of spontaneous sedimentation and/or by Stoll’s quantitative method. We were able to repeat the stool examinations in 186 cases who initially had negative results in both examinations and after examination 32 patients (17.2%) were found positive. Stool examinations were made in 1,087 of the 1,212 inhabitants, which represents 90% of the population. Of those examined, 344 were excreting viable S. mansoni eggs in the stools, giving a prevalence of 31.6%.

Excluding pregnant women and children under two years of age, we treated in one day all the 313 patients present in the area (152 males and 161 females). The physical exami-

Study carried out with the support of the “Conselho Nacional de Desenvolvimento Científico e Tecnológico” (CNPq)
(1) School of Medicine, Federal University of Bahia; Gonçalo Muniz Central Laboratory and “Gonçalo Muniz” Research Center
(2) Faculty of Health Sciences, University of Brasilia
nation showed 301 patients to have the hepatointestinal form of the disease, 11 to have the hepatosplenic form and one with the pseudoneoplastici form (Table I). Only four of the 11 hepatosplenic patients had a splenomegaly in which the spleen exceeded the left costal margin. The percentage of hepatosplenics in this area is, therefore, 3.1% considering all palpable spleens, and 1.1% considering only the spleens surpassing the left costal margin. Oxamnique was given only as a syrup in the dosage of 20.0 mg/kg to the patients weighing up to 30.0 kg (children between 2 and 10 years of age), and as capsules in the dosage of 12.5 — 15.0 mg/kg to patients over 30.0 kg (Table II).

**TABLE I**

Clinical form of the schistosomiasis in the patients treated with oxamnique Mirangaba, Ba. — 1975

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Clinical form of the schistosomiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>Hepato-intestinal</td>
</tr>
<tr>
<td>11</td>
<td>Hepatosplenic</td>
</tr>
<tr>
<td>1</td>
<td>Pseudoneoplastici</td>
</tr>
<tr>
<td>Total</td>
<td>313</td>
</tr>
</tbody>
</table>

**TABLE II**

Treatment of the schistosomiasis with oxamnique in rural area, according to the weight, dose and drug formulation. Mirangaba — Ba. — 1975

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose (mg/kg)</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 30</td>
<td>20.0</td>
<td>Syrup</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>12.5 — 15.0</td>
<td>Capsule</td>
</tr>
</tbody>
</table>

Evidences of intolerance to the drug was evaluated by the complaints which were made by the patients, who had been asked to return to the Health Station on the day following treatment.

The evaluation of cure started four months after treatment and lasted three months, during which time five stool examinations were made for each patient. Fecal egg counts were made in non-cured patients in order to evaluate possible reductions in the parasite load.

One year after treatment, we carried out another evaluation of cure by means of two stool examinations in 243 patients who were in the area; three years and seven months later, a new stool examination was made in 168 patients of the 313 initially treated.

**RESULTS**

Of the 313 patients treated, 141 (45.04%) experienced one or more of the following side effects: dizziness, drowsiness, headache, nausea and, occasionally, vomiting. These side effects disappeared within the first two hours after drug had been given, with no need for ancillary medication. In this group, there was no difference in tolerance among adults treated with capsules and the children treated with syrup (Table III).

**TABLE III**

Tolerance of oxamnique in the schistosomiasis treatment in rural area, according to the drug formulation. Mirangaba — Ba. — 1975

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Patients treated No.</th>
<th>Patients with complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule</td>
<td>280</td>
<td>128</td>
</tr>
<tr>
<td>Syrup</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>313</td>
<td>141</td>
</tr>
</tbody>
</table>

The efficacy of oxamnique was confirmed by cures in 257 of the 313 patients treated. The global cure rate was 83.2%, which derived from 84.6% for adult patients given capsules and 72.4% for children given syrup (Table IV). The non-cured patients showed significant fecal egg reduction, proved by statistical test (Table V). One year after treatment, two stool examinations were made in 243 persons. This revealed 13 patients excreting *S. mansoni* eggs in the stools and who had been considered as cured in the five examinations in the initial evaluation. These data permitted us to calculate a probable reinfection rate of 5.3% for this area in this year of observation. Three years and seven months later, the reinfection rate was 12.5%, corresponding to 21 patients excreting *S. mansoni* eggs in the stools, and the cure rate had fallen to 65.4% (Table VI). The mean age of the positive patients one year after treatment was 21 years, while that three years and seven months after treatment was 30 years.
TABLE IV
Efficacy of oxamniquine in the schistosomiasis treatment in rural area, according to the drug formulation. Mirangaba, Ba. — 1975

<table>
<thead>
<tr>
<th>Formulation (mg/kg)</th>
<th>Patients treated No.</th>
<th>Patients controlled No.</th>
<th>Patients cured No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule 12.5 — 15</td>
<td>280</td>
<td>228</td>
<td>194</td>
<td>68.6</td>
</tr>
<tr>
<td>Syrup 20</td>
<td>33</td>
<td>29</td>
<td>21</td>
<td>72.4</td>
</tr>
<tr>
<td>Total</td>
<td>313</td>
<td>257</td>
<td>215</td>
<td>63.2</td>
</tr>
</tbody>
</table>

TABLE V
Mean of the number of eggs in the stools of the non-cured patients, before and after the treatment with oxamniquine. Mirangaba, Ba. — 1975

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean $\bar{x}$ Standard deviation</th>
<th>Difference $\bar{x}$ Standard deviation</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>349.3 ± 429.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>107.9 ± 80.8</td>
<td></td>
<td>$T_{25} = 2.54; P &gt; 0.05$</td>
</tr>
</tbody>
</table>

TABLE VI
Initial and final efficacy of oxamniquine with its re-infection rates. Mirangaba — Ba. — 1975

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Cure percentage (%)</th>
<th>Re-infection percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>83.2</td>
<td>--</td>
</tr>
<tr>
<td>(seven months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One year</td>
<td>77.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Three years and</td>
<td>65.4</td>
<td>12.5</td>
</tr>
<tr>
<td>seven months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COMMENTS

Our results in Mirangaba showed that oxamniquine is a good therapeutic agent for the large scale treatment of schistosomiasis. Those side effects reported were well tolerated by the population. In this group of patients, we have not observed any CNS reactions, as reported in other publications, although we have treated a relatively large number of patients. The drug is easy to give and a physician, with only the help of an orderly to weigh the patients, may administer it to at least 300 individuals in one day. Of course, in Mirangaba the physical examinations had already been done before the treatment day.

The cure rate observed, over 80%, after a 7-month follow-up, is very satisfactory, and there was no significant difference between the cure rates obtained with capsules and those obtained with syrup, although in a previous study we had obtained a cure rate of nearly 95% with dosages similar to those used in the present trial. It is possible that the great difference in the number of patients who were given capsules and syrup and the delay in beginning evaluation of the cure account for this apparent discrepancy. The later evaluations have demonstrated that, in the course of time, the cure rate diminishes, that is, the patients begin to excrete viable S. mansoni eggs in the stools again. Unlike the results in other localities described in previous studies, the reinfections occurred faster, which perhaps reflects a more active transmission in the locality of Mirangaba.

There was difference in the mean ages of the patients infected after one year of treatment and those infected after three years and seven months, but we were not able to determine a statistically significant difference between the means because the population evaluated after three years and seven months was just a little more than half the initial population. In other words: while in the evaluation after one year we were able to examine the stools of 78% of the initial population, in the evaluation after three years and seven months we examined just 53%.

