EFFECTS OF A DECADE OF CHEMOTHERAPEUTICS ON THE PREVALENCE OF BILHARZIASIS IN A SETTLED COMMUNITY

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Chemotherapy as a method of control, alone and in combination with molluscicides, used at Limpopo Irrigation Scheme Mozambique, and Philadelphia Mission Dennilton.

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ABSTRACT

Bilharziasis is a world problem affecting 124 million persons. On the African continent some 91 million are infected, while on the subcontinent it is calculated that about 11,25 million are infected. The prognosis is serious as the increase of the disease is linked, amongst other factors, with improvement of the agronomy and water recreation facilities in the area. Today bilharziasis can be considered as an occupational hazard for all agricultural labourers.

Reports of control measures appearing in the literature largely contain inadequate data for various reasons, while no long-term large-scale project relying on chemotherapy with the new schistosomicides has been reported for the subcontinent. A study fulfilling these inadequacies would, therefore, be worthwhile.

A short-term pilot project was commenced at Dennilton, Transvaal and a long-term major project involving a community of 7 400 over a period of 10 years followed at Limpopo Irrigation Scheme, Mozambique. Here the total population was examined at approximately quarterly intervals for ten years and those infected received therapy. Later this was combined with periodic snail control. Schistosomicides used fell mainly into Winthrop's series of thioxanthenones (oral and parenteral) and Ciba's nitrothiazole (oral).

Preliminary surveys at both project centres showed that egg excretion by patients and haematuria was more severe in Africans than Caucasians and that the severity of the disease was similar to that found at Komatipoort previously, but not so severe as found in Egypt. Haematology and blood biochemistry tests carried out on limited random groups did not show much deviation from normal accepted values.

Short-term results of mass chemotherapy at both centres showed clinical improvement of the recipients and almost total suppression of egg excretion for observation periods up to 8 months. Haematology values were largely undisturbed with the exception of eosinophile counts and sedimentation rates which deteriorated immediately after therapy then improved as compared with pre-therapy values. Most

transaminase values showed a transient increase post-therapy, but returned to within the range of normal accepted values shortly afterwards, indicating clinical improvement of patients treated.

Long-term results obtained at Limpopo showed that chemotherapy reduced the total prevalence of the disease in the population from 23,1% to 7,7% within four months, and maintained this rate over considerable periods by sequential treatment, later interspersed with periodic snail control, when prevalence was reduced to the lowest point, 3,3%. MacDonald in 1965 had considered that a reduction of prevalence in a population to 10% was the breakpoint from where eradication would proceed. This did not happen in Limpopo, although total prevalence in the population was maintained by chemotherapy over long periods at a figure lower than this. Advantages of chemotherapy were found to be speed in application and results and ease of administration of the new schistosomicides used; particularly hycanthone in a single injection and ambilhar in an oral course, compared with antimonials accompanied by greater risks and lower cure rates.

Loss to the national productivity of the Southern African population due to the disease is difficult to assess. Estimates for the subcontinent place this figure at US $ 71 337 500, as compared with estimates by Wright (1968) of $ 445 866 945 for all Africa and $ 641 790 130 for the world. Control and therapy costs at Limpopo and Dennilton amounted to US $ 1,95 and $ 3,07 per person per annum respectively.

Suggestions for future investigations include parallel studies to establish bilharziasis as a priority disease; continued study of groups studied in the past by Powell (1967) and Walker et al (1970); continued study of chemical substances to perfect a selective schistosomicide and molluscicide; and intensified study of avian, animal and human schistosomes *in situ*, to establish the immunio-logical response leading to the production of a vaccine.

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SUMMARY

INTRODUCTION

From the earliest publications of Harley in 1864 setting out the cause of endemic haematuria in the Cape and Natal to the present day, many prominent investigators in South Africa have recorded their data on several aspects of the disease and many international congresses held here have made contributions. Yet basic data on the epidemiology and pathology of bilharziasis are still incomplete. In these circumstances some quantifications on the importance of the infection are justified to provide a basis for priority consideration.

Wright (1968) states that bilharziasis is endemic in 71 countries of the world having a total population of 1 362 million. Of these about 124 million are sick with the disease. On the African continent he considers that 91 million are infected. Similar calculations for the subcontinent show that 11,25 million are infected.

The subcontinent can be divided into the heavily infected areas with severe pathology, such as Malawi, Mozambique and Rhodesia: areas less heavily infected with lesser pathology, i.e., South Africa, Zambia and Swaziland: and the lightly infected areas with light pathology, i.e., Angola, Botswana and South West Africa, with no infection reported from Lesotho.

The spread of the disease is largely related to water impoundment and conservation. Rhodesia and the Republic of South Africa are at greatest risk because of expanded water programmes. One-third of the land area can be considered endemic for bilharziasis, inhabited by 11,25 million infected people. The magnitude of the disease can be appreciated by "the size of the population infected with these parasites, serious illness even for a minority of these constitutes a major health problem" (Gear 1974).

CONTROL METHODS REPORTED IN LITERATURE

Bilharziasis is the last unchallenged horizon in Tropical Medicine. The three main approaches to control are:- control of vector snails; control of the environment; and chemotherapy. Some small success in

lowering prevalence of the disease can be reported from a number of countries, eradication does not seem feasible at this stage.

In 1973 a World Health Organisation (WHO) Expert Committee reviewed 25 control programmes or pilot projects, based on various combinations of approaches. Snail control by molluscicides only resulted in lowering the prevalence of infection. This approach has disadvantages, mainly economic and toxicity to mammals (Pitchford (1962)). Clarke and Shiff (1968) report success from snail control in Rhodesia. Pitchford (1966) in South Africa favours environmental modification, although this is costly and slow. Walker, Walker and Richardson (1970) report ineffectivity of some aspects of environmental control. Control by chemotherapy was not considered effective in the past, mainly due to unsuitable schistosomicides (MacDonald (1965)). It has now become more attractive due to improvements in newer schistosomicides. Advantages of this approach are the simultaneous improvement of the health of the individual and the curbing of transmission in the community.

PROGNOSIS OF BILHARZIASIS ON SUBCONTINENT

Bilharziasis is recognised on a world basis as an increasingly debilitating medical and economic problem (Wright (1968)), and deserving of more effort at control (WHO (1967: 1973)). WHO in 1975 began to establish regional laboratories for eradication of 7 tropical diseases including bilharziasis. On the subcontinent it has become recognised as an occupational hazard to agricultural workers, while the sequelae are recognised as becoming increasingly serious (Prates (1961): Gelfand (1968): Gear (1974): Bhagwandeen (1973)).

Need exists for well planned study on chemotherapeutics

Extensive research reveals that essential data are lacking in most previous chemotherapeutic projects, and that there were disadvantages in the older schistosomicides used, as these were far more toxic and not as easily administered as those now available. Also no large-scale project covering several years has been reported from the subcontinent. A well planned project based on therapy alone, or in conjunction with other control measures conducted in statistically

significant numbers over a long enough period would show the feasibility of using such measures for the control or eradication of bilharziasis from the large communities affected by the disease.

PLANNING, METHODS AND RESULTS OF PRELIMINARY INVESTIGATION

Two areas were chosen for the study because of accessibility, stability of population and prevalence of the disease; the first, Philadelphia Mission at Dennilton to serve as a small pilot project, and the second at Limpopo Irrigation Scheme in Mozambique as the large-scale project. At Dennilton two groups "A" and "B" consisting of 106 patients participated for about 8 months while the Limpopo project involved the total settled community of some 7 400 persons over a period of 10 years.

Specimens of urine and faeces were taken from the Limpopo community on twenty-four occasions in 10 years. Specimens were prepared and microscopically examined to establish which persons were infected. These then received therapy. Some rectal biopsies were taken to confirm diagnostic findings. Haematology and blood biochemistry studies were carried out on limited groups where specific schistosomicides were used. At Dennilton the two groups tested and treated were intensively followed up in the same way for a shorter period.

A total of 163 000 urine and stool specimens were examined during the years 1963 - 1972; 1 108 of these were done personally. Twenty-thousand therapies were administered using four different schistosomicides, mainly in the Winthrop thioxanthenone series WIN 4 304, WIN 13 820 (becanthone), WIN 24 933-2 (hycanthone) and Ciba's nitrothiazole, administered parenterally and orally. The administration of 1 700 therapies was personally supervised.

Five components were examined in 12 050 haematology tests, plus the same number of blood biochemistry tests; of which 1 707 were done personally.

Results of the preliminary studies (pre-treatment) were:-

total prevalence at Limpopo was 23% with a bias of highest infections towards males in the lower ages

in both ethnic groups. Africans had a much higher prevalence than Caucasians, especially amongst females. S. haematobium infections predominated over S. mansoni. Individual egg counts from patients were higher in the Africans than in Caucasians, showing a higher intensity of the disease. Haematuria was also higher. At Dennilton the prevalence for Africans was about the same as for the African group at Limpopo, with the same high intensity of infection, and severe haematuria in most patients;

haematology studies, including sedimentation rates, haemoglobin concentration, mean corpuscular haemoglobin concentration (MCHC), haemocrit and eosinophile counts, did not vary significantly from accepted values for both groups at Limpopo and for Africans at Dennilton. Sedimentation rates were highest for Africans, and both ethnic groups had raised eosinophile counts;

blood biochemistry studies included tests for Bilirubin, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), and in some cases Serum Urea Nitrogen (SUN). Frequency distribution for all tests were over 90% within the accepted range of normal values, with Africans having slightly higher values for SGOT and Bilirubin tests.

Comparison of the study groups with Africans surveyed by Walker et al (1970) at Komatipoort showed that overall prevalence of infection at Dennilton resembled that at Komatipoort, while the prevalence in Africans at Limpopo was slightly less. Prevalence in the Caucasians at Limpopo was about one-third of the prevalence amongst the other African groups.

Infection was highest in Africans in the puberty-adolescent age group, in the Caucasians in the juvenile-adolescent age range. Except for African females at Limpopo there was a male bias for high rates of infection in all study groups.

Mean egg counts for African males at Dennilton and at Limpopo were similar. These groups had lower counts than those at Komatipoort. Caucasians at Limpopo had relatively low egg counts.

Haematuria was heaviest at Dennilton, but at both study centres haematuria was heavier than at Komatipoort. All urine specimens at the two study centres had some range of turbidity. No correlation existed between grades of haematuria and egg counts.

The haematology studies indicated that sedimentation rates were lower for both ethnic groups at Limpopo than at Komatipoort, with some high values in Caucasians with S. mansoni and mixed infections. All values for other tests were within the normal range of values with no apparent anaemia found anywhere.

Mean eosinophile rates were higher amongst all Africans than in Caucasians.

ASSESSMENT OF RESULTS OF CHEMOTHERAPY IN STUDY AREAS

The results of mass chemotherapy can be divided into short and long-term categories.

Assessment of the short-term results of chemotherapy in the study areas as compared with results obtained in similar short-term studies in Swaziland was as follows:-

> No haematology or biochemical studies were carried out in Swaziland. However, the results for the study areas of Limpopo and Dennilton did not show greatly significant changes for haematology values before or after treatment, as compared with the accepted normal values for healthy individuals. There was some speed-up in sedimentation rates at about one month after treatment and white blood cell counts (WBC) rose after a week in patients treated at Dennilton with subsequent decrease some time afterwards.
>
> Transaminases studies did not show much divergence, pre- or post-treatment, from accepted normal values

for either study area. It could be that the tests employed are not sensitive enough to record significant changes. The disease, or the drugs used may not have, in fact, upset the biochemical balance of treated patients sufficiently for this to become apparent.

There appears to be a very good response to therapy. About 80% patients became negative for viable eggs usually one month after treatment. This trend was maintained or even increased for Dennilton Group "A" and for the Limpopo where nearly all patients treated became negative within 3 months and remained so for 6 - 8 months after treatment. For Swaziland the trend was a little different as an increasing number of patients again became positive for viable eggs over a similar period.

MacDonald (1965) calculated the probabilities of success of four apparently equivalent control measures. He showed that reduction of contamination and exposure would be too inefficient and slow to influence transmission, this has been experienced at Limpopo, where each family had a piped water supply and waterborne sewerage, yet the disease prevalence remained at 231 per 1 000. Mass chemotherapy alone was responsible for reducing the mean prevalence from 231 to 77 per 1 000 within 4 months, and maintained this rate over considerable periods of time by sequential treatment. Later when periodic snail control was combined with therapy prevalence was reduced to its lowest point, 33 per 1 000. Based on the new infection rate during the early years of control, the prevalence would have doubled itself in 10 years in the absence of control by chemotherapy and later by chemotherapy plus molluscicides. MacDonald (1965) considered that a reduction of prevalence in a population to 10% was the breakpoint from where reduction could proceed to eradication within 4 - 5 years. However, at Limpopo eradication was not complete after 10 years although the prevalence had been reduced to 8%.

The external appearance of eggs excreted changed after treatment. These were seen to be dead and deformed in urine specimens and rectal biopsies. Some dead and black eggs continued to be excreted in urine, a normal occurrence after successful treatment as confirmed by Weber, Blair and Clarke (1969), and Jordan (1967). By standards used elsewhere, where the degree of success was judged by interrupted egg laying (MacDonald, Clarke, Gaddie and Atkinson (1968)), control by chemotherapy at Limpopo was successful, excepting for the group of older African women, in whom reduction in egg excretion had not yet reached the breakpoint, and the parasite pool continued. The schistosomicide used at Dennilton and Limpopo was hycanthone, far superior to any available to MacDonald in 1965. He maintained that therapy to be successful as a control measure must be systematic, regular and supplemented by other intensive measures to reach the breakpoint and proceed on to eradication. This was true for Limpopo.

The advantages of chemotherapy were found to be ease and speed of administration of the new schistosomicides used, particularly hycanthone in a single parenteral shot and ambilhar in an oral course, when compared with the longer courses needed for the antimonials accompanied by greater risks and lower cure rates.

Some of the negative factors obscuring priority rating for control of the disease are firstly the physical tolerance or lack of external manifestations in many sufferers. The dangers of treatment based on the peculiar intravascular and intratissue parasitosis has also resulted in a cautious approach. So has the long list of natural contraindications to treatment, the chief being an acute tender liver. Liver disease of many causes is common in the African, and its presence must be heeded in chemotherapy. For this reason polypharmacy during treatment, including use of hepatotoxic drugs, must be avoided. Another factor influencing the official attitude to therapy is the possibility of a cured person becoming reinfected on immediate return to an endemic area, with possibility of "lost immunity" after his worm load is killed off. At Limpopo and Dennilton it has been shown that the possibility of reinfection can be discarded for at least 6 - 8 months after therapy. Work elsewhere (Jordan (1967): Cook, Jordan and Bartholomew (1975)) confirms the existence of a re-infection-free period of even longer duration following successful

therapy. This gives time in which to space sequential therapy at economic intervals. One of the most important factors to contend with in the control of bilharziasis is that the disease increases with efforts to improve the agronomy. The great man-made lakes of Africa, of vital importance to the population, have all increased the health problems, including bilharziasis.

In the absence of statistics on the subject the economic impact of the disease on the national productivity of the population of Southern Africa is difficult to determine. However, it has already been estimated that there are 11,25 million sufferers and that about one-third of the subcontinent is endemic to bilharziasis. An estimate of losses based on two days per annum by each person sick from bilharziasis shows that the total loss on the subcontinent could amount to US $ 71 337 500. Compare this estimate with estimates of losses calculated by Wright (1968) of $ 445 866 945 for all Africa, and $ 641 790 130 for the world. The cost of the 10 years control programme for Limpopo was approximately US $ 1,95 per person protected: the short-term therapy at Dennilton cost about $ 3,07 per person treated.

FUTURE DEVELOPMENT AND INVESTIGATIONS

Future development of control measures could be by application and intensification of environmental and social improvement, research and development of new schistosomicides and molluscicides and the development of an effective vaccine. Adaption of biological control to local conditions would be of secondary importance.

Suggestions for future investigations are as follows:-

a) To establish the priority of bilharziasis as a debilitating disease, parallel studies should be set up in different parts of Africa.

b) Groups observed in the past, studied by Powell (1967) and Walker et al (1970) and others should be studied again to determine the progressive results of the disease.

c) Intensive study of all schistosome species, avian, animal and human, *in situ* if possible, to establish disease response and determine its relation to worm load. This could possibly accelerate the discovery of the immunological response from which a vaccine may result.

CHAPTER 1

INTRODUCTION

1.1 BILHARZIASIS AS A WORLD PROBLEM

There can be no doubt that bilharziasis is at present one of the most important problems in tropical medicine, if only considered in terms of total numbers of sufferers.

Wright (1968) states in a global appreciation that bilharziasis is endemic in 71 Countries or islands having a total population of 1 362 million. Of this total 592 million are exposed with about 124 million actually infected.

On the African Continent alone he estimates that 226 million are exposed to infection out of a total population of 308 million. He calculates 91 million are actually infected. On the basis of these figures the problem is indeed formidable on a world-wide front. Refer to Table 1 "Bilharziasis: World, Africa and Subcontinental Populations at Risk", page 3.

1.2 THE PROBLEM AS RELATED TO THE AFRICAN SUBCONTINENT

Included in the study are all African countries south of approximately 7^{o} lat, as follows:-

Angola	Republic of South Africa
Botswana	Rhodesia
Lesotho	Swaziland
Malawi	Zambia
Mozambique	

This will be referred to as the "subcontinent".

HISTORICAL NOTE

From the earliest publications of Harley (1864) setting out the cause of endemic haematuria in the Cape and Natal to the present day, many prominent investigators in South Africa have recorded their data on several aspects of the disease and many international congresses held here have made contributions to the understanding of the disease. (See Annexure "A" Listing of prominent early South African authors). Yet basic data on the epidemiology and pathology of bilharziasis is still incomplete. In these circumstances some quantifications on the importance of the infection are justified to provide a basis for priority.

TABLE 1

BILHARZIASIS

WORLD, AFRICA AND SUBCONTINENTAL POPULATIONS AT RISK, IN MILLIONS

	REGION	POPULATION	EXPOSED	INCIDENCE % RANGE	INFECTED
(1)	WORLD	1 362	592		124
(1)	AFRICA	308	226		91
(2)	SUBCONTINENT				
	Malawi	4½ (1965)	3½	(60/100)	2¾
	Mozambique	8 (1970)	3	(23/100)	1¾
	Rhodesia	5½ (1971)	3½	(15/90)	1¾
	Republic of South Africa	22 (1971)	6	(5/95)	2¾
	Zambia	4 (1970)	2½	(3/60)	¾
	Angola	6 (1970)	2	(7/60)	¾
	All Other States	5½ (Est.)	1½	(2/60)	½
	TOTAL FOR SUBCONTINENT	55½	22	-	11½

(1) Taken from Wright (1968)

(2) Quantifications based on personal communications

1.2.1 THE SUBCONTINENTAL CONTEXT

Table 1 on page 3 shows quantifications, based on personal communications, for the study area on the subcontinent. Approximately 22 million persons, in a total population of 55,5 million, are exposed to bilharzial infection, while 11,25 million can be considered as infected.

A further breakdown of prevalence of the disease by Country gives an insight into the problem on a national basis.

Republic of South Africa

An estimated 2,25 million persons are infected out of a total population of 22 million (1973). The incidence of both forms of the disease may range from 3% - 80% in endemic areas.

Porter (1938) was the first to outline the endemic areas. (See Annexure "B" Bilharziasis: Distribution according to Porter 1920 - 1938). Unfortunately, most early work does not give actual prevalence in the various areas. Porter defined these by vector snails shedding cercariae. According to her distribution of S. haematobium in the Cape was restricted to the Eastern Province with heaviest infections at Port Elizabeth and King William's Town. All but the mountain areas of Natal were infected with S. haematobium. The heaviest infections were found near Durban along the North and South Coast coinciding with the agricultural and sugar growing areas. The most heavy and extensive S. haematobium infections in the Transvaal were reported from the Limpopo and Crocodile River systems. No infection was found in the Vaal River basin or on the Witwatersrand, although S. haematobium was reported from Krugersdorp, Klipspruit and Muldersdrift.

She also established that S. mansoni infections in Natal were present in Durban, Umvoti, Verulum and Tongaat, and in the Transvaal at Brakpan (an obvious error) and Oogies River at Onderstepoort. The sparse distribution of this species was thought to be due to its recent introduction into the Southern part of the subcontinent.

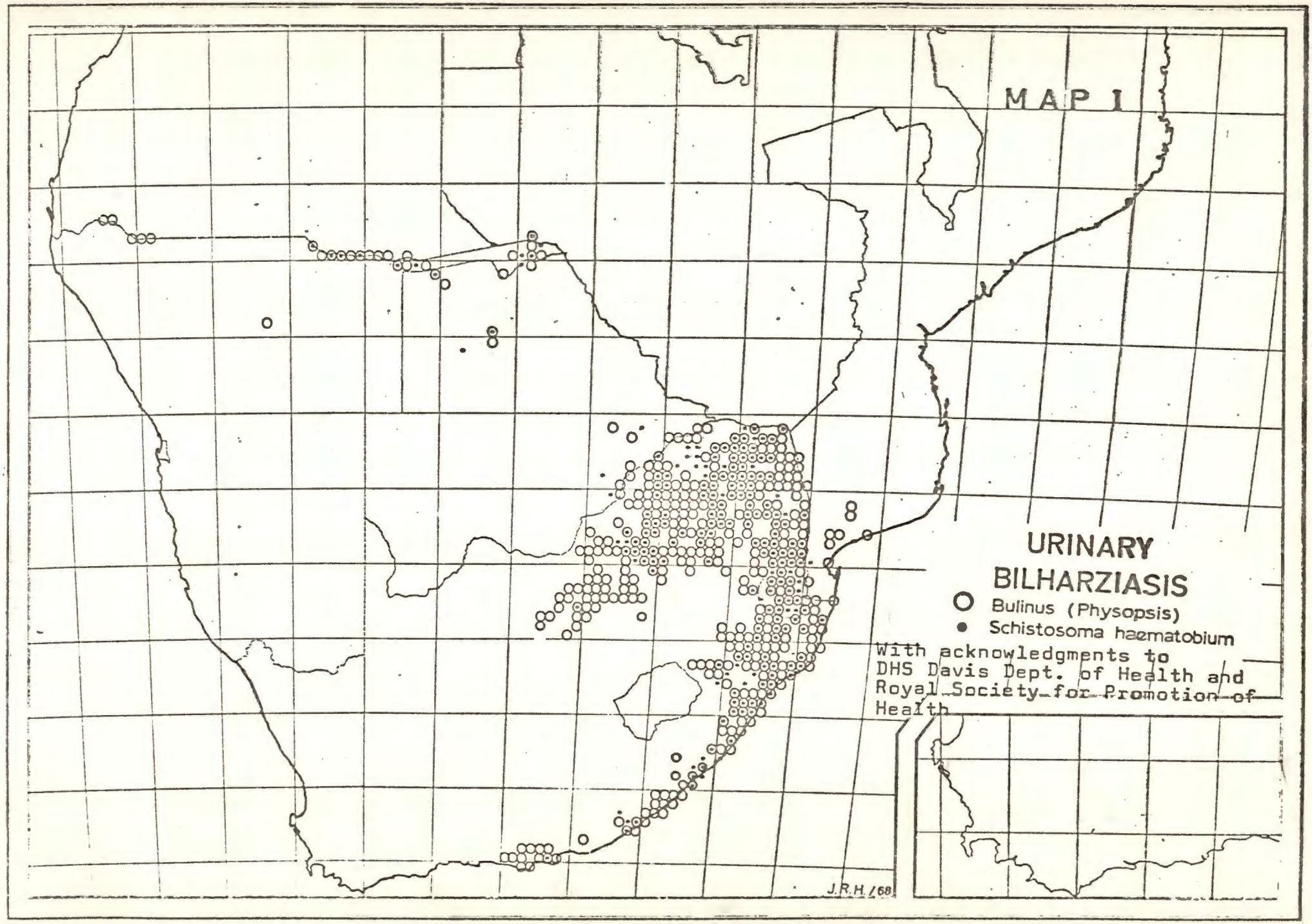
Cawston (1930) and Porter (1938) reported finding S. japonicum near Durban. Both thought this to be an accidental occurrence, and was probably a spurious infection of S. margriebowei.

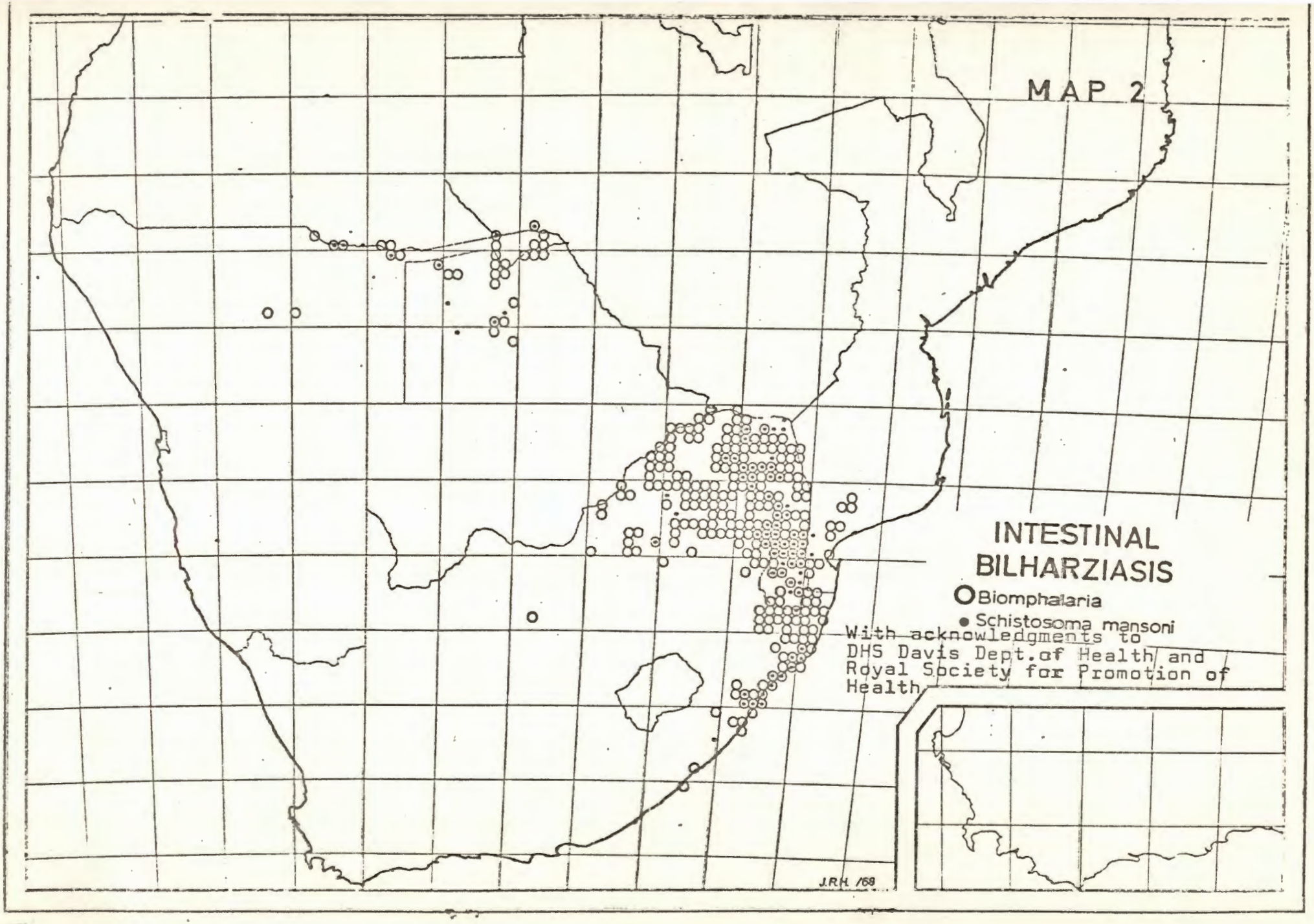
According to Pitchford and Geldenhuys (1960): Pitchford (1968) and

Davis (1968), present day distribution of S. haematobium infections follow this outline with small variations and only slight geographical extensions, although decreasing prevalence of both species have been reported from the areas round Umtata, King William's Town, Uitenhage and Humansdorp. Refer to Maps 1 and 2 on pages 6 and 7 outlining present distribution of snail vectors and bilharzial infections of both species. According to Davis (1968) snail vectors of S. haematobium have a larger distribution than the disease, but follow Porter's delineations with some new areas on the Vaal tributaries. Geographical distribution of S. mansoni infections have increased throughout the lowveld of the Transvaal and coast of Natal up to the borders of the Transkei. The snail vectors of S. mansoni, being more susceptible to extremes of climate, are more limited in distribution than those of S. haematobium.

A further spread of vector snails and disease would be related to extension of human activity, although Pitchford and Visser's (1969) investigations show this to be unlikely to happen in the new catchment areas constructed on the Orange River. In spite of lack of comprehensive data, it is felt on clinical grounds that the prevalence and pathology of S. haematobium are increasing (personal communications (1963 - 1969)). Only in the tail end of infection towards the Transkei has any recession of the disease occurred (Pitchford and Geldenhuys (1960)). Surveys carried out during 1963 - 1969 while monitoring clinical trials on groups of school children in endemic areas confirm these observations. Pitchford (1968) remarked that the "Schistosomes are experiencing a population explosion".

Never has there been such a divergence of medical opinion on the importance of a disease which all research workers admit has the greatest distribution of all tropical diseases. The Symmers liver and Cor Pulmonale are not commonly reported (Bnagwandeen (1964): Schneider (1970): Winship et al (1969)). Diffuse lesions in the urinary tract and calcification of the bladder are far more common (Bhagwandeen (1967): Kisner (1952)). Hydronephrosis and renal failure may be responsible for the severe results of obstructive uropathy seen, although secondary infection has also to be considered. Large numbers of individual focal lesions in genitalia and elsewhere are reported in both male and female patients (Gibson (1925): Charlewood et al (1949): Jopling (1958): Schneider (1970)). Bilharzial allergy


MAP I
URINARY
BILHARZIASIS
Bulinus (Physopsis)
Schistosoma haematobium
With acknowledgments to
DHS Davis Dept. of Health and
Royal Society for Promotion of
Health
J.R.H./68


MAP 2
INTESTINAL BILHARZIASIS
Biomphalaria
Schistosoma mansoni
With acknowledgments to DHS Davis Dept.of Health and Royal Society for Promotion of Health
J.R.H. /68

(Katayama Syndrome) is thought to be uncommon (Lurie (1953): Walt (1954): Lachman (1961)). Physical fitness and intelligence are not impaired according to Walker et al (1970), nor can any deaths be directly attributed to the disease (Powell (1967): Walker et al (1970)). Physicians such as Powell (1967) contend that bilharziasis is not a serious disease. Surgeons and urologists as Winship et al (1969) and Kisner (1952) agree that it is. All accept that the existing data is inadequate.

RHODESIA

From Rhodesia there is more positive evidence in the literature published of the grave sequelae of bilharziasis. Data compiled from personal communications (1963 - 1969) show that the prevalence of both forms of the disease is about 30% throughout the Country. This confirms early observations made by Turner in 1908. The pathology is far more serious than that attributed to the disease in South Africa (Gelfand (1968): Simpson (1965): Harvey et al (1960): Dukes et al (1970): Kingsley (1969): Levy et al (1969): Clarke et al (1970): Zilberg (1970)). Gelfand and these authors have published in detail the results of bilharzial infection, but make some distinction between pathology as seen in whites and in blacks, the latter having more grave sequelae.

MOZAMBIQUE

The prevalence of infection in Mozambique, as estimated from personal communications (1963 - 1969), exceeds 22%. S. haematobium infections are more prevalent than S. mansoni. Turner (1908) reported an overall prevalence of 25,8% S. haematobium infection in mine labourers recruited from the "East Coast". There is lack of detailed data on pathology. Prates (1948: 1961) and Prates and Gillman (1959) consider this to be serious and commented that the relationship between bladder carcinoma and calcification of this organ in Mozambique was significant.

MALAWI

An estimate of the prevalence of infection, based on personal

communications (1963 - 1969) in Malawi is 61%, with perhaps close parity in both infections. Turner (1908) had already reported 36,3% infections of S. haematobium in mine labourers recruited from the Lake, while Wiltshire (1925) found an incidence of 16% S. mansoni. There are no publications dealing specifically with the pathology of bilharziasis in Malawi.

ZAMBIA

The overall prevalence of bilharziasis as based on personal communications (1963 - 1969) is estimated to be 19%. Statements published by the Ministry of Health (1974) place this between 20% - 80% in teenagers for S. haematobium, and Henderson (1969) reported a prevalence of 57,7% for S. mansoni in limited studies. Published data on pathology is scant. Bhagwandeen (1973) reported bilharzial pipestem portal fibrosis from necropsy studies, although previously both Gore (1968) and Fine (1969) concluded that bilharzial disease was of no consequence in Zambia.

ANGOLA

Prevalence of the disease is thought to be sporadic throughout Angola, amounting to 12% Countrywise as estimated on personal communications (1963 - 1969). Several local foci have high incidences. Some pure S. mansoni foci exist, otherwise there is a preponderance of S. haematobium. There is a lack of published data on pathology, though this could be severe when coupled with high incidences of S. mansoni.

SWAZILAND

Swaziland has a high incidence related to severe pathology which resembles that found in South Africa.

Turner (1908) found a prevalence of 18,1% in labourers recruited from Swaziland. Eastman-Nagle (1956) found 23 - 70% S. haematobium and 22 - 46% S. mansoni infections in surveys carried out in the middleveld and lowveld. Pitchford (1958) found incidences ranging

from 3 - 75%, related to water surfaces, for S. haematobium with lower rates for S. mansoni.

Other countries (South West Africa, Botswana, Lesotho)

Since desert or adverse climatic conditions exist over the remainder of the subcontinent, only isolated foci of infections are found there, associated with waterholes or along a few permanent waterways and swamps. Lesotho can be stated as the only Country free from bilharzial infection on the subcontinent.

1.3 STATUS OF THE DISEASE ON SUBCONTINENT

In 1967 an international group of experts under the auspices of World Health Organisation (WHO) introduced the subject of assessment of the importance of bilharziasis as follows:-

> "Basically, the evaluation of the public health importance of any disease is different; the difficulty is increased when the condition is not solely characterised by acute readily recognisable aspects of disability which can be counted and measured, and it is worsened when disease typically occurs in places not well served by hospitals and pathological services".

We are still faced with basic lack of essential data on bilharziasis. Expert opinions still disagree or contradict each other outright on the importance of infection. Often such opinions are based on meagre evidence or limited studies which relate only to specific areas or conditions.

However, an assessment of available data which have already been briefly reviewed will be made.

1.3.1 PARAMETERS OF ASSESSMENT

PREVALENCE AND DISTRIBUTION

Prevalence rates of the disease for the subcontinent, where these exist, have been determined for small areas and groups, such as pupils attending local schools. They are sometimes based on the examination of single specimens of urine or faeces only. (See Annexure "C" Bilharziasis: Prevalence, according to published data).

Quantifications based on these factors have shown that of the subcontinent's total population of 55,5 million people, 22 million are exposed to the danger of infection, and of these 11,25 million persons could be actively suffering from bilharziasis. (Table 1, page 3).

One person in every five could be infected on the subcontinent. Wright estimated in 1968 that 91 million persons on the African Continent were infected with bilharziasis. The 11,25 million sufferers estimated for the study area on the subcontinent would then be 11% of all sufferers in Africa, including those present in heavily infected Egypt.

According to quantifications, based on personal communications (1963 - 1969), which have already been discussed, the most heavily infected Country on the subcontinent is considered to be Malawi with 61% sufferers out of a population of 4,5 million. This is followed by Rhodesia with 32% and Mozambique with 22%.

It is estimated that there are 2,75 million infected persons in the Republic of South Africa. This compares with the number infected in Malawi.

These two Countries each have the greatest number of actual sufferers on the subcontinent, although the Republic, with a larger population, has a lower percentage prevalence. Swaziland is relatively heavily infected.

Least affected are Lesotho, South West Africa and Botswana.

The geographical distribution of the disease is sketched out in previous discussions for the subcontinent. Collectively the area endemic to bilharziasis is impressive. Refer to Table 2 "Bilharziasis: Habitable, as related to endemic areas on the subcontinent", page 12. An estimate makes this over 1,5 million km^2.

TABLE 2

BILHARZIASIS

HABITABLE, AS RELATED TO ENDEMIC AREAS ON THE SUBCONTINENT

	Infected Area
Mozambique	540 000
Zambia	350 000
Republic of South Africa	270 000
Rhodesia	210 000
Malawi	120 000
Angola	120 000
Swaziland	22 100
Botswana	20 000
South West Africa	9 000
Lesotho	-
	1 661 100 km^2

Total Area	5 500 000
Desert Areas	160 000
Habitable Areas	5 340 000 km^2

According to quantifications based on personal communications (1963 - 1969)

When the desert and other arid areas of the Namib, the Kalahari and the Karoo are excluded because of absence of suitable water surfaces, it becomes obvious that bilharziasis casts a deep shadow over the most fertile parts of Southern Africa where human populations are most concentrated.

