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### THE UNIVERSITY OF OKLAHOMA

## GRADUATE COLLEGE

A MATHEMATICAL MODEL FOR THE DESIGN AND EVALUATION OF SCHISTOSOMIASIS CONTROL PROGRAMS

## A DISSERTATION

# SUBMITTED TO THE GRADUATE FACULTY

# in partial fulfillment of the requirements for the

degree of

DOCTOR OF PHILOSOPHY

BY

# CHARLES E. HUFFMAN

# Oklahoma City, Oklahoma

A MATHEMATICAL MODEL FOR THE DESIGN AND EVALUATION OF SCHISTOSOMIASIS CONTROL PROGRAMS



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# A MATHEMATICAL MODEL FOR THE DESIGN AND EVALUATION OF SCHISTOSOMIASIS CONTROL PROGRAMS

#### CHAPTER I

#### INTRODUCTION

Schistosomiasis is one of the world's most important diseases. In many ways it is the greatest unconquered parasitic disease now afflicting mankind, and it is increasing in importance in underdeveloped areas where people are attempting to raise their level of well-being by improvements in agriculture, particularly, in Africa and South America where newly constructed irrigation systems provide ideal breeding places for the intermediate snail hosts of the parasite (102). There are increasing opportunities for the disease to spread throughout the world with the increased movements of mankind across the globe. The disease, a rarity outside endemic areas until a few years ago, has become widely known with several thousands of cases being seen in Europe and America each year (33). The economic burden of schistosomiasis is difficult to determine, but in Egypt, Farooq (14) estimated the disease cost \$560 million annually. Although many attempts have been made to

control the disease (8, 15, 18, 37, 45, 71, 72), few have been effective, and schistosomiasis continues to be an increasing burden for mankind. Weir (102) states,

... that it is the greatest unconquered disease afflicting man and animals; that it is 'man made,' resulting from man's own unsanitary practices...yet no effective program of control of the disease nor any effective treatment on a mass basis for human beings or animals has been developed anywhere in the world.

Although schistosomiasis has become of general interest in western nations only recently, it has been recognized for several thousand years. A disease with urinary symptoms, probably haematobiasis, was described in Egyptian papyrus (Ebers Papyrus) writings of about 1500 B.C. (60, 102). Eggs of the parasite have been found in mummies of the twentieth dynasty (1250-1000 B.C.) in Egypt. It has been suggested that the decline of the ancient Egyptians may have been due to the presence of schistosomiasis and hookworms (60). Symptoms of the disease have been clearly described in Babylonian inscriptions and later, in literature of medieval period. The Napoleonic army developed hematuria during the Egyptian campaign. indicating the presence of schistosomiasis in man at the end of the 18th century (60). The parasitic worm responsible for the disease was first identified by Bilharz, in 1851 (44). The full explanation of the complex life cycle of the parasite was demonstrated by Leiper in 1915 (54). Differentiation of separate species of schistosomiasis was made in 1903 by Manson (54). Apparently the disease was not known in the Americas until it was introduced by the slave trade. Since then only Schistosoma mansoni has been

identified in the Western Hemisphere (60). During World War II, attention was drawn to schistosomiasis due to the incidence of cases among service men in the Pacific and to the large number of Puerto Ricans deferred from military service because they were infected with the disease (76). Since then the Department of Defense and the National Institutes of Health have promoted the study of schistosomiasis. The World Health Organization, since 1950, has taken an active part in promoting knowledge and in establishing schistosomiasis control programs. Much of this work, however, has contributed only to the general knowledge of the organism, with few improvements in medical or public health practice. New irrigation and agricultural projects, such as those in Colombia and Ecuador, and an exceptional world population growth offer opportunities for the future establishment of the parasite.

Schistosomiasis manifests itself primarily by an overall deterioration in health. In areas such as Egypt where detailed surveys have been undertaken, the mortality rate due to the parasite has been estimated to vary from one per 1,000 to one percent according to the rate of infection in the locality (14). Generally, however, instead of causing death directly, schistosomiasis leads to an associated mortal disease.