On the basis of the above, we think that the large scale treatment of populations who live in areas of low transmission is the best...
way to control schistosomiasis, because even
the non-cured patients showed a statistically
significant reduction in the number of eggs
excreted. We believe, however, that specific
treatment constitutes only one of the measures
to be adopted for schistosomiasis control and
eradication. We believe also that the selec-
tive treatment of the patients with schisto-
omiasis, even in hyperendemic areas, is in-
dicated, once there is evidence that treatment
prevents the development of the severe forms
of the disease. However, on the basis of the
present state of knowledge, we do not think
the time for general mass treatment is ideal
because of the existence of absolute and rela-
tive contraindications to treatment and beca-
use examinations of stool are not confirmatory
of diagnosis in all the cases. Neverthe-
less, the results obtained in Mirangaba prompt
us to treat other populations in endemic areas
of schistosomiasis with oxamnique.

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Clinical trials with oral oxamnique (UK 4271) for the

SAEZ-ALQUEZAR, A.; FUNSKAS, J. A. & RAIA, S. —
Further clinical trials with oxamnique (UK 4271), a

DISCUSSION OF DR. BINA'S AND DR.
PRATA'S PAPER — OXAMNIQUE IN THE
TREATMENT OF A LOW ENDEMICITY
SCHISTOSOMIASIS-INFECTED POPULATION

Prof. PRATA

I would like to emphasize that these re-
results are from an area in which transmis-
sion was low. It used to be an endemic area but
with sanitary improvements, supply of clean
water, and the draining of an infested lake,
transmission was greatly reduced. We feel
that most reinfections occurred when mem-
bers of the population were away from the
area. The reinfection rate, using five stool
examinations, was 22% after one year and
35% after three years and seven months. This
is less than figures seen in endemic areas and
proves that we are seeing reinfection, and
that transmission has been decreased. The
other problem is that in this population of
2,000 people we detected 300 positive cases
after a single stool examination. When we
performed a second examination of those that
were initially negative, we found 17 positive
cases. To treat everyone in an area such as
this does not make sense, but how many stool
examinations should be performed prior to
treatment? These are the practical difficul-
ties of schistosomiasis control.
THE ROLE OF CHEMOTHERAPY IN THE SPECIAL PROGRAM FOR CONTROL OF SCHISTOSOMIASIS

Solon de CAMARGO (1)

INTRODUCTION

The programs against schistosomiasis in Brazil, or better to say, the work against the endemic disease was always hindered by deficiencies or difficulties in the application of measures against the several phases in the epidemiological cycle of the disease.

The concept is that the disease is due to socio-economical causes and consequently would need measures to raise the economic and social level of the population. This is theoretically feasible if, at the same time, the people had the technical resources and the ability to change the ecology to cut one of the rings in the transmission chain.

The disease, however, is usually confined to areas of poor sanitary conditions, and to populations, even though they are conscious of the cause of the problem, which can do very little to minimize it. It is Utopia to think that modifying one of the causes of the permanence of the disease, the conomical problems of vast areas of the country, one can eliminate the disease.

Therefore, the governing bodies try to find a way to control the problem, by preventing the contact of the excreta with the liquid medium, or by eliminating the intermediate host of the disease by preventing the contact of man with the infectious agents.

It is widely accepted and was recently mentioned again by the Minister of Health, that the fight against schistosomiasis should include simultaneous and correlated actions which synergistically will cut the transmission of the disease.

Those measures are based on environmental sanitation and housing improvement, health education, control of snails that are the intermediary hosts of the disease, and in the specific treatment of the positive patients. Additional action for individual protection or the isolation of areas can be taken when and if it is found to be necessary.

This integrated approach seldom could be achieved due to the high cost of environmental sanitation, the long time period required to obtain awareness of the population, by the capacity of the snails to protect themselves and by the lack of specific therapeutic agents that could be used easily with high efficacy levels and lack of serious side effects.

The therapeutic arsenal used in the past is a long list, from the empiric preparations, usually from plants, such as the oil of "mas-truço", pumpkin seeds, etc., which were followed by tartar emetic, tartarate of sodium and antimonies, Fuadin, Repodral, Stibofen, Sulfantimmon, Triostib, Ambilhar, to the more recent ones, hycanthone (ETRENOL) and oxamniquine (MANSIL), to some others in the experimentation phase.

Amongst the products to control the snail, from the application of lime, pentachlorophenol, copper sulfate and others, we have now in the market, Frescon (from Shell), TPTO (an organoth) and Bayluscide (Bayer) and, under trial, the juice of SISAL (Agave) and FIOCRUZ-002, a copper abietate.

PREPARATORY WORK

The government, studying the matter of schistosomiasis and following the research done, both by foreign and Brazilian researchers, considered the oral treatment with oxamniquine a great step ahead. More than

(1) Superintendence of Public Health Campaigns, Ministry of Health — Brazil
30,000 treatments had been done with Etenol but the care necessary in the selection before the treatment and the follow-up for 48 hours after treatment restricted a large scale use in a public health campaign.

Oxamniquine, with the easiness of oral administration in one dose and with a high index of cure, which was reported in several published papers, has allowed its use in a larger and more effective way.

Through the responsible service, the “Superintendência de Campanhas de Saúde Pública”, the Ministry of Health decided to test oxamniquine using their field personnel.

Initially, the test was done in an area without transmission, to check the curative capacity of oxamniquine without the re-infection problem. The country of Guia, in the West of Paraná State, has a population comprised almost totally of newcomers, who come from schistosomiasis areas. The snail found was Biomphalaria tenagoplia and in thousands of examinations not one cercariae of Schistosoma mansoni was found. Stool examinations were done in 26,530 persons with the finding of 828 positives, all of whom came from other endemic areas.

Seven hundred and sixty two (762) adults and children were treated, with a dosage of 12.5 mg/kg body weight. All persons treated were checked by the doctor to determine the incidence of side effects. The cure index was 96% but the long-term follow-up could not be done due to the arrival of winter and the emigration of the people.

As a second stage, it was decided to treat people in a highly endemic area of the city of Touro, in Rio Grande do Norte. This city has a long history of schistosomiasis. The census of the population was 2,259 and the index of positive cases, by one stool examination using the Kato method in 1,985 persons was 53.4% (1,065 positive for Schistosoma mansoni). As oxamniquine, provided by the manufacturers, Pfizer Quimica Ltda., was available in capsule and syrup form, the treatment scheme was of 20 mg/kg for persons of less than 15 kg, 15 mg/kg for those from 16 to 20 kg and 12.5 mg/kg for those above 21 kg body weight. The index positivity went down as measured in the first evaluation after treatment to 3.4% but went up again slowly. In an annex table we show the successive evaluations in Touro.

As was mentioned above, the work in Touro was limited to chemotherapy. The only measure taken concerning the snails was to start a continuing study of its population dynamics, with the collection of snails in stations 50 meters apart along the Macel river and around the Jiqui lagoon.

As a third stage, an isolated community in the middle of the sugar cane plantations in the humid region of Pernambuco, county of Palmares, the locality Santo Antonio dos Palmares (or das Trempes) was first evaluated by a socio-economic survey followed by coproscopic and malacological evaluation of the hydrographic basin. Piped water was installed in all the houses, along with a shower, a latrine and a washing basin. In addition, a communal laundry building was provided. The river was found to have B. straminea and the snails were controlled with Bayluscide.

Santo Antonio dos Palmares has a population of 571 persons, distributed by sex with 49% masculine and 51% feminine. 57% of the population was below 19 years of age; 31% between 20 and 49 years and 12% above 50 years. All 571 persons had one stool examination done by the Kato method and 289 (or 50.43%) were found positive for Schistosoma mansoni.