A breakdown of the total figure shows that Mozambique and Zambia have the greatest areas affected by the disease (540 000 and 350 000 km^2); followed by South Africa and Rhodesia (270 000 and 210 000 km^2), then comes Malawi (a small Country) and Angola, each with 120 000 km^2. Swaziland, Botswana and South West Africa have the smallest endemic areas (22 000, 20 000, 9 000 km^2), while Lesotho has none.

When surveyed collectively the problem is formidable. Of a total population of 55,5 million on the subcontinent, nearly half are living in or near endemic areas and are exposed to infection.

Of the total population 20% or 11,25 million suffer from the disease in various degrees.

In terms of land area endemic to the disease the situation is just as depressing. Of the total habitable area comprising 5 340 000 km^2 about 1 661 100 km^2 are within the endemic area, i.e., nearly 31% of the human habitable area is endemic for bilharziasis.

Dramatic evidence of expansion and increased prevalence

At the turn of the Century, Turner (1908) examining labourers recruited for the Witwatersrand Gold Mines, tried to define areas where urinary bilharziasis was found, while several early reports on urinary infection in British soldiers serving mainly in the Cape of Good Hope were made about the same time (Felkin (1895): Stock (1906): Temple-Mursell et al (1908)). Porter (1938) outlined the geographical distribution of the two forms of infection in the Republic of South Africa.

Since then there has been dramatic evidence of the geographical expansion of vector snails and increasing rates of prevalence of S. mansoni in South Africa. In 1908 Turner stated that there was some mansoni infection present, but that it was confined to the lowveld. Cawston in 1930 stated in his opinion this form of the

disease had been seen only after local troops had returned from foreign service in Egypt.

Orenstein (1930), Holland (1934), Rijper (1934), and Porter (1938) all stated S. mansoni was rarely found. Only after 1940 did Gear (1941), Kark et al (1944), and de Meillon (1948) determine increases in prevalence of S. mansoni infections. Annecke and Peacock (1951), Pitchford (1952), and Annecke et al (1955) have confirmed this increased distribution and prevalence (See Annexure "E" Bilharziasis: Evidence of increase of S. mansoni in South Africa).

No data exist for any other Country to serve as a base line to judge the movement of the disease, and recent surveys are not sufficient or extensive enough to give data for accurate comparison.

Data which have already been discussed can be used to describe the problem in terms of saturation as related to prevalence and distribution for the various Countries.

TABLE 3

BILHARZIASIS

Status of prevalence and distribution
Listed by Country

Country	Incidence	Distribution
Mozambique	saturated:	saturated:
Malawi	saturated:	saturated:
Rhodesia	saturated in endemic areas but could move into new areas	not saturated: possibility for expansion in new irrigation areas
South Africa	not saturated:	saturated: with little opportunity of expansion to new area
Zambia	not saturated:	not saturated:
Swaziland	not saturated: but nearing this	not saturated: but nearing this
Angola	not saturated: relatively small areas suitable	not saturated: relatively small areas
Botswana	not saturated:	confined to definite area
South West Africa	not saturated:	small local areas
Lesotho	Nil (few imported cases)	Nil

MAGNITUDE OF PROBLEM AS EXPRESSED IN DISABILITY AND SUFFERING

Some aspects of the problem as expressed in disability and suffering on the part of the individual have already been discussed in reference to pathology of the disease where available for a few Countries.

Data on morbidity of bilharziasis on the subcontinent are scant, a little more is available in individual publications on organ involvement. Some appreciation of disability and suffering may be based on these.

For the Countries most seriously affected some references are available. Prates (1948: 1961) and Prates and Gillman (1959) discourse on the seriousness of organ involvement in bilharziasis as found in Mozambique, particularly in regard to the possibility of carcinoma of the bladder. These observations have been confirmed by Fraga de Asevedo et al (1957).

For Malawi there is little published data available. However, personal communications from Bijl (1970) and Tozer (1970) confirm that there is serious organ involvement in patients seen and autopsies carried out in Blantyre.

Gelfand (1974) presents the greatest amount of detailed pathology data on record, for Rhodesia, to substantiate his emphatic statement that bilharziasis is a serious disorder there. He gives data on extensive organ involvement much of which he maintains is irrevocable. He quotes a 1,1% incidence for Symmers liver, mentions the presence of bilharzial lung disease and Cor Pulmonale, diffuse lesions in the urinary tract, including bladder calcification (4,8%), the morbidity of chronic bilharziasis and hydronephrosis and the possibility of renal failure as a result of untreated cases. Recently there has also been published data on the increase of Katayama Syndrome caused by S. mansoni infection, which approaches epidemic proportions. (Clarke et al (1970): Zilberg (1970)).

The morbidity of bilharziasis in South Africa is the subject of serious dispute. Craib (1968) considers that claims of crippling effects of bilharziasis have not been substantiated. Elsdon-Dew (1947: 1958) supports these views. Powell (1967) denies that the pathology of bilharziasis in the Durban area is serious and gives evidence that it is a self limiting disease, with possibility of

reversal of early sequelae in later life, but admits that it has the largest admission rate at King George's Hospital. Walker et al (1970) support Powell's statements in assessing the bilharzial problem in the Transvaal lowveld. Condemning evidence against the disease comes from surgeons, urologists and pathologists. Kark (1962), Chapman (1964), Kisner (1952: 1964) and Vermooten (1937) maintain the seriousness of ureter and kidney involvement which does not resolve in later years. Bhagwandeen (1964) gives data from autopsies and necropsies that it should be regarded seriously. Gear (1974) supports this vein and states that it is serious even though may be only for a minority who become infected.

The remainder of the Countries have little published data on the description of pathology of the disease, except Zambia. There Bhagwandeen (1973) has described serious sequelae of bilharziasis from necropsy studies, although Gore (1968) and Fine (1969) had previously denied serious sequelae existed.

1.3.2 CONCLUSION

With 11,5 million infected persons living on 1 661 100 km^2 of the subcontinent there can be very little argument against the provision of measures aimed at the curbing of such a disease, even though ".....only a minority develop serious signs and symptoms" (Gear (1974)), as this minority can amount to a considerable number of human beings proportionately to the 11,5 million sick.

While the geographical distribution of S. haematobium has remained constant in some areas of the subcontinent during the past 50 years, in other areas it has spread to man-made water surfaces, with rising rates of prevalence and increasing pathogenicity. The more severe form of the disease, S. mansoni, has in the same time not only greatly increased in prevalence but has been introduced into extensive new areas with changing ecological conditions. Whereas the schistosome worm load may have become stabilised in the black population after many centuries of infection resulting in some simbiosis, today this balance is rapidly becoming upset with increases in water conservation and irrigation farming until bilharziasis must be regarded as an economic hazard and an occupational risk in the agronomy of all countries on the sub-continent. Furthermore, in a water-hungry land where large

artificial lakes are being created the non-infected urbanised population is placing itself at increased risk by using these potential infection foci for recreational purposes.

With the possibility of increased prevalence of infection and severity of the disease, linked with the need for expanding food production, a method of eradication or control of bilharziasis has become urgent.

1.4 CONTROL IS FEASIBLE

For all the negative probabilities the logistics for schistosome population maintenance and increase are simple and depend on the necessity for some human excreta containing schistosome ova to reach dense vector snail populations co-existing with large concentrations of people.

Control measures can be aimed at breaking this sequence of happenings in the easiest and quickest manner.

MacDonald (1965) constructed a model to assess the effectiveness of control by reference to a curve showing the progress of the calculated mean worm load of a theoretical population living within the area of a particular control measure. Hypothetical progress of one of four apparently equivalent control measures, i.e., reduction of contamination, reduction of snails, reduction of exposure and treatment associated with less exposure or less snails, can be measured on the curve. The contrast is based on the reduction of one of the factors involved to 1/5 of its original value. He concluded that the effect of reducing excretal contamination to 1/5 its former volume would be almost negligible over 20 years. Control of exposure by persons to infected water to the same degree would also take a period of time, whereas reduction of snail populations would be equally effective, without coercion of the population or disturbing the traditional behaviour patterns. The fourth, that of chemotherapy had not been adequately assessed at that time.

He stated "The mass treatment of human infections seems, in the abstract, a promising means for bilharziasis control, but alone it would not be effective under present conditions. The available drugs cannot be counted upon to eradicate human infections in a

large enough population of persons treated". This opinion was expressed in 1965; since then the synthesis and development of more efficient and easily administered schistosomicides changed the prospects of chemotherapy as a potentially effective control measure.

The rationale of placing emphasis on chemotherapy as a control measure, but not ignoring other pertinent factors of possible control measures, would rest on consideration of the role humans play in perpetuating the schistosome life cycle.

It seems logical to free the human patient from his parasite pool by reducing the longevity of the worm, thus improving his own state of health and at the same time preventing further infection of snail hosts by suppression of egg excretion. Reduction in numbers of the snail host would assist to cut the cycle. Prevention of pollution of water by human excreta (or modification of the environment), would control the aquatic life cycle of the schistosome. All these methods could be adjuncts to control, should the new chemotherapeutic agents prove effective.

Abdalla (1961) stated that eradication was not feasible, and that control efforts should be aimed at infection foci to reduce the prevalence of bilharziasis, to a point where it is no longer a major health problem, including the prevention of transmission by reduction of the load of infection in the affected people. However, he mentioned that to date no prophylactic drug was available, health education fell short, and molluscicide programmes have not yet proved their effect on transmission.

1.4.1 ASSESSMENT OF CONTROL METHODS REPORTED IN LITERATURE

In 1973 a WHO Expert Committee reviewed some 25 control programmes or pilot projects, almost all open to some criticism on lack of evaluation or comparison data, an almost inherent condition in all work done for control of bilharziasis in the past.

Six of these control projects used only molluscicides, four attempts were by chemotherapy alone, some by use of environmental modification, and several combined two or more control measures.

CONTROL BY MOLLUSCICIDES

The WHO Expert Committee (1973) review referred to analysed results of five control programmes based only on molluscicides. Results were based on theprevalence of infection as an indicator of change that responds most rapidly and because data on this was available. The analysis shows that all five projects had a clear impact on lowering the prevalence ofinfection.

TABLE 4

CONTROL BY MOLLUSCICIDES ALONE
REDUCTION IN PERCENTAGE PREVALENCE OF BILHARZIASIS

Country	Species of Schistosome	Molluscicide	Relative % After 1 Year	Incidence % After 2 Years
Ghana	S. haematobium	niclosamide	41	34
Tanzania	S. haematobium	niclosamide	90	49
Egypt	S. haematobium	niclosamide	32	36
Egypt	S. mansoni	niclosamide	73	22
Japan	S. japonicum	sodium penta-chlorophenate	14 - 20	0

Adapted from W.H.O. Tech.Series 515

In addition to the data given above the results on similar mollusciciding campaigns available from Rhodesia (Shiff et al (1967)) were given in some detail. These show year to year differences in relative incidence of infection, as well as differences according to the kind of irrigation used. These results do not show such an impact as those for the five quoted above although various degrees of control were established relative to untreated irrigated areas.

Results from other mollusciciding projects reported on were evalued by a variety of other methods. In three instances, Belo Horizonte, Warrag el Arab and Kyle, satisfying decreases in prevalence were obtained.

However, the Expert Committee (1973) speculated on the possibility of a tendency, reported from some sources, for results to

deteriorate after initial success due to various assumed causes.

These examples give convincing evidence of the effectiveness of molluscicididing on reduction of prevalence of transmission which over a long period will have a beneficial effect on public health.

Molluscicides available are shown in Table 5 page 21. Their effectivity, specific mode of action and effects on snails and other inhabitants of water treated, as well as side effects can be gauged from this table.

All molluscicides are poisonous to varying degrees. Depending on concentration they will affect animal and plant life as well as the microfauna and flora of water treated while concentrations remain effectively stable. Their use could also change the snail and other aquatic species population in a treated snail habitat. Their effectiveness against vector snails is determined by concentration depending upon dilution of water volume and flooding. Sunlight and suspended matter in the water treated could also modify effectiveness.

Clarke and Shiff (1968) set out the rationale of bilharziasis control in Rhodesia where snail control operations extended over some 4 000 sq. miles of territory. The rationale is based on the ecological balance between snail, schistosome, and man by influencing population curbs on the snail by means of molluscicides.

The results of control from 1960 - 1966 in the Kyle Dam catchment area has resulted not only in the overall reduction of infection in each age group of the population but more significantly there has been a progressive absence of infection in the younger age groups. Costs were relatively low, but would increase significantly if the technique were to be applied to more intensely watered areas of an irrigation scheme.

Pitchford (1962) strongly opposed the use of molluscicides in the Transvaal lowveld stating "the general use of molluscicides cannot be recommended as a reliable method of reducing bilharziasis ..... and it is doubtful if the method would be more efficient ..... than mass treatment .....".

Endemic areas in the Republic of South Africa and most other Countries are too large and inaccessible for the profitable use of molluscicides. Not only do the important smaller irrigation schemes become reinfected very rapidly, but some evidence exists on the

TABLE 5
SURVEY OF MOLLUSCICIDES AND THEIR PROPERTIES
ADAPTED FROM WHO TECHNICAL SERIES NO.515

Characteristic	Niclosamide	N-trityl morpholine	NaPCP	Yurimin
Active Ingredient	2'5-dichloro-4'-nitro-salicylanide ethanolamine salt	N-trityl-morpholine	sodium penta-chlorophenate	3,5-dibromo 4-hydroxy-4'-nitroazo benzene
Physical properties				
Form of technical material	crystalline solid	crystalline solid	crystalline solid	crystalline solid
Solubility in water	230mg/l (pH dependent)	<1mg/l	33%	very slight
Toxicity				
Snail LC_{90} (mg/lxh)[a]	3-8	0,5-4	20-100	4-5
Snail eggs LC_{90}(mg/lxh)[a]	2-4	240	3-30	-
Cercariae LC_{90}(mg/l)	0,3	No effect	-	-
Fish LC_{90} (mg/l)	0,05-0,3 (LC_{50})	2-4	-	0,16-0,83(L
Rats, acute oral, LD_{50}(mg/kg)	5 000	1 400	40-250	168 (mice)
Herbicidal activity	none	none	none	none
Stability (affected by)				
U.V.Light	no	no	yes	no
Mud, turbidity	yes	no	no	yes
pH	optimum 6-8	yes	no	slight
algae, plants	no	no	no	-
storage	no	no	no	-
Handling qualities				
Safe	yes	yes	varies	yes
Simple	yes	yes	yes	yes

increase of young highly susceptible snail populations which can result in increased transmission regardless of the time of year. Neither can molluscicides solve the problem of polluted water supplies. Earlier on in 1962 Pitchford outlined the reasons for failure of molluscicides used in an attempt to reduce bilharzial prevalence.

Types of irrigation can also influence results, as can temperatures. Prinsloo and van Eedan (1969) have drawn attention to difference of performance of molluscicides on different snail vectors (L. natalensis and B. tropicus) at various temperature levels.

Techniques for the use of molluscicides in overhead spray irrigation areas have still to be perfected.

CONTROL BY ENVIRONMENTAL MODIFICATION

Modification of the environment can be aimed at the elimination or radical alteration of the snail vector habitats. Human behaviour can be modified so as to minimise contamination or exposure to snail infested water.

Good sanitary engineering at the commencement of construction of irrigation schemes could already ensure some measure of success in maintaining snail populations at a low level and could result in control measures being more effective.

Success has been reported in reducing the prevalence of the disease in the Philippines by elimination or reduction of snail habitats. Attempts to change human habits have not been easy, nor has this been shown conclusively to be effective in the control of the disease.

Jordan (1967), reporting on progress of pilot control projects at St.Lucia, states that the prevalence and intensity of S. mansoni infection was markedly reduced with reduction in frequency of human contact with water at streams after a piped water supply had been in operation for 12 months.

Pitchford (1970) gives details of environmental measures used for control on an irrigation farm in the Transvaal lowveld. Piped water had been laid on to villages and swimming facilities provided, while contact with contaminated water had been minimised in various other ways. He reports a gradual decline of S. haematobium and S. mansoni infection rates in school children in these areas, and

in subsequent years children born there showed gradually decreasing infection rates of both parasites.

Walker et al (1970) studied the prevalence of infection at Komatipoort in the Transvaal lowveld. Students enrolled at the African School came from two villages. "The Railway Village" had piped water laid on to three points for each house and was situated about two miles distant from the Komati River, heavily infested with B. africana and B. pfeifferi, vectors of S. haematobium and S. mansoni respectively. The second township, named the "Town Village" had piped water to one central point from which all inhabitants drew water. The nearest river was fenced against game poaching and this acted as a partial human deterrent to access. Prevalence of infection for each village was:-

Railway Village	-	Males (7-8 years)	10% S. haematobium
Town Village	-	Males (7-8 years)	42% S. haematobium

They state that a piped supply of potable water alone does not lower prevalence in an endemic area, this should be supplemented by non-infected water supplies for bathing and recreational purposes to be of value as a factor in reducing transmission.

Pitchford (1958) determined prevalence for various human habitats in the Transvaal. He found that infection rates for S. haematobium in the Eastern Transvaal, a highly endemic area, were independent of whether people lived on reserves, farms or towns, nor were they correlated with living conditions or water supply, as all inhabitants had free access to highly infected natural or irrigation water. With S. mansoni he found that infection rates were low in reserve areas due to scattered population and small streams. However, where people were concentrated along banks of streams with limited water, the rates rose sharply. In irrigation areas rates were high. S. mansoni rates were low in towns with latrines and piped water supplies where streams were more distant.

In Northern Transvaal he found conditions were somewhat similar but with lower rates except for some special places having more limited water sources.

In the arid Western Transvaal where natural water supplies are exceedingly limited serving concentrated populations, the S. haematobium rates are low, with no cases of S. mansoni.

He states that siting of habitations is important and while environmental control is expensive the costs are non-recurrent. The fixtures required consist only of basic water supplies, cheap swimming pools and a certain amount of fencing.

Latrines play very little part in preventing pollution because of the promiscuous excretory habits of the black rural population.

MacDonald as far back as 1965 was critical of the role that "improvement of sanitation" could play as a method of control. He considered that even when a good level in reduction of contamination reaching water had been achieved, the number of miracidiae in such water could remain higher than the number of snails, maintaining an unbroken chain of infection.

CONTROL BY CHEMOTHERAPY

Since 1965 a major development has taken place in chemotherapy which had until then been ineffectual as a control measure because of unsuitable schistosomicides. Several new schistosomicides, superior to those previously available, have now been developed. While none of these can be described as suitable for chemoprophylaxis, they seem to hold promise of successful chemotherapy, far greater than the older type of schistosomicides for which published data report but small measure of success. Refer to Table 7 "Rating of Schistosomicides for Mass Chemotherapy", page 25 (Also refer to Annexure "F" Schistosomicides and their Properties).

The WHO Expert Committee (1973) reported on five attempts to control bilharziasis by the use of schistosomicides alone. Refer to Table 6 "Control by Chemotherapy, Reduction of Percentage Incidence of Bilharziasis", page 24.

TABLE 6

CONTROL BY CHEMOTHERAPY
REDUCTION OF PERCENTAGE PREVALENCE OF BILHARZIASIS

Country	Species	Therapy	% Prevalence before	% Prevalence after-years 1	% Prevalence after-years 3-5
Iran	S. haematobium	niridazole	39	1	14
Brazil	S. mansoni	hycanthone	46	26	-
Egypt	Mixed	tartar emetic) stibophen)		prevalence declined by $\frac{1}{3}$	
Gisa	Mixed	hycanthone	29	20	-

Adapted from W.H.O. Tech.Series 515

TABLE 7

RATING OF SCHISTOSOMICIDES FOR MASS CHEMOTHERAPY*

Property	Type of schisto-somiasis	Antimonials		Nonantimonials			
		antimony sodium tartrate (i.v.)	stibo-captate (i.m.)	niri-dazole	metrifo-nate	lucan-thone hydro-chloride	hycan-thone mesylate
Therapeutic efficacy; cure and associated egg reduction [a]	S. mansoni	++-+++	++-+++	+-++	poor	+-++	++-+++
	S. haematobium	+++	+++	++-+++	++-+++	++	++-+++
Estimated population coverage [b]		+	++	++-+++	++-+++	++-+++	+++
Estimated population tolerance [c]		+	+-++	++-+++	+++	+-++	++
Mode of administration [d]		+	++	++	++ [f]	++	+++
Cost [e]		+++	++	++	++-+++	+-++	+
Overall ranking (sum of ranks for individual properties) [g]	S. mansoni	9	11	12	not applic-able	11	12
	S. haematobium	9	11	13	14	11	12

* Throughout the table, +,++,and +++ signify ranks,1, 2, and 3 respectively.

a+= 0-40%,++=40-75%,+++= 75%.

b Varies markedly with age;+=0-33%,++=34-66%,+++= 66%.

c Varies markedly with age;+=poor, ++=moderate,+++=good.

d+= 10 days,i.v.or i.m.,++=5-10 days, oral or i.m.,+++=short course, no i.v.i.

e+= high,++=moderate,+++=low.

f An exception;spaced doses every 2 weeks x 3.

g Where a range is given the upper rank is taken

Adapted from W.H.O. (1973) Tech.Series No.515

It seems from the small reduction in prevalence after therapy that the results were inconclusive, with the exception of the studies using hycanthone in Brazil and Gisa. These showed promise.

Results obtained in these projects determined by decreasing prevalence as well as several other projects not mentioned here, give the impression that the use of a combination of chemotherapy and molluscicides results in lower prevalence over a shorter period of time than those obtained from all other control methods.

It will be noted that results obtained by use of the modern schistosomicides, hycanthone and niridazole, are far superior to those reported in the past for antimonial compounds. Their use as control measures on a mass scale, either alone or in combination with other methods, should be further investigated.

When the advantages of chemotherapy, either alone or in combination are considered, it is apparent that this method of control merits far greater importance than given it in the past.

1.5 PROGNOSIS OF BILHARZIASIS ON THE SUBCONTINENT

Bilharziasis is a growing medical problem in Southern Africa where it is linked with an expanding agronomy trying to keep pace with a rapidly increasing population. At present an estimated 11,25 million sufferers live on approximately 31% of inhabitable land endemic to the disease on the subcontinent.

Bilharziasis is now considered to be an occupational hazard to irrigation farmers and labourers, and is beginning to affect recreational facilities provided in the new man-made lakes.

Pitchford (1968) states that schistosome populations are increasing, hence worm loads of individual sufferers must be increasing with consequential aggravation of the sequelae of the disease caused by increased ova excretion. The sequelae are considered by Gear (1974), Gelfand (1968), Prates (1961) and Bhagwandeen (1973) to be serious for sufferers, even though these be in the minority of those affected.

Bilharziasis is recognised on a world-wide basis as an increasingly debilitating medical and economic problem (Wright (1968)), and deserving of more effort at control than given at present (WHO

(1967: 1973)). It is the last unchallenged horizon of tropical medicine with a distribution greater than Malaria. The problem is considered so important that WHO has recently (1975) formulated a policy to establish regional research laboratories on a global basis charged with finding solutions to the control or eradication of bilharziasis and other major tropical diseases.

1.5.1 PAUCITY OF DATA FROM PREVIOUS CONTROL PROJECTS

MacDonald (1965) and others (Pitchford (1968): Clarke et al (1968)) reported on extensive research conducted over several years on control measures used in the past, mostly unsuccessful because of time and economic factors involved. He and Abdalla (1970) commented on the lack of efficient chemotherapy agents which limited the useful purpose of this control measure at that time. Since then the development of more efficient and easily administered schistosomicides have changed the prospects of chemotherapy as a potentially effective control measure.

An Expert Committee convened by WHO in 1973 reviewed some 25 control programmes or pilot projects, some dating back more than a decade. Of these four used chemotherapy only, but none were reported from the African subcontinent. The assessment of nearly all was defective because of lack of some basic data either before or after control had begun.

1.5.2 NEED EXISTS FOR WELL PLANNED STUDY ON CHEMOTHERAPEUTICS

A study planned to provide such data was desirable, based chiefly on chemotherapy as a control measure. Sufficient basic data could be collected before the initiation of control measures followed by data which could show trends by comparison, on improvement or otherwise of health standards of the population involved, including short-term effects of the therapy itself on the individual treated. Such a study would have to be conducted on a statistically significant number of persons, followed up for a long enough period of time to indicate the long-term consequences of chemotherapy and other control measures used.

The study would show the feasibility of using chemotherapy now available for either control or eradication of the disease from a community, and for improving the health and well-being of the individual without having toxic side effects. The model developed and results obtained from such a study could be used as an example for large-scale control projects in Southern Africa. This could also be useful for the WHO regional research plans to control or eradicate bilharziasis elsewhere.

CHAPTER 2

PLANNING AND METHODS OF INVESTIGATION

2.1 CHOICE OF PROJECT AREAS

Two areas were required, the first small, where operational techniques could be applied and worked out to meet field requirements and preliminary commitments would be economical in case of error. Afterwards the techniques found successful on a small scale could be expanded to suit the requirements of a larger area where results obtained with a larger population would have greater statistical significance.

In both instances choice would be determined by easy accessability with some isolation to minimise movement in an otherwise stable population. A high rate of infection would be desirable with both forms of the disease present. Hospital and laboratory facilities well staffed would be needed for medical surveillance.

These conditions were fulfilled in two of the centres where clinical trials of new formulae schistosomicides were proceeding.

The Philadelphia Mission Hospital at Dennilton in the Eastern Transvaal, with restricted population and facilities, would serve as the pilot project area, while the Limpopo Irrigation Scheme in Mozambique, with larger population and expanded facilities, would become the major project area. Refer to Map 3, page 31 "Location of Project Areas".

2.2 DESCRIPTION OF PROJECT AREAS

PHILADELPHIA MISSION HOSPITAL, DENNILTON

The Philadelphia Mission Hospital at Dennilton, where the pilot study was conducted, is situated in the Eastern Transvaal. The Mission serves as a medical centre with ancillary services for an area about 80 km^2 in which live a population of approximately 25 000, mostly Ndebele and North Sotho Tribes.

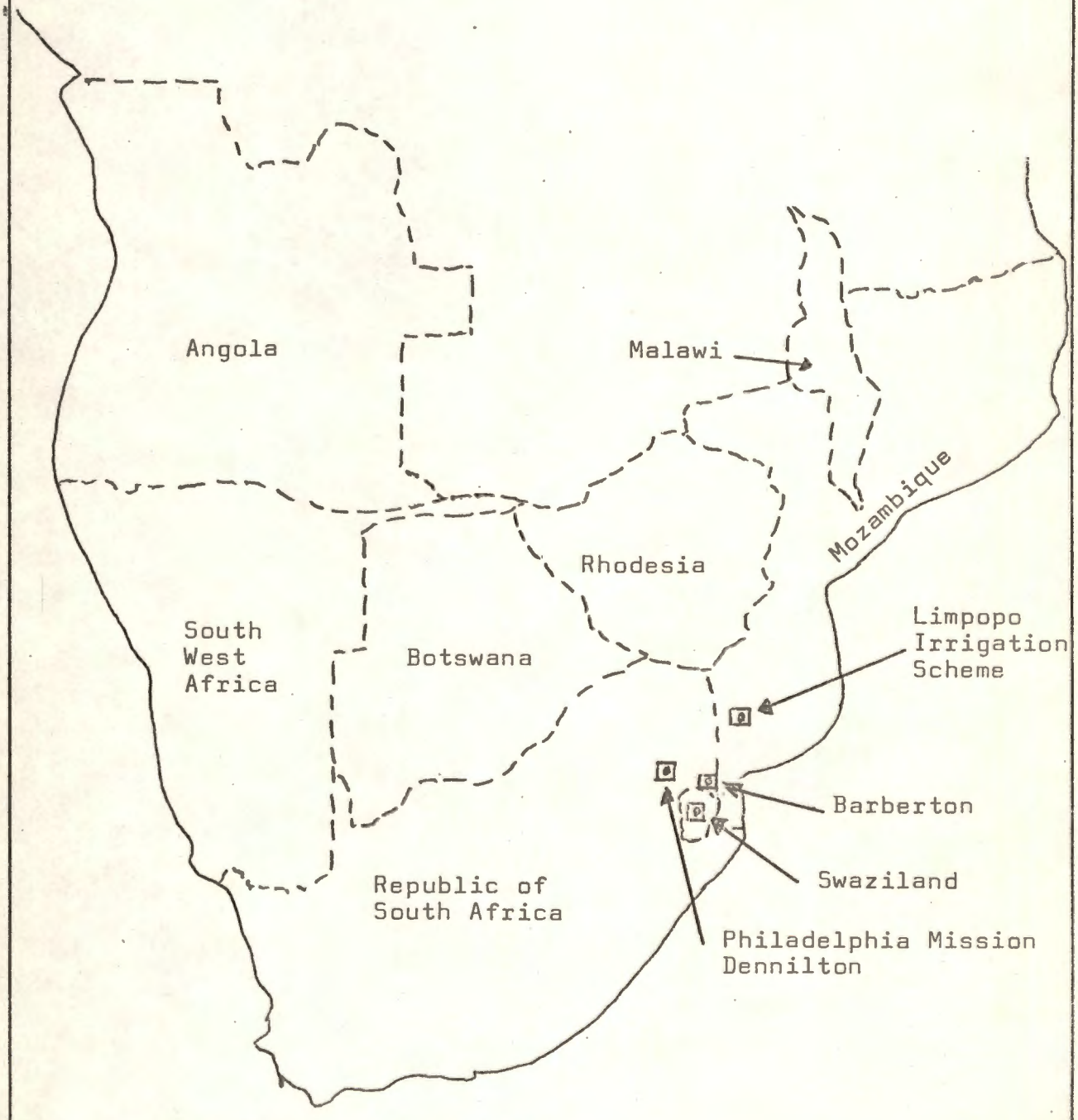
The area is just off the high continental plateau with an altitude of about 1 200 m. Surface vegetation consists of grass savannah, interspersed with sparse scrub-bush. Rainfall, with long dry spells, varies around 350 mm per annum in summer. Summer is very hot and winter varies from mild to cold. There is no noteworthy river system, although several small streams are present. These only run when it rains. The Moses River is exceptional as it is perennial but small

MAP 3

STUDY AREA ON SUBCONTINENT

OF AFRICA

LOCATION OF PROJECT AREAS



Redrawn from Philips School Atlas
K. Hechter-Schulz 1977

and serves as a focal contact for a large part of the population. About 35 km to the South lies the Loskop Dam from which concrete channels conduct water to irrigation farms outside the project area.

Housing is mostly of the local rural type, constructed of mud walls with thatched roofs. Water for domestic purposes is obtained from waterholes alongside streams, there are but few constructed wells. Little regard is given by the population to sanitation.

Students from the Weltevreden School formed the study groups. They come from a radius of about 30 km. Two groups, "A" group consisting of 56 patients, and "B" of 50, were included. Many others in the area were also treated with schistosomicides. In fact, most of the early studies on hycanthone were carried out here (Maritz (1969)). However, the periods of observation of these early studies were too short for inclusion in the project. No other control measures were carried out at Dennilton during the study period.

Limpopo Irrigation Scheme, Mozambique

The Irrigation Scheme lies alongside the Limpopo River in South-Central Mozambique, about 160 km from the sea. The region is a vast marine terrace not exceeding an elevation of 400 m, drained by the Limpopo River system. Surface vegetation consists of typical African scrub-bush. Climate consists of hot summers and warm winters. Rainfall is torrential, received at intervals throughout the summer from September to April. Little or no rainfall is received during winter. Because of the low, flat elevation, the region is inundated by heavy rains and overflow of the Limpopo and its tributaries.

Shangaans, of the Nguni ethnic group, inhabit the region. Before the commencement of the Scheme the population numbered not more than 5 per km^2.

Water for the Irrigation Scheme is fed from an earthen barrage across the River forming a coffer dam from which water is conducted by a main canal constructed with earthen levees about 2,50 m above ground level. From the main canal water is dispersed to the irrigated areas by several minor canals. Alongside the main canal are borrow pits from which earth has been excavated to build the levees. These borrow pits form permanent seepage areas and drain the high surface water table. During the years 1965 - 1970 the area was adversely

affected by the passage of several tornadoes. The irrigated area, including land on which the villages have been built, is about 8 km wide by 50 km long, strung out alongside the Limpopo River.

The settled population live in dispersed villages built away from the irrigated lands. Each family has a well-constructed brick house with enough rooms for family purposes including bathrooms and water closets. Piped chlorinated water and electricity is laid on to each house. Sewage disposal is by means of giant septic tanks. There are 14 self-contained villages. In 1963 at the commencement of the study period, the population consisted of about 1 250 families totalling some 7 400 persons of Caucasians and Africans.

The Irrigation Scheme is surrounded by an uncontrolled African squatter population about 5 times its own number, attracted by the benefits to the fringe of the Scheme. Primitive living conditions here are reflected in a low general standard of health. The squatters cultivate rice and other crops by poor irrigation methods from flood and drainage water overflowing from the Scheme.

From August 1963 to date the settled population has been under constant medical surveillance, particularly for bilharziasis and malaria. Several schistosomicide and molluscicide studies and investigations have been carried out here, to the benefit of the population. Supplies of these products have usually been sufficient to carry on periodical control work after the studies have been completed (Ruas (1974)).

2.3 METHODS OF INVESTIGATION

Methods developed at Dennilton, the pilot project area, were adapted and applied to the major project area at Limpopo. The main differences in techniques and methods were in the limitation of time and population participating at Dennilton, whereas at Limpopo observations extended over a decade and the total population participated. Methods used at Limpopo will be described in full, any deviation from these at Dennilton will be commented on separately.

Collection of specimens

A socio-medical welfare scheme was already established at Limpopo and all residents had to participate. The first surveys were completed August 1963 to October 1964. Surveys then continued over a period of 10 years at approximately quarterly intervals to December 1972. Altogether 24 surveys were carried out.

The large number of persons, varying at times from 5 648 to 7 311 living at Limpopo, from whom specimens had to be collected, required the procedure to be extended over a 3 months period at each survey. However, as the population was divided into groups for this purpose, each group could be processed at regular intervals. As the Irrigation Scheme is populated by a closed community, discipline was no problem.

All persons were required to report at the central medical clinic at given times, when record cards were completed for each individual indicating name, sex, age, address, period of residence and previous history of bilharziasis. A small identity card was handed to each to be produced on subsequent visits to the clinic. Each participant was examined physically by the medical staff, including pulse rate, heart, chest, liver and spleen.

Although it is known that peak excretion of S. haematobium ova in urine from infected persons is maximal around midday, urine specimens could not always be collected at this time because of the vast numbers involved. However, times of collection of specimens were standardised between 10h00 and 15h00.

Persons attending each survey were handed two marked and serially numbered 120 ml screw-topped bottles and the serial number noted on the record card. An area was marked off with hessian screens behind the clinic building and appropriate furniture supplied, where urination and defecation into the bottles could take place. The bottles were returned and checked by the medical staff.

On return of the urine specimen this was allowed to stand for not more than 30 minutes before processing.

About 50 ml of 2% saline solution was added to each faeces specimen returned and the contents well shaken in the bottle until emulsified.

Rectal biopsy material from a very small number of persons was taken from near the mucosal fold of the anterior rectum. Sections obtained

in this manner were pressed between two glass slides and examined microscopically immediately. Rectal biopsy is painful and had to be discontinued in the interests of individual co-operation.

Biochemical analysis of blood was done on a limited number of persons. For this purpose blood was drawn from the patient by standard methods into vacitubes packed in ice and taken to the Public Health Research Laboratories in Lourenco Marques where analysis was commenced immediately.

LABORATORY TECHNIQUES

A standard technique was used throughout:-

a) Microscopic Examination of Urine for Schistosome ova and Red Blood Corpuscles or degree of haematuria (RBC)

Each urine specimen was treated as follows:-

After agitation, 8 - 10 ml was centrifuged in graduated conical tubes at 1 000 - 1 500 rpm for 1 - 2 minutes. The supernatant fluid (SNE) was removed by decanting and a volume of 0,2 ml was reconstituted with some of the supernatant fluid, or with isotonic solution. The reconstituted specimen was then well shaken and 0,05 ml drawn off and examined microscopically under 10 x magnification.

Results were estimated and reported with the following symbols:-

i OVA

0	=	None
F	=	1 or 2
±	=	3 to 10
1+	=	11 to 30
2+	=	30 to 99
3+	=	100 to 199
4+	=	200 to 299 or 100+ on 2 days
5+	=	More than 300 on one or more days

The symbols ϑ and Ø were used after the counts:

ϑ	=	Mostly (50% or more) dead or deformed
Ø	=	Dead ova only

ii RBC

F	=	Occasional
±	=	1 - 2 per field
1+	=	Several per field
2+	=	Numerous but not crowded field
3+	=	Crowded field - not macroscopic haematuria but perhaps visible layer of RBC after centrifuging
4+	=	Macroscopic haematuria and sediment, may require dilution to search for eggs

NOTE

The symbols Θ and Ø were used after ova counts to denote (a) mostly (or more) dead or deformed eggs, and (b) dead eggs only. Viability was determined by observing embryonic development and flame cell movement, or by hatching test.

b) Microscopic Examination of Faeces for Schistosome Ova

Examination of faeces was based on a modification of Bell's Method (1963). A single specimen, mixed with saline as already described, was agitated for 15 minutes. About 50 ml were decanted and washed through coarse gauze wire to remove the coarser debris. One ml of the strained suspension was syphoned off and filtered through Whatman's No. 541 filter paper and stained in a flat bottomed dish. The stained filter paper was wetted before microscopic examination under 10 x magnification.