Schistosomiasis produces obstruction of the bladder neck and leads to infection and bilateral renal destruction. The most serious clinical manifestation of the disease, however, is found in the liver. It is produced when eggs drift into the liver from the primary sites of infestation (61). In Egypt, the chance of a

given case of cirrhosis being of schistosomal origin has been found to be greater than 70 percent with half of these being caused by the parasitic infection alone, and the other half being complicated by nutritional deficiencies or viral hepatitis (9). The incidence of bladder cancer in Egypt is 19 percent of all cancer cases; 83.1 percent of all bladder cancers in Egypt have schistosomal bladders; 6.5 percent of chronic schistosomal bladders show malignant changes (9). The incidence of cancer of the bladder associated with schistosomiasis follows the same age pattern as schistosomiasis. The incidence reaches a peak and then declines with age; whereas the incidence of cases of non-schistosomal bladder cancer steadily increases with age. Of patients with schistosomiasis, one-third show pulmonary involvement. Patients with lesions in their lungs complain of easy fatigue, weakness, giddiness, palpitation and thoracic pains. In some instances, schistosomiasis has been found to cause damage to the brain and nervous system. The morbidity and mortality caused by the disease exacts a great toll within areas where it is established.

The association of schistosomiasis with water resources makes obvious the effect it will have on plans for increasing food production throughout the world. In developing countries, it is primarily a rural disease affecting farmers and farm production. Many of the projects under way for increasing food production and raising economic levels call for extensive irrigation works. These networks will increase the likelihood of the spread of the disease across wide areas. Agricultural production will be affected and

medical costs will rise. In the Philippines, loss to the community resulting from schistosomiasis japonicum has been estimated at \$1,350,000 from lost wages for 125,000 adults while under treatment. Total direct medical costs per 100,000 were put at \$5,282,500 (102, 72). The disease not only reduces human productivity, but also causes substantial losses in other hosts such as cattle and sheep. The economic loss and decreased productivity indicate the need to establish controls if projects to increase food production such as those being undertaken in many parts of the Middle East, Africa and South America are to be successful.

Schistosomiasis has an almost universal distribution throughout countries of the Far East, Middle East, Africa, western South America and the islands of the Caribbean. In the Far East, schistosomiasis japonicum infests the populations of Japan, the Philippines, Taiwan, China, the Celebes and Thailand. Adjoining countries will probably be found to contain foci of infection when specific searches are undertaken. Throughout the Eastern Mediterranean and in all of the African countries, schistosomiasis hematobium may be found. Schistosomiasis mansoni is found through the Middle East, Africa and in many countries of the Americas. Particularly important to the United States is the incidence of the disease in Puerto Rico.

The total incidence of the disease is not accurately known. The incidence varies from place to place across the globe. Unfortunately, since the disease is not generally a killing disease, its ill-effects are often underestimated. Other diseases often

appear on the death certificate, obscuring the infection which causes a gradual deterioration of health. In countries where the problem has been recognized, such as in Egypt, surveys of the population show that essentially 100 percent of the population over two years of age is infected. Incidence rates of 70-80 percent are common (9). Levels of infection similar to those found in Egypt have been noted in the Philippines and in Japan. In Puerto Rico, laboratory data and clinical records indicate that the prevalence of schistosomiasis probably has remained in the range of 10 to 20 percent during most of this century (20).

Weir (102), points out that in rural populations of developing countries, surveys have shown that any individual who is old enough to walk to the village watering spot will become infected. Incidence may easily be underestimated since the presence of eggs in excreta is not determined completely by one examination, and in remote areas it is difficult to conduct multiple examinations. In 1948, the World Health Organization of the United Nations (102) estimated that over 150 million people were infected. Later surveys indicate that this estimate should be raised to over 200 million. Schistosomiasis is second only to malaria in global importance, and with the constant attack on malaria gradually reducing its importance, schistosomiasis is becoming the major parasitic disease for which we have no solution.

#### CHAPTER II

#### LITERATURE REVIEW

The term schistosomiasis indicates infection with dioecious trematodes belonging to the family <u>Schistosomatoidea</u>, genus <u>Schisto-</u> <u>soma</u> (61). Three species, <u>Schistosoma mansoni</u>, <u>Schistosoma haema-</u> <u>tobium</u> and <u>Schistosoma japonicum</u>, are the major species afflicting man, although infections from other species are not unknown (54).

The natural history of schistosomiasis is complicated (16). Figure 1 illustrates the life cycle of the schistosome organism. Adult schistosomes live within abdominal veins; hence they have been termed blood flukes. <u>Schistosoma haematobium</u> deposits its eggs inside the veins of the urinary bladder and lower gut. <u>Schistosoma mansoni</u> and <u>Schistosoma japonicum</u> lay eggs in the inferior intestinal tract. The <u>Schistosoma haematobium</u> eggs escape with the urine and feces. Eggs from the other two species escape in stools from the infected mammals. In a few days, the eggs hatch, producing a free swimming stage called a miracidium. The miracidia seek out and penetrate an appropriate snail host. Within the snail the miracidia form mother cysts which produce multiple generations of the second free swimming form called a cercaria. The cercariae penetrate the skin of an



Figure 1 - Schistosome life cycle.

appropriate mammalian host, migrate to the lungs and liver, and after maturation, migrate to the abdominal veins. If mating occurs, oviposition begins and the cycle is repeated.