The average number of egg per gram of feces was 7.28 and in the river 5,894 snails B. straminea were found to be negative.

A large scale treatment was done in two days, by four trained men under medical supervision. 547 (96%) of the population was treated. Seventeen (17) pregnant women, 3 persons suffering of cardiac lesions, one with cerebral thrombosis and one person that refused, were not treated.

Treatment evaluation was done every 90 days as shown in annex table.

“PROGRAMA ESPECIAL DE CONTROLE DA ESQUISTOSOMOSE — PECE”

(Special Program for Control of Schistosomiasis)

The government, based on acquired experience, accepted the challenge to control the
disease at a national level. The available drug, oxamniquine — MANSIL — was able to be used on a large scale, with ease of administration, small number of mild non-serious side effects, and a cure rate of about 95%.

The Social Development Council with approval of the President of the Republic, proposed the “Programa Especial de Controle da Esquistossomose” to cover the entire endemic area at a cost of Cr$ 1,700,000,000 (one billion seven hundred million cruzeiros) plus funds for environment sanitation work.

The methodology adopted, to be applied in continuous and contiguous areas and following the ecological characteristics of each hydrographic region was: 1) Geographic survey, marking houses, trails, streams and other bodies of water; 2) Malacological survey of the water sites classifying them as: 2.1. Breeding places — water collections with snails; 2.2. Breeding places of epidemiological importance — places used by humans and contaminated by their excreta. In this way, molluscicide application could concentrate on those places with risk, therefore, obviating the need of blanket coverage; 3) Coproscopic survey — with one stool examination by the Kato method. The age group 7-14 years was considered to be representative of the population and the survey was made in this group most often in rural areas in the periphery of towns; 4) To provide, as often as possible, environmental sanitation and housing improvement, building latrines, showers, washing basins and communal laundry buildings, with playgrounds where children could play under the supervision of their mothers; 5) Treatment of the population, using the following scheme: 5.1. When the positive rate is 20% and up, mass treatment of the population; 5.2. With the positive rate between less than 20% and more than 3%, treatment of the population from 1 to 25 years of age, and; 5.3. Active search and treatment of positives with the rate below 4%. All the work was to be followed by a health education campaign in order to obtain the understanding and cooperation of the population.

Based on the geographic and epidemiological situation, the Northeast, with a larger and older infestation of schistosomiasis, was to be starting point and the State of Rio Grande
do Norte was the first to finish the several phases of the program.

At this moment, 8 states, from Maranhão down to Sergipe, are engaged in the work and annexed is a summary of the work.

In two of those states, Rio Grande do Norte and Sergipe, the evaluation is now under way and some of the results are shown in the tables following.

There is some discrepancy in the results between one state and another and we believe besides the sampling error, we consider that the treatment of the snails with molluscicide is one of the causes of the greater reduction in the rate of infection.

In Rio Grande do Norte, in the Gravatá lagoon this question is under study, mainly as a result of the high rate of malacological positivity and the difficulty to effectively treat the lagoon, covered as it is with water hyacinths “Eichornia crassipes”. It was decided to remove this vegetation before applying molluscicide. The cost and time consumed will be evaluated.

COMMENTS

The purpose of the treatment is not to eliminate the disease but to reduce it to indices compatible with development.

Joining all the other measures with treatment, we achieve reduced rates which are slow to rise. Beside reducing the rate, another important point is the egg reduction in the stools and the almost complete disappearance of serious cases of schistosomiasis, especially if the lower age groups are treated who, as we know and has been reported by several authors, are the patients who are the serious cases and the ones in which hepatosplenomegaly begins to form.

There is a study now in progress of persons with splenomegaly to see if there is a regression of the lesions after treatment.

We believe that the role of chemotherapy is not only of treatment to the individual but also as prevention of serious cases and of the transmission of the disease by reducing the number of miracidia in the liquid media.
### Superintendence of Public Health Campaigns SUCAM
Special Program of Schistosomiasis Control PECE
Regional Board of Directors of Rio Grande do Norte
Results of the initial surveys, treatments and evaluations per municipality.

<table>
<thead>
<tr>
<th></th>
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<td>13 — Eduardo Gomes</td>
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<td>272</td>
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<td>3,011</td>
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<td>118</td>
<td>22.5</td>
<td>2,504</td>
<td>533</td>
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<td>20 — Vera Cruz</td>
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<td>0.3</td>
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<td>21 — Arês</td>
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<td>1,840</td>
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<td>22 — Espírito Santo</td>
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<td>9</td>
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<td>63</td>
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<td>23 — Golinhana</td>
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<td>41</td>
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<td>2,366</td>
<td>562</td>
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<td>24 — Sen. Georgino Avelino</td>
<td>888</td>
<td>200</td>
<td>35</td>
<td>17.5</td>
<td>840</td>
<td>201</td>
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<td>25 — Tibau do Sul</td>
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<td>4</td>
<td>0.8</td>
<td>1,151</td>
<td>465</td>
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<td>26 — Baía Formosa</td>
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<td>77</td>
<td>57.0</td>
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<td>108</td>
<td>15</td>
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<td>27 — Canguaretama</td>
<td>2,275</td>
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<td>70</td>
<td>12.9</td>
<td>2,305</td>
<td>509</td>
<td>6</td>
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<tr>
<td>28 — Pedro Velho</td>
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<td>364</td>
<td>113</td>
<td>29.4</td>
<td>1,628</td>
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<td>29 — Vila Flor</td>
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<td>12</td>
<td>2.4</td>
<td>1,816</td>
<td>475</td>
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**TOTAL** | **74,494** | **36,046** | **7,201** | **20.0** | **59,686** | **15,785** | **547** | **3.5** | **22,747** | **16,000** | **407** | **3.5**

Source: DR — Rio Grande do Norte
SC/cos
18/09/78

Ministry of Health Superintendence of Public Health Campaigns Medication Until August

<table>
<thead>
<tr>
<th>States</th>
<th>Treatments</th>
<th>Localities</th>
<th>Persons</th>
<th>Capsules</th>
<th>Syrup (ml)</th>
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<td>Pernambuco</td>
<td>1st Treatment</td>
<td>623</td>
<td>163,922</td>
<td>185,872</td>
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<td>1,211</td>
<td>234,101</td>
<td>432,749</td>
<td>499,735</td>
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<td>Tull July</td>
<td>2nd Treatment</td>
<td>507</td>
<td>80,771</td>
<td>141,383</td>
<td>196,901</td>
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<tr>
<td>Paraíba</td>
<td>1st Treatment</td>
<td>2,706</td>
<td>414,213</td>
<td>794,485</td>
<td>856,320</td>
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<td>Sergipe</td>
<td>1st Treatment</td>
<td>1,640</td>
<td>90,664</td>
<td>175,805</td>
<td>186,242</td>
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<td>2nd Treatment</td>
<td>336</td>
<td>14,952</td>
<td>29,429</td>
<td>25,403</td>
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<tr>
<td>Total</td>
<td>1st Treatment</td>
<td>6,080</td>
<td>843,900</td>
<td>1,730,320</td>
<td>1,194,016</td>
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<tr>
<td>Total</td>
<td>2nd Treatment</td>
<td>848</td>
<td>93,723</td>
<td></td>
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<tr>
<td>General Total</td>
<td></td>
<td>6,928</td>
<td>938,623</td>
<td>1,730,320</td>
<td>1,194,016</td>
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Superintendence of Public Health Campaigns (SUCAM) Regional Board of Directors in Pernambuco Special Program of Schistosomiasis Control (PECE) Special Project of Santo Antonio dos Palmares