The estimated number of ova was reported by cymbols as for urine examinations.

In some of the earlier surveys faeces specimens were submitted to acid ether extraction, when viability of the egg was judged by development of the embryonic miracidium.

c) Haematology Studies

Haematology studies were carried out on a limited number of patients, values for the components listed below were determined.

The Ames/BMI diagnostic reagents kit system was used, unless otherwise stated. (See Annexure "G" Instructions for using Ames Diagnostic Reagent Kits)

Components tested were as follows:-

Erytherocyte-Sedimentation Rates:

Normal Accepted Range: Males 0,9 - 3,7 females 0,20 - 9,6

Clinical Significance: A slow sedimentation rate may indicate inflammatory lesions or processes. The speed may vary with the severity of infection, and presence of excess plasma proteins may influence the rate. In the presence of liver disease the rate is very slow.

Haemoglobin:

Ames diagnostic reagent kit for determining haemoglobin values was used. This depends on oxyhaemoglobin reaction with colour stabilization values and the results are expressed as gm%.

Normal Accepted Range: Male 13,5 - 18,0 gm%
Female 12,5 - 16,5 gm%

Clinical Significance: Low values could indicate blood loss with anaemia or chronic infection. Abnormally high values could indicate abnormalities of pulmonary circulation.

Mean Corpuscular Haemoglobin Concentration (MCHC):

This was determined percentagewise with the following formula:-

$$MCHC = \frac{\text{Hb concentration in gm/100 ml} \times 100}{\text{Haemocrit}}$$

The values used were obtained from haemoglobin and haemocrit values from each patient tested. Values are expressed as percentage of the total cell weight.

Normal Accepted Range: 32 - 38%

Clinical Significance: A low value indicates that the RBC is not carrying its full quota of Hb.

Haemocrit:

Packed cell volume (PCV) was determined according to the method of Wintrobe (1929) and expressed as a volume percent of cellular elements of the blood.

Normal Accepted Values: Males 47% females 42%

Clinical Significance: Values can be looked on as an accurate determining of the degree of anaemia present in a patient.

Eosinophile Counts:

Eosinophile cells were determined by a differential count of the blood of patients.

Normal Accepted Value: 1 000 per c mm.

Clinical Significance: Increased values are taken as a sign of immune or allergic reactions in a patient, indicative of helminthic parasitism.

d) Blood Biochemical Studies

Four blood biochemistry components were studied in a limited number of patients.

Bilirubin:

Conjugate and total Bilirubin was determined by means of Ames diagnostic reagent kit for measurement of direct and total Bilirubin according to the procedure of Malloy and Evelyn (1937). Values are expressed as mg per 100 ml.

Normal Accepted Values: 0,2 - 1,0 mg/100 ml

Clinical Significance: Higher than normal values can signify hepatic disease or obstruction of the biliary tract. Hemolytic disease and pulmonary infarction can cause slight elevations.

Serum Glutamic Oxaloacetic Transaminase (SGOT):

This was determined according to Ames diagnostic reagent kit using the principle of vanillin pyruvate reaction. Values are expressed in Karmen units.

Normal Accepted Range: 10 - 40 Karmen units

Clinical Significance: Elevated values usually occur in acute liver disease or myocardial infarction, or in tissue cell damage of these organs, this can also indicate damage to muscle cells elsewhere.

Serum Glutamic Pyruvic Transaminase (SGPT):

Also determined according to Ames diagnostic reagent kit as for SGOT. Because pyruvate is formed directly at the 4th reaction, there is no need to continue to the final procedure as for SGOT. Values are expressed in Karmen units.

Normal Accepted Range: 8 - 35 Karmen units

Clinical Significance: Elevated SGOT/SGPT values are usually linked in diagnosing disease or damage mainly to the liver, also to the heart. In acute liver disease SGPT results are usually higher than SGOT.

Serum Urea Nitrogen (SUN):

Determined according to Ames seronic diagnostic reagents kit, based on reaction of diacetyl with urea in the presence of a colour developer, which can be measured on a colorimeter. Value is expressed in mg/100 ml.

Normal Accepted Range: 8 - 18 mg% (border 18 - 22)

Clinical Significance: High values may signify renal insufficiency.

CHEMOTHERAPY TECHNIQUES

While four chemotherapeutic agents were used during the study period at Limpopo, one from Ciba's nitrothiazole series, and three from Winthrop's thioxanthenone series, the technique of administering one, hycanthone (Winthrop), will be described fully as this was the major schistosomicide used under the supervision of the author throughout the period. It can also be considered, through experience, as being the most convenient and quickest to administer (Ruas (1974)). Also hycanthone has superceded all other analogs in this series.

Preparation of patient

All mass therapy campaigns must be carried out under the direct supervision of qualified medical staff, supervised by a medical practitioner in person who has been instructed in the use of the schistosomicide.

Mass therapy campaigns differ mainly from single patients reporting to a clinic, in that the latter usually presents with some other major complaint and the presence of bilharziasis is then discovered and treated, when the patient is in a poor physical state, while in former case the majority presenting for treatment are apparently in a good physical state. However, precautions must be observed in either instance and contraindications observed (Refer to Annexure "F" Chemotherapy agents available). Therapy administered under these conditions must, therefore, be qualified as "Selective Mass Chemotherapy", as unsuitable candidates are referred for treatment of other medical conditions before receiving a schistosomicide.

Approval for immediate therapy depends on the absence of an acute tender liver present in the candidate, and on a medical history excluding any contraindications to the use of the schistosomicide to obviate possibilities of a severe reaction. A drill to exclude such candidates in the field consists of rapid and hard palpation of the candidate's liver by a medical practitioner and examination of the eye for possible signs of icterus, while a case history is established by secondary medical staff.

Sections of the community to receive therapy were lined up, with the sexes separated, and these precautions applied to each person. Those selected passed on for therapy, those rejected were referred for further examination and treatment before reporting back. The rejection rate based on the drill outlined above amounted to less than 1% at both Dennilton and Limpopo.

Technique

Administration of hycanthone was carried out by a medical practitioner, or a registered nurse under his instruction. Hycanthone mesylate was supplied in 2 ml ampoules as a dry, yellow chrystalline powder, for reconstitution with 2 ml sterile water. The solution was made up fresh every 24 hours.

Dosage consisted of 3,00 ($\pm$ 0,5) mg per kg body weight of patient treated to a maximum of 200 mg base, administered as a single parenteral dose. Site of the injection was important, as the injection site can become painful. The site of injection was the gluteus minimus muscle high up under the iliac crest. Care was taken

to avoid intravenous injection. After therapy the patient was placed under house surveillance for 24 hours. Severe reactors to therapy were searched out and observed in the clinic for a further 24 hours. Reaction of mild nausea and/or vomit occurred in 15 - 20% of recipients, recovery usually occurred on the second day, with no medication necessary. A four page medical record was maintained for each patient treated.

2.4 SURVEY LOGISTICS FOR THE TWO STUDIES

Time: Length of survey periods

Dennilton Groups "A" and "B".

Surveys and tests were carried out during the months and years listed:-

1. January to June 1963
2. March 1965
3. June 1965
4. July 1965
5. October 1965
6. November 1965
7. February 1968
8. March 1968
9. April 1968

Limpopo

Surveys and tests covered a period of 10 years, carried out at approximately quarterly intervals from August 1963 to September 1972, and involved the total population of 7 311.

1st Aug 63/Oct 64	9th Sept 67/Dec 67	17th May 70/Aug 70
2nd Nov 64/Dec 65	10th Jan 68/Apr 68	18th Sept 70/Dec 70
3rd Aug 65/Dec 65	11th May 68/Aug 68	19th Jan 71/Apr 71
4th Jan 66/Apr 66	12th Sept 68/Dec 68	20th May 71/Aug 71
5th May 66/Aug 66	13th Jan 69/Apr 69	21st Sept 71/Dec 71
6th Sept 66/Dec 66	14th May 69/Aug 69	22nd Jan 72/Apr 72
7th Jan 67/Apr 67	15th Sept 69/Dec 69	23rd May 72/Aug 72
8th May 67/Aug 67	16th Jan 70/Apr 70	24th Sept 72/Dec 72

The processes repeated at each test period for each person tested were:-

PARASITOLOGY STUDIES:

consisting of collection and preservation of urine and stool specimens from all persons in community;
centrifuge and prepare specimens for examination: microscopical examination of specimens under low power (10 x magnification): estimation of numbers of schistosome ova, with viability;
recording of results for each person tested.

HAEMATOLOGY STUDIES:

the components which were studied in a random selection of patients -

erythrocyte-sedimentation rate
haemoglobin
MCHC
haemocrit
eosinophile counts

BLOOD BIOCHEMISTRY STUDIES:

components studied in a random selection of patients were -

bilirubin
SGOT
SGPT
SUN

CHEMOTHERAPY:

all persons found positive at each test were treated with a schistosomicide.

Total processes carried out during 10 years of study

Total population re-examined x 24	:	7 311	
Parasitology studies (urines and stools)	:	163 000	(1 108) (x)
Haematology studies (5 components)	:	12 050	(806) (x)
Blood biochemistry (4 components)	:	12 050	(901) (x)
Treatment of positive patients x 24 (4 schistosomicides)	:	20 400	(1 750) (x)

In addition the Author monitored the Winthrop Clinical Research Programme for Schistosomicides for Southern Africa in which 10 050 patients received therapy, mainly with hycanthone, observed and followed-up for varying periods up to 18 months. These drug trials were carried out under his instruction and supervision, and the recorded data computerised for submission to Dunlop Commission on the Safety of Drugs (London) for the registration of hycanthone for sale under the trade name "Etrenol".

Note (x) Signifies number of processes carried out or personally supervised by Author

CHAPTER 3

RESULTS OF PRELIMINARY SURVEYS

3.1 DENNILTON:

Prevalence and intensity of bilharziasis

Prevalence of infection was not established for the Dennilton population prior to the commencement of the study which commenced with clinical trials on new schistosomicides. Groups of school children were tested, those not excreting ova were rejected for further observations, while those found positive were treated and placed under observation for varying lengths of time. Consequently some basic data are lacking on the prevalence of the disease in the pilot project area. For these reasons Dennilton cannot be used as an example of control methods, only as a pilot study for the comparison of data values in infected persons pre- and post-treatment, and as a control to check the course of events within a small population subjected to chemotherapy of a particularly effective new schistosomicide, hycanthone. Only African school children at Dennilton participated in this study. Two groups were chosen because of continuity of follow-up tests after therapy. These were designated "A" and "B".

Prevalence for both species of bilharziasis

Prevalence of bilharziasis in the Dennilton area has been estimated on information available at clinics and out-patients attendance at between 60 - 80% of the total population, confirmed by clinical impressions gained in medical examinations made in schools and hospitals as a prelude to the schistosomicidal trials.

Prevalence by age

It seems that the older school-going age has the greatest prevalence of infection at Dennilton. Frequency distribution of the prevalence found in the two groups of students, "A" and "B" are listed in Table 8 "Dennilton: Frequency distribution of prevalence of infection by age in two groups of students", page 46.

TABLE 8

Dennilton: Frequency distribution of prevalence of infection by age in two groups of students

Group "A"			Group "B"		
Total infected	Age Group 6-11	Age Group 12-16	Total infected	Age Group 9-11	Age Group 12-16
56	12	44	16	1	15
Frequency distribution %	21,4	78,6	-	6,25	93,75

Species of schistosome infection

The species of infection in students studied at Dennilton was predominantly S. haematobium, with only a very small number of S. mansoni appearing in mixed infections with haematobium. Estimates based on results of clinical trials show that these mixed infections could not have exceeded 5% of the project population at the time of the study more than a decade ago. For this reason observations were limited to S. haematobium infections. Data for the study was based mainly on urine specimens taken from the students.

Egg counts

Estimates of the number of eggs excreted by individual patients were carried out on three consecutive days, and recorded in the symbols as set out on page 35. Conversion of these symbols to their numerical equivalent showed that the mean number of eggs excreted by patients from Group "A" was 179 viable and 18 dead per ml of urine, with a range of 1 - 250. Patients in Group "B", where the ages were higher, excreted less eggs, the mean being 62 viable eggs per ml, with a range of 5 - 150. Refer to Table 9 "Dennilton: Viable and dead ova excreted per ml of urine, or present in rectal biopsy, of students in two groups", page 47.

TABLE 9

Dennilton: Viable and dead ova excreted per ml of urine, or present in rectal biopsy, of students in two groups

	Group "A"		Group "B"		
	Urine	Rectal Biopsy	Urine	Rectal Biopsy	Mean for both groups
No. in group	56	56	16	16	72
Mean ova excreted viable/dead	179/18:	53 positive	62/0:	5 positive	120/9:
range viable ova only	1-250	-	5-150	-	1-250
RBC in urine	3+	-	3+	-	3+

The mean excretion for the two groups was 120 viable with 9 dead eggs, range was 1 - 250 eggs. Rectal biopsies from both groups showed numerous viable S. haematobium eggs, with about 10% of the total present dead in the tissues.

Haematuria

Most urine specimens were turbid, with vivid macroscopic haematuria. Microscopically the rating was high, 3+, with much debris which had to be diluted for egg counting.

Haematology studies

Only eosinophiles and white blood cells were estimated in the groups studied at Dennilton.

Eosinophile Count:

71 students in Groups "A" and "B" were tested for eosinophilia. Values obtained for each group were similar and well within the normal accepted eosinophile range.

White Blood Cell/mm^3:

Total WBC/mm^3 counts were carried out on the two age groups comprising Groups "A" and "B". Values obtained for Group "A" were

almost one-third higher than those obtained for Group "B". Frequency distribution of those patients in Group "A" whose values exceeded the accepted upper limit of 10 000 cells/mm^3 was 16% in the puberty-adolescent age (12 - 16 years) and 5,4% in the juvenile age (6 - 11 years). Frequency distribution for 14 children in Group "B" shows 7% in the puberty-adolescent age (12 - 16 years) above the accepted upper limit. One patient in this group was recorded as having an exceptionally "high eosinophile count". Refer to Table 10 "Dennilton: Haematology studies and frequency distribution for two groups, Preliminary Survey", page 49.

BLOOD BIOCHEMICAL STUDIES

Three components were studied in the two groups at Dennilton. Refer to Table 11 "Dennilton: Blood Biochemical Studies for 3 components, Preliminary Survey", page 50 and Table 12 "Dennilton: Frequency Distribution Blood Biochemical Studies, Preliminary Survey and Post-Therapy", page 51.

Bilirubin (total, conjugate):

80 patients in the two groups were studied for bilirubin values. Mean values for all ages within the two groups were within the normal accepted range, although those for Group "A" were higher than Group "B". The mean value for both groups was 0,5 with a range from 0,2 to 1,2.

Frequency distribution for the bilirubin component for all patients studied in Group "A" was 35% within the range of 0,0 - 0,5; 35% within 0,6 - 1,0; and 30% within 1,1 - 1,5. In Group "B" the distribution was 88% in the range 0 - 0,5 and 12% within 0,6 - 1,0; there being none in the range 1,1 - 1,5.

SGOT:

The same number of patients from both groups and ages were studied for SGOT values. Values were highest for Group "B", although these were within the normal accepted range. Mean value for both groups was 25, with a range of 10 to 105.

Frequency distribution of values for patients in Group "A" was 65% within the 10 - 20 units range; 16% within 21 - 30 units; and 18% with 31 - 40+. One patient in the latter range had the very high

TABLE 10

Dennilton: Haematology studies
for 3 components

Preliminary Survey

Component	Age Group	Group "A"	Group "B"	Mean for Group
Haemoglobin (gm/%)	Juvenile 6-11	13,8(10-16) (12)	13,3(12-14,5) (2)	13,5(10-16) (14)
Accepted values 12,5/18,0	Pub-adol 12-16	13,2(11-16) (42)	13,4(11,5-15) (14)	13,3(11-16) (5,6)
WBC(mm^3)	Juvenile 6-11	9 160(6 500-12 000) (12)	6 850(6 500-7 200) (2)	8 000(6 500-12 000) (14)
Accepted values 5 000-10 000	12-16	9 150(6 500-13 000) (42)	7 200(5 500-12 000) (14)	8 175(5 500-13 000) (56)
Eosinophiles Accepted values	Juvenile 6-11	-	1(1) (2)	1(1) (2)
1 000 c mm	Pub-adol 12-16	-	2(1-6) (8)	2(1-6) (8)

Calculated from computerised data obtained from clinical research programme Dennilton.

Monitor: K.Hechter-Schulz. Unpublished data on Winthrop Files Johannesburg

TABLE 11

Dennilton: Blood biochemical studies for 3 components

Preliminary Survey

Test	Age Group	Group "A" mean(range)	Group "B" mean(range)	Mean for 2 Groups mean(range)
Bilirubin (total conjugate) Accepted values (0,1-1,0)	Juvenile 6-11 years	0,9(0,4-1,2) 12 patients	0,2(0,2) 2 patients	0,6(0,2-1,2) 14 patients
	Pub/adol 12-16 years	0,7(0,2-1,2) 42 patients	0,2(0,2-1,1) 14 patients	0,5(0,2-1,2) 66 patients
	Mean for all patients mean(range)	0,5(L,2-1,2) 80 patients		
SGOT Accepted values (10-40)	Juvenile 6-11 years	23(14-35) 12 patients	27(21-32) 2 patients	25(14-35) 14 patients
	Pub/adol 12-16 years	20(10-35) 42 patients	32(19-105) 14 patients	26(10-105) 66 patients
	Mean for all patients mean(range)	25(10-105) 80 patients		
SGPT Accepted values (8-35)	Juvenile 6-11 years	22(12-33) 12 patients	-	22(12-33) 12 patients
	Pub/adol 12-16 years	17(7-33) 42 patients	-	17(7-33) 42 patients
	Mean for all patients mean(range)	20(7-33) 80 patients		

Calculated from computerised data obtained from clinical research programme Dennilton.

Monitor: K.Hechter-Schulz. Unpublished data on Winthrop Files Johannesburg

TABLE 12

Dennilton: Frequency distribution
blood biochemical studies

Preliminary Survey and Post-Therapy

	Group "A"				Group "B"			
	Pre-treatment		Post-treatment 1 week		Pre-treatment		Post-treatment 1 week	
Distribution	Patients		Patients		Patients		Patients	
Total Bilirubin								
0-0,5	19/54	35%	18/54	33%	14/16	88%	14/16	88%
0,6-1,0	19/54	35%	24/54	44%	2/16	12%	2/16	12%
1,1-1,5	16/54	30%	12/54	23%	-		-	
SGOT								
10-20	35/54	65%	28/54	53%	1/16	6%	2/12	17%
21-30	9/54	16%	16/54	29%	10/16	63%	4/12	33%
31-40+								
SGPT								
10-20	41/53	77%	35/53	66%				
21-30	7/53	13%	10/53	19%				
31-35	5/53	10%	8/53	15%				

Calculated from computerised data obtained from clinical research programme Dennilton.

Monitor: K.Hechter-Schulz. Unpublished data on Winthrop Files Johannesburg

value of 105 units. In Group "B" the distribution was 6% in the range 10 - 20 and 63% in the range 21 - 30.

SGPT:

Only patients in Group "A" were studied for SGPT values. The mean value for this group was 20 units, well within the accepted normal range of values. The younger age group had higher values, but these were still within the normal accepted values.

Frequency distribution of values for this group was 77% within the range 10 - 20; 13% within the range 21 - 30; and 10% within the range 31 - 35.

3.2 LIMPOPO:

PREVALENCE AND INTENSITY OF BILHARZIASIS

The preliminary survey preceding chemotherapy was conducted during the first test period from August 1963 to October 1964, when the control programme was commenced.

PREVALENCE OF BILHARZIASIS FOR ETHNIC AND AGE GROUPS

The percentage prevalence found in the tests suggest the following conclusions:-

For Caucasians the pattern of infection was:-

persons 10 - 14 years had the highest prevalence of the disease;

those 15 - 19 had lesser prevalence;

while those 5 - 9 years had almost half the first mentioned age groups prevalence;

groups with lowest prevalence were 0 - 4 and 20 - 50+.

In all age groups the male ratio of infection was greater than female, about 4 : 1: except for the infants where prevalence of infection for both sexes was about equal.

The pattern of infection in Africans was different.

Ages 5 to 19 years had highest prevalence compared with Caucasians in the age group of 10 to 19 years;

infants up to 4 years (male and female) had relatively high prevalence, much higher than the same Caucasian age group;

lower prevalence in Africans was found only in ages of 30 years onwards.

African females were more highly infected than males.

Africans became more heavily infected at an earlier age than Caucasians, and retained infection longer.

Male and female prevalence for the first test period were:-

Percentage prevalence by age and ethnic groups, pre-therapy

Caucasian males	24,1%	females	5,8%
African males	36,6%	females	41,7%
overall prevalence	23,1%		

(extracted from Tables 13A and B, pages 54 and 55)

Refer to Tables 13A and B "Limpopo: Test Periods, prevalence as percentage for ethnic and age groups; Caucasian and African", pages 54 and 55: also Table 14 "Limpopo: Test Periods, total prevalence and prevalence for males and females of ethnic groups", page 56.

SPECIES OF SCHISTOSOME INFECTION

Detailed observations were made on small unselected and random groups throughout the area to establish the frequency of either S. haematobium or S. mansoni infections in the Limpopo population. In this survey no pure cultures of S. mansoni infections were found, only S. haematobium infections alone; or mixed S. haematobium and mansoni infections. Later work did, in fact, bring to light the presence of pure S. mansoni infections. This will be commented on later.

From Table 15 "Limpopo: Preliminary, species infection by village and ethnic group", page 57, it will be seen that of 4 723 persons tested from 9 villages, 730 or 15,5% were found positive for

LIMPOPO TEST PERIODS

PREVALENCE AS A PERCENTAGE FOR ETHNIC AND AGE GROUPS

(A) CAUCASIAN AGE GROUPS

PERIOD	0 - 4	5 - 9	10 - 14	15 - 19	20 - 29	30 - 39	40 - 49	50 - +
	M F	M F	M F	M F	M F	M F	M F	M F
1	2,3 - 3,3	26,2 - 6,5	52,5 - 12,8	42,3 - 7,7	16,0 - 2,3	6,4 - 2,4	6,0 - 3,9	7,5 - 4,8
2	2,8 - 0,8	8,2 - 3,3	16,3 - 1,9	13,0 - 2,7	3,2 - 2,5	2,2 - 1,0	1,0 - 1,9	2,2 - 0,5
3	1,6 - 0,4	11,4 - 1,6	15,9 - 2,3	10,4 - 2,0	4,0 - 0,7	2,6 - 1,0	1,7 - 0,3	1,4 - 0,5
4	0,8 - 0,4	4,0 - 1,5	9,6 - 1,4	8,3 - 0,8	0,6 - 0,0	2,4 - 1,0	0,7 - 0,0	0,3 - 0,0
5	0,5 - 0,5	6,4 - 2,0	6,4 - 0,8	5,7 - 0,7	1,6 - 0,3	1,2 - 0,5	1,4 - 0,3	0,3 - 0,4
6	1,8 - 0,5	6,2 - 1,0	7,8 - 1,0	4,2 - 1,6	3,4 - 0,7	1,5 - 0,9	0,7 - 0,7	1,8 - 0,0
7	1,0 - 0,0	3,9 - 0,5	4,2 - 1,1	2,7 - 0,0	2,2 - 0,3	0,7 - 0,0	2,0 - 0,0	1,2 - 0,0
8	1,1 - 0,0	9,7 - 1,9	7,8 - 0,5	4,4 - 0,8	5,0 - 0,3	2,5 - 0,4	2,4 - 0,7	0,3 - 0,0
9	0,5 - 0,0	5,5 - 2,7	8,4 - 1,5	3,8 - 1,3	2,8 - 0,7	1,9 - 0,0	1,2 - 0,0	0,0 - 0,0
10	2,0 - 0,7	6,4 - 1,4	6,4 - 2,1	4,8 - 0,0	2,5 - 1,0	1,4 - 1,3	1,2 - 0,7	0,3 - 0,0
11	0,5 - 1,7	6,7 - 2,9	14,8 - 2,2	7,3 - 1,6	2,0 - 0,4	3,2 - 0,8	1,6 - 1,0	2,0 - 0,8
12	1,5 - 1,6	2,7 - 0,2	8,0 - 0,6	6,6 - 0,0	3,4 - 0,0	2,6 - 0,0	2,0 - 0,7	0,9 - 0,0
13	0,8 - 0,0	4,6 - 0,5	6,3 - 0,3	2,6 - 0,4	3,2 - 0,4	1,5 - 0,4	0,4 - 0,3	0,6 - 0,0
14	1,3 - 0,0	4,6 - 1,0	5,9 - 1,2	3,8 - 0,4	1,6 - 0,8	0,4 - 1,3	1,6 - 0,0	0,8 - 0,7
15	1,1 - 1,7	3,9 - 1,4	9,6 - 0,6	7,1 - 0,9	3,8 - 0,4	3,4 - 1,3	1,3 - 0,7	0,9 - 0,4
16	1,3 - 0,7	9,0 - 2,5	10,7 - 4,1	6,1 - 2,6	3,4 - 0,8	4,2 - 0,9	0,9 - 2,6	1,8 - 0,0
17	1,3 - 0,7	9,3 - 2,8	15,2 - 2,8	7,5 - 4,3	6,0 - 1,3	3,6 - 1,4	3,4 - 1,8	2,9 - 0,7
18	1,1 - 1,3	3,5 - 1,4	6,8 - 2,1	8,4 - 0,5	4,4 - 1,9	2,2 - 1,0	3,7 - 0,4	1,4 - 0,0
19	0,8 - 2,2	2,9 - 1,3	7,8 - 1,8	5,4 - 1,4	2,5 - 0,0	2,1 - 0,9	1,8 - 0,8	1,0 - 0,3
20	0,0 - 0,9	2,7 - 1,3	4,4 - 1,5	3,8 - 0,9	3,1 - 0,4	2,1 - 0,9	3,1 - 0,8	1,0 - 0,3
21	2,0 - 0,8	5,4 - 1,8	9,2 - 1,2	8,0 - 2,9	2,4 - 1,4	1,8 - 1,4	0,5 - 0,8	1,0 - 1,0
22	0,0 - 1,0	4,1 - 1,4	9,8 - 1,5	7,9 - 0,5	2,5 - 0,5	4,1 - 0,0	3,1 - 1,3	1,8 - 0,9
23	1,8 - 1,0	6,7 - 2,3	14,8 - 3,2	6,2 - 0,9	1,2 - 0,0	2,7 - 0,9	3,7 - 0,8	1,1 - 0,3
24	0,8 - 0,9	6,9 - 0,6	9,7 - 1,9	6,2 - 1,0	4,3 - 2,1	1,9 - 0,9	2,7 - 0,4	2,2 - 0,7

Calculated from computerised data of Limpopo Bilharziasis Control Project using hycanthone.

Monitor: K.Hechter-Schulz. Unpublished data on Winthrop Files Johannesburg.

LIMPOPO TEST PERIODS

PREVALENCE AS A PERCENTAGE FOR ETHNIC AND AGE GROUPS

(B) AFRICAN AGE GROUPS

PERIOD	0 - 4		5 - 9		10 - 14		15 - 19		20 - 29		30 - 39		40 - 49		50 - +	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1	16,9	17,7	51,1	44,1	63,1	58,5	63,5	67,1	38,6	42,9	25,3	42,0	19,2	42,0	14,6	17,1
2	6,1	6,8	24,0	23,1	26,4	21,6	25,7	23,9	12,0	14,4	6,8	13,0	3,7	14,1	5,9	10,9
3	10,6	10,9	32,6	31,1	26,6	34,4	27,3	20,8	11,0	14,9	5,8	9,9	8,9	9,2	2,1	2,0
4	2,5	2,1	15,8	17,1	28,8	18,1	19,4	15,5	6,8	8,2	1,8	8,2	1,0	4,3	2,0	11,1
5	13,2	12,2	19,1	20,4	18,9	18,7	13,4	14,7	3,2	4,9	2,5	10,7	5,3	6,3	1,0	0,0
6	10,2	12,9	24,3	18,4	23,6	24,7	1,8	20,0	10,0	11,7	7,2	4,1	3,0	6,3	4,5	0,0
7	4,6	9,8	14,5	9,2	16,1	13,0	7,5	7,4	1,2	5,4	4,0	5,4	1,9	4,4	0,0	0,0
8	8,3	19,0	13,2	14,1	16,2	11,2	9,9	4,7	3,6	6,8	6,1	5,8	2,9	1,1	5,7	2,6
9	11,8	18,0	15,1	15,3	17,5	9,9	4,5	8,6	7,3	6,2	0,6	3,9	1,0	3,3	0,0	5,4
10	22,7	10,3	13,6	14,1	15,6	12,2	12,0	8,5	3,2	7,9	2,3	3,4	2,8	3,2	2,1	0,0
11	11,6	28,6	26,4	26,1	22,5	22,3	12,5	21,6	5,3	9,0	4,3	8,5	6,9	3,4	4,3	2,9
12	14,3	15,9	23,0	22,1	27,9	13,1	16,4	15,3	5,9	7,8	5,9	4,5	2,3	3,8	8,8	3,1
13	9,7	8,3	19,4	22,7	21,7	16,9	11,5	6,8	9,8	9,2	9,9	3,8	2,0	3,8	3,5	2,5
14	28,1	11,1	29,1	29,6	18,1	21,9	15,5	15,2	5,6	6,3	4,5	5,4	3,9	3,3	0,0	7,1
15	13,5	23,1	33,9	32,6	32,0	23,6	15,4	19,4	11,1	9,9	6,4	11,0	7,1	2,7	5,9	2,7
16	38,7	36,4	32,9	34,0	26,0	31,4	15,2	25,0	12,7	22,7	5,3	20,0	8,4	11,2	10,1	2,2
17	41,0	37,8	49,1	48,0	43,8	36,7	22,2	36,4	22,2	18,4	10,4	12,2	5,7	10,8	7,9	13,3
18	23,8	17,6	32,0	31,3	27,3	35,0	18,8	25,9	12,2	10,6	14,8	8,5	10,2	11,0	5,3	8,3
19	18,2	20,0	19,9	21,4	20,0	25,1	21,1	18,7	8,6	12,6	9,3	6,4	4,7	4,5	3,0	9,3
20	17,1	10,3	12,2	22,1	16,4	18,9	13,4	11,8	12,5	12,7	4,7	9,9	7,5	4,3	2,1	6,7
21	16,2	20,0	22,9	26,8	22,7	26,3	4,7	18,1	4,8	10,9	10,6	9,0	4,8	8,2	2,2	4,2
22	12,9	12,0	22,7	23,4	19,3	24,4	15,0	16,1	9,3	16,1	6,4	7,3	3,9	10,2	11,2	4,4
23	17,4	28,1	28,3	36,2	38,2	31,7	12,0	24,7	8,3	16,8	7,3	9,6	6,7	9,0	6,3	4,4
24	4,2	14,0	21,1	27,5	36,5	33,5	34,5	23,1	8,2	17,2	10,3	18,8	5,8	15,9	7,8	20,9

Calculated from computerised data of Limpopo Bilharziasis Control Project using hycanthone.

Monitor: K.Hechter-Schulz. Unpublished data on Winthrop Files Johannesburg.

TABLE 14

LIMPOPO TEST PERIODS

TOTAL PREVALENCE AND PREVALENCE FOR MALES AND FEMALES OF ETHNIC GROUPS

SURVEY PERIOD	TOTAL NO.	%	CAUCASIAN MALE	%	CAUCASIAN FEMALE	%	AFRICAN MALE	%	AFRICAN FEMALE	%
1 Aug 63/Oct 64	1712/7424	23,1	694/2882	24,1	132/2283	5,8	402/1099	36,6	484/1160	41,7
2 Nov 64/Jul 65	618/7422	8,3	217/2813	7,7 (4,2)	40/2308	1,7 (1,5)	161/1102	14,6 (9,3)	200/1199	16,7 (10,5)
3 Aug 65/Dec 65	628/714	8,8	202/2726	7,4 (4,6)	26/2248	1,2 (1,0)	182/1061	17,2 (8,7)	218/1108	19,7 (9,6)
4 Jan 66/Apr 66	337/6942	4,9	107/2695	4,0 (2,0)	16/2260	0,7 (0,4)	979/95	9,7 (2,6)	119/1008	11,8 (5,1)
5 May 66/Aug 66	355/7020	5,1	97/2706	3,6 (1,9)	18/2319	0,8 (0,5)	106/978	10,8 (4,0)	134/1023	13,1 (3,2)
6 Sep 66/Dec 66	397/6845	5,8	102/2603	3,9 (2,0)	18/2219	0,8 (0,7)	129/976	13,2 (3,7)	148/1047	14,1 (4,6)
7 Jan 67/Apr 67	226/6929	3,3	66/2632	2,5 (1,4)	7/2331	0,3 (0,2)	75/963	7,8 (1,8)	78/1003	7,8 (2,2)
8 May 67/Aug 67	319/6832	4,7	126/2587	4,9 (2,2)	16/2332	0,7 (0,6)	86/930	9,2 (3,1)	91/983	9,3 (2,7)
9 Sep 67/Dec 67	277/6558	4,2	86/2454	3,5 (1,5)	21/2203	1,0 (0,8)	79/938	8,4 (2,7)	91/963	9,4 (3,4)
10 Jan 68/Apr 68	285/6670	4,3	91/2510	3,6 (1,7)	22/2242	1,0 (0,9)	86/947	9,1 (3,8)	86/971	8,9 (2,7)
11 May 68/Aug 68	466/6703	7,0	144/2539	5,7	36/2305	1,6	126/903	14,0	162/956	16,9
12 Sep 68/Dec 68	329/6328	5,2	87/2419	3,6	8/2202	0,4	126/823	15,3	108/884	12,2
13 Jan 69/Apr 69	290/6325	4,6	69/2381	2,9	7/2232	0,3	108/834	12,9	106/878	12,1
14 May 69/Aug 69	347/6326	5,5	68/2336	2,9	16/2192	0,7	119/870	13,7	144/928	15,2
15 Sep 69/Dec 69	430/6091	7,1	91/2243	4,1	20/2167	0,9	155/817	19,0	164/864	19,0
16 Jan 70/Apr 70	538/6140	8,8	123/2279	5,4	42/2148	2,0	156/836	18,7	217/877	24,7
17 May 70/Aug 70	688/6117	11,2	159/2250	7,1	45/2137	2,1	232/851	27,3	252/879	28,7
18 Sep 70/Dec 70	471/5771	8,2	80/2058	3,9	21/1942	1,1	173/852	20,3	197/919	21,4
19 Jan 71/Apr 71	330/5773	5,7	70/2121	3,3	21/2047	1,0	106/774	13,7	133/831	16,0
20 May 71/Aug 71	286/5924	4,8	56/2137	2,6	19/2080	0,9	85/817	10,4	126/890	14,2
21 Sep 71/Dec 71	387/5907	6,6	90/2150	4,2	29/2038	1,4	109/818	13,3	159/901	17,6
22 Jan 72/Apr 72	368/5680	6,5	95/2049	4,6	19/1980	1,0	108/779	13,9	146/872	16,7
23 May 72/Aug 72	503/5775	8,7	118/2065	5,7	27/1918	1,4	155/823	18,8	203/906	22,4
24 Sep 72/Dec 72	575/5640	8,4	97/1994	4,9	20/1928	1,0	144/787	18,3	214/939	22,8

Calculated from computerised data of Limpopo Bilharziasis Control Project using hycanthone.

Monitor: K.Hechter-Schulz. Unpublished data on Winthrop Files Johannesburg.

TABLE 15

LIMPOPO, PRELIMINARY

SPECIES INFECTION BY VILLAGE AND ETHNIC GROUP

VILLAGE	Caucasian				African				Total			
	S. h Positive	%	S. m Positive	%	S. h Positive	%	S. m Positive	%	S. h Positive	%	S. m Positive	%
GUIJA	97/823	11,8	13/823	1,6	29/823	3,5	3/823	3,5	126/823	15,3	16/823	1,9
TRIGO	19/179	10,6	1/179	0,5	3/179	1,6	0/179	0	22/179	12,2	1/179	0,5
FREIXIEL	21/1220	1,7	4/1220	0,3	219/1220	18	36/1220	2,9	240/1220	19,6	40/1220	3,3
S.JOSE	35/161	21,7	7/161	4,3	0/161	0	0/161	0	35/161	21,7	7/161	4,3
FOLGARES	68/1874	3,6	5/1874	0,3	87/1874	4,6	12/1874	0,6	155/1874	8,3	17/1874	0,9
SAGRES	28/356	7,8	4/356	1,1	14/356	3,9	3/356	0,8	42/356	11,7	7/356	1,9
PEGOES	19/130	14,6	2/130	1,5	12/130	9,2	0/130	0	31/130	23,8	2/130	1,5
OURIQUE	21/237	8,9	0/237	0	0/237	0	0/237	0	21/237	8,8	0/237	0

Calculated from computerised data of Limpopo Bilharziasis Control Project using hycanthone.
Monitor: K.Hechter-Schulz. Unpublished data on Winthrop Files Johannesburg.

S. haematobium and 95 or 2,0% for mixed S. haematobium and mansoni infections. Prevalence of S. haematobium infections were alike for Caucasians and Africans (7,6 and 7,8%), but Africans had slightly more mixed S. haematobium and mansoni infections than did Caucasians (1,1 and 0,9%). San Jose Village had the highest prevalence of both S. haematobium and mixed haematobium and mansoni infections. Pegoes Village had the highest prevalence of S. haematobium. The total prevalence as a percentage per village over the 24 test periods is shown in Table 16 "Limpopo: Total prevalence as a percentage per village for each test period throughout study", page 59.

Egg counts

Data on the numbers and species of ova excreted per person are available for a group specifically observed for this and presented in Table 17 "Limpopo: Preliminary study, egg excretion by ethnic group and species, also Haematuria", page 60.

Of 27 Caucasians who had specimens of both urine and faeces tested on three consecutive days, 11 were passing S. haematobium eggs in urine and S. mansoni eggs were found in the faeces of 15. Four had mixed infections; i.e., haematobium eggs in urine and mansoni eggs in the faeces of the same person. Three out of four rectal biopsies taken from the same group were positive for S. mansoni, although all eggs embedded in the biopsy tissue were dead.

The average number of eggs excreted per person for S. haematobium were 39 viable and 3 dead with a range of 1 to 320. Viability of the eggs was established by the hatch test.

Estimated average number of eggs excreted per person for S. mansoni and mixed infections ranged from 1 - 108, no actual counts having been made.

Seventy-four Africans tested under similar conditions excreted an average of 196 viable and 15 dead S. haematobium eggs in urine per person. Some excreted only S. mansoni eggs in faeces, others excreted eggs of both species. Egg counts ranged from 0 - 2 052 for S. haematobium; 1 - 2 for S. mansoni and 3 - 12 in mixed infections. Rectal biopsies were done on 16 persons of whom 10 were positive for S. mansoni with a range of 2 - 48 eggs per biopsy. All eggs embedded in the biopsy tissue were dead.

TABLE 16

LIMPOPO

TOTAL PREVALENCE AS A PERCENTAGE PER VILLAGE
FOR EACH TEST PERIOD THROUGHOUT STUDY

PERIOD	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
TRIGO DE MORAIS	18,9	9,3	3,6	4,7	1,4	2,8	1,8	1,4	0,3	0,4	4,7	4,6	2,1	1,1	1,4	2,0	2,2	1,6	0,9	1,2	0,7	1,4	0,9	3,0
BARRAGEM	16,0	8,3	2,0	1,5	1,0	0,5	1,1	2,2	0,0	-	-	4,3	2,6	0,7	5,8	0,7	2,9	3,1	1,8	1,7	0,9	1,0	1,0	2,4
LEONDE	20,6	6,6	2,3	3,0	4,8	3,1	2,2	1,3	0,6	0,8	2,7	2,8	1,1	1,7	4,5	3,4	3,7	2,9	5,4	3,0	3,0	3,0	3,3	3,1
FREIXIEL	22,7	8,3	14,7	7,2	6,4	11,1	4,3	3,9	4,5	3,9	8,6	8,6	8,4	7,3	13,3	13,7	15,3	12,9	11,0	9,9	10,0	10,2	13,3	18,5
S.J.de RIBAMAR	26,1	1,5	6,4	1,6	2,5	-	-	0,9	2,0	-	1,0	1,1	1,1	1,0	2,3	11,0	2,1	1,3	1,9	2,0	1,9	2,9	3,4	3,8
FOLGARES	13,6	3,0	6,5	2,4	2,0	2,0	2,5	1,3	1,5	1,8	3,0	3,3	2,2	1,5	3,5	5,4	5,3	5,8	2,4	2,8	2,8	5,3	6,5	5,4
SAGRES	14,2	2,6	4,7	1,7	0,7	3,3	2,4	8,6	7,9	6,3	8,0	4,9	2,5	3,2	5,8	10,0	12,3	10,0	7,6	5,4	2,9	8,9	9,0	4,9
SANTIAGO	24,0	12,6	14,7	7,9	8,8	4,8	6,7	3,5	1,0	2,2	8,9	9,9	6,3	3,3	3,7	2,5	31,2	13,3	12,7	14,5	12,7	7,1	19,3	15,7
OURIQUE	9,4	1,8	2,6	2,7	1,4	1,7	0,9	0,6	0,3	1,6	7,7	1,7	0,3	0,0	2,1	1,7	1,9	0,4	3,0	0,4	3,1	0,9	2,7	2,3
SRA.da GRACA	22,4	8,6	5,9	2,5	1,3	2,2	2,0	1,9	3,5	4,1	5,8	2,7	1,7	3,1	3,6	4,3	7,5	4,2	2,8	2,2	6,6	5,2	7,5	5,0
MADRAGOA	31,6	13,4	13,5	8,7	12,6	6,7	5,3	12,2	9,7	10,5	13,4	7,9	8,9	14,0	12,0	18,4	24,8	15,7	8,5	6,6	12,4	9,5	12,7	11,5
SANTA COMBA	34,2	11,8	8,1	2,7	6,0	6,5	6,3	2,8	8,4	3,5	7,0	2,9	6,4	6,5	8,7	5,1	3,8	3,4	2,3	3,7	0,4	3,8	8,6	5,1
SANTANA	43,9	17,3	9,2	3,5	9,8	7,2	3,9	15,4	5,3	5,9	3,3	4,4	3,0	9,6	6,0	8,4	11,4	8,5	4,1	1,6	3,5	9,3	3,8	4,0
PEGOES	44,7	7,1	8,5	9,9	6,6	4,9	2,8	11,8	3,9	8,1	6,0	7,3	4,3	7,2	0,9	14,7	8,4	3,1	5,3	4,7	9,6	2,0	5,2	2,1
TOTAL %	23,1	8,3	8,8	4,9	5,1	5,8	3,3	4,7	4,2	4,3	7,0	5,2	4,6	5,5	7,1	8,8	11,2	8,2	5,7	4,8	6,6	6,5	8,7	8,4

Calculated from computerised data of Limpopo Bilharziasis Control Project using hycanthone.

Monitor: K. Hechter-Schulz. Unpublished data on Winthrop Files Johannesburg.

TABLE 17

LIMPOPO PRELIMINARY STUDY

EGG EXCRETION, (VIABLE/DEAD) BY ETHNIC GROUP AND SPECIES

ALSO HAEMATURIA

Group	Caucasian				African				Total			
Species	S H	S M	Mixed	Rect. Biop.	S H	S M	Mixed	Rect. Biop.	S H	S M	Mixed	Rect. Biop.
Patients	11	18	4	4	42	2	4	16	53	20	8	20
Average eggs/ patient viable/dead	39/3	15Pos	4Pos	3Pos	196/15	2Pos	3Pos	10Pos	117/9	17Pos	7Pos	13Pos
range of viable eggs	1/320	1/14	1/108	-	0/2052	1/2	3/12	2/48 (dead)	1/2052	1/14	1/108	2/48 (dead)
Haematuria	2+		2+		4+				3+			

1. Per low pwer field of 0,05ml of centrifuged sample, or 1ml of faeces emulsified with 2% saline.
2. Average counts over three consecutive days.
3. Viable ova confirmed by hatch test.

Calculated from computerised data obtained for Hycanthone Clinical Studies at Limpopo.

Monitor: K.Hechter-Schulz. Unpublished data Winthrop Files Johannesburg.

In both ethnic groups average excretion of S. haematobium eggs in urine were 97 viable and 6 dead, ranging from 1 - 2 052 per count. In this sample a few Africans had only S. mansoni but many in both ethnic groups had mixed S. haematobium and mansoni infections.

Haematuria

Microscopically very few stools were seen to contain RBC, observations were then confined to urine samples.

Nearly all urine specimens from both ethnic groups in Limpopo were turbid.

On an average Africans passed more RBC in urine than did Caucasians, showing macroscopic haematuria and containing gross sediment, scoring mostly 4+, requiring further dilution to search for eggs. Urine specimens from Caucasians showed numerous RBC, although not a crowded microscopic field, with little sediment, in contrast to urine from Africans.

Haematology studies

These were carried out on random unselected groups of infected patients who were divided into groups according to species of infection, i.e., Group 1 S. haematobium, Group 2 S. mansoni and Group 3 mixed infections of haematobium and mansoni. Age groups tested were:-

3 - 5 years	18 - 23 years
6 - 11 years	24 - 39 years
12 - 17 years	40 years onwards

Age groups were later consolidated into 3, i.e.,

juvenile	12 - 23 years
3 - 11 years	mature 24 - 40+ years
puberty-adolescent	

Refer to Table 18 "Limpopo: Preliminary haematology for 3 groups of infection, by ethnic and age groups", page 62.

Three groups of infection for ethnic and age groups

Group 1: S. haematobium infections
Group 2: S. mansoni infections
Group 3: S. haematobium and S. mansoni mixed infections

TABLE 18

LIMPOPO
PRELIMINARY STUDIES
HAEMATOLOGY
3 GROUPS OF INFECTION

Five components tested for each patient

NOTE: (a) Sedimentation rate, haemaglobin, MCH concentrate, haemocrit and eosinophiles: figures denote mean values followed by range in brackets
(b) Number of patients tested is placed in brackets beneath mean and range-(1)

TEST	AGE	GROUP 1 Patients		GROUP 2		GROUP 3		AVERAGE/3 GROUPS	
		African	Caucasian	African	Caucasian	African	Caucasian	African	Caucasian
		mean and range							
Constant	3-5	-	-	-	-	-	-	-	-
(a)Sedimentation rate normal values male 0,9-3,7 female 0,20-9,6	6-11	12(12) (b) (1)	-	-	-	-	-	12(12) (1)	-
	12-17	3(3) (b) (1)	-	-	-	-	3(3) (1)	3(3) (1)	3(3) (1)
	18-23	6(3-9) (b) (2)	2(1-3) (4)	-	6(1-16) (13)	-	14(7-27) (3)	6(3-9) (2)	13(1-27) (20)
	24-39	-	6(6) (1)	19(15-22) (2)	4(1-10) (5)	15(12-18) (2)	-	17(12-22) (2)	4(1-10) (6)
	40+	-	-	-	-	-	-	-	-
(b)Haemoglobin g-% normal value male 13,5-18,0 female 12,5-16,5	3-5	-	13,5(12,9-14)	-	-	-	-	-	13,5(12,9-14) (2)
	6-11	12,6(11,2-13,5) (b) (4)	14(14) (1)	-	-	-	-	12,6(11,2-13,5) (4)	14(14) (1)
	12-17	13,5(10,3-15,6) (b) (9)	12,9(12,9) (1)	-	-	14,7(12,6-17) (2)	16,6(16,4-17) (1)	17(17) (1)	14,7(12,9-17) (2)
	18-23	15,0(12,6-17,9) (b) (14)	16,8(16,4-17) (4)	-	15,7(14-17,4) (13)	-	16,6(13,3-16) (3)	15(12,6-17,9) (14)	16,3(13,3-17,4) (20)
	24-39	15,5(12,9-17,4) (b) (13)	15(14,4-17) (3)	12,6(12,4-13,3) (2)	16,3(15,6-17,4) (5)	15,7(15,2-16,5) (2)	-	14,6(12,4-17,4) (17)	15,6(14,4-17,4) (8)
	40+	14,7(14,0-15,6) (b) (2)	-	-	-	-	-	14,7(14,0-15,6) (2)	-
(a)MCH concentration % normal value 32-36	3-5	-	33(33) (2)	-	-	-	-	-	33(33) (2)
	6-11	31(30-34) (b) (4)	33(33) (1)	-	-	-	-	31(30-34) (4)	33(32-34) (2)
	12-17	31(28-50) (b) (9)	33(33) (1)	-	-	31(31-32) (2)	33(32-34) (1)	31(28-50) (11)	33(32-34) (2)
	18-23	32(28-34) (b) (14)	33(32-35) (4)	-	32(30-33) (13)	-	32(31-32) (3)	32(28-34) (14)	32(30-35) (20)
	24-39	32(29-33) (b) (13)	33(32-34) (3)	30(29-31) (2)	32(31-34) (5)	32(31-33) (2)	-	31(29-33) (17)	32(31-34) (7)
	40+	32(31-33) (b) (2)	-	-	-	-	-	32(31-33) (2)	-
(a)Haemocrit % normal value male 47 female 42	3-5	-	40(39-42) (2)	-	-	-	-	-	40(39-42) (2)
	6-11	40(35-45) (b) (4)	42(42) (1)	-	-	-	-	40(35-45) (4)	42(42) (1)
	12-17	43(35-50) (b) (9)	39(39) (1)	-	-	47(40-54) (2)	50(50-50) (1)	45(35-54) (11)	44(39-50) (12)
	18-23	47(39-54) (b) (14)	50(48-52) (4)	-	47(41-54) (13)	-	46(45-50) (3)	47(38-54) (14)	47(41-50) (20)
	24-39	49(47-54) (b) (13)	45(43-49) (3)	42(42-43) (2)	49(46-52) (5)	49(47-50) (2)	-	46(42-54) (17)	47(43-52) (8)
	40+	45(42-49) (b) (12)	-	-	-	-	-	45(42-49) (2)	-
(a)Eosinophiles per c mm normal value 1 000	3-5	-	14,5(6-23) (2)	-	-	-	-	-	14,5(6-23) (2)
	6-11	33(21-53) (b) (4)	3(3) (1)	-	-	-	-	33(21-53) (4)	3(3) (1)
	12-17	24,8(8-62) (b) (10)	5(5) (1)	-	-	18,5(18-19) (2)	5(5) (1)	21,6(8-62) (12)	5(5) (2)
	18-23	15,4(2-30) (b) (12)	9,3(3-15) (4)	-	8(4-29) (13)	-	6,6(4-11) (3)	15,4(2-30) (12)	7,9(3-20) (20)
	24-39	17,4(4-36) (b) (13)	6,6(5-9) (3)	8(5-11) (2)	16,8(13-23) (5)	18(10-26) (2)	-	14,4(4-36) (17)	11,7(5-23) (8)
	40+	3,5(2-5) (b) (2)	-	-	-	-	-	3,5(2-5) (2)	-

Calculated from computerised data obtained for haematology studies carried out for Hycanthone Clinical Studies at Limpopo by Lourenco Marques Public Health Laboratories.
Monitor: K.Hechter-Schulz. Unpublished data Winthrop files Johannesburg.

Sedimentation Rate:

The number of African patients tested was amall, 6 in all. The values obtained in the tests suggested that mean sedimentation rates for Africans were higher in the juvenile and mature age groups than in the puberty-adolescent group. The latter group had values falling within the normal accepted range of values. Group 2 with S. mansoni infections had highest values (19).

Twenty-seven Caucasian patients tested had relatively low values, all within the normal accepted range; with the exception of the puberty-adolescent age group in Group 3 with mixed haematobium and mansoni infections, where values were significantly high.

Collectively Africans had higher values than did Caucasians. Individually some Caucasians ranged far in excess (27), of Africans as well as of normal accepted values.

Haemoglobin Concentration:

A total of 38 Africans and 33 Caucasians were tested for haemoglobin concentration.

All African and Caucasian groups had higher mean values than the lowest normal accepted value, an indication that anaemia was not present in either ethnic group. However, some Africans in the juvenile and puberty-adolescent age groups of Africans in Group 1 with S. haematobium ranged below the minimum normal value of 12,5 but still above the absolute minimum value of 10 mg percent indicative of anaemia.

MCH Concentration:

Forty-eight Africans were tested for mean corpuscular haemoglobin.

All ages in Group 1 having S. haematobium infections had low values, these being within the normal accepted range.

Thirty-one Caucasians who were tested had higher than normal accepted values. There was little difference in the range of values between the age groups and of the various ethnic groups.

Haemocrit:

Forty-eight Africans and 41 Caucasians were tested for packed cell volume.

There was little difference in the range of values between the various age and ethnic groups. The age group "juvenile" had the lowest values in each ethnic group, but still within the normal accepted range.

Eosinophile Count:

Eosinophile counts were carried out on 47 Africans. Significantly high values were observed in the juvenile age, these values became progressively nearer normal in the puberty-adolescent and mature age group. The youngest age group had the highest degree of eosinophilia. Highest values, indicative of pronounced eosinophilia, were found in persons infected with S. haematobium.

Thirty-three Caucasians had eosinophile counts. In the lowest and highest age groups the values rose above the normal accepted range. The young Caucasians had much lower values than did Africans. Those in Group 3 with mixed infections had lowest values.

BLOOD BIOCHEMICAL STUDIES

Bilirubin (total, conjugate):

Thirty-eight Africans and 33 Caucasians were studied for bilirubin, total and conjugate. Mean values for all ages in both ethnic groups were very similar, all falling within the normal accepted range. Refer to Table 19 "Limpopo: Preliminary survey, blood biochemistry for 3 groups of infection by ethnic and age groups", page 65.

In Table 20 "Limpopo: Frequency distribution, blood biochemistry, bilirubin, SGOT, SGPT and SUN", page 66, the frequency distribution of bilirubin values for all persons studied was 99% within the range 0 - 1,0 and 1% within the range of 1,1 - 1,5.

SGOT:

Forty-seven Africans were studied for SGOT values. Values were lowest for juveniles (20) progressing to higher values (28) in the older groups, but still remaining within the normal accepted range.

Thirty-three Caucasians were studied. Mean values obtained for these were higher than for the Africans, but still within the normal accepted range. Highest mean value (34) was recorded for the juvenile age group.

Three groups of infection for ethnic and age groups

Group 1: S. haematobium infections

Group 2: S. vaginali infections

Group 3: S. haematobium and S. mansoni mixed infections

TABLE 19

LIMPOPO
PRELIMINARY

BLOOD BIOCHEMICAL STUDIES
3 GROUPS OF INFECTION

Four components tested for each patient

NOTE: (a) Bilirubin: figures denote values for total/conjugate-0,54/0,12
(b) SGOT,SGPT and SUN: figures denote mean values followed by range in brackets-20(18-31)
(c) Number of patients tested is placed in brackets beneath mean and range-(4)

TEST	AGE	GROUP 1 Patients		GROUP 2		GROUP 3		AVERAGE/3 GROUPS	
		African	Caucasian	African	Caucasian	African	Caucasian	African	Caucasian
		mean and range							
	3-5	-	0,48/0,13 (2)	-	-	-	-	-	0,48/0,13 (2)
(a)Bilirubin mg% (Total conjugate) normal value 0,20/1,0 mg%	6-11	0,54/0,12 (c) (4)	0,54/0,09 (1)	-	-	-	-	0,54/0,12 (4)	0,54/0,09 (1)
	12-17	0,49/0,11 (c) (10)	0,54/0,13 (1)	-	-	0,56/0,11 (2)	0,75/0,13 (1)	0,52/0,11 (2)	0,64/0,13 (2)
	18-23	0,59/0,13 (c) (13)	0,58/0,11 (4)	-	0,52/0,10 (13)	-	0,46/0,08 (3)	0,59/0,13 (13)	0,52/0,09 (20)
	24-39	0,67/0,14 (c) (13)	0,63/0,10 (3)	0,58/0,11 (2)	0,54/0,08 (5)	0,45/0,13 (2)	-	0,56/0,12 (17)	0,58/0,09 (8)
	40+	0,65/0,13 (c) (2)	-	-	-	-	-	0,65/0,13 (2)	-
	3-5	-	34(30-40) (2)	-	-	-	-	-	34(30-40) (2)
(b)SGOT Karman units normal value 10-40 units	6-11	20(18-31) (c) (4)	34(28-40) (1)	-	-	-	-	20(18-31) (4)	34(28-40) (1)
	12-17	28(18-42) (c) (9)	21(21) (1)	-	-	27(21-33) (2)	30(30) (1)	28(18-42) (11)	23(21-30) (2)
	18-23	28(12-48) (c) (13)	23(10-30) (4)	-	25(10-44) (13)	-	24(20-28) (3)	28(12-48) (13)	24(10-44) (20)
	24-39	29(16-48) (c) (13)	24(10-40) (3)	26(21-33) (2)	28(15-38) (5)	23(21-28) (2)	-	26(15-48) (17)	26(10-40) (8)
	40+	31(12-48) (c) (2)	-	-	-	-	-	31(12-48) (2)	-
	3-5	-	9(3-13) (2)	-	-	-	-	-	9(3-13) (2)
(b)SGPT Karman units normal value 8-35 units	6-11	8(4-14) (c) (4)	15(15) (1)	-	-	-	-	8(4-14) (4)	15(15) (1)
	12-17	9(4-22) (c) (9)	2(2) (1)	-	-	8(5-12) (2)	9(9) (1)	9(4-22) (11)	6(2-9) (2)
	18-23	10(5-21) (c) (13)	8(2-12) (4)	-	9(4-19) (13)	-	9(7-11) (3)	10(5-21) (13)	9(2-19) (20)
	24-39	13(3-32) (c) (13)	10(2-17) (3)	9(5-12) (2)	13(9-21) (5)	11(4-14) (2)	-	11(3-32) (17)	12(2-21) (8)
	40+	4(2-7) (c) (2)	-	-	-	-	-	-	-
	3-5	-	-	-	-	-	-	-	-
(b)SUN mg% normal value 8-18 mg%	6-11	14(13-15) (c) (4)	-	-	-	-	-	14(13-15) (4)	-
	12-17	14(13-15) (c) (9)	-	-	-	14(14-14) (2)	-	14(13-15) (11)	-
	18-23	15(13-17) (c) (10)	17(13-20) (3)	-	15(13-17) (8)	-	15(15) (1)	15(13-17) (10)	16(13-20) (12)
	24-39	17(14-30) (c) (11)	14(14) (1)	14(14) (2)	16(13-24) (8)	14(13-14) (2)	-	15(13-30) (15)	15(13-24) (9)
	40+	15(15-16) (c) (2)	-	-	-	-	-	15(15-16) (2)	-

Calculated from computerised data obtained for biochemical studies carried out for hycanthone Clinical Studies at Limpopo by Lourenco Marques Public Health Laboratories.
Monitor: K.Hechter-Schulz. Unpublished data Winthrop Files Johannesburg.

Four components tested for each patient

TABLE 20 A, B, C & D

LIMPOPO PRELIMINARY AND POST-CHEMOTHERAPY STUDIES

FREQUENCY DISTRIBUTION

BLOOD BIOCHEMISTRY

BILIRUBIN, SGOT, SGPT AND SUN

NOTE: (a) Bilirubin: 1st line-conjugate distribution: 2nd line-patients/total tested: 3rd line-% frequency: 1st column-total distribution.
(b) SGOT: 1st line-patients/total: 2nd line-% frequency: 1st column-distribution.
(c) SGPT: 1st line-patients/total tested: 2nd line-% frequency: 1st column-distribution.
(d) SUN: 1st line-patients/total tested: 2nd line-% frequency: 1st column-distribution.

A.(a) Total BILIRUBIN mg %

	PRE-TREATMENT	POST-TREATMENT													
		Day-1		Day-2		Day-3		Day-8		2 Wks		1 Mo		2 Mos		3 Mos		4 Mos	
	Conjugate	Conjugate		Conjugate		Conjugate		Conjugate		Conjugate		Conjugate		Conjugate		Conjugate		Conjugate	
	0-,19	0-,19	≥ 0,2	0-,19	≥ 0,2	0-,19	≥ 0,2	0-,19	≥ 0,2	0-,19	≥ 0,2	0-,19	≥ 0,2	0-,19	≥ 0,2	0-,19	≥ 0,2	0-,19	≥ 0,2
0-1,0	79/80	59/68	5/68	56/59	1/59	42/46	2/46	64/65		29/29		21/21		9/9		10/11		4/4	
	99%	87%	7%	95%	1,7%	91%	4%	98%		100%		100%		100%		90%		100%	
1,1-1,5	1/80	1/68	2/68		1/59	1/46	2/46		1/65							1/11			
	1%	1,5%	3%		1,7%	2%	2%		1%							9%			
> 5,0			1/68		1/59														
			1,5%		1,7%														

B.(b) SGOT

	PRE-Rx	Day-1	Day-2	Day-3	Day-8	2 Wks	1 Mo	2 Mos	3 Mos	4 Mos
≤ 50	80/80	34/68	35/61	41/46	66/66	29/29	21/21	6/6	11/11	4/4
	100%	50%	57%	89%	100%	100%	100%	100%	100%	100%
51-100		25/68	21/61	4/46						
		37%	34%	9%						
101-200		5/68	2/61	1/46						
		7%	3%	2%						
201-300		3/68	3/61							
		4,4%	5%							
> 300		1/68								
		1,5%								

C.(c) SGPT

	PRE-Rx	Day-1	Day-2	Day-3	Day-8	2 Wks	1 Mo	2 Mos	3 Mos	4 Mos
< 50	80/80	60/68	55/61	43/46	64/64	29/29	20/20	5/5	11/11	4/4
	100%	88,3%	90,0%	93,3%	100%	100%	100%	100%	100%	100%
51-100		5/68	3/61	2/46						
		7,4%	5,0%	4,4%						
101-200		2/68	1/61							
		3,0%	1,6%							
201-300			1/61							
			1,6%							
> 300		1/68	1/61	1/46						
		0,5%	1,6%	2,2%						

D.(d) SUN

	PRE-Rx	Day-1	Day-2	Day-3	Day-8	2 Wks	1 Mo	2 Mos	3 Mos	4 Mos
< 10										
10-20	58/58	36/38	25/27	26/28	30/30	13/15	12/12	5/5		
	95%	94,5%	93%	93%	100%	86,7%	100%	100%		
20-25	2/58	1/38	2/27	2/28		2/15				
	3,5%	2,6%	7%	7%		13,3%				
> 25	1/58	1/38								
	1,7%	2,6%								

Calculated from computerised data obtained from biochemical studies carried out for hycanthone at Lourenco Marques Public Health Laboratories.
Monitor: K.Hechter-Schulz. Unpublished data Winthrop Files Johannesburg.

Frequency distribution for all persons studied was 100% within a range of less than 50 units. Table 20B "Limpopo: Frequency distribution, blood biochemistry, bilirubin, SGOT, SGPT and SUN, page 66).

SGPT:

SGPT values were obtained for 45 Africans and 33 Caucasians. Mean values for all age groups within the two ethnic groups did not seem to differ. All were within the normal accepted range of values.

Frequency distribution of all persons studied was 100% within a range of less than 50 units. (Table 20C "Limpopo: Frequency distribution, blood biochemistry, bilirubin, SGOT, SGPT and SUN", page 66).

SUN:

Forty-two Africans and 21 Caucasians were studied for SUN values. The values obtained for each ethnic group, age group and group of infection were remarkably constant and within the normal accepted range of values.

Frequency distribution of persons tested was 95% within the range of 10 - 20 mg percent; and 4,5% within the range 20 - 25 mg percent (Table 20D "Limpopo: Frequency distribution, blood biochemistry, bilirubin, SGOT, SGPT and SUN", page 66).

3.3 SIGNIFICANCE OF PRELIMINARY SURVEYS

Discussion of comparative areas

The two study areas are unlike each other in geography, climate and agronomy. Whereas at Limpopo two ethnic groups, African and Caucasian, were included in the study, at Dennilton only Africans were included.

The epidemiology of bilharziasis could be expected to differ in each study area, i.e., prevalence of the disease in the population, the intensity of infection and pathology in the individual could possibly follow variable patterns.

Significant factors could be lost in a direct comparison of the data

obtained. An intermediate standard to which each area in turn could be compared would, therefore, give a clearer picture of the status of the disease in the study areas before chemotherapy was commenced.

Comparisons with an intermediate area nearby could produce useful data, while also acting as a control on results obtained from the study areas.

It is intended to carry out such comparisons. The common standard of comparison used will be Komatipoort on the border of the Transvaal where a study was conducted in 1967 - 69 by Walker et al (1970). Komatipoort was chosen because of detailed and independent data available from there.

Komatipoort is situated in the lowveld, almost intermediate between Dennilton and Limpopo. Geographical and climatic factors resemble more those found at Limpopo, the ethnic grouping and agronomy resemble those found at Dennilton.

For establishing the status of the disease in terms of known standards data obtained from the study areas will be compared also with accepted assessments reported from Egypt.

3.3.1 DENNILTON: COMPARISON WITH KOMATIPOORT

PREVALENCE OF THE DISEASE

No disease prevalence surveys were carried out at Dennilton prior to the commencement of studies. Two groups were studied, "A" and "B", the latter group included older persons. Refer to Table 8 "Dennilton: Frequency distribution of prevalence of infection by age in two groups of students", page 46.

Prevalence of infection at Dennilton, based on limited data obtained from selection of patients for clinical trials, is estimated at 60 - 80% for S. haematobium infections, little data being available for mansoni infections. Walker et al (1970) found prevalence to be 62,5% for S. haematobium and 58,5% for S. mansoni infections at Komatipoort. Refer to Table 21 "Dennilton: Compared with Komatipoort and Limpopo. Preliminary prevalence egg counts haematology and blood biochemistry", page 69.

DENNILTON COMPARED WITH KOMATIPOORT AND LIMPOPO
PRELIMINARY PREVALENCE EGG COUNTS HAEMATOLOGY
AND BLOOD BIOCHEMISTRY

PRE-TREATMENT

	LIMPOPO	DENNILTON	KOMATIPOORT(according to Walker et al (1970)
PREVALENCE %	23% Total all races and ages Afr. highest in years 10-14 Cauc. highest in years 5-19 All males high 22,1/36,1% Afr. females highest 41,7%	60-80% Total population all ages and study groups. Highest infection in 12-16 age group	Afr. *S. h* 62,5% overall prevalence. Highest in ages 10-14. *S. m* 58,5% highest in ages 15+ with male-bias
EGGS *S. h*	Afr. 196/15: Cauc. 39/3	"A" 179/18: "B" 62/0	Afr. *S. h* Mean Male and Female 380
S. m	Afr. 2 : 14		*S. m* Mean Male and Female 44
S. h + *S. m*	Afr. 12 : 108		
HAEMATOLOGY			
Haematuria	2+/4+ High in all races	4+ High in both groups	Afr. *S. h* 2+ estimate
Sed Rate	Afr. 5/17 Higher in all ages. Highest in *S. h* + *S. m* (mixed). Cauc. 4/5 low rate with highest in *S. m*		Afr. Infected 20/32. Not infected 14/21. Highest values in juvenile group
Haemoglobin	12,6/15,6 Normal in all ages + races	13,5 for both groups. Normal for both groups and all ages	Afr. Infected 12,3/14,6. Not infected 12,4/14,9. Normal in both groups and all ages
MCH	31/33 normal in all ages + races		
Haemocrit	40/47 normal in all ages + races	1/2 for group "B". Highest in puberty-adolescent ages	Afr. Infected 38,5/46. Not infected 39,5/47,5. Normal in both groups
Eosinophilia	Afr. 9/33. Highest in mature decreasing in young ages. Highest in *S. h*. Cauc. 6,4/11,7. Low rate. High in young and mature ages for *S. h* + *S. m* (mixed)		Afr. Infected 22,0% over 1 000. Not infected 12,5% over 1 000. Not abnormal
WBC		8 175 for both groups. Lowest in group "B"	
BIO-CHEMICAL			
Bilirubin	0,51/0,11-0,60/0,13 Normal in all races and ages	Mean for two groups 0,5 Normal for both groups and all ages. Highest values for group "A".	
SGOT	Afr. 20/28. Higher rate in mature age and *S. h*. Cauc. 24/34. Highest in young and *S. h*	Mean for two groups 25 units. Norman for both groups and all ages. Highest for group "B"	
SGPT	8/12 Normal in all ages + races	Mean for "A" group 20 units. Normal for all age groups. Highest for juvenile age	
SUN	14/16 Normal in all ages + races		

Compiled from Tables 8, 9, 10, 11, pages 46, 47, 49, 50 and Tables 13A and 13B, 17, 18, 19 pages 54, 55, 60, 62, 65.

The puberty-adolescent age group (12 - 16 years) was most affected at Dennilton, similar to Komatipoort. Infection prevalence at both places had a male-bias.

Infections at Dennilton were almost exclusively S. haematobium, whereas at Komatipoort prevalence of infection was almost evenly distributed for S. haematobium and mansoni.

Egg excretion

Egg excretion was only studied in urine specimens at Dennilton where infection was almost exclusively S. haematobium. "B" group was examined about three years before "A" group when the mean number of eggs passed per patient (62/0) was much less than the mean for "A" (179/18). Mean egg counts for Dennilton were about half the mean for patients excreting S. haematobium eggs at Komatipoort.

Haematuria

At Dennilton haematuria was high in both groups (4+), almost double that estimated for Komatipoort (2+). About one-third of all urine specimens examined at Dennilton were macroscopically coloured ranging from deep brown (turbid) to bright crimson (frank haematuria), all containing much sediment. The remaining two-thirds specimens were less turbid. Contrast this with Komatipoort where turbidity and frank haematuria was much less. No apparent correlation existed between degree of haematuria and rate of egg excretion at either place.

Haematology studies

Sedimentation rates were not studied at Dennilton. Mean haemoglobin concentration values were normal for both groups and all ages at Dennilton (13,5), and for the infected group at Komatipoort (14,6). No anaemia was found in any of the groups studied at the two centres.

At Dennilton WBC counts were higher in the older Group "B" studied two years earlier (8 175) than in Group "A" (8 000). These values were within the normal accepted range. Eosinophile counts were

highest in Group "B" (1 - 2) in the puberty-adolescent ages. At Komatipoort the counts were comparable, although uninfected persons had lower counts. All values of infected persons at both centres were considered to exceed normal accepted values.

BLOOD BIOCHEMICAL STUDIES

Biochemical studies at Dennilton included bilirubin, SGOT and SGPT. None of these were reported for Komatipoort.

Mean values for bilirubin were within normal accepted range for both groups and all ages (0,5). Highest values were found in Group "A", consisting of younger patients and studied two years later than Group "B".

Mean values for SGOT were normal (25) for all groups and ages, with highest values found in Group "B".

SGPT mean values were available only for Group "A". These were normal (20), with highest values found amongst the juvenile ages.

SUMMARY

The comparison between groups from Dennilton and Komatipoort show that the overall prevalence of infection was almost equal, bearing in mind that the prevalence at the former place was an estimate. The same age groups were similarly affected, but S. haematobium infections predominated at Dennilton. There was a male-bias of infection at both places.

Although percentage prevalence was thought to be more or less equal at both places, the egg counts at Dennilton were less than half those at Komatipoort, accompanied by a greater degree of haematuria. One-third of all urine specimens at Dennilton were turbid with large amounts of sediment present, and many showed frank haematuria.

Haematology studies reveal no anaemia but some raised eosinophile values present amongst the older ages, which was comparable with Komatipoort.

Biochemical studies at Dennilton showed that mean values for bilirubin, SGOT and SGPT were all within the normal range of values for both

groups, although values varied slightly for the various age groups. Bilirubin and SGPT values were higher in younger ages. Higher values were obtained in older ages for SGOT. No data on similar studies are available for Komatipoort.

3.3.2 LIMPOPO: COMPARISON WITH KOMATIPOORT

PREVALENCE OF THE DISEASE

Table 21 "Limpopo and Dennilton compared with Komatipoort, preliminary prevalence, egg counts, haematology and blood biochemistry, page 69 indicates the various standards of comparison.

At the first test period (pre-treatment) in 1963/64 the overall prevalence of bilharziasis in the two ethnic groups at Limpopo was 23%. This compared with Turner's (1908) prevalence of 25,8% based on urine surveys of African mine labourers recruited from Mozambique in 1907. Prates (1948: 1961) has placed the prevalence at between 40 and 100% for specific localities, based mostly on the examination of limited and insignificant groups. Walker et al (1970) found the prevalence amongst African school children in Komatipoort to be 62,5% for S. haematobium and 58,5% for S. mansoni in 1968/69.

The highest prevalence in Limpopo was found in African women and in children aged 10 - 14 years. Overall there was a male-bias in prevalence for all ethnic and age groups. At Komatipoort the highest prevalence was in the 10 - 14 years age group for S. haematobium and in an older age group for S. mansoni, coinciding with similar data for Africans at Limpopo. However, amongst the Caucasians at Limpopo the greatest prevalence was in older ages ranging in intensity from juvenile (5 years) to the mature age group (19 years).

Prevalence of infection at Limpopo was apparently low compared with Turner's findings for selected Mozambique African mine labourers more than 50 years ago. However, recent prevalence for Africans only was higher than that reported by Turner: 36,6% for males and 41,7% for females respectively.

Compared with prevalence in Africans at Komatipoort (61% for both species of infection), the prevalence for all African groups and ages at Limpopo was almost half (39,1%). The overall Caucasian prevalence was even lower (15%). Prevalence in the African age groups followed the same pattern as at Komatipoort, with the greatest prevalence in the puberty-adolescent age group. However, the highest single prevalence in Limpopo was female-biased, opposite to that found at Komatipoort. Caucasian prevalence had a male-bias.

The species of infection at Limpopo was greatest for S. haematobium as compared with S. mansoni in a ratio of 7 : 1, whereas the ratio for both species at Komatipoort was nearly equal. In addition, at Limpopo there were many mixed S. haematobium and mansoni infections, mostly in Africans.