<table>
<thead>
<tr>
<th>Period</th>
<th>Persons examined</th>
<th>Exam. done</th>
<th>Result</th>
<th>Medicated</th>
<th>Non-medicated</th>
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<tr>
<td>April 77</td>
<td>in the survey</td>
<td>571</td>
<td>286</td>
<td>283</td>
<td>50.4</td>
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<tr>
<td>July 77</td>
<td>1st Evaluation</td>
<td>515</td>
<td>17</td>
<td>498</td>
<td>3.3</td>
</tr>
<tr>
<td>Sept 77</td>
<td>2nd Evaluation</td>
<td>499</td>
<td>33</td>
<td>466</td>
<td>6.6</td>
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<tr>
<td>Oct 77</td>
<td>3rd Evaluation</td>
<td>477</td>
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<td>457</td>
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<tr>
<td>Dec 77</td>
<td>4th Evaluation</td>
<td>464</td>
<td>14</td>
<td>450</td>
<td>3.0</td>
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<tr>
<td>Feb 78</td>
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<td>20</td>
<td>428</td>
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<tr>
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<td>6th Evaluation</td>
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<td>19</td>
<td>422</td>
<td>4.3</td>
</tr>
<tr>
<td>May 78</td>
<td>7th Evaluation</td>
<td>431</td>
<td>13</td>
<td>418</td>
<td>3.0</td>
</tr>
<tr>
<td>Jul 78</td>
<td>8th Evaluation</td>
<td>425</td>
<td>14</td>
<td>411</td>
<td>3.3</td>
</tr>
<tr>
<td>Aug 78</td>
<td>9th Evaluation</td>
<td>418</td>
<td>7</td>
<td>411</td>
<td>1.7</td>
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</tbody>
</table>

Observation: Of the persons examined up to the 9th evaluation, only 4 failed to be medicated for the following reasons: 1 — asthmatic patient with stroke, 2 — move to another locality, 1 — refusal.

Project Touros — RN — Coproscopic results of the 1st Examination and of the 11 Evaluation. Dec. 75 — March 78

<table>
<thead>
<tr>
<th>Specification</th>
<th>Exame</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>6th</th>
<th>7th</th>
<th>8th</th>
<th>9th</th>
<th>10th</th>
<th>11th</th>
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<tr>
<td>Negative</td>
<td>930</td>
<td>1.726</td>
<td>1.627</td>
<td>1.643</td>
<td>1.301</td>
<td>1.309</td>
<td>1.404</td>
<td>1.429</td>
<td>1.425</td>
<td>1.184</td>
<td>1.971</td>
<td>1.613</td>
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<td>1.49</td>
<td>53</td>
<td>67</td>
<td>86</td>
<td>186</td>
<td>194</td>
<td>334</td>
<td>230</td>
<td>238</td>
<td>306</td>
<td>81</td>
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<td>% Positivity</td>
<td>50.5</td>
<td>7.1</td>
<td>2.5</td>
<td>3.2</td>
<td>4.6</td>
<td>8.8</td>
<td>9.3</td>
<td>15.8</td>
<td>10.9</td>
<td>11.3</td>
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<td>% Positive adjusted</td>
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<td>6.6</td>
<td>12.4</td>
<td>12.1</td>
<td>18.9</td>
<td>13.9</td>
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<td>4.8</td>
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<td>236</td>
<td>431</td>
<td>401</td>
<td>632</td>
<td>616</td>
<td>513</td>
<td>348</td>
<td>456</td>
<td>689</td>
<td>454</td>
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<td>Total</td>
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<td>2.111</td>
<td>2.111</td>
<td>2.111</td>
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SOURCE: SUCAM/D.R.R.N./DEP/CAD—SP
Ministry of Health
SUCAM — PECE

Drawing: José Ronaldo de Menezes
Date: May/78

102
SCHISTOSOMIASIS ENDEMIC AREA
BRASIL

- Area with medium & high endemicity
- Area with low endemicity
- Isolated foci
- Area without transmission or not surveyed
Evaluation of treatment — Sergipe

<table>
<thead>
<tr>
<th>Municipalities</th>
<th>Initial Rate (%)</th>
<th>Control (%)</th>
<th>Reduction of the Rate</th>
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</thead>
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<tr>
<td>Pirambu</td>
<td>26.4</td>
<td>16.3</td>
<td>33.4</td>
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<tr>
<td>Capela</td>
<td>57.0</td>
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<td>78.2</td>
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<tr>
<td>Maruim</td>
<td>58.6</td>
<td>24.9</td>
<td>77.3</td>
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<tr>
<td>Gal. Maynard</td>
<td>75.5</td>
<td>32.2</td>
<td>56.0</td>
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<tr>
<td>Rosário</td>
<td>76.7</td>
<td>31.4</td>
<td>58.0</td>
</tr>
<tr>
<td>Japaratuba</td>
<td>42.2</td>
<td>13.7</td>
<td>67.5</td>
</tr>
<tr>
<td>St. Amaro das Brotas</td>
<td>64.2</td>
<td>19.7</td>
<td>69.3</td>
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<tr>
<td>Carmópolis</td>
<td>76.7</td>
<td>21.4</td>
<td>72.1</td>
</tr>
<tr>
<td>S. Francisco</td>
<td>21.9</td>
<td>9.7</td>
<td>55.7</td>
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<tr>
<td>Siriri</td>
<td>27.0</td>
<td>8.7</td>
<td>67.8</td>
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<td>Divina Pastora</td>
<td>53.2</td>
<td>13.6</td>
<td>74.4</td>
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<td>Japoaia</td>
<td>31.6</td>
<td>4.5</td>
<td>85.8</td>
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<td>Matinha dos Bois</td>
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<td>70.7</td>
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<td>Muribeca</td>
<td>28.6</td>
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<td>94.6</td>
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<td>Riachuelo</td>
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<td>71.4</td>
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<tr>
<td><strong>Total mean</strong></td>
<td><strong>48</strong></td>
<td><strong>16.05</strong></td>
<td><strong>67.1</strong></td>
</tr>
</tbody>
</table>

DISCUSSION ON DR. CAMARGO’S PAPER — THE ROLE OF CHEMOTHERAPY IN THE SPECIAL PROGRAM FOR CONTROL OF SCHISTOSOMIASIS

Prof. PRATA

Thank you, Dr. Camargo, for your paper on the status of the special program of schistosomiasis control in Brazil. I would like to ask several questions to start the discussion. How many people have been treated, were they all treated in the same period, and did you treat entire areas?

Dr. CAMARGO

Approximately one million people have been treated so far. They have been treated at different times because the different aspects of the program all have their own speed of activity. The treatment program is the least time-consuming; but coprological surveys and malacological surveys take time, and general sanitation improvements are much slower. However, we do try to treat continuous and contiguous areas that make up a "water shed" trying not to leave gaps that could be a source of reinfection.

Prof. PRATA

The reason why I asked the question was that, in my own studies of an isolated area, the people moved to other areas and became reinfected. By treating large areas, I would hope that we could get better results than treating isolated areas.

Dr. CAMARGO

This is why we try to treat entire areas. Before commencing we fully map the area, note every house, the behavior of the people and where they go in their daily activities.

Dr. ANDRADE (Salvador)

Dr. Camargo, from your tables you showed that 59.856 people were treated in one area, but only 7,200 were positive. Can you explain why you treated ten times more people than were found to be positive?

Dr. CAMARGO

Yes, we performed a sample on those 7-14 years old. If in this sample the incidence was over 70%, then the entire population was given treatment. We did not survey the entire population.

Prof. PRATA

We can all disagree on different details of the program, but overall very useful information is likely to emerge. I hope that this mass treatment can show benefits in decreasing the incidence of severe forms of the disease and maybe in the general control of schistosomiasis. With the careful statistics that you are keeping, we look forward to these answers in the future.
SERUM ENZYMATIC CHANGES IN PATIENTS WITH SCHISTOSOMIASIS TREATED WITH OXAMNIQUE OR HYCANTHONE: COMPARATIVE STUDY

A. SAEZ-ALQUEZAR (1), N. OHTSUKI (1), H. SETTE JR. (2), A. C. MAGNANELLI (1), S. RAIA (3) and L. C. DA SILVA (4)

INTRODUCTION

In a previous work, the Authors have shown that hycanthone in the dose of 2.5 mg/kg produced greater serum aminotransferases changes than oxamnique in the dose of 12.5 mg/kg of b.w.

Smaller doses of hycanthone (2.0 mg/kg) were recomended by CUNHA, with rather satisfactory results. Furthermore, oxamnique has been used in the minimal dose of 15.0 mg/kg.

In view of the results previously mentioned, showing greater rises in the serum levels of aminotransferases after hycanthone, the authors considered it wise to perform a comparative study between hycanthone and oxamnique in the doses of 2.0 mg and 15.0 mg/kg, respectively. For a better evaluation of a possible hepatotoxic effect of the drugs, the following determinations were included in the study design: serum levels of the guanase activity (GDS) gamma-glutamyltransferase (GGT), alkaline phosphatase (AP) and bilirubin concentration.

CASUISTICS AND METHODS

CASUISTICS

Initially, 39 patients with active schistosomiasis were treated. The majority had the hepato-intestinal form of the disease. Patients were distributed into two groups according to a table of random numbers:

Group I — 20 patients, of whom 15 with the hepato-intestinal form (HI) and 5 with the hepatosplenic form (HS); all received hycanthone in single IM dose of 2.0 mg/kg.

Group II — 19 patients, of whom 13 with the HI form and 6 with the HS form; all received oxamnique in single oral dose of 15.0 mg/kg.

In a second stage, 14 more patients (10 HI and 4 HS) were treated with oxamnique (Group III).

METHODS

Selection of patients

After detection of viable eggs in the feces, the patients were treated with hycanthone or oxamnique according to a table of random numbers.

Collection of blood specimens

It was performed before treatment and day 4, day 8 and day 12 after treatment. The biochemical profile was also studied on day 30 after treatment in 15 patients of group I and in 7 of the Groups II and III.

Biochemical profile

Besides determination of the serum bilirubins, the serum activity of the following enzymes were studied: alanine aminotransferase (ALT), aspartate aminotransferase (AST), guanase (GDS), gamma-glutamyl transferase (GGT) and alkaline phosphatase (AP). The techniques used and the normal values are shown in Table I.

(1) Biochemist of the Liver Unit of the Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo
(2) Assistant-Physician of the Hospital das Clinicas da Faculdade de Medicina da USP
(3) Assistant Professor of Liver Surgery and Portal Hypertension Service of the Faculdade de Medicina da USP
(4) Chief of the Hepatology Laboratory of the Instituto de Medicina Tropical de Sao Paulo
**TABLE I**

Components of the biochemical profile, methods and normal values 3a

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Methods</th>
<th>Normal values</th>
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<tr>
<td>Alanine aminotransferase (ALT) (E.C. 2.6.1.2.)</td>
<td>colorimetric</td>
<td>5 — 35 URF/ml</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST) (E.C. 2.6.1.1.)</td>
<td>colorimetric</td>
<td>8 — 40 URF/ml</td>
</tr>
<tr>
<td>Guanase (GDS) (E.C. 5.3.4.3.)</td>
<td>colorimetric</td>
<td>0.6 — 3.6 U/l</td>
</tr>
<tr>
<td>Gammaglutamyltransferase (GGT) (E.C. 2.3.2.3.)</td>
<td>kinetic (m.)</td>
<td>6 — 28 U/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(L.) 4 — 18 U/l</td>
</tr>
<tr>
<td>Alkaline phosphatase (AP) (E.C. 3.1.3.1.)</td>
<td>colorimetric</td>
<td>15 — 69 U/l</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>colorimetric</td>
<td>0.3 — 1.3 mg%</td>
</tr>
</tbody>
</table>

**Statistical Analysis**

The statistical analysis used the paired "t" test for comparison of each post-period with the pre-period, and Student’s "t" test for comparison between same periods of the groups treated with hycanthone and oxamniquine.

**RESULTS**

Tables II, III and IV show the results obtained in the different periods of each group in relation to the mean, standard deviation and upper and lower limits (UL and LL) of the mean.

**TABLE II**

Serum levels of aspartate (AST) and alanine aminotransferase (ALT) activities in patients with schistosomiasis in the pre-treatment and on day 4, day 8, day 12 and day 30 after treatment with hycanthone (Hy, group I) or Oxamnique (Ox, group II and III)

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<tr>
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<tr>
<td>Pre</td>
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<td>22.11</td>
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<td>48.96</td>
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<tr>
<td>G II</td>
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<td>19.83</td>
<td>2.55</td>
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<td>77.67</td>
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<td>4.º</td>
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</tr>
<tr>
<td>G I</td>
<td>29.85</td>
<td>28.17</td>
<td>6.83</td>
<td>44.34</td>
</tr>
<tr>
<td>G II</td>
<td>32.76</td>
<td>23.55</td>
<td>5.81</td>
<td>45.08</td>
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<tr>
<td>G III</td>
<td>54.69</td>
<td>40.69</td>
<td>11.29</td>
<td>79.28</td>
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<td></td>
</tr>
<tr>
<td>G I</td>
<td>25.50</td>
<td>12.33</td>
<td>3.14</td>
<td>32.13</td>
</tr>
<tr>
<td>G II</td>
<td>39.89</td>
<td>43.51</td>
<td>9.88</td>
<td>57.87</td>
</tr>
<tr>
<td>G III</td>
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<td>48.95</td>
<td>13.08</td>
<td>84.61</td>
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<tr>
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<td>31.61</td>
<td>24.43</td>
<td>5.60</td>
<td>43.37</td>
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<td>25.79</td>
<td>11.41</td>
<td>3.05</td>
<td>32.37</td>
</tr>
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<td>G III</td>
<td>58.18</td>
<td>45.63</td>
<td>13.99</td>
<td>86.97</td>
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<td>30.º</td>
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<td>29.40</td>
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<td>30.70</td>
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<td>7.85</td>
<td>2.97</td>
<td>31.54</td>
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<tr>
<td>G III</td>
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</table>
**TABLE II**

Serum levels of guanase (GDS) and gammaglutamyltransferase (GGT) activities in patients with schistosomiasis in the pre-treatment and on day 4, day 8, day 12 and day 30 after treatment with hyancione (Hy, group I) or Oxanquine (Ox, group II and III).