Egg excretion

Egg excretion of each schistosome species followed the same pattern in both areas, being far heavier for S. haematobium than for S. mansoni. The mean egg counts per person were far higher at Komatipoort (S. haematobium = 380, S. mansoni = 44) than at Limpopo. In Limpopo Africans excreted more eggs than Caucasians for S. haematobium, but less for S. mansoni.

Egg excretion in Limpopo for the various species was as follows:-

Live/dead egg excretion for species of infection

	African	Caucasian
S. haematobium infection	196/15	39/3
S. mansoni infection	2	14
mixed infections	12	108

(extracted from Table 17, page 60)

Ratio of eggs excreted by Africans at Limpopo as compared with Komatipoort was almost half.

Haematuria

Haematuria was heavier at Limpopo ranging from 2+ to 4+, than at

Komatipoort (2+). Africans passed more RBC in urine than did Caucasians, necessitating further dilution of centrifuged samples when these were examined microscopically. The macroscopic appearance of nearly all urine specimens was red tinted and turbid.

There was no apparent correlation between severity of haematuria and numbers of eggs excreted at either place.

Haematology studies

At Limpopo mean sedimentation rates for Africans (range 5 - 17) were higher than those for Caucasians (range 4 - 5), but both ethnic groups had considerably lower values than Africans at Komatipoort (infected range 20 - 32: not infected range 14 - 21) where the values were high. Africans had highest values for mixed infections while highest values for Caucasians were for S. mansoni infections. Some Caucasians had higher values than normally accepted.

Mean haemoglobin concentration values at Limpopo were normal for all ages and ethnic groups (range 12,6 - 15,6) and equal to infected and uninfected groups at Komatipoort. Anaemia is not present in the infected persons examined at Limpopo.

MCH concentration was normal for all ages and ethnic groups at Limpopo (range 31 - 33) and more or less resembled the values found at Komatipoort.

Blood biochemical studies

Studies at Limpopo included the determination of values for bilirubin, SGOT, SGPT and SUN. Unfortunately, similar studies have not been published for Komatipoort. However, all mean values obtained at Limpopo were considered to be within the normal accepted range in all age and ethnic groups, as follows:-

Mean values for blood biochemical studies (Limpopo)

	Africans	Caucasians
Bilirubin	0,51-0,11	0,60-0,13
SGOT	20-28	24-34
SGPT	8-12	8-12
SUN	14-16	14-16

(extracted from Table 19, page 65)

Highest values in all studies were found in S. haematobium infections.

SUMMARY

In this investigation the overall mean prevalence of infection at Limpopo was almost half that at Komatipoort. Prevalence in the Limpopo Caucasian group was much lower than in Africans at both Limpopo and Komatipoort.

Highest disease prevalence in the investigation was found in puberty-adolescent age groups at both places. There was a male-bias of infection in Africans at Komatipoort and Caucasians in Limpopo, but an older female-bias in Africans at Limpopo.

With lower prevalence of infection, egg excretion was much lower at Limpopo than at Komatipoort. Africans at Limpopo excreted larger egg numbers than Caucasians. Larger numbers of S. haematobium eggs were excreted than S. mansoni, especially by Africans. Haematuria seemed to be heavier at Limpopo than at Komatipoort, especially amongst Africans whose urine specimens tended to be turbid with macroscopic haematuria.

Haematology studies showed that while Caucasians had higher eosinophile values than Africans at Limpopo, both these groups had lower values than Africans at Komatipoort. Some had values raised above normal, especially in S. mansoni infections. Mean values for tests of haemoglobin concentration, MCH concentration and haemocrit values were comparable for all groups and ages at both places and considered to be within normal accepted range.

Blood biochemical studies included SGOT, SGPT and SUN. Values for these tests can be considered within normal accepted range for both groups at Limpopo. A comparison was not possible with Komatipoort.

On the evidence of prevalence of infection and rate of excretion of eggs by the two communities suggested by the investigations, Africans infected at Komatipoort must be considered as having a heavier and more intensive bilharziasis infection than both Caucasians and Africans infected at Limpopo. All other components studied seem fairly equal for both communities.

3.3.3 STUDY AREAS COMPARED: LIMPOPO/DENNILTON

PREVALENCE OF THE DISEASE

Overall prevalence of infection was 23% at Limpopo in 1963/64 at the commencement of the study and before treatment, with sharp differences between the ethnic groups as well as the sexes, as follows:-

Percentage of prevalence by sex of ethnic group

	Males	Females
Africans	36,6	41,7
Caucasians	24,1	5,8

(extracted from Tables 13A and B, pages 54 and 55)

Prevalence of infection at Dennilton, shortly after this time and prior to chemotherapy, was estimated at 70 - 80%. This resembled Komatipoort where the mean prevalence for both species of infection was 60,5% in 1968/69.

At Dennilton and Komatipoort there was a male-bias of infection, at Limpopo the bias was more towards female, due to the high infection rate amongst older African females. The Caucasian juvenile-adolescent age groups (5 - 19 years) were mostly affected at Limpopo, while for Africans the puberty-adolescent age group (10 - 14 years) had the greatest prevalence.

EGG EXCRETION

Mean egg counts for S. haematobium for Africans at Limpopo and Dennilton's Group "A" were very similar (190/15 : 179/18). Group "B" which had been studied 2 years previously had a smaller mean count (62/0).

Caucasians having haematobium infections at Limpopo also had a smaller mean egg count (39/3).

Mean egg counts for Africans at Komatipoort with S. haematobium were almost double that for Africans elsewhere.

Egg counts for S. mansoni and mixed infections were not done at

Dennilton. At Limpopo counts for these infections in Africans were low (12 and 108 respectively), while at Komatipoort they were higher for S. mansoni (44).

Haematuria

Haematuria accompanying S. haematobium infections was heavier at both Limpopo and Dennilton than at Komatipoort. Most urine specimens from Limpopo and Dennilton ranged from turbid to bright red in colour. The degree of haematuria was not related to egg counts.

Haematology studies

Sedimentation rates at Limpopo for both ethnic groups were considerably lower than those for Africans at Komatipoort. Some Caucasians at Limpopo had values higher than the normal accepted range. S. mansoni and mixed S. haematobium and mansoni infections had highest sedimentation rates. Mean haemoglobin concentration values were within normal accepted values for all three study centres, with no anaemia present.

Mean MCH and haemocrit values were comparable and within normal accepted values at all three study centres.

Mean eosinophile counts were higher amongst Africans than in Caucasians at Limpopo, but comparable with Africans at Komatipoort where these were not considered as unduly raised. WBC counts at Dennilton were highest in the earlier Group "B" studied although still within normal accepted values.

Blood biochemical studies

These studies included bilirubin, SGOT, SGPT and SUN at Limpopo, the latter component was not studied at Dennilton. Values for such studies have not been published for Komatipoort.

All values for blood biochemical studies at these centres were within the normal accepted range, although the values inclined towards the upper limits. Highest values were found in the younger age groups and for S. haematobium infections.

3.4 CONCLUSIONS ON PREVALENCE AND INTENSITY OF BILHARZIASIS IN THE STUDY AREAS

Jordan (1968) having carried out extensive studies relevant to the subject, considers that whereas worm loads in individuals cannot be directly measured, egg counts can be accepted as some indication of intensity of infection. He quotes Annecke et al (1955) and Pitchford (1952) from the Transvaal in support. However, prevalence alone could be insufficient as an index where this is very high. Many factors, including times of collection of specimens, etc., would have to be taken into consideration to make valid assessments, but egg counts can and are used to establish the intensity of infection, and can also be used as a measure to demonstrate the efficacy of control measures.

While there was a great variability of conditions under which data had been collected and processed at the study centres of Limpopo and Dennilton, this was largely offset by standardisation of the parameters as far as possible and standardisation of data obtained by using simple mean values.

When a direct comparison was made of the prevalence of infection with egg loads for the two study areas of Limpopo and Dennilton and the comparison area of Komatipoort, results showed that while the pattern outlined by Jordan of prevalence of infection related to egg counts was true for Africans studied at Komatipoort, i.e., high prevalence related to high egg counts, also for Africans at Limpopo with high prevalence and high egg counts, Caucasians with low prevalence and low egg counts, this does not hold for Africans at Dennilton where a high prevalence was related to a low egg count. Refer to Fig 9 "Komatipoort/Limpopo/Dennilton comparison of egg counts related to prevalence of infection", page 79.

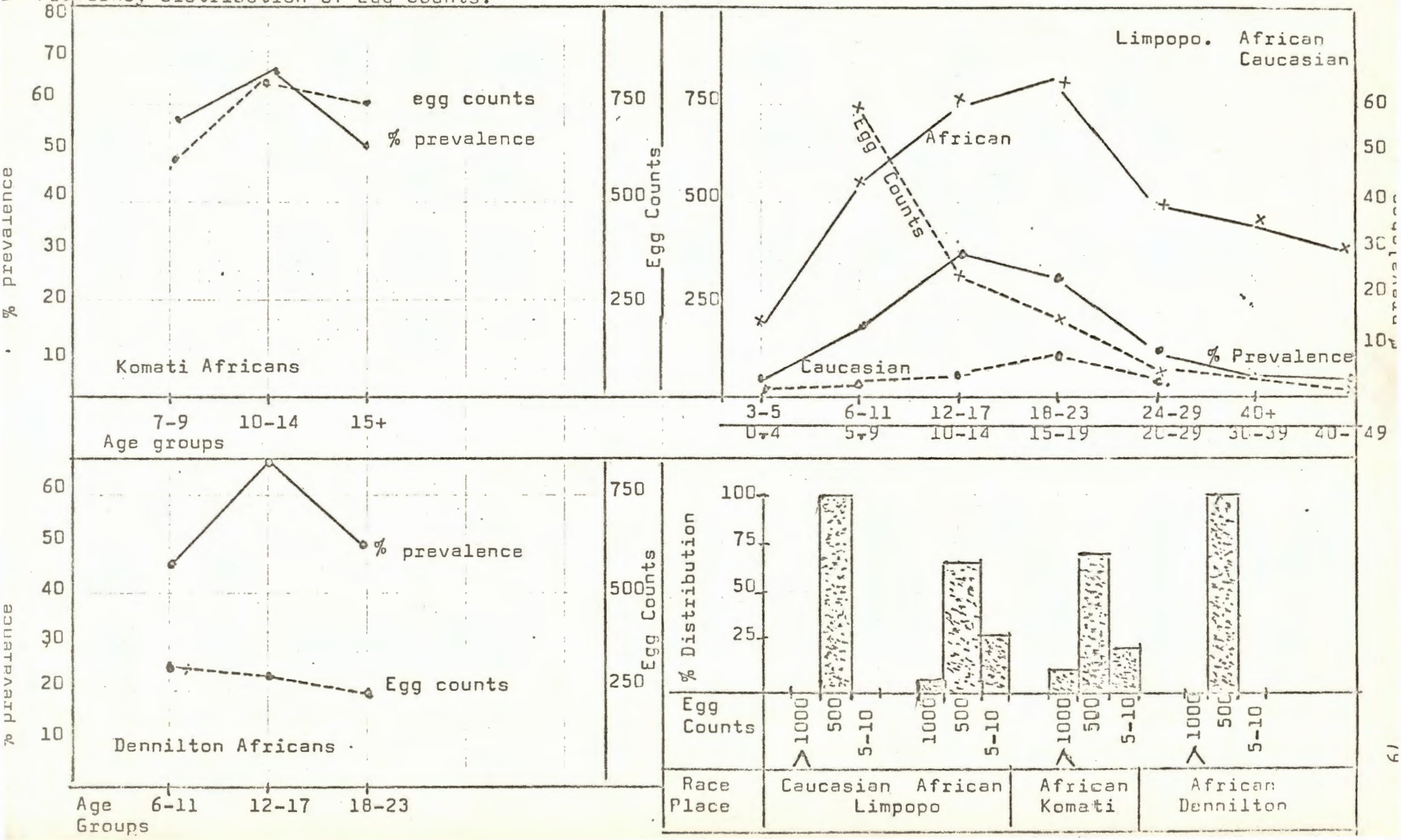
Also the percentage distribution of egg counts for Africans at Limpopo and Komatipoort was predictable, with individual mean counts of about one-third of each group studied excreting over 500 eggs. But Caucasians at Limpopo with a low prevalence and Africans at Dennilton with a high prevalence, all had comparatively low egg counts, less than 500 eggs per individual in each group.

Values obtained for blood biochemical tests of SGOT and SGPT are accepted as relating to the release of transaminases from tissue,

FIGURE 9

A" Egg counts related to prevalence of infection.
B" Frequency distribution of Egg Counts.

S. haematobium - Komati, Limpopo and Dennilton



including liver or heart tissue, circulating in the blood. The values of these tests are elevated when these tissues are damaged. Liver damage, contrary to heart damage, results in rises of SGOT and SGPT to about the same level. Such elevated values could decline gradually over weeks or months after an episode of liver damage as in carbon tetrachloride poisoning.

Values for the tests can be elevated before any change in liver function appears. Elevation can also be caused by various acute and chronic imflammatory diseases or allergic and degenerative conditions not necessarily only by damage due to toxic substances.

Saif et al (1964), studying the effects of bilharziasis on the values of these tests in Egypt, concluded that in all its forms there is an appreciable increase in both SGOT and SGPT, and that values in individuals are higher for intestinal (S. mansoni) than in urinary bilharziasis (S. haematobium) and that the values are significantly higher for SGOT than SGPT. When associated with hepatosplenomegaly values of both tests are much higher in the presence of ascites, conforming with the progress of pathology due to hepatocellular necrosis resulting from ishaemic changes. Elevation may also be due to destruction of worms and allergic reaction of the host, and could also be due to toxic drug reaction when the value increase would be uniform.

The values for SGOT and SGPT at Limpopo and Dennilton were not considered to be higher than the top range of accepted normal values for healthy individuals. Values for these tests were not published for Komatipoort.

The Limpopo mean values for SGOT were highest in the youngest age group of Caucasians (34, range 30 - 40) followed by Africans in the oldest ages (31, range 12 - 48) in S. haematobium infections. At Dennilton the mean value was 25 (range 10 - 105), compared with values given by Saif et al for sick persons in Egypt of 46,51 ($\pm$ 9,75) for S. haematobium and 58,19 ($\pm$ 16,25) for S. mansoni infections.

In the case of SGPT the values were highest for both Africans and Caucasians at Limpopo in the older ages (11, range 3 - 32, and 12, range 2 - 21), more or less similar for both species of infection. For Africans at Dennilton the mean value was 20, range 7 - 33, as

compared with Egypt of 41,8 (± 10,69 : range 15 - 66) for S. haematobium. For S. mansoni the Egyptian values are 52,71 (± 17,78 : range 18 - 85). Refer to Table 22 "Comparison of biochemical values for Limpopo, Dennilton and Egypt", page 81.

There was no hepatosplenomegaly of any marked degree present in any age or group at either Limpopo or at Dennilton, and no great degree of involvement of the liver was apparent as based on results obtained from SGOT and SGPT studies, such as is reported from Egypt.

High eosinophile counts and some degree of anaemia have been reported from other centres for parasitic diseases, the values varying in proportion to the load of parasites carried by the individual. Haematology studies at the two study areas and at the comparison area of Komatipoort showed that there was only a slight degree of eosinophilia and no anaemia present there.

The conclusion on the prevalence and intensity of bilharziasis present in the study areas is that while the prevalence of infection is high amongst Africans at both Limpopo and Dennilton as compared with Komatipoort, it is much less so than in Egypt. The degree of intensity is less than at Komatipoort and very much less than the classical illness extensively reported from Egypt. Intensity of infection in Caucasians at Limpopo was less than Africans.

TABLE 22

COMPARISON OF BLOOD BIOCHEMICAL VALUES FOR LIMPOPO, DENNILTON AND EGYPT

		Mean values for			
		SGOT		SGPT	
		S. haematobium	S. mansoni	S. haematobium	S. mansoni
(1) Limpopo	Caucasian	34(30-40)		12(2-21)	
	African	31(12-48)		11(3-32)	
(1) Dennilton		25(10-105)		20(7-33)	
(2) Egypt		46,5(20-68)	58,19(30-90)	41,48(15-66)	52,7(18-85)

(1) Author's data

(2) Data from Saif et al (1964)

CHAPTER 4

RESULTS OF 10 YEARS CHEMOTHERAPY ALONE AND IN COMBINATION WITH OTHER CONTROL MEASURES

4.1 INTRODUCTION

The results of mass chemotherapy can be divided into two categories:-

a) as short-term, where the individual is expected to benefit from treatment; and

b) as long-term, when the community as a whole could benefit by an appreciable decrease in the rate of transmission.

If the individual benefits from mass treatment of the population, this could be measured in degrees of clinical improvement, based on improvement in blood biochemical function values, haematology values and organ functional improvement, all coupled with a dramatic reduction in the numbers of eggs excreted by the individual. These improvements, except for some irreversible sequelae of the infection, would become evident a relatively short time after therapy. For some individuals therapy would only be necessary on one or two occasions, to obtain these improvements, for the bulk of an infected population therapy would have to be sequential over many years for community benefits to be demonstrated. However, significant increases in values after therapy in haematology and especially blood biochemical tests could also indicate toxic effects of the schistosomicide used, as well as possible allergic and autoimmune reactions of the host to schistosomes damaged by such treatment. Some of these changes in values, particularly of the transaminases, would become evident in a matter of hours after treatment. If they are temporary with no lasting effects on the patient, values would return to acceptable normal limits within a few days. If values become significantly high after use of a schistosomicide and these do not subside after approximately a week, tissue damage to the host can be suspected, with the process even ending in fatality. Should high values return to normal within days the reason could be due to absorption by the hose of foreign tissue released by damaged schistosomes. Clinical improvement for a patient would be indicated by return to normal accepted values shortly after therapy.

At no time can an actual assessment be made of the individual's parasite load. Interpretation of the pattern of egg excretion, dead or alive, is the nearest approach to such assessment. Egg

excretion patterns are, therefore, extremely important. Many of the schistosomes may be severely damaged by the schistosomicide used, some only slightly so. Damage may occur first to the gonads of the female resulting in an abrupt cessation of egg laying. Severely damaged schistosomes, male and female, rarely recover and they die during varying periods of time resulting in permanent termination of egg laying. Those schistosomes only slightly damaged could reconstitute damaged tissue and egg laying would commence again within several weeks. Not one of the schistosomicides now available is known to affect the growing schistosomule. As persons living in endemic areas are exposed to constant re-infestation, schistosomules may reach maturity after therapy with subsequent egg laying. This may be seen as continued egg laying but at a lower rate than before therapy. This can be confused with the recovery of a few slightly damaged females coming into production again. Reinfection shortly after treatment is a reality but not as likely to occur as previously presumed. When this happens there is usually an appreciable increase in egg excretion about 6 - 8 weeks after cessation of egg laying. Refer to Fig 1, page 85. "Pattern of egg excretion after chemotherapy". Viable eggs can be excreted by a person for some time after all schistosomes have been killed, while dead eggs can be passed in urine for lengthy periods afterwards. As severity of the disease is related to the number of eggs excreted the individual pathology is not only improved by therapy but this also lessens the rate of infection in a community.

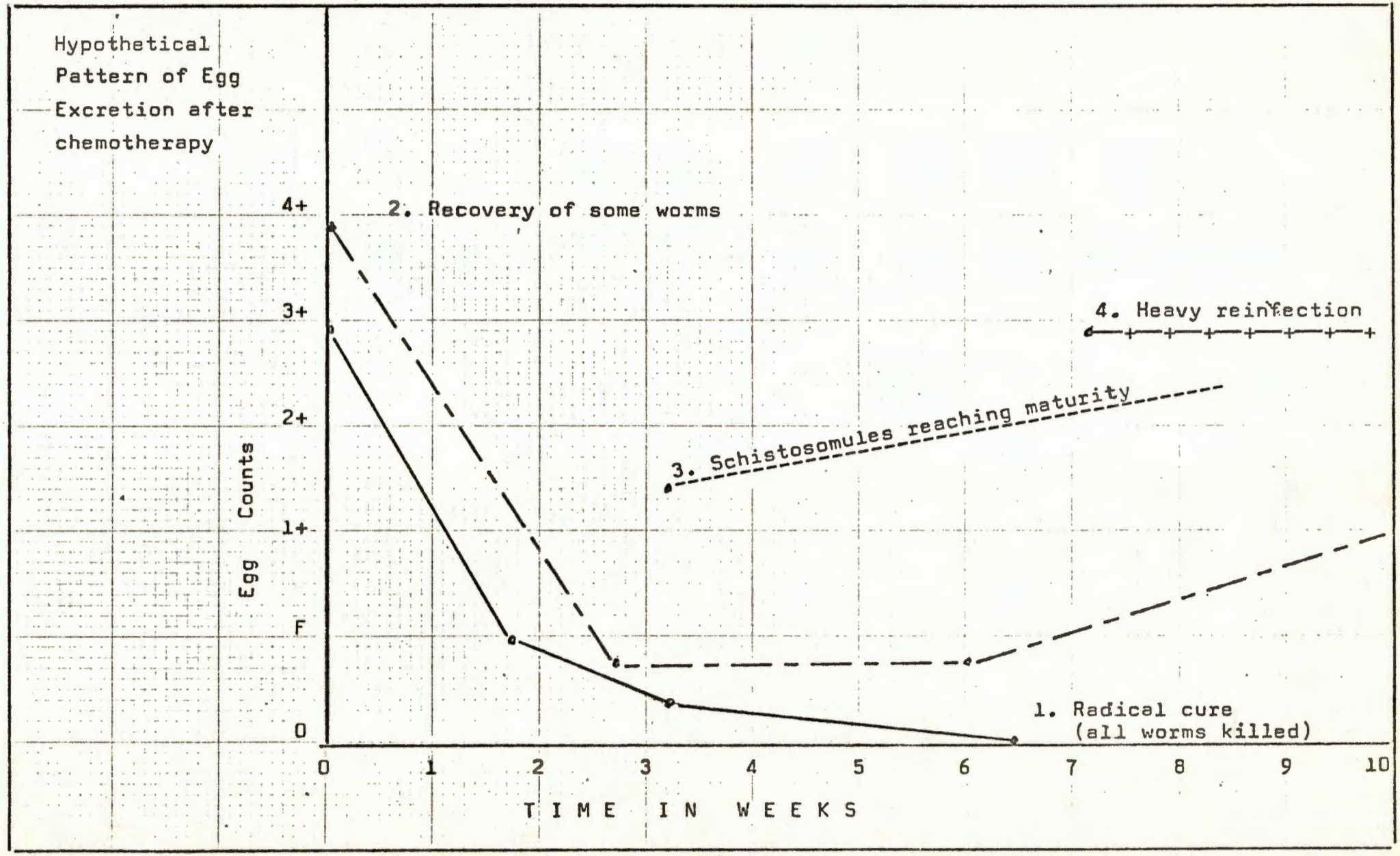
Long-term benefit to the total community coming from an appreciable decrease in the rate of transmission would be linked to reduced egg excretion, resulting from mass treatment of the population on many occasions spread over an extended period.

Measurement of this mass benefit could be detected by <u>incidence</u> of infection (rate at which uninfected people become positive), or the <u>prevalence</u> of infection (the proportion of the population infected), or the <u>intensity</u> of infection. Conclusions could be based on egg output of part or the total community.

The various parameters of possible improvement and benefits derived from mass chemotherapy of a community will be considered for the two study areas of Dennilton and Limpopo.

Two sets of data are available for assessment of possible improvement

FIGURE 1


Hypothetical Pattern of Egg Excretion after chemotherapy
4+
3+
2+
1+
F
0
Egg Counts
2. Recovery of some worms
4. Heavy reinfection
3. Schistosomules reaching maturity
1. Radical cure (all worms killed)
0
1
2
3
4
5
6
7
8
9
10
TIME IN WEEKS

after chemotherapy in the community at Limpopo: These are:-

a) short-term intensive studies of limited numbers of individual patients followed up for various periods to 150 days, for haematological, blood biochemical, and in some instances parasitological studies, including quantitative egg counts, and,

b) periodical large-scale prevalence studies of the infection in the total population. Some data are available on new infections in limited groups, when egg excretion by individuals newly infected was measured quantitatively.

Several different schistosomicides were used over the 10 year period of control.

For Dennilton the data are limited to follow-up studies of small groups treated with hycanthone in clinical trials. Egg excretion by individuals in these groups was measured quantitatively. In each study area the short-term results for the individual obtained from mass treatment will be considered first: followed by consideration of long-term results in which the community could be expected to benefit.

4.2 SHORT-TERM RESULTS

4.2.1 LIMPOPO: POST-CHEMOTHERAPY SHORT-TERM SURVEYS FOR ETHNIC GROUPS AND INFECTIONS

BLOOD BIOCHEMICAL STUDIES

Compare Tables 19 (pre-therapy) and 23 (post-therapy), pages 65 and 87, 88, 89, 90 in which the mean values obtained for tests are set out for infections of S. haematobium, S. mansoni and mixed S. haematobium and mansoni for all age groups of the two ethnic groups.

Three groups of infection for ethnic and age groups

Group 1: S. haematobium infections

Group 2: S. mansoni infections

Group 3: S. haematobium and S. mansoni mixed infections

"D"

TABLE 23

LIMPOPO

POST-CHEMOTHERAPY STUDIES

BLOOD BIOCHEMICAL STUDIES

GROUP 1: S. HAEMATOBIUM

Four components tested for each patient

NOTE: (a) Bilirubin: figures denote mean values for total/conjugate-0,56/0,12

(b) SGOT,SGPT and SUN: figures denote mean values 13,7

(c) Number of patients tested is placed in brackets beneath mean and range-(4)

TEST	AGE	PRE-THERAPY	DAYS POST-CHEMOTHERAPY 7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS
AFRICANS	3-5	-	-	-	-	-	-	-
(a)Bilirubin	6-11	0,54	0,56/0,12 (c) (4)	0,49/0,11 (2)	-	-	-	-
mg% (Total conjugate) normal value 0,20/1,0 mg%	12-17	0,49	0,51/0,11 (c) (10)	0,54/0,13 (1)	-	-	-	-
	18-23	0,59	1,04/0,31 (*) (c) (11)	0,64/0,14 (8)	0,57/0,13 (4)	-	0,59/0,13 (3)	-
	24-39	0,67	0,67/0,16 (c) (11)	0,53/0,13 (9)	0,59/0,13 (-*) (8)	0,62/0,13 (7)	0,57/0,14 (-*) (8)	
	40+	0,65	0,75/0,15 (c) (2)	0,69/0,13 (2)	-	0,51/0,13 (-*) (2)	-	-
CAUCASIANS	3-5	0,40	0,51/0,13 (c) (2)	-	-	-	-	0,44/0,13 (-*) (1)
(a)Bilirubin	6-11	0,54	0,54/0,13 (c) (1)	-	-	-	-	0,44/0,13 (-*) (1)
	12-17	0,54	0,54/0,13 (c) (1)	-	0,44/0,13 (1)	-	-	0,44/0,13 (-*) (1)
	18-23	0,58	0,64/0,11 (*) (c) (4)	0,45/0,09 (2)	0,59/0,11 (2)	-	-	-
	24-39	0,63	0,60/0,11 (c) (3)	0,44/0,13 (1)	0,64/0,13 (1)	-	-	0,92/0,13 (**) (1)
	40+		-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SUN	6-11	14	13,7 (c) (3)	14 (1)	-	-	-	-
mg% normal value 8-16 mg%	12-17	14	14,2 (c) (7)	-	-	-	-	-
	18-23	15	14,7 (c) (10)	15,8 (1)	14,9 (1)	-	-	-
	24-39	17	15,4 (c) (4)	15,9 (5)	16,2 (5)	11,7 (5)	-	-
	40+	15	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(b)SUN	6-11	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-
	18-23	17	15,0 (c) (3)	14,5 (2)	14,0 (2)	-	-	-
	24-39	14	14,6 (c) (1)	14 (1)	14,9 (1)	-	-	-
	40+	-	-	-	-	-	-	-

* significant rise (— 10%)

** highly significant rise (— 5%)

-* significant fall

"D" Comparative values from Table 19, page 65

Calculated from computerised data obtained from biochemical studies carried out for hycanthone studies at Lourenco Marques Public Health Laboratories.

Monitor: K.Hechter-Schulz. Unpublished data Winthrop Files Johannesburg.

Three groups of infection for ethnic and age groups

Group 1: S. haematobium infections
Group 2: S. mansoni infections
Group 3: S. haematobium and S. mansoni mixed infections

TABLE 23 (Continued)

LIMPOPO
POST-CHEMOTHERAPY STUDIES
BLOOD BIOCHEMICAL STUDIES
GROUP 1: S. HAEMATOBIUM

Four components tested for each patient

NOTE: (a) Bilirubin: figures denote mean values for total/conjugate- 0,56/0,12
(b) SGOT, SGPT and SLV: figures denote mean values 13,7
(c) Number of patients tested is placed in brackets beneath mean and range-(4)

TEST	AGE	PRE-THERAPY	DAYS POST-CHEMOTHERAPY 7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SGOT	6-11	20	38,4 (••) (4)	24 (2)	-	-	-	-
Karmen units	12-17	28	56,3 (••) (10)	21 (1)	-	-	-	-
normal value	18-23	28	109,9 (••) (11)	28,4 (7)	29,2 (4)	-	22,1 (-•) (3)	-
10-40 units	24-39	29.	55,5 (••) (11)	26,5 (10)	26,1 (9)	27,7 (6)	27,5 (-•) (8)	-
	40+	31	33,8 (2)	27 (2)	-	-	-	-
CAUCASIANS	3-5	34	22,3 (-•) (2)	-	-	-	-	30 (-•) (1)
(b)SGOT	6-11	34	26 (-•) (1)	-	-	-	-	18 (-•) (1)
	12-17	21	28,5 (••) (1)	16 (1)	26 (1)	-	-	9 (-•) (1)
	18-23	23	38,5 (••) (4)	33 (2)	27 (3)	-	-	-
	24-39	24	39,7 (••) (3)	15 (1)	38 (1)	-	-	20 (-•) (1)
	40+	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SGPT	6-11	8	12,3 (••) (4)	5,3 (-•) (2)	-	-	-	-
Karmen units	12-17	9	26,5 (••) (10)	7,5 (-•) (1)	-	-	-	-
normal value	18-23	10	155,9 (••) (11)	13,6 (6)	8,5 (4)	-	9,9 (3)	-
8-35 units	24-39	13	22,7 (••) (11)	11,7 (9)	10 (9)	5,3 (5)	13,8 (8)	-
	40+	4	3,8 (2)	4,5 (2)	-	-	-	-
CAUCASIANS	3-5	9	5,7 (-•) (2)	-	-	-	-	20 (••) (1)
(b)SGPT	6-11	9	3 (-•) (1)	-	-	-	-	20 (••) (1)
	12-17	2	2 (1)	2 (1)	-	-	-	5 (•) (1)
	18-23	8	13,0 (•) (4)	16,5 (2)	10,3 (3)	-	-	-
	24-39	10	20,4 (••) (3)	3 (1)	26 (••) (1)	-	-	7 (••) (1)
	40+	-	-	-	-	-	-	-

• significant rise (< 10%)

•• highly significant rise (< 5%)

-• significant fall

"p" Comparative values from Table 19, page 65

Calculated from computerised data obtained from biochemical studies carried out for Mycenthone studies at Lourenco Marques Public Health Laboratories.
Monitor: K.Hechter-Schulz. Unpublished data Winthrop Files Johannesburg.

Three groups of infection for ethnic and age groups

Group 1: S. haematobium infections

Group 2: S. mansoni infections

Group 3: S. haematobium and S. mansoni mixed infections

TABLE 23 (Continued)

LIMPOPO

POST-CHEMOTHERAPY STUDIES

BLOOD BIOCHEMICAL STUDIES

GROUP 2: S. MANSONI

Four components tested for each patient

NOTE: (a) Bilirubin: figures denote mean values for total/conjugate- 0,56/0,12

(b) SGOT, SGPT and SUN: figures denote mean values 13,7

(c) Number of patients tested is placed in brackets beneath mean and range-(4)

TEST	AGE	PRE THERAPY "p"	DAYS POST-CHEMOTHERAPY 7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS
AFRICANS	3-5	-	-	-	-	-	-	-
(a)Bilirubin	6-11	-	-	-	-	-	-	-
mg% (total conjugate)	12-17	-	-	-	-	-	-	-
normal	18-23	-	-	-	-	-	-	-
value 0,20/1,0	24-39	0,58	0,72/0,13 (*) (2)	0,44/0,09 (-*) (1)	-	-	-	-
mg%	40+	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(a)Bilirubin	6-11	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-
	18-23	0,52	0,58/0,12 (*) (13)	0,72/0,09 (**) (1)	-	-	-	-
	24-39	0,54	0,58/0,09 (*) (4)	0,49/0,11 (-*) (2)	0,64/0,13 (**) (1)	-	-	-
	40+	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SGOT	6-11	-	-	-	-	-	-	-
Karmen units	12-17	-	-	-	-	-	-	-
normal	18-23	-	-	-	-	-	-	-
value 10-40 units	24-39	26	83,5 (**) (2)	35 (**) (1)	-	-	-	-
	40+	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(b)SGOT	6-11	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-
	18-23	26	36,2 (**) (13)	22 (-*) (1)	-	-	-	-
	24-39	28	29,7 (**) (4)	17,5 (2)	22 (-*) (1)	-	-	-
	40+	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SGOT	6-11	-	-	-	-	-	-	-
Karmen units	12-17	-	-	-	-	-	-	-
normal	18-23	-	-	-	-	-	-	-
value 10-40 units	24-39	26	83,5 (**) (2)	35 (**) (1)	-	-	-	-
	40+	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(b)SGOT	6-11	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-
	18-23	26	36,2 (**) (13)	22 (-*) (1)	-	-	-	-
	24-39	28	29,7 (**) (4)	17,5 (2)	22 (-*) (1)	-	-	-
	40+	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SGPT	6-11	-	-	-	-	-	-	-
Karmen units	12-17	-	-	-	-	-	-	-
normal	18-23	-	-	-	-	-	-	-
value 8-35 units	24-39	9	59,3 (**) (2)	15 (*) (1)	-	-	-	-
	40+	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(b)SGPT	6-11	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-
	18-23	9	16,1 (**) (13)	7,5 (-*) (1)	-	-	-	-
	24-39	13	11,3 (4)	9,3 (2)	7,5 (-*) (1)	-	-	-
	40+	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SUN	6-11	-	-	-	-	-	-	-
mg%	12-17	-	-	-	-	-	-	-
normal value	18-23	-	-	-	-	-	-	-
8-18 mg%	24-39	14	21,6 (**) (2)	-	-	-	-	-
	40+	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(b)SUN	6-11	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-
	18-23	15	15,2 (8)	22,4 (**) (1)	-	-	-	-
	24-39	16	16,5 (3)	18,2 (2)	13 (-*) (1)	-	-	-
	40+	-	-	-	-	-	-	-

*p= significant rise (≤ 10%) ** highly significant rise (≤ 5%) -* significant fall

Comparative values from Table 19, page 65

Calculated from computerised data obtained from biochemical studies carried out for Hyconthone studies at Lourenco Marques Public Health Laboratories.

Monitors: K.Hechter-Schulz. Unpublished data Winthrop Files Johannesburg.

Three groups of infection for ethnic and age groups

Group 1: S. haematobium infections

Group 2: S. mansoni infections

Group 3: S. haematobium and S. mansoni mixed infections

TABLE 23 (Continued)

LIMPOPO

POST-CHEMOTHERAPY STUDIES

BLOOD BIOCHEMICAL STUDIES

GROUP 3: MIXED INFECTIONS

Four components tested for each patient

NOTE: (a) Bilirubin: figures denote mean values for total/conjugate= 0,56/0,12

(b) SGOT, SGPT and SUN: figures denote mean values 13,7

(c) Number of patients tested is placed in brackets beneath mean and range=(4)

TEST	AGE	PRE-THERAPY	DAYS POST-CHEMOTHERAPY 7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS
AFRICANS	3-5	-	-	-	-	-	-	-
(a)Bilirubin	6-11	-	-	-	-	-	-	-
mg% (total conjugate)	12-17	0,56	0,55/0,12 (2)	0,54/0,13 (1)	0,64/0,13 (**) (1)	-	-	-
normal value	18-23	-	-	-	-	-	-	-
0,20/1,0	24-39	0,45	0,64/0,12 (**) (2)	0,54/0,13 (1)	0,54/0,13 (**) (1)	-	-	-
mg%	40+	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(a)Bilirubin	6-11	-	-	-	-	-	-	-
	12-17	0,75	0,77/0,13 (1)	-	-	-	-	-
	18-23	0,46	0,48/0,10 (3)	0,54/0,13 (**) (1)	0,54/0,09 (**) (1)	-	-	-
	24-39	-	-	-	-	-	-	-
	40+	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SGOT	6-11	-	-	-	-	-	-	-
Karmen units	12-17	27	36,7 (**) (2)	14 (-*) (1)	28 (1)	-	-	-
normal value	18-23	-	-	-	-	-	-	-
10-40 units	24-39	23	44,3 (**) (2)	31 (**) (1)	-	-	-	-
	40+	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(b)SGOT	6-11	-	-	-	-	-	-	-
	12-17	24	52 (**) (1)	-	-	-	-	-
	18-23	24	41 (**) (3)	20 (1)	18 (-*) (1)	-	-	-
	24-39	-	-	-	-	-	-	-
	40+	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SGPT	6-11	-	-	-	-	-	-	-
Karmen units	12-17	8	14,4 (**) (2)	8 (1)	11,5 (1)	-	-	-
normal value	18-23	-	-	-	-	-	-	-
8-35	24-39	11	19,1 (**) (2)	26 (**) (1)	-	-	-	-
units	40+	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(b)SGPT	6-11	-	-	-	-	-	-	-
	12-17	9	14,8 (**) (1)	-	-	-	-	-
	18-23	9	21 (**) (3)	5 (1)	6 (-*) (1)	-	-	-
	24-39	-	-	-	-	-	-	-
	40+	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-
(b)SUN	6-11	-	-	-	-	-	-	-
mg%	12-17	14	14,6 (2)	13 (1)	13 (1)	-	-	-
normal value	18-23	-	-	-	-	-	-	-
8-18	24-39	14	14 (2)	-	-	-	-	-
mg%	40+	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-
(b)SUN	6-11	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-
	18-23	15	14,5 (1)	14,9 (1)	14,9 (1)	-	-	-
	24-39	-	-	-	-	-	-	-
	40+	-	-	-	-	-	-	-

* significant rise (< 10%) ** highly significant rise (< 5%) -* significant fall

*p= Comparative values from Table 19, page 65

Calculated from computerised data obtained from biochemical studies carried out for hycanthone studies at Lourenco Marques Public Health Laboratories.