<table>
<thead>
<tr>
<th>GDS</th>
<th>X</th>
<th>S</th>
<th>Sx</th>
<th>UL</th>
<th>LL</th>
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<tbody>
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<td>Prd</td>
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<tr>
<td>G I</td>
<td>1.40</td>
<td>1.50</td>
<td>0.34</td>
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<td>0.70</td>
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<td>G II</td>
<td>1.33</td>
<td>1.49</td>
<td>0.35</td>
<td>2.08</td>
<td>0.59</td>
</tr>
<tr>
<td>G III</td>
<td>0.95</td>
<td>1.20</td>
<td>0.33</td>
<td>1.68</td>
<td>0.23</td>
</tr>
</tbody>
</table>

|    |    |    |    |    |    |
|    |    |    |    |    |    |
| 4.° |    |    |    |    |    |
| G I | 1.32 | 1.44 | 0.35 | 2.06 | 0.58 |
| G II | 1.49 | 1.92 | 0.47 | 2.48 | 0.50 |
| G III | 1.58 | 1.67 | 0.46 | 2.39 | 0.57 |

|    |    |    |    |    |    |
|    |    |    |    |    |    |
| 8.° |    |    |    |    |    |
| G I | 1.93 | 1.12 | 0.26 | 1.59 | 0.46 |
| G II | 2.01 | 2.12 | 0.49 | 3.36 | 1.21 |
| G III | 1.41 | 1.57 | 0.42 | 2.32 | 0.51 |

|    |    |    |    |    |    |
|    |    |    |    |    |    |
| 12.° |    |    |    |    |    |
| G I | 1.33 | 1.27 | 0.20 | 1.84 | 0.72 |
| G II | 2.09 | 2.57 | 0.69 | 3.57 | 0.60 |
| G III | 1.75 | 1.75 | 0.53 | 2.93 | 0.58 |

|    |    |    |    |    |    |
|    |    |    |    |    |    |
| 30.° |    |    |    |    |    |
| G I | 1.40 | 2.24 | 0.58 | 2.64 | 0.16 |
| G II | 1.27 | 1.94 | 0.76 | 3.07 | 0.00 |
| G III |    |    |    |    |    |

**TABLE IV**

Serum levels of alkaline phosphatase (AP) activity and serum levels of total bilirubin (BT) in patients with schistosomiasis in the pre-treatment and on day 4, day 8, day 12 and day 30 after treatment with hyancione (Hy, group I) or Oxanquine (Ox, group II and III).

<table>
<thead>
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<th>AP</th>
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<th>LL</th>
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<tr>
<td>Prd</td>
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<td></td>
</tr>
<tr>
<td>G I</td>
<td>63.85</td>
<td>55.82</td>
<td>19.69</td>
<td>100.19</td>
<td>22.50</td>
</tr>
<tr>
<td>G II</td>
<td>63.96</td>
<td>45.41</td>
<td>18.12</td>
<td>81.92</td>
<td>46.89</td>
</tr>
<tr>
<td>G III</td>
<td>97.36</td>
<td>86.35</td>
<td>17.73</td>
<td>185.66</td>
<td>59.65</td>
</tr>
</tbody>
</table>

|    |    |    |    |    |    |
|    |    |    |    |    |    |
| 4.° |    |    |    |    |    |
| G I | 63.96 | 64.50 | 15.64 | 97.13 | 30.80 |
| G II | 62.78 | 25.30 | 6.14 | 75.79 | 48.77 |
| G III | 100.08 | 67.53 | 18.73 | 140.89 | 59.27 |

|    |    |    |    |    |    |
|    |    |    |    |    |    |
| 8.° |    |    |    |    |    |
| G I | 57.76 | 62.87 | 14.82 | 89.02 | 26.49 |
| G II | 78.57 | 47.06 | 10.80 | 89.26 | 52.89 |
| G III | 100.21 | 61.76 | 16.51 | 135.87 | 64.56 |

|    |    |    |    |    |    |
|    |    |    |    |    |    |
| 12.° |    |    |    |    |    |
| G I | 69.36 | 76.68 | 17.36 | 105.83 | 32.90 |
| G II | 74.43 | 60.98 | 10.86 | 91.12 | 51.73 |
| G III | 96.73 | 66.43 | 20.02 | 141.35 | 52.19 |

|    |    |    |    |    |    |
|    |    |    |    |    |    |
| 30.° |    |    |    |    |    |
| G I | 56.07 | 42.32 | 10.93 | 79.46 | 32.69 |
| G II | 43.67 | 27.94 | 10.56 | 69.51 | 17.83 |
| G III |    |    |    |    |    |
The comparison between group I and II in the pre-treatment and in day 4, day 8, day 12 and day 30 post-treatment did not show statistically significant differences, except for GDS (guanase) on day 8 (p < 0.05).

The comparison between group II and III in relation to the same parameters mentioned above did not show statistically significant differences.

In some patients, evident changes of the serum enzyme activity were observed, as can be seen in Table V.

<table>
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<tr>
<th>Patient</th>
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<th>Post (days)</th>
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<td>LGS</td>
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<tr>
<td></td>
<td>GDS</td>
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</tr>
<tr>
<td></td>
<td>GGT</td>
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<td>46</td>
</tr>
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<td>JSS</td>
<td>ALT</td>
<td>58</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>GDS</td>
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<td>0.00</td>
</tr>
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<td>GGT</td>
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<td>GDS</td>
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<tr>
<td></td>
<td>GGT</td>
<td>40</td>
<td>22</td>
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</tbody>
</table>

* ALT (U/L); GDS and GGT (U/L)

Figures 1 and 2 show cases illustrating changes of GDS (guanase) and ALT (alanine aminotransferase).

**DISCUSSION**

While hydantoin has shown direct hepatotoxic potential, producing severe hepatitis or even fatal hepatitis, oxamnique has not caused noteworthy changes after single oral dose of 15 mg/kg, after higher doses or even after doses as high as 60 mg/kg. In a previous report, the authors have shown that intramuscular hydantoin (2.5 mg/kg single dose) actually produced aminotransferase changes more significant than those produced by oral oxamnique (12.5 mg/kg single dose).

In different published papers there is lack of uniformity in relation to the enzymatic control periods after the treatment. There is predominance of studies conducted between day 2 and day 3, 4, 13, 12, 14, 15, and day 10, 3, 9, 13 after...
treatment. As regards hyacanthone, the most evident changes were observed early, that is, around day 2. A few Authors, who studied the serum levels of the enzymatic activity for longer periods, have reported normalization after two to three weeks. Such facts, coupled with the constant and diffuse changes of the endoplasmatic reticulum observed under electron microscope, suggest that the drug possesses apparent hepatotoxic potential. According to ANDRADE et al. the diffuse and early character of the lesion indicates a direct action of hyacanthone and not a result of a worm embolism.

As to oxamniquine, several Authors pointed out the absence of evident hepatotoxic potential. KATZ et al. observed significant changes of aminotransferases on day 3 after treatment, but the serum levels did not exceed 60 units. In some individual cases, changes of aminotransferases over 100 URF/ml, were ob-
served by the authors on both day 2 and day 10.17. The significance of such increases is not yet defined, since so far there is no report of severe hepatitis caused by the drug.

In the present study, the Authors did not observe differences statistically significant in relation to the aminotransferase levels after use of hyancanthone (2.0 mg/kg) and of oxamnique (15 mg/kg). However, in some cases, the serum levels of the enzymatic activity of ALT (alanine aminotransferase) and ASAT (aspartate aminotransferase) distinctly changed, particularly from day 4 to day 12 after treatment, as can be seen in Figures 1 and 2. Furthermore, GDS (guanase), a specific enzyme of hepatic lesion — also raised in some individual cases in the same period of time.

The late enzymatic changes, for instance, from day 8 on, could be due to focal hepatic necrosis resulting from embolism and death of worms, although one cannot exclude the possibility of occurrence of such mechanism in earlier periods.

The variable behavior of the enzymes in individual cases points to the need for systematic studies in different periods after treatment using, whenever possible, enzymes specific for hepatic lesions.