Monitor: K.Hechter-Schulz. Unpublished data Winthrop Files Johannesburg.

Bilirubin (total, conjugate):

S. haematobium infections:

Africans; all young age groups maintained fairly constant values for 14 days post-therapy. Older groups (18 - 40+ years) had a significant ($0,1 > P > 0,05$) rise in this time followed by significant decreases at 30, 60 and 90 days.

Caucasians; young age groups had significant falls in values after 7 to 120 days post-therapy. Persons in the older groups (18 - 39 years) had significant increases at 7 days, with reduction at 14 days and highly significant increases at 30 days. One person in this group had steadily increasing and highly significant values to 120 days.

S. mansoni infections:

Africans; the older age groups (24 - 39 years) had a highly significant increase at 7 days falling slightly again at 30 days post-therapy, while the younger group had steadily increasing and highly significant values at 30 days.

Caucasians; the limited number of persons evaluated had slight but insignificant increases at 7 days, while one person maintained a highly significant value to 30 days post-therapy.

FOOTNOTE

The terms "significant" and insignificant" as used throughout the text of this Chapter have statistical values.

Throughout the text the term "significant" must be understood in this statistical sense. In the tables, containing the data on which the conclusions appearing in the text are based, the notation "*" means significant rise; while "**" means highly significant rise in comparison with pre-therapy values. In some cases where a significant fall in values occurred, an additional minus sign is used; thus "-*".

Mixed infections:

Africans; a small number of persons in the age group 24 - 39 years showed significant rises at 7 days post-therapy, but these decreased significantly at 14 days post-therapy.

Caucasians; all age groups had a significant rise at 7 days post-therapy. Two persons had a further highly significant increase at 30 days post-therapy.

SGOT:

S. haematobium infections:

Africans; all age groups had highly significant rises in values 7 days post-therapy, but all values decreased (some significantly) at 30 and 90 days post-therapy.

Caucasians; the younger age groups (3 - 11 years) had significant decreased values 7 days post-therapy while the older ages (12 - 39 years) had highly significant increases. At 120 days these values had decreased significantly.

S. mansoni infections:

Africans; only two persons were followed up, showing highly significant increased values at 7 and 14 days post-therapy.

Caucasians; all persons 18 - 39 years showed highly significant increases at 7 days with significant decreases at 14 and 30 days post-therapy.

Mixed infections:

Africans; all age groups had highly significant increases in values 7 days post-therapy, with only some significant decreases at 14 days.

Caucasians; all age groups had highly significant increases in values 7 days post-therapy. One person followed up for 30 days showed a significant decrease in value.

SGPT:

S. haematobium infections:

Africans; all age groups had significant rises at 7 days post-therapy and significant falls in values again at 14, 30 and 90 days.

Caucasians; young age groups (3 - 17 years) had significant reductions at 7 days post-therapy followed by highly significant increases at 120 days. The older groups had a significant rise at 7 days post-therapy with significant falls in values at 30 and 120 days.

S. mansoni infections:

Africans; the only age group tested (24 - 39 years) had a highly significant rise at 7 days post-therapy, falling at 14 days although remaining higher than at pre-therapy.

Caucasians; older groups (18 - 39 years) had highly significant rises at 7 days post-therapy with significant falls at 14 and 30 days.

Mixed infections:

Africans; all age groups had significant rises at 7 days post-therapy, values remained high at 14 and 30 days.

Caucasians; all age groups had highly significant rises at 7 days post-therapy with significant falls at 14 and 30 days.

SUN:

S. haematobium infections and mixed infections:

Africans; all age groups had a remarkable steady value at 7, 14, 30 and 60 days post-therapy.

Caucasians; results for tests of the older groups were similar to these.

S. mansoni infections:

Africans; the older group tested had a highly significant rise at 7 days post-therapy.

Caucasians; some older groups tested had highly significant rises at 7 days post-therapy.

Haematology studies

Compare Tables 18 (pre-therapy) and 24 (post-therapy), pages 62 and 95, 96, 97 in which the mean values obtained for tests are set out for infections of S. haematobium, S. mansoni and mixed S. haematobium and mansoni, for all age groups of the two ethnic groups.

Sedimentation Rate:

S. haematobium:

Africans; had a significant fall in sedimentation rates after therapy.

Caucasians; no data available.

S. mansoni:

Africans; in age groups 24 - 39 years, had a significant rise two weeks post-therapy.

Caucasians; in age groups 18 - 23 years, had a significant rise two weeks post-therapy.

Mixed infections:

Africans; in some age groups, had a highly significant rise two weeks post-therapy.

Caucasians; in age group 12 - 17 years, had a small but significant rise at 30 days: age group 18 - 23 years had a highly significant fall at 2 weeks post-therapy.

Haemoglobin Concentration:

S. haematobium:

Africans; no significant changes in values occurred to 120 days post-therapy.

Three groups of infection for ethnic and age groups

Group 1: S. haematobium infections
Group 2: S. mansoni infections
Group 3: S. haematobium and S. mansoni mixed infections

TABLE 24

LIMPOPO
POST-CHEMOTHERAPY
HAEMATOLOGY STUDIES
GROUP 1: S. HAEMATOBIUM

Four components tested for each patient

NOTE: (a) Sedimentation rate, haemeglobin, MCH concentration, and haemocrit: figures denote mean values followed by range in brackets
(b) Number of patients tested is placed in brackets beneath mean and range-(1)

TEST	AGE	(c) PRE-THERAPY	DAYS POST-CHEMOTHERAPY 7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS	150 DAYS
AFRICANS	3-5	-	-	-	-	-	-	-	-
(a)Sedimentation Rates	6-11	12	9(9) (b) (1)	21(21) (**) (1)	-	-	-	-	-
normal values	12-17	3	3(3) (b) (1)	3(3) (1)	-	-	-	-	-
male 0,9-3,7	18-23	6	8(5-11) (b) (2)	14(6-25) (5)	11(2-20) (**) (4)	-	-	-	-
female 0,20-9,6	24-39	-	-	4(3-5) (4)	8(1-18) (5)	6(1-16) (5)	-	-	-
	40+	-	-	23(9-40) (2)	-	-	-	-	-
CAUCASIANS		(a) Sedimentation Rates NIL							
AFRICANS	3-5	-	-	-	-	-	-	-	-
(a)Haemaglobin gm%	6-11	12,6	12,6(11,1-13,6) (b) (9)	12,4(11,2-12,9) (8)	12,3(11,6-12,9) (4)	12,7(12,6-12,8) (3)	12,9(12,9) (1)	-	-
normal value	12-17	13,5	13,5(10,2-15,4) (b) (9)	13,1(0,98-14,4) (9)	14,1(13,3-14,5) (4)	14,0(14,0) (1)	-	-	-
male 13,5-18,0	18-23	15,0	14,7(12,0-17,9) (b) (10)	14,6(12,0-17,4) (12)	14,9(12,9-17,9) (7)	14,2(14,2) (1)	15,4(13,6-17,4) (4)	15,0(15,0) (1)	
female 12,5-16,5	24-39	15,5	15,9(14,0-17,0) (b) (8)	15,2(12,9-17,0) (12)	15,1(13,5-17,0) (11)	14,7(12,2-17,0) (7)	15,8(13,6-17,6) (8)	-	-
	40+	14,7	-	13,0(11,8-15,2) (2)	14,0(13,3-16,4) (2)	14,7(13,3-16,0) (2)	-	-	-
CAUCASIANS	3-5	13,5	-	13,7(13,3-14,0) (2)	12,9(12,9) (1)	-	14,6(14,6) (1)	13,5(12,9-14,0) (2)	17,2(17,2)(**) (1)
(a)Haemeglobin	6-11	14	-	13,3(13,3) (1)	-	13,3(13,3) (1)	14,0(14,0) (1)	14,0(14,0) (1)	13,8(13,8) (1)
	12-17	12,9	12,6(12,6) (b) (1)	13,6(13,6) (1)	14,4(14,4) (1)	14,4(14,4) (1)	-	14,4(14,4) (1)	13,6(13,6) (1)
	18-23	16,8	16,6(16,2-17,2) (b) (4)	16,2(15,6-16,4) (4)	16,2(15,6-16,4) (4)	15,6(15,6) (1)	-	-	-
	24-39	15	14,8(14,4-15,4) (b) (2)	15,5(15,0-16,0) (2)	15,3(14,4-16,0) (3)	15,8(15,2-16,0) (2)	16,1(15,4-17,0) (2)	17,4(17,4) (*) (1)	-
	40+	-	-	-	-	-	-	-	-

(a) Comparison with Table 18, page 62

(*) significant rise (≤10%)
(**) highly significant rise (≤ 5%)

Calculated from computerised data obtained for haematology studies carried out for hycanthone Clinical Studies at Limpopo by Lourenco Marques Public Health Laboratories.
Monitor: K.Hechter-Schulz. Unpublished data Winthrop Files Johannesburg.

Three groups of infection for ethnic and age groups

Group 1: S. haematobium infections
Group 2: S. mansoni infections
Group 3: S. haematobium and S. mansoni mixed infections

TABLE 24

LIMPOPO
POST-CHEMOTHERAPY
HAEMATOLOGY STUDIES
GROUP 2: S. MANSONI

Four components tested for each patient

NOTE: (a) Sedimentation rate, haemaglobin, MCH concentration, and haemocrit: figures denote mean values followed by range in brackets
(b) Number of patients tested is placed in brackets beneath mean and range-(1)

TEST	AGE	(c) PRE-THERAPY	DAYS POST-CHEMOTHERAPY 7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS	150 DAYS
AFRICANS	3-5	-	-	-	-	-	-	-	-
(a)Sedimentation	6-11	-	-	-	-	-	-	-	-
Rates	12-17	-	-	-	-	-	-	-	-
normal values	18-23	-	-	-	-	-	-	-	-
male 0,9-3,7	24-39	19	32(32) (1)	34(34) (**) (b) (1)	-	-	-	-	-
female 0,20-9,6	40+	-	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-	-
(a)Sedimentation	6-11	-	-	-	-	-	-	-	-
Rates	12-17	-	-	-	-	-	-	-	-
	18-23	6	5(1-12) (6)	10(2-35) (**) (6)	-	-	-	-	-
	24-39	4	-	-	-	-	-	-	-
	40+	-	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-	-
(a)Haemaglobin gm%	6-11	-	-	-	-	-	-	-	-
normal	12-17	-	-	-	-	-	-	-	-
value	18-23	-	-	-	-	-	-	-	-
male 13,5-18,0	24-39	12,6	12,9(12,6-13,3) (2)	12,6(11,8-13,3) (2)	-	-	-	-	-
female 12,5-16,5	40+	-	-	-	-	-	-	-	-
CAUCASIANS	3-5	-	-	-	-	-	-	-	-
(a)Haemaglobin	6-11	-	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-	-
	18-23	15,7	15,6(13,6-17,4) (13)	15,5(13,6-17,0) (10)	15,4(14,0-16,2) (4)	15,0(13,0-16,0) (3)	16,0(15,6-16,4) (3)		
	24-39	16,3	16,2(14,8-17,4) (5)	16,5(15,8-17,0) (3)	17,0(17,0) (1)	12,0(12,0) (-*) (1)	-	-	-
	40+	-	-	-	-	-	-	-	-

(b) Comparison with Table 18, page 62

(**) highly significant rise (≤ 5%)
(-*) significant fall

Calculated from computerised data obtained for haematology studies carried out for hycenthone Clinical Studies at Limpopo by Lourenco Marques Public Health Laboratories.

Monitor: K.Hechter-Schulz. Unpublished data Winthrop Files Johannesburg.

Three groups of infection for ethnic and age groups

Group 1: S. haematobium infections
Group 2: S. mansoni infections
Group 3: S. haematobium and S. mansoni mixed infections

TABLE 24

LIMPOPO
POST-CHEMOTHERAPY
HAEMATOLOGY STUDIES
GROUP 3: MIXED INFECTIONS

Four components tested for each patient

NOTE: (a) Sedimentation rate, haemoglobin, MCH concentration, and haemocrit: figures denote mean values followed by range in brackets
(b) Number of patients tested is placed in brackets beneath mean and range-(1)

TEST	AGE	(c) PRE-THERAPY	DAYS POST-CHEMOTHERAPY 7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS	150 DAYS
AFRICANS	3-5	-	-	-	-	-	-	-	-
(a)MCH Concentration	6-11	31	30(30-31) (3)	30(30-31) (4)	31(31-33) (2)	33(33) (1)	33(33) (*) (1)	-	-
% normal value 32-38	12-17	31	31(28-34) (9)	31(29-34) (9)	33(32-33) (4)	31(31) (1)	-	-	-
	18-23	32	31(28-34) (10)	31(28-34) (12)	32(30-37) (7)	33(33) (1)	31(30-33) (4)	32(32) (1)	-
	24-39	32	32(31-33) (8)	32(29-34) (12)	31(29-33) (10)	31(30-32) (7)	32(31-33) (8)	-	-
	40+	32	-	32(31-33) (2)	33(32-33) (2)	31(30-32) (2)	-	-	-
CAUCASIANS	3-5	33	-	34(33-34) (2)	-	-	33(33) (1)	32(32) (1)	34(34) (1)
(a)MCH Concentration	6-11	33	-	33(33) (1)	-	33(33) (1)	34(34) (1)	33(33) (1)	34(34) (1)
	12-17	33	32(32) (1)	34(34) (1)	34(34) (1)	32(32) (1)	-	32(32) (1)	32(32) (1)
	18-23	33	33(32-35) (4)	33(31-34) (4)	32(32-33) (4)	33(33) (1)	-	-	-
	24-39	33	33(32-33) (2)	32(32-33) (2)	33(32-33) (3)	32(32) (2)	32(31-34) (2)	33(33) (1)	-
	40+	-	-	-	-	-	-	-	-
AFRICANS	3-5	-	-	-	-	-	-	-	-
(a)Haemocrit % normal value male 47 female 42	6-11	40	41(35-45) (3)	39(35-42) (4)	39(37-40) (2)	38(38) (1)	39(39) (1)	-	-
	12-17	43	32(36-50) (9)	42(38-44) (9)	43(42-45) (4)	45(45) (*) (1)	-	-	-
	18-23	47	47(36-55) (10)	46(36-53) (12)	47(40-53) (7)	43(43) (1)	49(44-52) (4)	47(47) (1)	-
	24-39	49	49(43-52) (8)	46(44-53) (12)	48(44-54) (11)	47(41-54) (7)	50(42-56) (8)	-	-
	40+	45	-	43(35-49) (2)	45(40-50) (2)	46(43-49) (2)	-	-	-
CAUCASIANS	3-5	40	-	41(41) (1)	-	-	43(43) (1)	40(40) (1)	41(41) (1)
(a)Haemocrit	6-11	42	-	40(40) (1)	-	40(40) (1)	41(41) (1)	42(42) (1)	38(38) (-*) (1)
	12-17	39	39(39) (1)	40(40) (1)	42(42) (1)	45(45) (1)	-	45(45) (1)	42(42) (*) (1)
	18-23	50	50(48-51) (4)	50(50) (4)	50(48-51) (4)	42(42) (-*) (1)	-	-	-
	24-39	45	44(43-46) (2)	47(46-49) (2)	46(43-39) (2)	49(47-50) (2)	50(48-51) (2)	53(53) (**) (1)	-
	40+	-	-	-	-	-	-	-	-

(c) Comparison with Table 18, page 62

(*) significant rise (< 10%)
(**) highly significant rise (< 5%)
(-*) significant fall

Calculated from computerised data obtained for haematology studies carried out for hycanthone Clinical Studies at Limpopo by Lourenco Marques Public Health Laboratories.

Monitor: K.Hechter-Schulz. Unpublished data Winthrop Films Johannesburg.

Caucasians; only in age group 24 - 39 years did a significant rise occur at 120 days.

S. mansoni:

Africans; no change in values occurred for the only age group tested (24 - 39 years) at 14 days post-therapy.

Caucasians; a significant fall in values occurred in age group 24 - 39 years at 60 days.

Mixed infections:

There were no significant changes post-therapy for either ethnic group in the limited number of persons tested.

MCH Concentration:

S. haematobium:

One African in age group 6 - 11 years had a significant rise in values 90 days post-therapy. All others in both ethnic groups remained fairly constant.

S. mansoni:

No significant changes in values occurred in either ethnic groups after therapy.

Mixed infections:

No significant changes in values occurred in either ethnic groups after therapy.

Haemocrit:

S. haematobium:

Africans; only in age group 12 - 17 years did a significant rise in values occur 60 days post-therapy.

Caucasians; in ages 6 - 39 years, a significant reduction in values occurred at 40, 120 and 150 days post-therapy.

S. mansoni:

A significant decrease in values occurred in age group 18 - 23 years at 90 days, post-therapy. No change was recorded for Africans.

Mixed infections:

A significant increase in values occurred in one person in the African age group 12 - 17 years at 30 days post-therapy. No changes were recorded for Caucasians.

Eosinophile Counts:

All ages within the ethnic groups had significantly high eosinophile counts.

PARASITOLOGY STUDIES

Compare Tables 17 and 25, pages 60 and 100)

Egg Counts:

Urine specimens were examined from small groups of Africans and Caucasians for various ages to determine egg excretion patterns before and after treatment. Live and dead eggs were noted separately. In most instances the hatching test was applied to eggs to confirm viability otherwise viability was judged by miracidium development and flame-cell movement.

Africans with S. haematobium infections excreted more live and dead eggs in all age groups pre- and post-therapy than did Caucasians. The intensity of infection, based on egg counts was heaviest in all Africans particularly in age groups 6 - 11 years. Intensity of infection decreased steadily in each advancing age group. In Caucasians the age group 18 - 23 years excreted most eggs combined with highest intensity of infection.

Before treatment only few dead eggs were excreted as compared with the large numbers of live eggs excreted by both ethnic groups. Only S. haematobium eggs, live and dead, were excreted in urine by either Africans or Caucasians.

In S. haematobium infections reduction but not cessation in egg excretion was noted for both Africans and Caucasians within the first week; with the exception of the Caucasian age group 3 - 5 years where there was an increase in eggs excreted at this time by one patient. The reduction was dramatic for Africans, especially

Three groups of infection for ethnic and age groups
Group 1: S. haematobium infections
Group 2: S. mansoni infections
Group 3: S. haematobium and S. mansoni mixed infections

TABLE 25

LIMPOPO
PARASITOLOGY
POST-CHEMOTHERAPY STUDIES

Hycanthone single parenteral dose.
Effects on the excretion of ova of S. haematobium and S. mansoni.

Group 1: S. haematobium infections — AFRICANS

	AGE	7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS	150 DAYS	180 DAYS	210 DAYS
URINE EXAM.	3-5	-	-	-	-	-	-	-	-	-
	6-11	11,3/116,7+ (1)	40/560- (1)	8/263,5- (3)	14,4/213,7- (3)	2,4/8,6- (3)	0/12- (1)	-	-	-
	12-17	-	3,4/5- (2)	8/4,5- (7)	9,3/30,4- (5)	-	-	-	-	-
	18-23	-	12,8/3,3- (3)	2/4,3- (10)	1,6/15,7- (7)	0/0- (4)	0/0- (1)	0/0- (1)	-	0/0,9- (3)
	24-39	-	12,4/1,4- (10)	0/5,2- (6)	0,5/0,4- (11)	0/1,2- (9)	0/0- (6)	0/0- (1)	4/0- (1)	0/0,2- (10)
	40+	0/0- (2)	-	-	0/0- (2)	-	-	0/0- (1)	-	-

Group 1: S. haematobium infections — CAUCASIANS

	AGE	7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS	150 DAYS	180 DAYS	210 DAYS
URINE EXAM.	3-5	57,5/4+ (1)	3,5/1+ (2)	0- (2)	0- (2)	0- (2)	0- (2)	0- (2)	0- (1)	0- (1)
	6-11	-	-	0- (1)	0- (1)	0- (1)	0- (1)	0- (1)	-	-
	12-17	-	0/2- (1)	0/2,5- (1)	0- (1)	0- (1)	0- (1)	-	0- (1)	-
	18-23	0- (1)	-	0- (1)	0- (3)	0- (3)	-	-	-	-
	24-39	-	2/6- (2)	2/2- (3)	2/2- (3)	4/0- (3)	0- (2)	-	-	-
	40+	-	-	-	-	-	-	-	-	-

Group 2: S. mansoni infections — AFRICANS

	AGE	7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS	150 DAYS	180 DAYS	210 DAYS
URINE EXAM.	3-5	-	-	-	-	-	-	-	-	-
	6-11	-	-	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-	-	-
	18-23	-	-	-	-	-	-	-	-	-
	24-39	-	-	-	0 (1)	-	-	-	-	-
	40+	-	-	-	-	-	-	-	-	-

Group 2: S. mansoni infections — CAUCASIANS

	AGE	7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS	150 DAYS	180 DAYS	210 DAYS
URINE EXAM.	3-5	-	-	-	-	-	-	-	-	-
	6-11	-	-	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-	-	-
	18-23	0- (2)	-	0- (8)	-	-	-	-	-	-
	24-39	0 (1)	-	0- (2)	-	-	-	-	-	-
	40+	-	-	-	-	-	-	-	-	-

Group 3: S. haematobium & S. mansoni-Mixed infections — AFRICANS

	AGE	7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS	150 DAYS	180 DAYS	210 DAYS
URINE EXAM.	3-5	-	-	-	-	-	-	-	-	-
	6-11	-	-	-	-	-	-	-	-	-
	12-17	-	-	-	-	-	-	-	-	-
	18-23	-	-	-	-	-	-	-	-	-
	24-39	-	0- (1)	0- (1)	-	0- (1)	0- (1)	-	-	-
	40+	-	-	-	-	-	-	-	-	-

Group 3: S. haematobium & S. mansoni-Mixed infections — CAUCASIANS

	AGE	7 DAYS	14 DAYS	30 DAYS	60 DAYS	90 DAYS	120 DAYS	150 DAYS	180 DAYS	210 DAYS
URINE EXAM.	3-5	-	-	-	-	-	-	-	-	-
	6-11	-	-	-	-	-	-	-	-	-
	12-17	-	-	0- (1)	0- (1)	-	-	-	-	-
	18-23	-	-	6/0- (3)	0- (3)	0- (1)	-	-	-	-
	24-39	-	-	-	-	-	-	-	-	-
	40+	-	-	-	-	-	-	-	-	-

NOTE: Mean range of egg excretion over 3 consecutive days: live eggs/dead eggs.

Symbol - denotes no haematuria
+ denotes some haematuria

Calculated from computerised data obtained from Hycanthone studies carried out at Limpopo Irrigation Scheme Mozambique.

Monitor: K. Mechter-Schulz. Unpublished data Winthrop Files Johannesburg.

in ages 6 - 11 years where egg excretion had been heaviest before treatment.

Numbers of live eggs excreted by Africans of all ages, particularly those with the highest egg counts, showed definite reduction 30 days after treatment. At about the same time the number of dead eggs began to increase. Zero live counts were recorded for persons with initial low counts within 90 days, while the age group with highest initial counts had none within 120 days. The older ages seemed to be the first to have zero egg counts. All persons tested up to 210 days when observations terminated excreted zero live eggs: while the numbers of dead eggs also decreased to almost zero.

Caucasians in the age group 12 - 23 years who had highest egg counts pre-treatment, had zero counts within the first week. This was maintained until the termination of observation at 90 days. All other age groups except that of 24 - 39 years had zero counts within 30 days, remaining zero until the last observation carried out between 180 - 210 days after therapy. At no time were many dead eggs excreted by the various Caucasian age groups, these became even less as time proceeded. The few persons in the age group 24 - 39 years who persisted in excreting eggs became zero for live and dead eggs at 120 days post-treatment when observations were terminated. Refer to Fig 2, page 102.

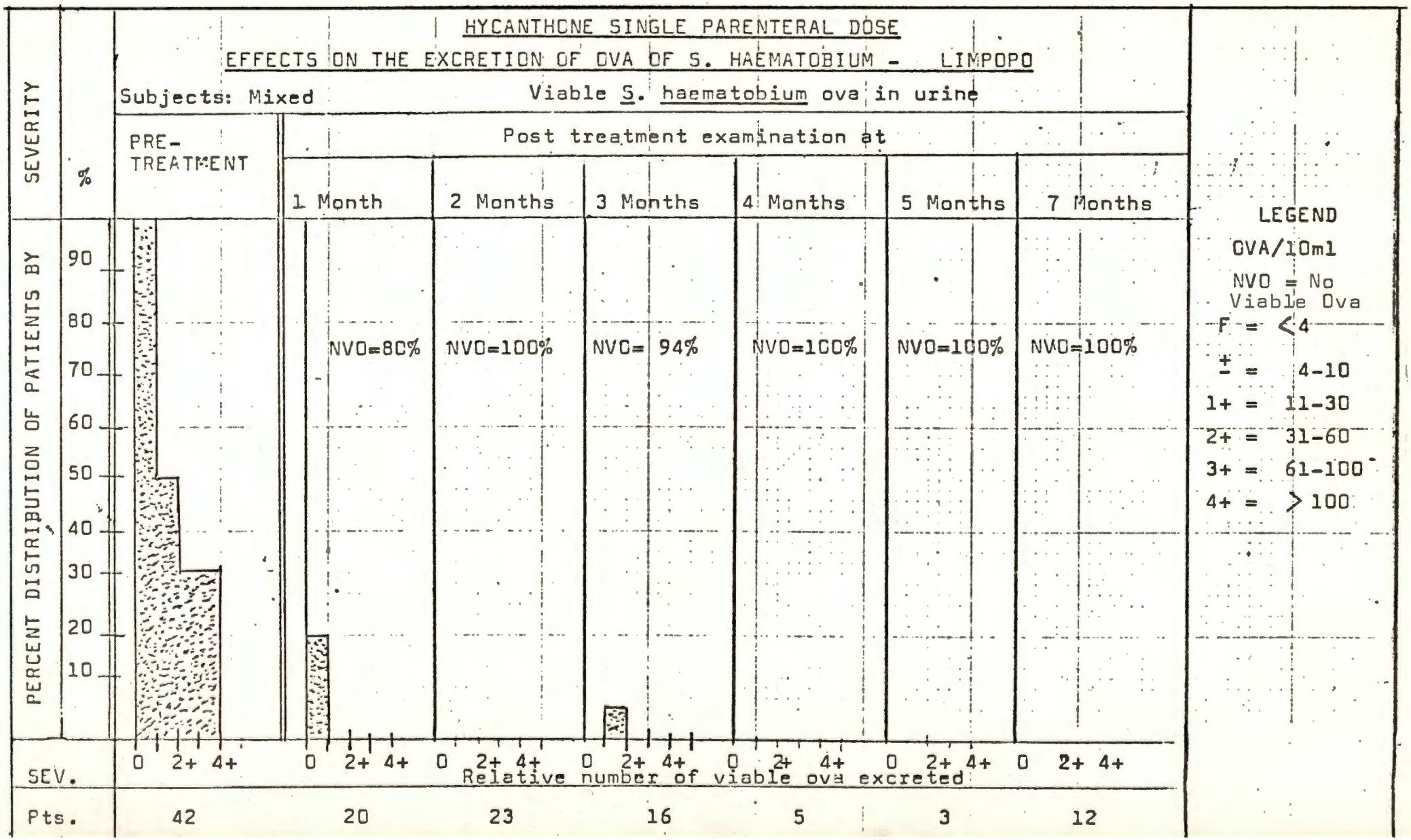
Caucasians and Africans treated and observed remained in the endemic environment, where they were constantly exposed to snails shedding cercariae.

Haematuria studies

Frank and heavy haematuria was present in all Africans before treatment, but in Caucasians haematuria was less so in intensity. Haematuria decreased then terminated in most Africans after treatment, but in a few persons persisted into the third month. Few still had occasional erythrocytes in urine specimens 212 days after treatment. This condition was associated with the occasional excretion of dead eggs, excretion of live eggs having ceased long ago.

A few Caucasians were still passing occasional erythrocytes nearly three months after effective treatment, unassociated with the passing of live or dead eggs.

FIGURE 2


HYCANTHONE SINGLE PARENTERAL DOSE
EFFECTS ON THE EXCRETION OF OVA OF S. HAEMATOBIUM - LIMPOPO
Subjects: Mixed
Viable S. haematobium ova in urine
SEVERITY
%
PRE-TREATMENT
Post treatment examination at
1 Month
2 Months
3 Months
4 Months
5 Months
7 Months
PERCENT DISTRIBUTION OF PATIENTS BY
90
80
70
60
50
40
30
20
10
NVO=80%
NVO=100%
NVO= 94%
NVO=100%
NVO=100%
NVO=100%
LEGEND
OVA/10ml
NVO = No Viable Ova
F = <4
± = 4-10
1+ = 11-30
2+ = 31-60
3+ = 61-100
4+ = >100
SEV.
0 2+ 4+
Relative number of viable ova excreted
Pts.
42
20
23
16
5
3
12

4.2.2 DENNILTON: Post-therapy sirveys

Blood biochemical studies

Compare Tables 11 (pre-therapy) and 26 (post-therapy), pages 50 & 104.

Data available for post-therapy surveys on biochemical studies on patients at Dennilton are available for one test period at 4 - 7 days after treatment. These data are only sufficient to determine any immediate toxic reaction to the drug used; or possible allergic reaction of the person to foreign protein from damaged schistosomes caused by therapy.

Bilirubin (total, conjugate):

There were no significant changes in post-therapy values for all ages in Groups "A" and "B".

SGOT:

Values for all ages in Group "A" were slightly, but not significantly raised after treatment, while those for Group "B" increased significantly. The increased values for older patients in Group "B" were high, although only slightly higher than the accepted normal values. Values for this age group had been high before treatment.

SGPT:

There was no significant change in post-therapy values for all ages in Group "A". Patients in Group "B" were not tested for SGPT values after therapy.

Haematology studies

Compare Tables 10 and 27, pages 49 and 105.

Haemoglobin Concentration:

There was no appreciable difference in haemoglobin values before and after therapy for both groups after 7 and 30 days respectively.

White Blood Cell Counts:

In Group "A" the WBC count had decreased by almost one-third of the

TABLE 26

DENNILTON
BLOOD BIOCHEMISTRY
POST-CHEMOTHERAPY STUDIES

S. haematobium infections

TEST	AGE GROUP	GROUP "A"	GROUP "B"	MEAN FOR 2 GROUPS
Bilirubin:		Day 4	Day 7	Day 4 - 7
	6-11	0,88(0,5-1,8) (12)	0,3(0,2-0,4) (1)	0,59(0,2-1,8) (13)
Total/ conjugate	12-16	0,81(0,4-1,4) (41	0,38(0,2-1,0) (11)	0,59(0,2-1,4) (52)
SGOT	6-11	25(14-36) (12)	18(18) (1)	21,5(14-36) (13)
	12-16	23(12-45) (41)	44,5(14-119) (11)	33,7(12-119) (52)
SGPT	6-11	23(13-38) (12)	-	23(13-38) (12)
	12-16	19(8-34) (40)	-	19(8-34) (40)

Calculated from computerised data obtained from clinical research programme Dennilton.

Monitor: K. Hechter-Schulz.

Unpublished data on Winthrop Files Johannesburg.

TABLE 27

HAEMATOLOGY STUDIES

POST-TREATMENT SURVEY

DENNILTON GROUP "B" + 7 DAYS S. HAEMATOBIUM INFECTIONS

Age	Hb	WBC	Eosinophile
Group 6-11	13,5(13-14) (2)	7 000(6 000-7 400) (2)	4,5(2-7) (2)
12-16	13,4(12,5-5-15) (14)	7 380(6 000-14 000) (14)	2,4(0,9) (14)
	GROUP "A" + 30 DAYS		
6-11	15,7(12,5-19) (2)	6 400(6 000-6 800) (2)	8(3-13) (2)
12-16	13,2(12,5-5-14) (14)	6 990(1 000-8 000) (14)	4,6(0-9) (12)

Calculated from computerised data obtained from clinical research programme Dennilton.

Monitor: K. Hechter-Schulz.

Unpublished data on Winthrop Files Johannesburg.

former value at 30 days after therapy. There was no change for Group "B" at 7 days after therapy.

Eosinophile Counts:

There was a marked increase in eosinophilia at 7 and 30 days respectively post-therapy for both groups.

Parasitology studies

Refer to Figs 3 and 4, "Effects on excretion of eggs after single treatment", pages 107 and 108.

Egg Excretion:

Within 5 weeks of therapy individuals experienced a dramatic decrease in egg excretion. Severity scores based on egg counts recorded for Group "B" had decreased by 56,3% within the first week. At 8 months when the final observation was made the decrease remained around 80%.

The larger Group "A" followed the same pattern of decrease in egg excretion. Within 5 weeks after therapy 86% were negative for viable ova, although 50% still excreted some dead eggs, which in a few cases included one or two live eggs. After 10 - 14 weeks all patients in this group excreted no viable eggs, and 82% were free from all eggs. This was the best period for this group, as eggs were again observed in about 15% of patients after 20 - 25 weeks. The number of patients excreting live eggs at 32 weeks when the study terminated did not increase beyond this percentage (15%).

Only one course of treatment had been given at the commencement of this study period, and all patients participating in the study remained in the endemic area, in constant contact with snails shedding cercariae.