REFERENCES


OXAMNIQUINE SYMPOSIUM

SUMMARY OF ROUND-TABLE DISCUSSIONS
MODERATOR: Professor A. PRATA

Prof. PRATA (Brasilia)

To open the round table discussion, I would initially like to give my personal point of view. Many of us have been working in the field of schistosomiasis for many years and well remember the time when treatment required multiple doses of antimony compounds or niridazole. At that time we did not suspect that the possibility of single dose treatment for schistosomiasis would come so quickly. However, the practicality of a drug with efficacy as a single dose and with good toleration came with hydantoin.

With the arrival of oxamniquine, we saw that it was possible to treat and cure a large number of patients with a single oral dose, and with good toleration; in fact I think that it would be difficult to get better toleration. Perhaps it is still possible to have a drug with better efficacy, and this may occur in the future. But in my personal opinion we now have a good drug for the treatment of schistosomiasis, and I congratulate Pfizer on their achievement.

However, the role of the pharmaceutical company in developing a drug and proving its safety and efficacy is only one aspect of the problem. In terms of the drug, there are admittedly further areas in which study is required, such as its use in pregnancy and so on. But the other important aspect is to develop information on how to utilize the drug properly, particularly as it applies to the community, and how we can prevent severe forms of the disease, and when and who should be retreated in order to achieve these aims. Before commencing the discussion we should make it clear that we are discussing the drug in terms of its use as a tool in controlling the disease. The treatment of a single patient in office practice is a different matter, as he presents asking for treatment and requesting a complete cure.

But important aspects for discussion in terms of the community are the goals of treatment, the relationship of treatment and retreatment to transmission of the disease, and whether to treat or retreat children and/or adults. The first question for discussion is who should be treated, when, and for what purpose.

Dr. N. KATZ (Belo Horizonte)

The aim of a treatment program is to decrease the incidence of severe disease as well as decrease transmission of the disease. The minimal time for retreatment would be four to six months, based on the findings that in some patients after a single treatment stool examinations may remain positive for up to two months in individuals who are later found to be completely cured. The amount of disease transmission should also be taken into account; for example, in an area of low endemic incidence, a retreatment after six months may decrease the prevalence in the community sufficiently to stop transmission. However, in an area of high endemic incidence, two treatments are probably inadequate for control. In such areas where control is possible, two or three treatments could be given at yearly intervals with the aim of controlling severe disease and decreasing prevalence. A further treatment program would probably then be required in two or three years when the disease prevalence starts to rise again. The other important question is how many courses of retreatment can be usefully given. We have seen that the results of a second treatment give cure rates similar to that of the first treatment, but we do not know what the results will be after a third, fourth, or fifth treatment with the same agent. The cost-benefit of such retreatments will need to be taken into account, for instance, if the cure after the third treatment is 85%, it is acceptable; but if it is only 50% it is probably not worth it.

In summary I believe that up to three treatments at yearly intervals will be useful, and the retreatment program should be repeated in two to three years depending on epidemiological conditions, reinfection rates, and so on.
Dr. L. CAETANO (São Paulo)

We should keep in mind that the disease incidence in a community in an endemic area rises in children over the age of two or three years and that the rate of reinfection is higher in the younger age group. It has also been shown that treatment can decrease the severity of hepatic lesions. For these reasons I feel that retreatment should be restricted to the age groups between 3 and 20 years and agree with Dr. Katz that the same drug can usefully be given two or three times. Retreatment should be performed after two or three years with priority given to hyperendemic areas.

Dr. A. COUTINHO (Recife)

I agree that if we wish to stop transmission of the disease in an area of low prevalence then it is essential to retreat patients. I also agree that in a hyperendemic area the priority is to treat the younger age groups in order to avoid severe forms of the disease. Consequently retreatment should be applied after one or two years, but it is not known for how long it will be required.

Prof. PRATA

In a community it can be seen that it takes some years to acquire the disease. In one endemic area that we have studied, the infection rate began after the first year of life, and at five years of age everybody was infected.

However severe manifestations of the disease are not seen for at least the first years of infection. There have been reports that severe forms of the disease can develop rapidly; but I think this is an exception, and normally the severe form takes at least two years to develop.

Dr. J. COURIA (Rio de Janeiro)

Therefore Professor Prata has the answer. We should treat patients before they develop severe forms of the disease.

Prof. PRATA

We have preliminary evidence that we can prevent severe forms of the disease after giving a single treatment. We also agree that patients should be treated before the age of 5 or 6 years to prevent severe forms of the disease, and that preventative treatment in those over 20 years is not useful. My question is why should we retreat when we know that severe forms can be prevented following a single treatment.

Dr. COURIA

Because they are reinfected with schistosomiasis. The schools are an excellent place to meet those candidates who are at risk of developing severe forms of the disease. I think that we should treat school-children between the ages of 6 and 15 and perform a survey every two to five years and retreat those with egg loads over 300 eggs per gram.

Prof. PRATA

Dr. Davis, would you like to comment?

Dr. A. DAVIS (Geneva)

You are arguing from incomplete evidence because you are talking as physicians and not as epidemiologists dealing with population groups. I think that there is a fairly well defined relationship between the incidence of severe disease and the worm load, which in turn depends on water contact. I would have thought it policy, whether it be scientific policy or political policy, to treat the younger age groups repetitively because they are the most economically productive of your community, and they are the people to whom you look to in the future. So I would go along with retreatment of people that are from the 5 to 16, or 5 to 17 age groups, who have the maximal worm load, the maximal water contact, and the longest life expectancy.

Dr. Z. ANDRADE (Salvador)

We are faced with the problem of schistosomiasis being a widespread disease in Brazil. The life cycle of the parasite is understood, and we know that if we could interrupt the life cycle at any point the disease could be eradicated. We now have a useful drug that can cure schistosomiasis in a high proportion of cases with negligible side effects. However, it is unlikely that drug therapy alone can eliminate schistosomiasis even for a small isolated area. Consequently drug therapy should be directed toward those at the highest risk, both in terms of themselves and the community. I advocate that the drug should be used in selective or target-treatment groups. The first group that I would treat are children below
the age of 15 years living in an endemic area. We have heard in previous discussions that hepatosplenic disease very rarely occurs in endemic areas in persons over the age of 15 years. Thus if we treat all people below this age, we are acting in a preventative way to avoid hepatosplenic disease, which is an important public health problem.

The second group that I would treat are those who are infected and are migrating from an endemic area to a nonendemic area. Migration of people in large numbers occurs because of drought or other environmental conditions, or for the prospect of improved working conditions in the cities, or major development projects such as hydroelectric dams, etc. These people should be treated when they leave the endemic area or immediately on arrival at the nonendemic area.

The third group for treatment would be symptomatic patients. At times it is difficult to decide whether schistosomiasis is the cause of their symptoms, but if eggs are found in the stools they should be treated.

I think that we should do pilot control projects using chemotherapy plus some other measure, such as mollusciciding or community education. By trying several methods we should be able to find the key to schistosomiasis eradication.

Prof. PRATA

Thank you Dr. Andrade. Let us now move to another point, the problem of cure versus egg reduction. I think that everyone will agree that it is necessary to achieve a complete cure to prevent severe forms of the disease. Egg reduction can be used as an indicator of control of the intensity of the infection.

Dr. KATZ

In a recent study we observed two communities for a period of two years. One community was given chemotherapy, the other acted as a control. In the control group, 50% of the people maintained similar egg outputs; 25% had fewer eggs; and 25% had a greater number of eggs. In the treated group after reinfection, 50% of the patients presented with a lower number of eggs than prior to treatment; 25% had a higher level of eggs; and 25% the same. Consequently following treatment 50% of patients will acquire lower level of infection.

Prof. PRATA

The real question is to decide whether it is better for a patient to have a benign infection rather than a complete cure. If a patient has a mild infection, it rarely becomes clinically important, but I am not convinced that if a patient is cured he will later acquire a severe infection. My question is what happens when a patient who has been cured returns to an endemic area.

Dr. COURÁ

We know from animal studies that if an animal that has been cured is reexposed to the parasites he becomes reinfeected. If the animal has not been cured, no reinfection occurs. For patients in endemic areas, I think that it is better for them to retain a mild infection, because those that are completely cured run a risk of reinfection and acquiring severe forms of the disease. If they have a light infection they will not get the severe form of the disease and they have concomitant immunity.

Prof. PRATA

What is the evidence in man that concomitant immunity exists?

Dr. COURÁ

If there was no concomitant immunity, everybody in the community would die of the infection because of their continual exposure.

Prof. PRATA

Is this immunity or concomitant immunity? I think that is immunity.

Dr. CAETANO

I wonder whether any drug really removes all of the worms from the body. With a technique of detecting increased antibodies after retreatment of "cured" patients, we have shown that a significant number of patients who do not have eggs in their stools do still have worms in their body.

Prof. PRATA

Dr. Caetano, do you think it will be possible to assess the efficacy of therapy by means other than fecal egg counts?
Dr. CAETANO

There are two methods. One is by perfusion of the blood, but this can only be done in man if the patient is having an operation for portal hypertension. So the only practical way, I think, is by immunological means. We can study the antibody response to a drug challenge. But I must confess that we have not been successful in finding circulating antigens in patients with low egg counts.

Dr. ANDRADE

At this time we do not have the proper techniques, but one possibility is a circulating polysaccharide that is produced by worms and not by the eggs. This antigen appears only in heavy infection and in patients with portal hypertension; presumably in patients with a normal liver the antigen is taken up by the Kupffer cells and other reticular cells, and does not circulate. With improved techniques, say radio immune assay, we should be able to show the presence of the circulating antigen, and by this prove that the patient harbors worms. The polysaccharide has been found in cercariae, schistosomula, and the adult worms but not in the eggs.

Prof. PRATA

Your work is proving that some adult worms do remain in the body following treatment. But we need a more practical method to prove the point, one that does not require a treatment challenge. Certainly more research is warranted in finding something in the serum or urine that correlates with the worm load.

Prof. PRATA

The next topic to address in whether or not we see drug resistance in our patients with S. mansoni infestation and what do we mean by the term "resistance".

Dr. KATZ

The term "resistance" is often used broadly and is often applied to a failure of treatment. With the dosage that we are currently using, we are obtaining cure rates of 85-90%. Therefore we should look at the 10-15% of patients who are not cured and ask why. Two factors are clear. The first is a true resistance of the particular strain of S. mansoni to the drug, with the problem in the parasite; the second is altered metabolism or absorption of the drug, where the problem is in the patient.

In order to shown true resistance of a particular strain it must be transmitted to mice and resistance experimentally demonstrated. I believe that the problem of resistance is overemphasized and is not a major problem in clinical practice. We are aware of this problem in the treatment of bacterial infections, but the practical point in treating schistosomiasis is to know whether a strain is initially resistant, or whether resistance can be induced by repeated treatments. We have seen that in treating a population one, two, or three times that similar therapeutic efficacy can be achieved, but on the fourth or fifth treatments, there is less therapeutic activity. For this reason it is better to use another drug if multiple retreatments are required.

Dr. CAETANO

I believe that we have been able to demonstrate true resistance. Yesterday I presented a case of a patient who failed to respond to treatment and had oxamniquine blood levels and urinary excretion similar to that of patients who were cured. When we transmitted the infection to mice it was not cured by a 50 mg/kg dose of oxamniquine, a dose that was effective in the control group. I believe that this is a case of true resistance. Other patients are not cured because of the metabolism of the drug, some patients may vomit, but is unusual. In other patients there are variable serum levels with the intramuscular formulation and more so after oral administration.

The other point is that patients who are not cured usually have very low egg counts and can be easily treated with other drugs, such as niridazole. The problem of resistance should not be taken as an argument against large scale treatment of priority areas, because of it appears we can use another drug in those individuals.

Dr. RAIZ

I agree that we should only use the term "resistance" when we can isolate the strain in mice or another animal model and prove that the strain is resistant to oxamniquine or hycazone. In our studies in São Paulo where the incidence of schistosomiasis is low and transmission is low, we can easily follow patients to determine reinfection. At this time we have 11 cases who have received three or
more doses of oxamniquine or hycanthone and are not parasitologically cured. We are now transmitting the strains to mice to see whether there is true resistance. The incidence of resistance may be more common than we previously thought.

Dr. R. FOSTER (UK)

I think that a lot of the confusion and the source of a lot of discussion on the question of so-called resistance is basically due to the fact that everybody has their own idea of what they mean by the word "resistance". People are tending to speak of resistance as though it is an absolute entity, as though an organism is either resistant or it is not, and that there is no degree of resistance. This is not true. The fact that a patient has not been cured by our definition means that the infection was not eradicated. But suppose that 95% of the worms were killed and the egg load reduced by 95%. It is time to say that this patient was not cured, but I submit that it is not time to say that these worms are resistant, because 95% died.

The other point concerns dosage. In discussions of oxamniquine here in Brazil, from your own experience you look upon the therapeutic dose of oxamniquine as being around 15 mg/kg. But if we look at our overall experience with oxamniquine, the therapeutic doses is anywhere from 15 to 60 mg/kg.

These patients in Brazil that are described as having resistant infections means that the patient has not been totally cured by a dose of 15 mg/kg. Has anyone tried repeating the treatment by using 20, 25, or 30 mg/kg? I think that some of these patients may have responded to a higher dose, because we know that patients elsewhere require a higher dose.

When we talk about a patient with a resistant infection in Brazil, we are really narrowing the definition down to the point where it is almost meaningless. We are selecting a dose level, an arbitrary dose of 15 mg/kg, and saying that this does not eliminate 100% of the worms. This is far too tight a definition for resistance. We must talk in terms of relative susceptibilities to this or any drug.

Dr. M. SCHULTZ (USA)

The concept of relative resistance is recognized in malariology, and there is a standard terminology for \( R_1 \), \( R_2 \), \( R_n \) resistance depending on the clinical cure and what happens to the parasitemia. I wonder whether it may be a useful concept to adapt to schistosomiasis therapy.

Dr. DAVIS

I think, again, that we are arguing from incomplete evidence and we are in danger of regarding \( S. mansoni \) as one particular organism. In fact, even in Brazil, there are numerous varieties of organisms and any family of \( Schistosoma mansoni \) has different genetic subtypes within it; it passes through different snails, it has different enteric properties and therefore it seems fair to assume that it has differential susceptibilities to chemotherapy. It is fair to assume that a certain amount of hybridization goes on in nature, and it does not surprise me that there is a range of susceptibility to any given therapeutic agent.

So, I think, when we talk about resistance, we are not talking about one thing, we are talking about a frequency distribution of strains or families of schistosomes, some of which are hybrids.

Prof. PRATA

It is evident that we are not using the same terminology. We are using the term resistance to mean resistance proven in an animal model as well as failure of treatment. There are other problems because patients do not always respond in the same way. If I treat 100 patients, 10% will not respond, but if I give a second treatment they do respond. However, there are a small percentage of patients that do not respond to multiple courses of therapy, and here we suspect resistance.

That concludes our panel discussion, and I would like to thank Pfizer for organizing the symposia and what has proved to be an interesting session. We have not only discussed the drug oxamniquine in detail but have also taken the opportunity to discuss many other important problems related to schistosomiasis control. Thank you.