Haematuria studies

Patients with frank haematuria when the study commenced showed great improvement in the post-therapy period. 68% of the patients had highest RBC counts of 3+ - 4+ at the commencement of the study. At three months post-therapy these high counts were nearly all reduced

FIGURE 3

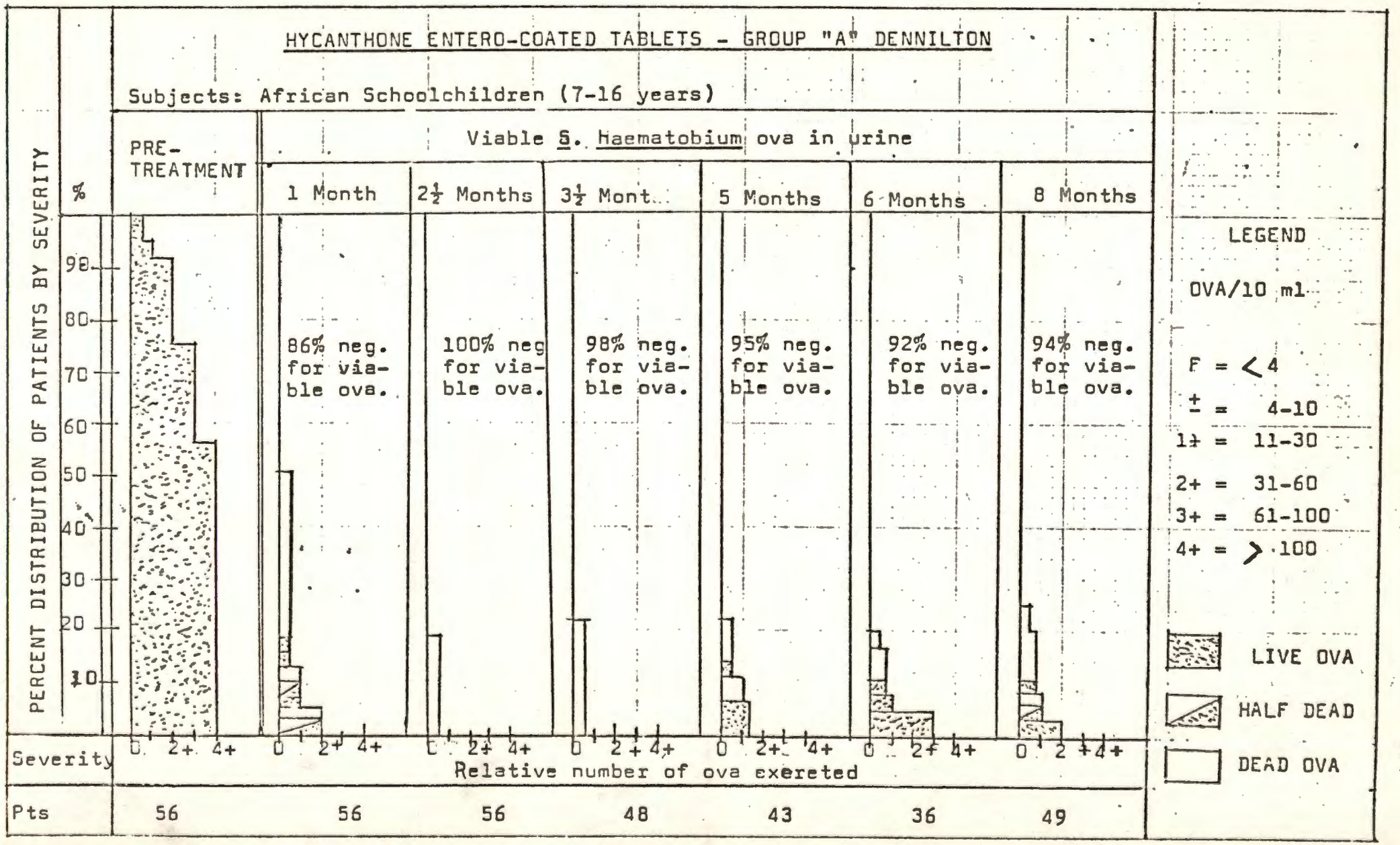
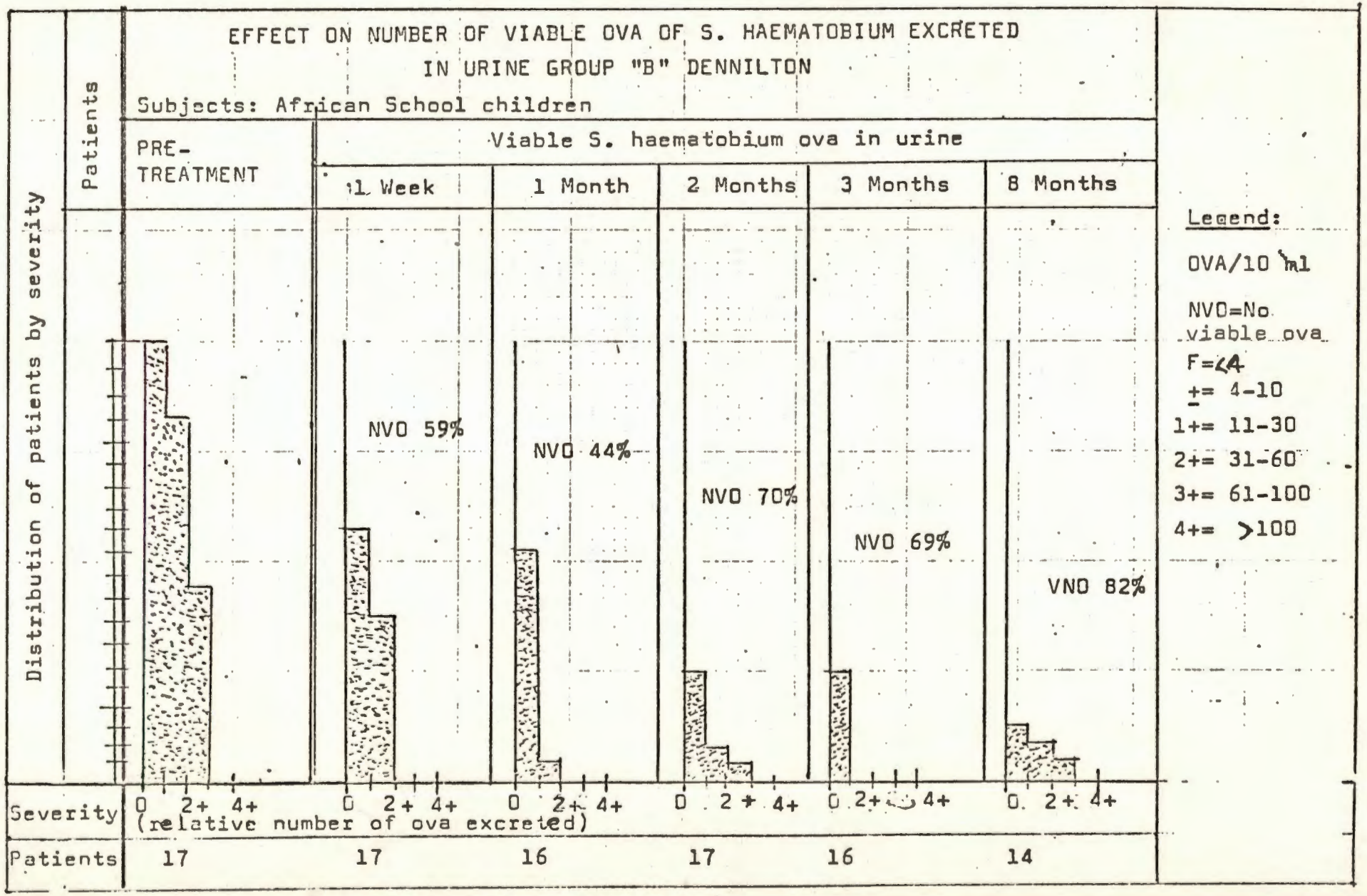

HYCANTHONE ENTERO-COATED TABLETS - GROUP "A" DENNILTON
Subjects: African Schoolchildren (7-16 years)
Viable S. Haematobium ova in urine
PRE-TREATMENT
1 Month
2½ Months
3½ Mont...
5 Months
6 Months
8 Months
%
PERCENT DISTRIBUTION OF PATIENTS BY SEVERITY
98
80
70
60
50
40
30
20
10
86% neg. for viable ova.
100% neg for viable ova.
98% neg. for viable ova.
95% neg. for viable ova.
92% neg. for viable ova.
94% neg. for viable ova.
Severity
0 2+ 4+
Relative number of ova excreted
Pts
56
56
56
48
43
36
49
LEGEND
OVA/10 ml
F = < 4
± = 4-10
1+ = 11-30
2+ = 31-60
3+ = 61-100
4+ = > 100
LIVE OVA
HALF DEAD
DEAD OVA

FIGURE 4

BECANTHONE ENTERO-COATED TABLETS



to 0. In 13% of patients treated did haematuria persist.

4.3 LONG-TERM RESULTS: REDUCTION IN PREVALENCE OVER 10 YEARS

Data over a long-term period are available from Limpopo when the total population was surveyed for bilharzial infection quarterly for 10 years: i.e., the prevalence of the disease was determined for S. haematobium in 24 periods during 10 years with the objective of treatment of all those found positive. Refer to Tables 13 (A and B) and 14, pages 54, 55 and 56: also Fig 5 "Long-term results of control", page 110.

At each determination of infection the individual found positive received therapy with a schistosomicide. Many of the schistosomicides used were in the clinical trial stage. Thus at various times during the 10 years patients received either becanthone, niridazole or hycanthone. No attempt will be made to differentiate between the various schistosomicides used at various times, nor will any attempt be made to assess and compare efficacy and tolerance of these, as basically the study was planned to show the results of mass chemotherapy by a schistosomicide and not to convey the advantages or disadvantages of any particular one.

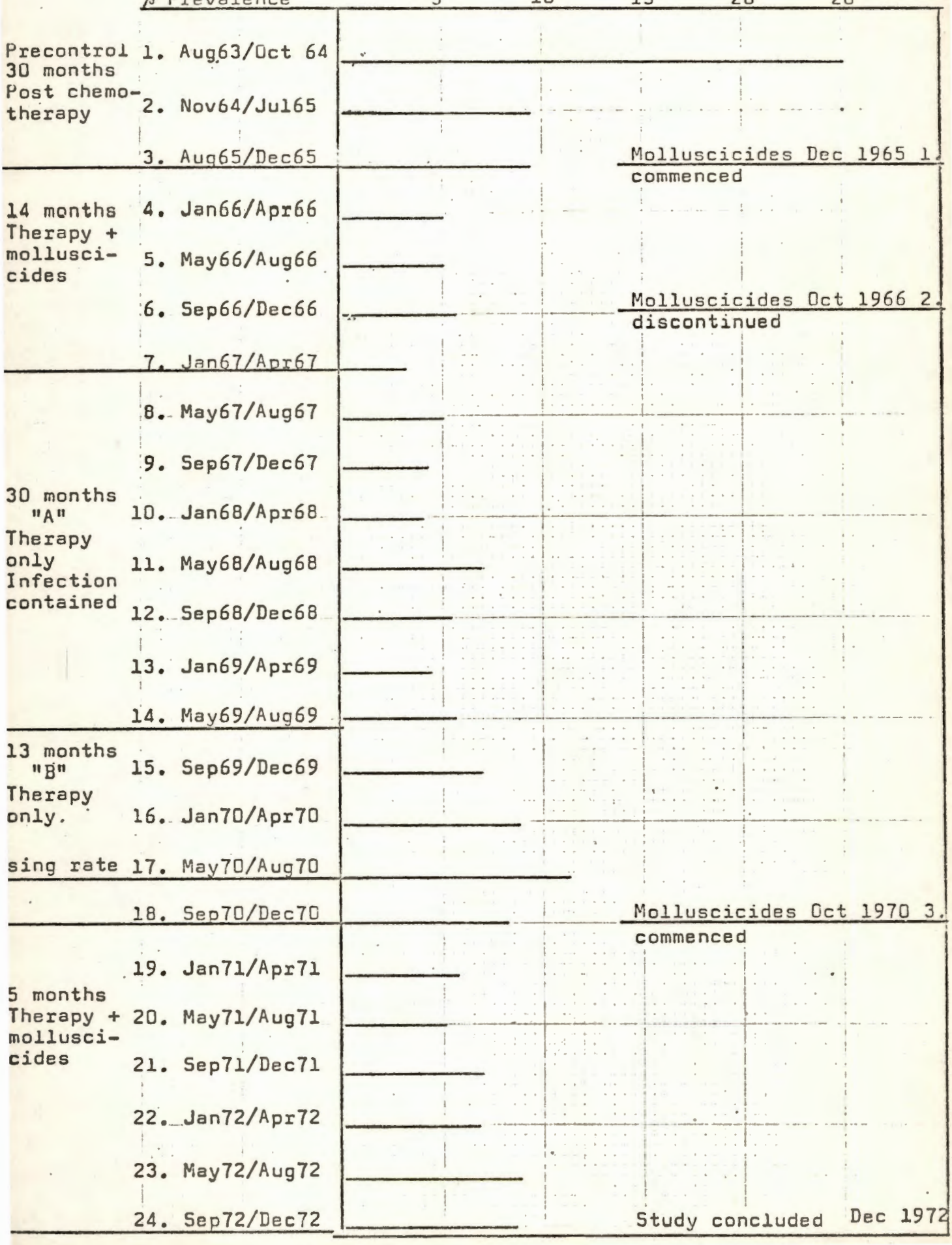
At certain periods after the study was initiated molluscicides were also used, thus introducing a secondary control measure in an attempt to reduce theprevalence of the disease in as short a time as possible.

The study was initiated in August 1963 when the first chemotherapy of the total population commenced. In July 1965 the first mollusciciding with Bayluscide was commenced in the borrow pits alongside the canals. From then onwards mollusciciding was carried out at irregular intervals until 1973 when this study was terminated (Fig 5, page 110).

The results of mass chemotherapy will be considered in several stages, firstly, from its commencement in August 1963 to the end of December 1965, when the first mollusciciding of the irrigation scheme was completed. This will show directly the results of only chemotherapy on the prevalence of the disease. Then the impact of mollusciciding combined with chemotherapy will become apparent from the early part of 1966 until October 1966. The next period from October 1966 until

FIGURE 5

S. haematobium. Limpopo. Results of 10 years control



October 1970 will show the results of only chemotherapy. After this until the study terminated the combined results of the two methods will again become obvious. Refer to Fig 6 "Limpopo: Long-term results "A. Percentage decrease, and B. Prevalence at various stages of control", page 112.

1963 - 1965 Chemotherapy only

The initial prevalence of infection in the population fell from 23,1% for both ethnic and all age groups in the first test period (August 1963 - October 1964) to 8,3% in the second test period (November 1964 - July 1965) after commencement of chemotherapy. A year later the prevalence was held at nearly the same figure, 8,8%, in the third test period (August 1965 - December 1965), after the population had been treated twice and all other factors remained static. Time lapse from the first chemotherapy was 30 months. At the second test period the group showing greatest improvement after therapy were Caucasian females, the prevalence having been reduced from 5,8% to 1,7%. They also had the lowest pre-therapy prevalence. African males had least improvement: prevalence having been reduced from 36,6% to 14,6%. In between these extremes were African females, who had the highest pre-therapy prevalence, which was reduced from 41,7% to 10,5%: and Caucasian males, reduced from 24,1% to 4,2%.

All groups showed clinical improvement and a dramatic fall in prevalence after chemotherapy. After the initial reduction the prevalence for each of the various groups remained fairly constant until the second treatment in December 1965. Percentage prevalence for African and Caucasian males and females after 30 months at the third test period were:-

Percentage prevalence at 30 months post-therapy

	Caucasian	African
Male	7,4	17,2
Female	1,2	19,7

(extracted from Tables 13A and B, pages 54 and 55)

While these prevalence rates are very similar to those obtained on the previous test period, it must be noted they had risen again,

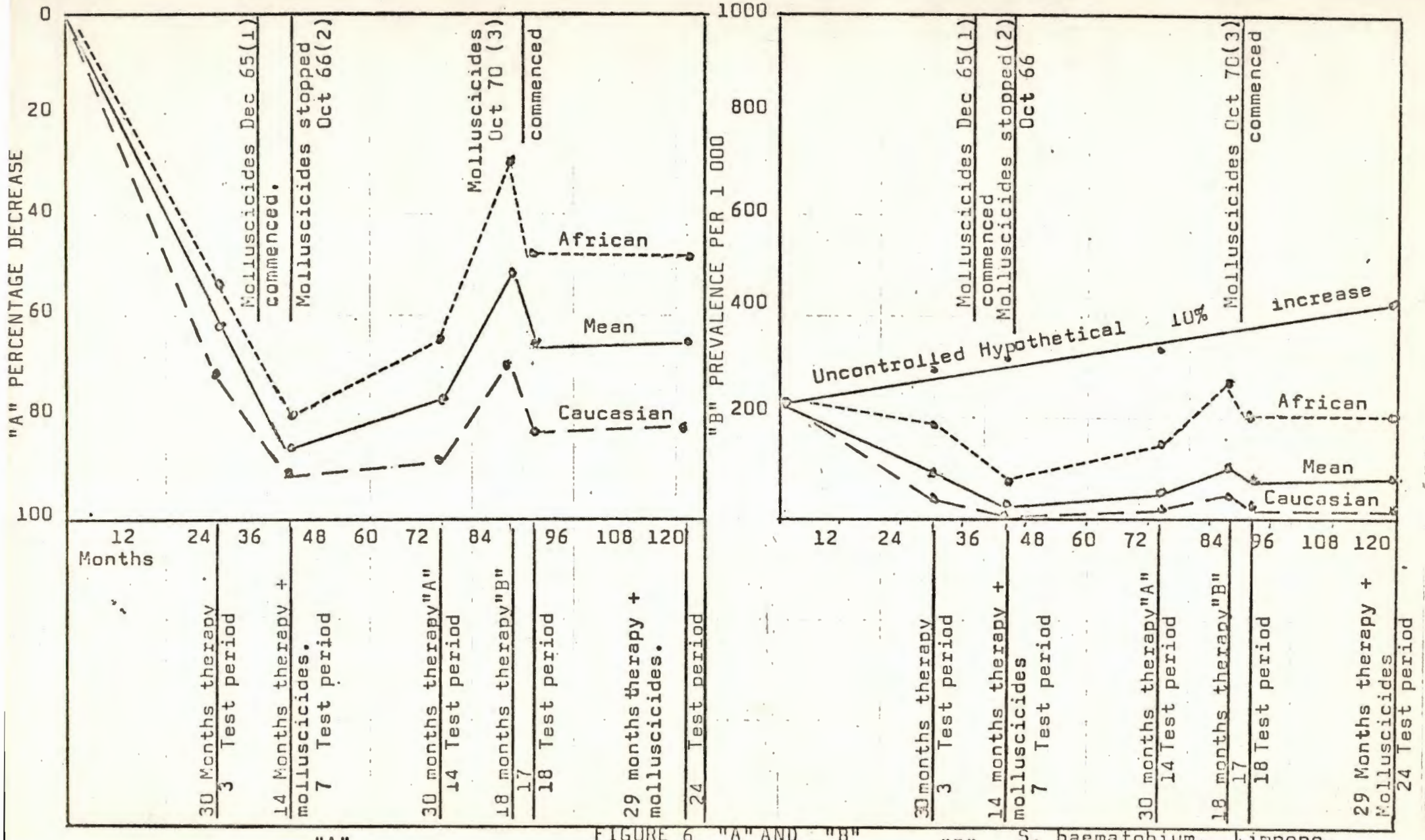


FIGURE 6 "A" AND "B" S. haematobium. Limpopo.

"A"

Percentage decrease from precontrol prevalence at various stages of control by chemotherapy only; and chemotherapy plus molluscicides.

"B"

Prevalence at various stages of control by chemotherapy only; and chemotherapy plus molluscicides.

although not significantly so ($x \geq P \geq y$) for the higher risk groups, i.e., African males and females.

New infection rates included in the prevalence quoted above, for second and third test periods and for the various groups were respectively:-

New infection percentage rates post-therapy

	Caucasian		African	
	Male	Female	Male	Female
2nd Test Period (post-therapy)	4,2	1,5	9,3	10,5
3rd Test Period (post-therapy)	4,6	1,0	8,7	9,6

(extracted from Tables 13A and B, pages 54 and 55)

Prevalence is remarkably constant for the various groups, while again it is obvious that the Africans constitute the higher risk groups as shown by the highest new infection rates.

Tables 13A and B, pages 54,and 55,and 14, page 56, show that overall pre-therapy prevalence is highest in the Caucasian male and female age groups of 10 - 14 years: they show the greatest improvement after therapy. In Africans the highest pre-therapy prevalence was in males and females aged 5 - 19 years. Highest prevalence after therapy was retained by them even though this was reduced by almost two-thirds, as follows:-

Percentage prevalence in age and ethnic groups pre- and post-therapy

	Caucasian				African			
Age Group	Male		Female		Male		Female	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
5 - 9	-	-	-	-	51,1/24,0		44,1/23,0	
10 - 14	52,5/16,3		12,8/ 1,9		63,1/26,4		58,5/21,6	
19 -					63,5/25,7		67,1/23,9	

(extracted from Tables 13A and B, pages 54 and 55)

Villages where inhabitants collectively benefited most are listed in the following order:-

Percentage prevalence by village, pre- and post-therapy

	1st Test(Pre-)	2nd Test(Post-)	3rd Test(Post-)
Pegoes	44,7	7,1	8,5
Santana	43,9	17,3	9,2
Santa Comba	34,2	11,8	8,1

(extracted from Table 15, page 57)

1965 - 1966 Chemotherapy combined with molluscicides

December 1965 saw the completion of the first period of molluscicides throughout the entire irrigation scheme which took nearly six months to complete. The next test period for the population to show up any influence on the prevalence of infection would be that of the fourth period, from January - April 1966.

The previous prevalence, during 30 months from commencement of chemotherapy, had been stabilised at 8,3% - 8,8% total prevalence. Within five months after more than half the study area had been controlled with molluscicides combined with chemotherapy, the overall prevalence of infection for the population fell to 4,9% and then to 3,3% at the seventh test. This was the lowest prevalence reached during the study period of 10 years, as can be seen in the following listing:-

Percentage prevalence post-therapy plus molluscicides

	Caucasian		African		Total
	Male	Female	Male	Female	Population
4th Test Period (post-therapy)	4,0	0,7	9,7	11,8	4,9
5th Test Period (post-therapy)	3,6	0,8	10,8	13,1	5,1
6th Test Period (post-therapy)	3,9	0,8	13,2	14,1	6,8
7th Test Period (post-therapy)	2,5	0,3	7,8	7,8	3,3

(extracted from Tables 13A and B, pages 54 and 55)

This reduced prevalence determined over periods of 6 and 14 months after the additional control measure of molluscicide had been introduced seem more or less stable. Time lapse from first commencement of chemotherapy was nearly 4 years. Also note that after a considerable reduction in prevalence for African males and females after molluscicide began, prevalence rises again slightly but significantly about 6 months afterwards ($x > P > y$).

The rate of the new infections is also of interest as these are almost halved again from the previous test periods when only chemotherapy took place.

New infection percentage rates, therapy plus molluscicides

	Caucasian		African	
	Male	Female	Male	Female
4th Test Period (post-therapy)	2,0	0,4	2,6	5,1
5th Test Period (post-therapy)	1,9	0,5	4,0	3,2
6th Test Period (post-therapy)	2,0	0,7	3,7	4,6
7th Test Period (post-therapy)	1,4	0,2	1,8	2,2

(extracted from Tables 13A and B, pages 54 and 55)

With control now established by means of chemotherapy twice per annum and molluscicide at longer and more irregular intervals the prevalence for the total population remained fairly constant, with little variation between 3,3% at the 7th Test Period (January - April 1967) and 4,3% at the 10th Test Period (January - April 1968).

The rate of new infections remained fairly constant during chemotherapy plus molluscicide, shown by the following incidences:-

New infections percentage rates, continued therapy plus molluscicides

	Caucasian		African	
	Male	Female	Male	Female
7th Test Period (post-therapy)	1,4	0,2	1,8	2,2
8th Test Period (post-therapy)	2,2	0,6	3,1	2,7
9th Test Period (post-therapy)	1,5	0,8	2,7	3,4
10th Test Period (post-therapy)	1,7	0,9	3,8	2,7

(extracted from Tables 13A and B, pages 54 and 55)

1966 – 1970 Chemotherapy only

Molluscicíding was now discontinued for 4 years from October 1966 to October 1970. The results of this action are clearly seen in Fig 5, page 110 showing changes in prevalence rates having two trends:

> "A" for 30 months (May 1967 - August 1969) when prevalence, although slightly erratic, tended to remain low with a computed rate of increase of 0,146% per test period for the total percentage prevalence: and
>
> "B" when in the following 13 months (September 1969 - August 1970) prevalence rose steadily and significantly 2,05% per test period to the highest recorded prevalence for the post-treatment period.

This was in the 7th year after commencement of chemotherapy, and 5 years after molluscicíding had been discontinued.

At this 7th Test Period (May 1970 - August 1970), prevalence had increased mostly for all males, with greatest gains by Africans. African females also had a slight but significant increase. Caucasian females had no advance on the previous Test Period, but showed an appreciable increase over that recorded about 6 months previously. The rise in prevalence during the latter part of the lapse in molluscicíding, but with continued therapy, can be expressed as follows:-

Percentage prevalence pre-therapy and therapy after lapse of molluscicides

Test Period	Total Incidence	Caucasian Male	Caucasian Female	African Male	African Female
1st (start) (pre-therapy)	23,1	24,1	5,8	36,6	41,7
13th (post-therapy)	4,6	2,9	0,3	12,9	12,1
14th	5,5	2,9	0,7	13,7	15,2
15th	7,1	4,1	0,9	19,0	19,0
16th	8,8	5,4	2,0	18,7	24,7
17th	11,2	7,1	2,1	27,3	28,7

(extracted from Tables 13A and B, pages 54 and 55)

However, in spite of the significant rise in prevalence in all groups from the 13th to the 17th period, these were still at an advantage when compared to the pre-treatment prevalence seven years ago.

A breakdown of figures for the 17th Test Period shows that the most highly infected groups were Caucasian males 10 - 14 years; and African males 5 - 14 years. These groups contributed most towards increased incidence recorded for this Test Period, which can be regarded as the climax in the control period of 10 years, as follows:-

Percentage prevalence at post-therapy climax

	Caucasian		African	
Age Group	Male	Female	Male	Female
5 - 9	9,3	2,8	49,1	48,0
10 - 14	15,2	2,8	43,8	36,7
15 - 19	7,5	4,3	22,2	36,4
20 - 29	6,0	1,3	22,2	18,4

(extracted from Tables 13A and B, pages 54 and 55)

At this time villages with highest prevalence of infection were Santiago where the increase was about 15 fold in four months, Madragoa which nearly doubled in the same time, and Freixiel where the prevalence mounted slowly but surely over a period of nearly two years.

Percentage prevalence for selected villages

Village	13th Test	14th Test	15th Test	16th Test	17th Test
Santiago	6,3	3,3	3,7	2,5	31,2
Madragoa	8,9	14,0	12,0	18,4	24,8
Freixiel	8,4	7,3	13,3	13,7	15,3

(extracted from Table 16, page 59)

1970 - 1972 Chemotherapy combined with molluscicides

Molluscicide of the total study area followed almost immediately after the results of the 17th Test Period (May - August 1970) became known, and continued annually combined with chemotherapy which had

been decreased to three times per annum, until the conclusion of the study period.

A sharp drop in the prevalence of infection became apparent after combined control measures were reinstituted. The downward trend continued until the 22nd Test Period (January - April 1972) when the rates increased again to about 8,7% and remained so for the last two Test Periods at the conclusion of the study.

The prevalence of infection in the total population at the initiation of the study had been 23,1% and after 10 years at termination had decreased to 8,4%. Within the 3rd year after chemotherapy had been instituted as a measure of control, prevalence had been reduced to 8,8%. With molluscicidiing in addition to chemotherapy in the next year, this fell to 4,9%. These rates remained more or less static until September - December 1969 when prevalence began to rise again ending in the climax of control in May - August 1970, of 11,2%. At this time molluscicidiing had been discontinued for nearly 5 years. After molluscicidiing was again instituted in October 1970, prevalence dropped back to 8,2%. At the termination of the study in September - December 1972 bilharzial infection in the total population was 8,4%. The lowest prevalence recorded during the 10 year study was 3,3%, approximately 3 years after commencement of regular periodic chemotherapy and one year following the first use of molluscicides.

The reduction of prevalence at selected times can be expressed as follows:-

Prevalence at selected control periods

Test Period	Years	Chemotherapy	Molluscicidiing	Total Prevalence %
1 1963(start) (pre-therapy)		0 pre-control	0	23,1
3 (post-therapy)	2nd	x post-control	-	8,8
4	3rd	x	x	4,9
7	3rd	x	x	3,3
15	5th	x	-	7,1
17 (climax)	5-6th	x	-	11,2
18	6th	x	x	8,2
24 1972(final)	10th	x	x	8,4

(extract from Tables 13A and B, pages 54 and 55) and Fig 6, page 112)

The group of persons who benefited most from control measures, chemotherapy and molluscicididing, were Caucasian males aged 10 - 19 years, followed by African males and females aged 20 - 49 years. In particular African females benefited, as previous to control they seemed to retain a very high prevalence of infection throughout life.

Percentage prevalence by age and ethnic groups pre-control and 10 years post-control

a) Caucasian

Age	Start Pre-control		Final Post-control	
	Males	Females	Males	Females
5 - 9	26,2	6,5	6,9	0,6
10 - 14	52,5	12,8	9,7	1,9
15 - 19	42,3	7,7	6,2	1,0
20 - 29	16,0	2,3	4,3	2,k

(extracted from Tables 13A and B, pages 54 and 55)

b) African

Age	Start Pre-control		Final Post-control	
	Males	Females	Males	Females
5 - 9	51,1	44,1	21,1	27,5
10 - 14	63,1	58,5	36,5	33,5
15 - 19	63,5	67,1	34,5	23,1
20 - 29	38,6	42,9	8,2	17,2
30 - 39	23,3	42,0	10,3	18,8
40 - 49	19,2	42,0	5,8	15,9

Refer to Fig 8 "A. African male and female age groups prevalence before control and at conclusion of study", and "B. Caucasian male and female age groups prevalence before control and at conclusion of study", pages 120 and 121.

4.4 ASSESSMENT OF CHEMOTHERAPY IN STUDY AREAS COMPARED WITH RESULTS OBTAINED ELSEWHERE

The study at Dennilton was limited and of relatively short duration when compared with the overall study at Limpopo, and can only be considered as a check on data obtained from the latter. Hence a

FIGURE 8

S. haematobium. Limpopo. Prevalence by age groups before control and at conclusion of Study.

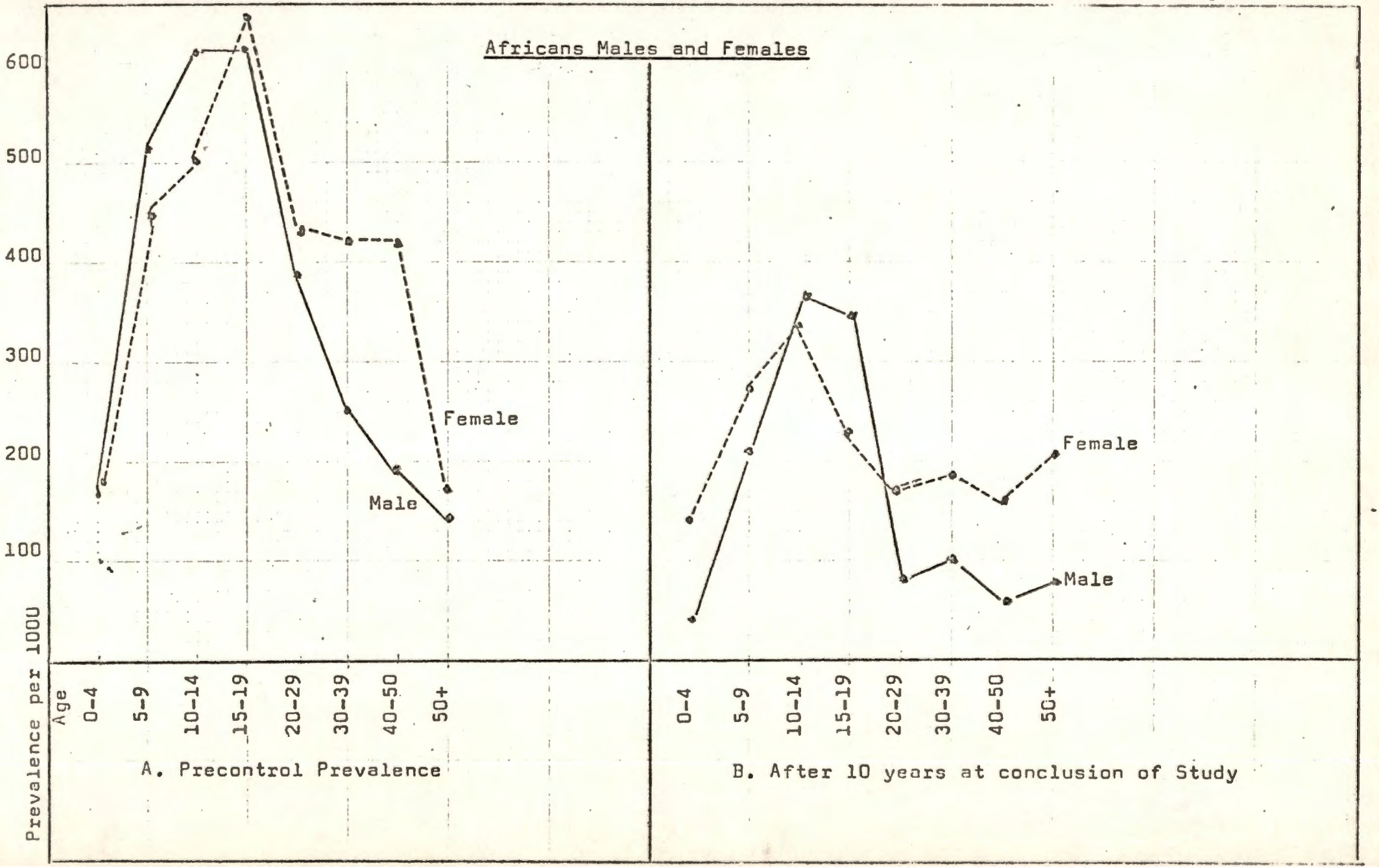
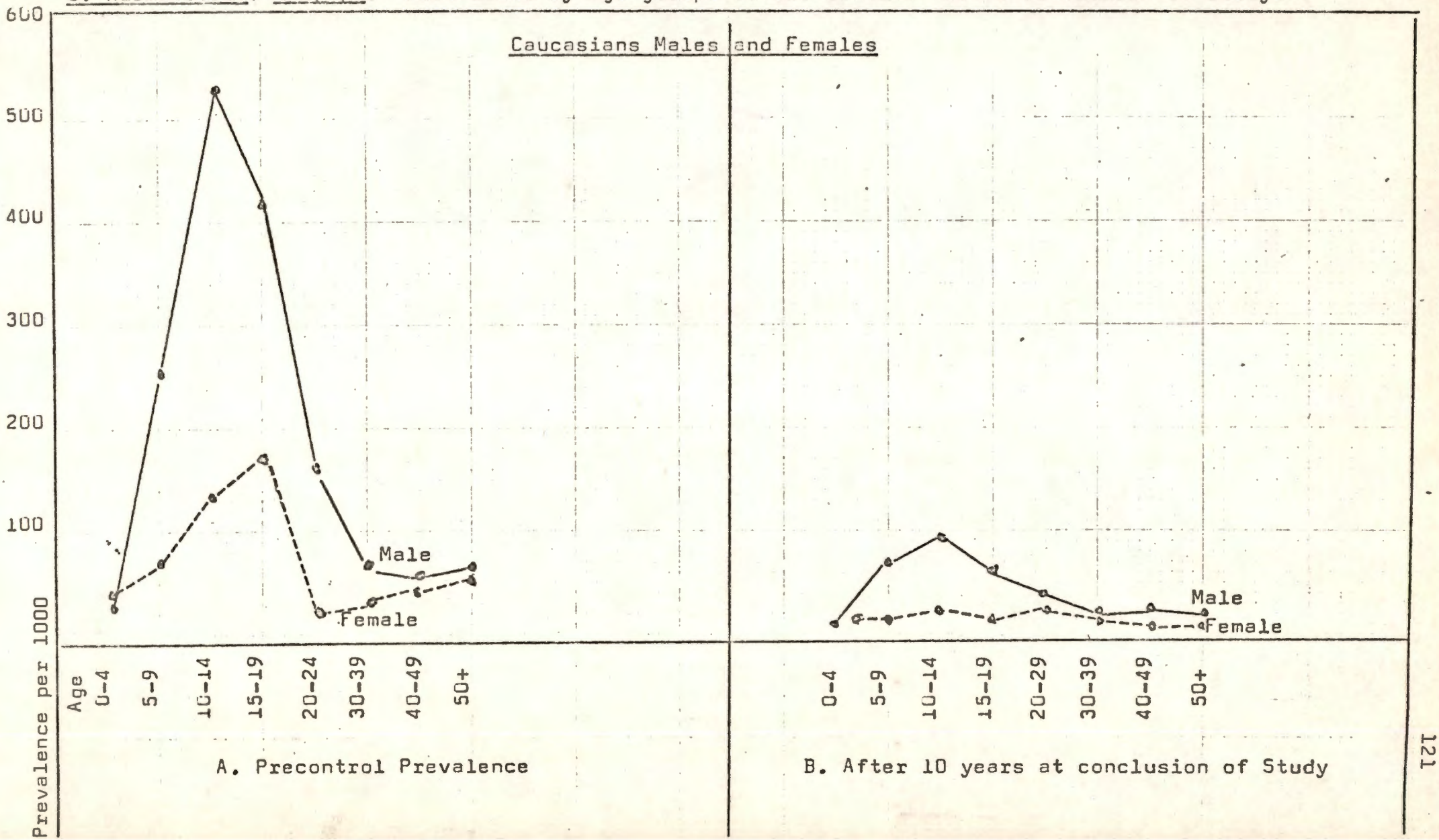


FIGURE 8

S. haematobium. Limpopo. Prevalence by age groups before control and at conclusion of Study.



further comparison of the results obtained with chemotherapy on small groups intensively followed up in Swaziland will be of value.

STUDY AREAS COMPARED WITH SWAZILAND

No haematology or biochemical studies were carried out on patients treated in Swaziland. Data from there relate solely to the efficacy of a drug trial with hycanthone, with pre- and post-therapy parasitological studies done in detail. The haematological and biochemical results from Dennilton and Limpopo will be assessed in terms of changes in values obtained for tests before and after therapy, as compared with accepted normal values for healthy individuals elsewhere.

Haematology and blood biochemistry tests carried out were aimed at determining the effects of parasitism on the individual by the schistosome.

HAEMATOLOGY STUDIES

Sedimentation rates were more generally disturbed beforehand in Africans and mainly in S. haematobium infections, than was evident in Caucasians. Immediate post-treatment values showed a clinical improvement for all ethnic groups in all types of infections, especially for Caucasians with mixed infections. No anaemia was indicated by the results of haemoglobin, MCH concentration and haemocrit tests either before or after therapy, and on long-term follow-up, although significant clinical improvement was observed in some young age groups (3 - 5 years) in Caucasians with S. haematobium infections.

Eosinophile values as well as some total WBC counts were mostly disturbed in all ethnic and age groups amongst individuals highly parasitised, i.e., in pre-puberty and puberty boys and girls. Most clinical improvement in all blood components studied was recorded in this field. Most age groups showed a response immediately post-therapy, due to host response to dead and dying schistosomes.

Blood biochemical studies

There was a transient rise in transaminase (SGOT and SGPT) values immediately after therapy in all groups, a few individuals having highly significant rises. The values fell again on long-term follow-up, comparable to pre-treatment values and within the accepted normal range. The most significant rises took place amongst Caucasians with S. mansoni infections and mixed infections. However, most individuals showed sufficient changed values on long-term follow-up to indicate a clinical improvement.

Transaminases studies did not show significant differences pre- and post-therapy from accepted normal values for either study area. This may be due to the fact that the tests employed are not sensitive enough to record significant changes or that the disease or the drugs used did, in fact, not upset the biochemical balance of patients receiving therapy sufficiently for this to become apparent. The apparent absence of severe hepatosplenomegaly from both areas confirms this.

Parasitology studies

Egg Counts:

This parameter is sufficiently sensitive to show change before and after therapy as quantitative increases or decreases in individual egg counts can easily be determined microscopically. As the period of observation in Swaziland was of short duration (3 months) only the short-term results of chemotherapy in Limpopo, Dennilton and Swaziland will be compared.

In all instances all persons receiving therapy were infected and remained in the endemic areas. The groups considered here were relatively small, and the periods of observation short:-

Numbers of patients and time observed

Swaziland	-	204 patients observed for 3 months
Dennilton		
"A" Group	-	56 patients observed for 8 months
"B" Group	-	17 patients observed for 8 months
Limpopo	-	42 patients observed for 7 months

All groups had been treated with hycanthone either orally or parenterally, except Group "B" at Dennilton, which received oral becanthone, a related schistosomicide. The objective of therapy was primarily to determine drug efficacy related to tolerance in patients treated.

Pre-therapy severity of infection in various places was based on egg counts and percentage frequency distribution can be listed as follows:-

Percentage pre-therapy frequency distribution of egg counts

	Severity		
	4+	1+/3+	Few
Swaziland	60	40	-
Dennilton "A"	57	43	-
"B"	47	35	18
Limpopo	36	14	50

Severity of infection relating to individual worm loads was significantly greater in Swaziland and Dennilton "A" than in Limpopo.

Percentage of patients excreting no viable eggs at various periods of observation after treatment was as follows:-

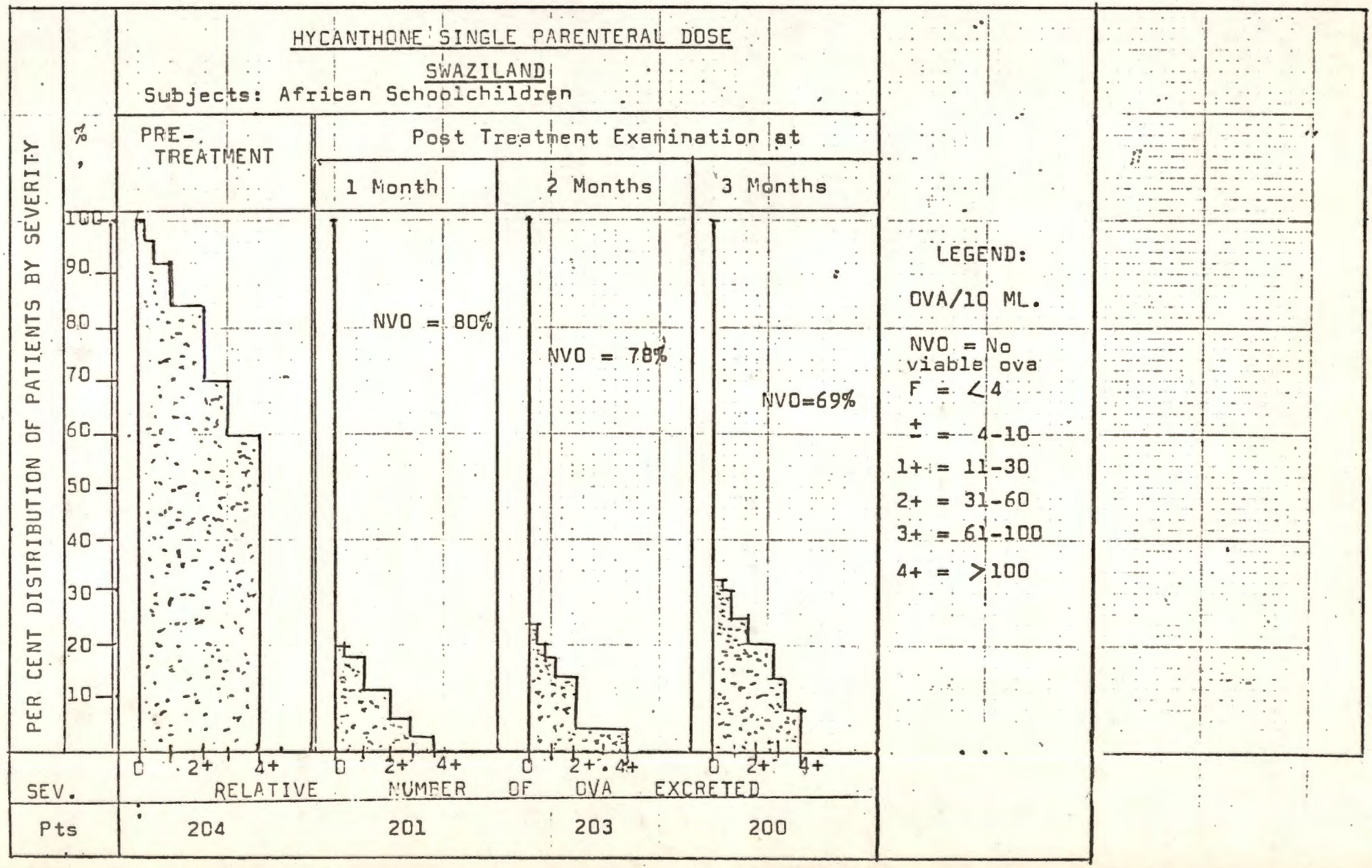
Percentage patients excreting no viable eggs, post-therapy

	1 month	2 months	3 months	7-8 months
Swaziland	80	78	69	-
Dennilton "A"	86	100	98	94
"B"	59	44	70	82
Limpopo	80	100	94	100

Refer to Figs 2, 3, 4 and 7, Effect of single therapy on ova excretion at Limpopo, Dennilton "A" and "B", and Swaziland respectively, on pages 102, 107, 108 and 125.

A regular pattern is apparent from the above figures, when considered for all groups treated with the same formulation drug, hycanthone, i.e., for Swaziland, Dennilton Group "A" and Limpopo. Omitted is "B" Dennilton, which received an inferior form of the drug, becanthone.

FIGURE 7


HYCANTHONE SINGLE PARENTERAL DOSE
SWAZILAND
Subjects: African Schoolchildren
PRE-TREATMENT
Post Treatment Examination at
1 Month
2 Months
3 Months
PER CENT DISTRIBUTION OF PATIENTS BY SEVERITY
%
100
90
80
70
60
50
40
30
20
10
NVO = 80%
NVO = 78%
NVO=69%
LEGEND:
OVA/10 ML.
NVO = No viable ova
F = < 4
+ = 4-10
1+ = 11-30
2+ = 31-60
3+ = 61-100
4+ = >100
0 2+ 4+
SEV.
RELATIVE NUMBER OF OVA EXCRETED
Pts
204
201
203
200

There appears to be a very good response in the former group of about 80% patients who became negative for viable eggs one month after therapy. This percentage was maintained or even increased for Dennilton "A" and Limpopo when nearly all patients treated became negative at 3 months and remained so 7 - 8 months when observations terminated. For Swaziland, where severity of infection was higher, the trend is a little different. An increasing number of patients again became positive for viable eggs over the observation period.

CHAPTER 5

COMMENTS AND CONCLUSIONS

5.1 GENERAL APPRECIATION

Changes observed in ova excreted after therapy

Weber et al (1969) stated that specific treatment, if successful, kills worms, thus interrupting the laying of further eggs. It does not, however, prevent the continued release of black or dead eggs from the bladder mucosa into the urine which may continue for some considerable time.

They report the presence of abnormal eggs in the intestinal wall after the use of several different schistosomicides, including niridazole and hycanthone. This supports Jordan's (1967) suggestions that the percentage reduction in egg load, rather than the absolute cure rate based on complete cessation of viable eggs, should be used to assess the effectiveness of suppressive - or chemotherapy.

The external appearance of eggs excreted by patients treated in the study areas changed, and embryonic development seemed affected.

Dead or deformed S. haematobium eggs, small in size, shape distorted, and embryo malformed or underdeveloped, were seen in rectal biopsy tissue taken from patients after treatment. Only few biopsies were done, some to the seventh month post-therapy, when this condition persisted.

Some fibrotic scar sites on the mucosal wall of specimens taken showed where apparently reabsorption of dead eggs had taken place towards the end of the observation period. Very little, if any, decrease in numbers of entrapped dead eggs was seen in specimens from patients under continuous observation.

Patterns of expectation

The changing pattern of egg excretion has already been described (see page106). Observations will now be made of the pattern in age groups and sexes of the ethnic groups, before chemotherapy and at the end of the 10 year study period.

MacDonald et al (1968) based their assessment of the results of control by chemotherapy and molluscicides in the Burma Valley

Rhodesia on patterns of egg excretion. The prevalence of S. haematobium infections was reduced from 39% to 22% after 2 years, while egg excretion was decreased by 29% in the first year and 38% after the second year of control.

By comparison in the Limpopo study the mean prevalence for both ethnic groups after 10 years of control was reduced from 23,1% to 8,4%: a ratio of 3 : 2 in favour of control results obtained at Limpopo.

Amongst Africans, males aged 10 - 19 years were still excreting large numbers of eggs, while females aged 5 - 14 were now amongst the biggest excretors of eggs. Before therapy ages 10 - 19 had excreted most eggs. Females aged 40 - 50+ became an increased source of egg excretion after therapy. The significance of this changing pattern is that the most physically active age groups, male and female adolescents, became the most intense egg excretors at the end of the study. Increasing egg excretion by older African women after therapy may be related to social habits. The parasite pool in Africans continued in sufficient quantity and the breakpoint in control had not been reached.

The pattern amongst Caucasian egg excretors was radically different from that of Africans. Egg excretion was reduced to almost nil in all female age groups and to small numbers in the ages 10 - 14 in males. Only an insignificant fraction of the parasite pool could have remained in Caucasians and the breakpoint in control leading to eradication would have been reached and passed some time previously, had infection been limited to only this group.

The frequency distribution of egg counts had also altered. For Caucasians all egg excretors now fell into a less severe category, i.e., 5 - 10 per ml urine specimen, as compared with 500+ before therapy. For Africans there was improvement too after 10 years of control, the high frequency distribution of egg excretors was now almost confined to the 5 - 10 category with only occasional higher excretion of 500+. Refer to Tables 17 and 25 pages 60 and 100.

MODERN SCHISTOSOMICIDES IN THE ROLE OF CONTROL OR ERADICATION

MacDonald (1965) considered that unless therapy was systematic, regular and supplemented by other intensive measures with the object of passing the control breakpoint and going on to eradication, it could be discounted as an effective method of control. The greatest weakness of therapy at that time was largely "inadequacy and toxicity of drugs available". The attributes of the new schistosomicide, hycanthone, which was used mainly in the study project, have completely offset this disadvantage by the speed and ease of administration, and by its high efficacy and relatively low toxicity (Ruas (1974)).

At Dennilton treatment was only carried out once, to test the efficacy of the new schistosomicide and was not accompanied by other measures aimed at controlling transmission. On the other hand, at Limpopo, treatment was systematic and regular, where the entire population was screened for infection and those positive treated in 24 periods in 10 years with the new effective schistosomicides. Concurrently contamination was kept at a low level and snail control proceeded at irregular intervals, very much in line with MacDonald's contentions. Evaluation of the results of this therapy, far exceeding anything available to MacDonald, have already been considered, both for short and long-term periods, in Chapter 4. Here therapy in relation to control or possible eradication will be discussed in terms of patterns which emerged from the study.

When the decrease in prevalence due to control measures at Limpopo is placed against MacDonald's contrast of four types of control it is seen that the breakpoint as defined by him is reached in a matter of months after initial therapy of all infected persons; whereas in his prediction, using the outdated schistosomicides, the breakpoint was only reached after several years. However, he predicted total control or eradication resulting from the most intensively applied measure of therapy plus control of entry to water and/or snail control to become absolute after 4 or 5 years. At Limpopo the addition of an extra control measure to therapy, i.e., snail control, forced the prevalence down to a basic 3%, but this was not low enough to bring about eradication or even to stabilize the parasite pool

at an acceptable low level in the population. When this additional control measure was relaxed the prevalence increased again.

Use of chemotherapy as a control measure was not enough to reduce the prevalence to a point from which eradication would result, while the combined measures of therapy plus snail control were not continued long enough to bring this about even though the prevalence was reduced by them to an almost negligible quantity.

MacDonald considered that his breakpoint would be reached when the infection rate in a community was reduced to roughly 10%, by a combination of control measures, therapy being one. But the results of similar combined measures used at Limpopo showed that the reduction in prevalence must be very much lower, even lower than 3%. Also, these measures would have to be maintained for long periods, exceeding the 30 months "A" Period during which the prevalence remained almost stable (see Fig 5, page 110). Where the control area is open and surrounded by uncontrolled conditions such as those found at Limpopo the measures may have to continue indefinitely to maintain this low prevalence in the protected population.

MacDonald stated "the significant point is that a sufficiently intense programme can be expected to pass a breakpoint and thereafter increase rapidly in efficiency and lead to eradication. While one falls short of the required degree of intensity, even by only a small measure, will have no hope of ever attaining anything other than a reduction of general prevalence".

Conclusions

The study project can be considered a successful exercise as pre- and post-therapy data have become available in a statistically significant number of persons observed over a long enough period, from which valid conclusions can now be drawn.

Data from selective mass chemotherapy, alone and in conjunction with other control measures, are now available of haematological, blood biochemical and egg excretionary responses of persons treated with a modern effective schistosomicide.

In addition, the effects of chemotherapy, on its own and related to

other control measures, have been studied on the prevalence of the disease in a community of 7 400 for a decade.

Stemming from this, it is considered that the experience and data gained at Limpopo can be used as a model on which future control programmes in large communities can be based. However, regardless of these conclusions, old dogmas may still hold back progress in the use of mass chemotherapy as a major method of bilharziasis control.

5.2 NEGATIVE FACTORS OBSCURING PRIORITY RATING FOR CONTROL

In the Republic of South Africa the controversy of "to treat or not to treat" goes on. Should the control of bilharziasis rank in priority with that given to tuberculosis, malaria, measles, venereal disease or other social diseases. Priorities for the control of any disease depends on its rating as a cause for lowering the productivity or physical well-being of the human population. Thus the physical tolerance or lack of external manifestations of a disease could determine its rating in a health budget.

In South Africa its priority ranks very low, although most facilities for control are present, such as adequate health budgets, trained personnel, etc. Elsewhere the need for high priority is recognised by health authorities, but the facilities of finance and staff are on short supply.

Apart from priority rating, several other factors tend to obscure a positive approach to the problem of therapy and control. Amongst these are the inherent dangers of treatment; possible relapses or reinfection after treatment if patients return to endemic foci; and other probable aggravating factors bound up with an expanding agronomy.

DANGERS OF TREATMENT

Because of its peculiar intravascular and intratissue parasitosis special knowledge is required and care must be taken in the treatment of bilharzial patients. Added to this the fact that all available schistosomicides have some potential toxicity, gives some risk to the patient in all forms of treatment. Other factors to be considered are concomitant illness and mixed treatment (polypharmacy) given simultaneously.

Apart from reactions which may be provoked by the toxicity peculiar to each of the available schistosomicides (see Annexure "F") all can cause some tissue and tumoral reaction related to worm mobilisation, shift into the liver or lungs, and by death of a variable quantity of worms with liberation of antigenic material (Coutinho (1969)). These reactions are almost unavoidable, but are fortunately unimportant at most times. When the liver or lungs are involved or a general state of allergy is invoked reactions can become serious or even fatal due to vascular or anaphylactic shock. Coutinho (1969) states that in such a case it is difficult to determine if the reaction is due to a specific drug sensitivity or to an intense allergic response to damaged worm substances liberated into the host.

We are, therefore, dealing in the first instance not only with the possible effects of a toxic substance on the patient, but also secondarily with the patient's reaction to debris from dead or dying worms as a result of the treatment. These responses could be aggravated by the presence of other diseases debilitating the patient or by the simultaneous use of other drugs known to cause toxic reactions.

It is interesting to note the contraindications to treatment as laid down by Coutinho in 1969, many years before the common use of the modern schistosomicides niridazole and hycanthone, whose listed contraindications could have been copied from these. He lists contraindications to treatment with any schistosomicide as follows:-

Pregnancy
Acute infections, acute broncho-pneumonia
Chronic infections, pulmonary tuberculosis
Accentuated malnutrition, marked loss of weight
Accentuated anaemias
Old age (over 55 years)
Advanced liver failure
Renal insufficiency
Cardiac disease
Neuro-psychic and electro-encephalogical disturbances
Gastritis, peptic ulcer
Specific drug sensitivity

This is a formidable list to heed when considering treatment, but in effect means the use of the physician's clinical judgement of offsetting the advantages for the patient against the risks of treatment.

No comprehensive statement on fatal reactions related to the use of any one schistosomicide has yet been published, with the exception of hycanthone. In an analysis of fatal reactions reported in Rhodesia and possibly related to the use of hycanthone Gane (1974) tabulates the reactions where two or more factors were implicated in the deaths of eight patients:-

FACTOR	PATIENTS
Error in dosage	3
Respiratory infections	4
Underlying cirrhosis	2
Operations under general anaesthetic	4
Wrong drug combinations	6
Chronic infections	2

It is apparent that most of the above reactions were due to an error in clinical judgement on the part of the doctor treating the patient. He concludes that hycanthone is usually only toxic to an already diseased liver and advises the careful reading of the manufacturer's package insert to use as few drugs concomitantly and to treat only patients who have been in good health for the past month.

In the field in Southern Africa, where the drug has been used in mass chemotherapy, Hansford (1974) Ruas (1974) and MacDonald et al (1968) considered the drug well-tolerated and side effects occurring were moderate. However, candidates for mass chemotherapy must be adequately examined under medical supervision.

Reaction rates of other schistosomicides are more difficult to come by. However, just as hycanthone can precipitate reactions all others can do the same. The toxicity for each would be peculiar to the target organs.

The antimonials have the worst record for fatal reactions, explaining their unpopularity in present day therapy. As most drugs introduced into the body are detoxified by the liver, this organ can be expected to be the target on most occasions for toxic reactions.

Gane's conclusion that drug toxicity can be expected with an already diseased liver and that we take too much for granted the resilience and powers of recovery of the liver, especially in the under-nourished, is so important that the liver and its illnesses in Southern Africa needs some further discussion.

The acute and chronic sick liver in the African is common in Southern Africa. In a short series of admissions for liver disease studied by Roberts (1970), he found that high prevalence of liver disease is one of the most striking differences between the European and the African in Southern Africa. In the African the high prevalence of cirrhosis and primary carcinoma of the liver is striking, possibly because the latter condition results from the former. Protein malnutrition has been considered as a predisposing factor. Kwashiokor may be responsible for the high prevalence of liver disease in after life for the African. Infective hepatitis which may give rise to a secondary post-necrotic cirrhosis also has a high prevalence. Wall and Gelfand (1972) in a study of African cirrhotic livers found that the condition is common in 8,3% of all autopsy material seen at Harari, several histological types being encountered - partial and post-necrotic cirrhosis, cirrhosis with siderosis, bilharzial fibrosis and chronic active hepatitis.

Kitsch and Saunders (1972) in a review on the subject of nutrition and liver disease established its importance and widespread occurrence, they discussed the relative importance of nutritional factors and alcohol in the pathogenisis of liver disease. The African sick liver is a widespread entity which must be catered for when considering mass therapy for the control of bilharziasis in the field.

Apart from reactions directly related to the use of schistosomicides, drug induced hepatotoxicity can also result from wrong combinations of drugs in polypharmacy, such combinations of drugs are more likely to be made in clinic or hospital treatment of individual patients than in mass therapy in the field.

Popper et al (1963) and Sherlock (1963) classify drug induced hepatic injury into various groups. Sherlock's classification is quoted here:-

Type	Example	Dose Dependance	Animal Prediction
Hemolytic	Sulfonamide	No	No
Interference with bilirubin			
Uptake	Flavaspidic acid	Yes	Yes
Conjugation	Novobiocin	Yes	Yes
Excretion	Norethandrolone	Yes	Yes
	Cholecystographic media	Yes	Yes
Direct hepatotoxicity	Tetracycline	Yes	Yes
Hepatitic	Phenelzine	No	No
Hypersensitivity			
Cholestatic	Chlorpromazine	No	No
General	p-Aminosalicylate		No
	Erythromycin estolate		No

The combination of schistosomicides with several of the drugs listed in Sherlock's classification have already been incriminated as causing severe adverse reactions by Gane. Of interest is the persistant use of Chloropromazine, under various trade names, as an antinausean, known for long as being hepatotoxic.

Relapses or reinfections after therapy

A major consideration maintaining official resistance to advancing the status of bilharziasis control in South Africa is the probability of immediate reinfection of a cured patient when returned to an endemic region. Also the question of "lost immunity" to super-infection is raised when therapy relieves the individual of the source of such possible immunity. Are there proven grounds for such fears? Relapses or reinfections after successful therapy are closely related to the probability of earlier acquisition of resistance to schistosomal infections by man. Leaving for the moment the possibility of prepatent infections (growing schistosomules) developing to maturity after therapy, or worms damaged by therapy reconstituting themselves, there is an apparent danger of new infection to a cured person returning to an endemic focus. However, observations made over varying periods of time of groups treated in

the study areas show that there is no immediate danger of this happening.

Data on cure rates in groups studied have already been presented in Chapter 4, and the significance of patterns which can be expected discussed. Here will be considered the probable length of time between therapy and re-appearance of positive reactors in relation to probabilities of reinfection. Should such time be short, then therapy cannot be considered as an economical or effective method of control, nor will therapy be of advantage to the individual.

In small groups mainly infected with S. haematobium intensively studied over short periods it has been shown that reinfection is not a serious factor for more than six months from date of treatment and that this may extend for even longer periods. In the Limpopo study area one group was followed through for more than 7 months without viable egg excretion again appearing. In Group "A" at Dennilton where excretion of dead eggs continued for more than 8 months post-treatment some viable eggs were only seen after 5 months and then the numbers of these remained minimal for more than 8 months. In Group "B" treated with a less effective schistosomicide a few live eggs persisted after maximum "cure rates" had been established within the second month and these few were present until after the 8th month when observations were discontinued. In the Swaziland control group where the maximum cure rates were obtained 1 - 2 months post-treatment a gradual build-up in numbers of viable eggs excreted by persons successfully treated commenced after the 3rd month. However, worm loads in Swaziland were very heavy, much more so than in Dennilton or Limpopo. According to these data, reinfection in the study areas would not be a factor to consider for 6 - 8 months from therapy for most persons. This is a reasonable period between sequential therapy periods for keeping transmission minimal and benefiting individual patients.

Observations on lack of immediate reinfections occurring in the study areas are confirmed elsewhere. Fripp (1969) in a resume on resistance to schistosomal infestation in man and experimental animals states that most opinion now favours the view that a partial immunity can be induced in man, but that the degree of resistance or its mechanism is still unknown. Although the elimination of infections in experimental animals with drugs usually results in a

loss of acquired resistance by them, Jordan (1967) in Tanzania observed during 2 years that reinfection by S. haematobium was slight in school children following successful therapy.

In a two-year follow-up in St.Lucia Cook et al (1974) state that the reinfection rate of S. mansoni was 15% after two years and was related to the geographical area to which the patient returned.

Walker et al (1970) state that the reason why some subjects are apparently not infected with schistosomiasis despite abundant exposure is a topic upon which insufficient research has been pursued. While studies on the production of heterologeous immunity are of considerable academic interest for the ultimate development of a vaccine, effective mass chemotherapy is feasible now and can immediately reduce the worm load and egg output by 90 - 100%, thereby arresting progress of pathological changes in individuals, reducing transmission in the community, retarding reinfection in the individual, and bringing the focus under control.

AGGRAVATING FACTORS

Because of lack of forethought some of the greatest ecological disasters in Africa are man-made; "..... the construction of the great man-made lakes of Africa - Lakes Volta, Kariba and Nasser have resulted in ecological disturbances that have produced formidable sociological and medical problems....." (Ecological Congress 1968).

On the subcontinent of Africa the increase in water conservation and supply has been described as the first priority for the continued existence of man there. Yet with every new water project the risk of man-made diseases is increased, foremost of these diseases being bilharziasis. Some assessment of the great water impoundment schemes along the Orange River in the Republic has shown that these are not likely to change the climate favouring introduction and establishment of bilharzial vector snails. However, other projects on the sub-continent are not so fortunate. Increase of the disease around Lake Kariba has already proved unmanageable for both Rhodesia and Zambia, and the effects of the great Kafue undertaking have still to be assessed. In Africa all irrigation projects are suspect.

While large-scale water conservation schemes are essential for maintaining and increasing the wellbeing of the subcontinent's

population, their planning should receive thought and attention beforehand for the prevention of man-made ecological disasters.

5.3 ECONOMIC IMPACT

The paucity of data on the morbidity and mortality due to bilharziasis in Southern Africa is matched by lack of data on which to base an estimate of its economic impact on the gross national productivity. Weisbrod (1961) believes that some quantification is justified because of its importance and Wright (1968) used quantification to arrive at an estimate of the economic importance of bilharziasis on a global scale.

It would be fantasy to attempt an accurate audit of the loss of productivity of the sick individual based on the meagre details available. However, in a few instances some data are available and this can be worked into an estimate of costs of the incapacity and losses caused by bilharziasis in Southern Africa. In the endemic region of the Transvaal Lowveld it is known that at three of the major medical centres the average out-patients attendance for bilharziasis is 3 per day (Personal communication 1969). Only occasionally are patients with gross sequelae of the disease admitted to the wards for treatment. In this region there are 35 Mission and State Hospitals of some consequence. If the average attendance is true for all these hospitals, then something like 35 000 patients could attend for treatment per annum. Average costs per patient day for the region is R3-00: with 2 days attendance this would make the direct cost of treatment for the disease something like R210 000 per annum. Add to this direct hospital cost the loss of earnings of, say, R2-50 per work day, then the total wage loss for patients attending hospitals would be about R175 000 per annum.

The direct costs of the disease based on this estimate would be:-

Hospital Costs	R210 000
Loss of Earnings	175 000
Total Loss	R385 000

This total loss is based on 35 000 patients seeking medical attention per annum, when we know that the total persons sick from only one

physically diagnosable symptom of the disease such as haematuria, far exceeds this estimate.

Again in Durban, Powell (1967) in a 9 year period from 1958 to 1966 treated only 1 374 patients admitted for bilharziasis to a large central hospital.

An estimate of direct costs based on 10 days incapacitation per patient for this hospital could be as follows:-

Hospital Costs	R 9 600
Loss of Earnings	8 000
Total Loss	R17 600

The same comment applies here as for the Transvaal, it is obvious that this amount is far below the actual losses for which the disease could be responsible.

Total losses based on two days loss of earnings and hospital costs per person for the estimated infected population in the Republic of South Africa would be nearer to the true position. For the 2,75 million estimated to be infected this loss would amount to R30 250 000: a sizeable slice cut from the gross national productivity.

The only other State on the subcontinent from which data for bilharziasis admissions to hospital are available is Malawi. The total out-patient attendance for bilharziasis for 1973/1974 was 129 044. The Gross National Product for Malawi was known to be about 1/10 that of the Republic of South Africa. Direct costs of incapacitation due to the disease based on this ratio would be K. 709 742. While this cost seems realistic, it could not reflect the true loss due to the disease when the total number of sufferers has been estimated at 2,75 million. An estimate of loss based on this number of persons sick from bilharziasis in Malawi each losing 2 days per annum would be K. 3 025 000. For a country which is still mainly dependant on subsistance such a loss to the economy must be enormous.

A guess estimate based on the method used, i.e., two days loss of earnings plus direct hospital costs per total number of sufferers estimated for each country, would give some indication of the economic loss caused by bilharziasis on the subcontinent. The local

currency has been converted and presented as US dollars for comparative purposes:-

COUNTRY	INFECTED	(x)LOSS IN US $(*)
Republic of South Africa	2,75 million	45 375 000
Malawi	2,75 "	4 537 500
Mozambique	1,75 "	1 925 000
Rhodesia	1,75 "	14 000 000
Angola	0,75 "	825 000
Zambia	0,75 "	4 125 000
All Other States	0,50 "	550 000
		71 337 500

It has already been stressed that the method of estimation is little more than a guess based on the direct loss of two days hospitalisation and earnings due to the disease by each of the infected persons. The loss is based on the difference in the G.N.P. of each country as compared to the Republic of South Africa. However, the method used does not totally invalidate the results obtained as these are based on very conservative considerations.

Of interest is the comparatively enormous economic loss by States such as Malawi, Mozambique and Zambia where the national economy is already low: while the losses for the Republic of South Africa and Rhodesia, where the national economies are somewhat stronger, are staggering. With the exception of Malawi, the losses due to the disease are greater in countries where the G.N.P. is higher.

Wright in his global estimate quotes the economic losses due to the disease for the world and for Africa. A comparison with his figures is invited, even though arrived at through a completely different method of calculation:-

Wright	Total for world	US $ 641 790 130
	Total for Africa	445 866 945
Author	Subcontinent of Africa	71 337 500

FOOTNOTE(*)
Converted from local currency to US dollars at ruling rate of exchange

The following estimate of the costs of chemotherapy in the study areas is offered as a basis for comparison with the estimated costs of the disease in loss to the national economy:-

DENNILTON. COST OF INITIAL TREATMENT PER PERSON

Chemotherapy per patient treated	Drug	US ¢	0,95
	Professional attendance		0,25
	Transport		2
	Equipment		10
	Laboratory Costs		1,50
	Administration and quarters		0,25
			3,07
Cost for total therapy for 400 patients			1 216,00

LIMPOPO. COST PER PERSON, AVERAGE OF 24 TREATMENTS IN 10 YEARS

Chemotherapy per patient treated	Drug	US ¢	0,60
	Professional attendance		0,10
	Transport		0,05
	Equipment		0,10
	Laboratory Costs		0,50
	Administration and quarters		0,25
			1,60
Other	Molluscicides		0,10
	Maintenance		0,25
			1,95
Cost for 7 400 persons protected per annum			14 625,00

At Dennilton the costs covered ± 400 patients participating in efficacy and tolerance drug trials for a limited period. While this was true also for Limpopo for part of the costs, these resembled more those which can be expected from a control project carried out continuously for 10 years for the protection of a population of 7 400 persons.

CHAPTER 6

FUTURE DEVELOPMENT OF CONTROL MEASURES

AND

SUGGESTIONS FOR FUTURE INVESTIGATIONS

6.1 DEVELOPMENT

According to experience obtained of the problem in the study areas, future bilharzial control measures could be developed along several lines. Those suggested are:-

application of "old methods" such as environmental and social improvement which have not yet received attention: and intensification of these methods where already applied;

research and development or improvement of the new field of schistosomicides and molluscicides;

the discovery of new methods; such as the development of an effective vaccine: and of biological control of transmission where this is feasible.

APPLICATION OR INTENSIFICATION OF OLD METHODS

The application of environmental and social improvement to regions where there is a possibility of isolating and destroying the focus of infection would make progress towards control of the disease. Intensification of such measures as the provision of piped water supplies and safe aquatic recreational facilities, adequate disposal of human wastes and isolating infested waters in rural communities would in time prove to be good investments other than for bilharzial control alone. Better placing of irrigation schemes and site selection of villages would be essential.

A commencement using these methods could be made in fringe areas of the infection such as in the Eastern Cape where the disease is reported to be on the wane (Pitchford et al (1960)). Isolated foci such as those reported from desert areas in Southern Botswana and South West Africa could be eliminated with such measures plus the judicious use of those which fall into the next category to be discussed.

RESEARCH AND DEVELOPMENT OF IMPROVED SCHISTOSOMICIDES AND MOLLUSCICIDES

The recent announcement by an international agency such as the

World Health Organisation (1975) that attention would be given in future to assisting in the discovery and production and testing of vaccines and drugs for the control and elimination of major tropical diseases which "until now have defied control", will assist private enterprise which has supplied all the initiative in this field in the past. The auro of commercialism tainting such activities in the past will now largely be removed by the official participation of national and international research laboratories in conjunction with those of commercial laboratories striving to produce new cures for old diseases.

While the new schistosomicides such as hycanthone, niridazole, oxamniquin and metrifonate have great advantages over the antimonials in efficacy and lesser toxicity, none of them is perfect. Further research on the chemical structures already known to have possibilities such as the thioxanthenones, nitrothiazoles, nitrofurans and organophosphoric compounds is urgently needed to discover the radicals which may reduce their human toxicity and increase a selective toxicity for the schistosome. Or the perfect schistosomicide of the future may lie completely outside these chemical structures.

The same is true for available molluscicides. While they remain toxic to organisms other than snails, their use will be limited. Intensive research is still needed to obtain the ideal molluscicide having selective properties for the snail species of Bulinus (Physopsis) and Biomphalaria.

Research into barrier creams for protecting the body before immersion into infected waters would also have a place in such a programme.

Vaccines and biological control

A vaccine is needed to prevent the antigenic disguise taken on by the adult schistosome and thus make it vulnerable to the human immune mechanisms or to destroy the invading cercariae on primary contact or penetration of the skin. The possibility of producing heterologous immunity has significance in limiting the severity of bilharziasis in regions of mixed human and animal infections.

Predator snail species have been introduced into new areas in the

hope that they will be able to control vector species, but so far have only had news value. The use of plants to render water toxic for the same purpose have progressed no further. However, this field of investigation should be continued in spite of its obvious shortcomings.

While all available measures should be developed and applied for the control and ultimate eradication of the scourge of bilharziasis, that of chemotherapy seems to be, on the evidence presented in this thesis, the most promising single measure for the foreseeable future. A commencement to control would be the suppression of egg excretion en mass by therapy in endemic areas, thereby arresting transmission and improving the lot of the individual patient.

Preliminary reports from the St.Lucia pilot project where chemotherapy is largely used support the conclusions based on the studies carried out at Dennilton and Limpopo. The use of chemotherapy was further confirmed by recommendations approved at a Plenary Session of the International Conference on Schistosomiasis held in Cairo in October 1975. Further recommendations made that closer collaboration between pharmaceutical companies and international health agencies in the development and testing of new therapeutic agents, were excellent and supported the call for this given earlier on by WHO (1975).

6.2 SUGGESTIONS FOR FUTURE INVESTIGATIONS

Control and eventual eradication of bilharziasis depends in the first instance on establishing the necessity for this. After more than a century during which the disease has been known and studied on the African subcontinent, and despite the existence of an enormous bibliography on the subject collected during that time, the authorities are not yet sure how to handle the rising tide of bilharziasis, this in spite of the evidence of the seriousness of the disease. The first need then is for an assessment of the importance of the disease sequelae today.

At the same time further development in the fields of chemotherapy and snail control is needed, while the subject of immunity and possible biological control methods should be explored.

A research programme, based on these needs, is suggested as follows:-

a) TO ESTABLISH THE PRIORITY OF BILHARZIASIS AS A DEBILITATING DISEASE

Parallel studies should be set up in different parts of Africa to study the reasons for apparent difference in observations made in the past and so to remove some of the anomalies which have clouded many aspects of the problem. These studies should include the pathogenisis and mortality in various age and ethnic groups and to establish possible variations of response in individuals to schistosomal invasion.

We should go back to individuals from groups which have been intensively studied in the past, when they were at a younger age, and by using sophisticated diagnostic aids determine what has happened to them after the passage of several decades. Powell's study (1967) in Durban and Walker et al (1970) in the Lowveld, should be duplicated and observations started now which can be projected into the future. While the assumption has been accepted that present sufferers may have heavier worm loads than in the past, no studies are ongoing to confirm this and to show what consequences can be expected.

b) MORE INTENSIVE STUDIES OF THE SCHISTOSOME

More intensive study is required on all schistosome species, avian, animal and human <u>in situ</u> to establish not only disease response, but also to relate egg excretion to worm load. At present there is only conjecture on the relationship of egg counts to worm loads, intensity and prevalence of infection. Studies already proceeding on possible heterologous immunity should be accelerated as the production of a vaccine would be greatly rewarding.

c) RESEARCH TO PRODUCE NEW SCHISTOSOMICIDES AND MOLLUSCICIDES

Now that the collective conscience of international health agencies has been quickened, co-operation between commercial pharmaceutical enterprise and these agencies should be speeded up to find new chemical formulations less toxic to humans and more selective for use as schistosomicides and molluscicides.

CHAPTER 7

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CHAPTER 8

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