Hairston (28) has found that a significant portion of the disease is transmitted through the human population, but that the disease is also transmitted through other mammals such as rats, dogs, pigs and monkeys. Movement of infected animals accounts for a significant portion of the spread of the disease.

In the adult form located within the mammalian host, the female moves into the surrounding body tissue approximately 12 times per day in order to deposit its eggs (28). In doing so it is often damaged or killed. Most necropsies reveal an excess of male organisms, but experimental evidence shows that initial infections by the male and female are approximately the same (28). The biology of the egg stage is not completely known, but extensive studies have been carried out to investigate the conditions under which the eggs hatch (55, 58, 62). Evidence indicates that hatching is sensitive to salinity, temperature and light, being more rapid under conditions similar to those occuring during rainy seasons, i.e., cool temperatures, low lighting and fresh water.

Once miracidia hatch, they appear to move about randomly until they contact a potential host. If the host is a snail, they penetrate its soft tissue at any point. Inside the snail the miracidium changes into a stage called a mother cyst. In 30 to 45 days the infected snails begin to release cercariae (88). It is theoretically possible for one miracidium to result in the production

of over 300,000 cercariae. There is some disagreement whether it is possible for a snail under natural conditions to receive more than one infection (32, 20, 57); however, in most cases multiple infections are probably rare. In Puerto Rico where infection rates in the human population are thought to be between 15 and 30 percent, the infection rate in the snail population, if one assumes only one infection per snail, is thought to be from 10 to 20 percent (20).

Conditions associated with the escape of cercariae from the molluskan host have been extensively studied (57, 84, 88, 93). The larvae emerge from the snail host during the late morning and early afternoon. The peak production appears to occur approximately at noon, with emergence being greatly reduced when snails are kept from light, or in water that is either too cold or too warm. Free swimming cercariae appear to concentrate at the surface of the water. Aggitation of the water, as when it is disturbed by an animal moving through it, causes an increase in the activity of the cercariae and increases the risk of infection (89). The cercariae activity, however, does not appear to be directed and contact with the appropriate host appears to occur randomly (79, 80). Cercariae have demonstrated the remarkable ability to penetrate materials such as wet sand columns, concrete pipe and clothing. Protective salves offer some protection to penetration and are recommended whenever it is necessary to contact infected waters (20). Cercariae do not tolerate salt water; consequently there is no problem in salt water lagoons or canals. In the areas where fresh and salt waters mix, however, the cercariae can survive long enough to penetrate the skin,

Cercariae penetrate the skin with a combined mechanical and chemical action (9). Once the body has been penetrated, the cercariae migrate through the lungs and eventually reach the portal veins where they mature, mate and produce more eggs.

The host snail has been the subject of much investigation. In most regions where the disease exists, more than one species of snail have been found which could accept the disease under laboratory conditions. In the natural condition, however, infection appears to be restricted to only a small number of species of possible hosts. For example, in Puerto Rico, only <u>Biophalaria</u> <u>glabrata</u> has been found infected in nature, but under laboratory circumstances (in descending order of frequency of penetration), <u>Biomphalaria obstructus, Biomphalaria glabrata, Biomphalaria riisei,</u> <u>Biomphalaria albicans, Aplexa marmorata, Plesiophysa hubendicki</u> and <u>Drepanotrema simmonsi accept miracidiae, and Biomphalaria</u> <u>riisei</u> and <u>Biomphalaria albicans</u> have been observed to become infected and to shed cercariae (21, 83).

A great variety of useful research has been performed in detailed fashion on the ecology of the vector snail (29, 31, 74, 80, 84, 91). The life cycle of <u>Biomphalaria glabrata</u> is typical and may be used to illustrate the history of snail populations in other regions. The eggs of <u>Biomphalaria glabrata</u> are deposited in flat masses on objects such as vegetation, rocks, other snails, toads or other animals. The snail produces an average of 11-28 eggs per clutch and from one to two clutches per day. The incubation period before the eggs hatch is about eight days. The time from hatching

to egg-laying requires only about 21 days and may begin when the snail is only about eight millimeters in diameter, thus, the eggto-egg cycle requires only about one month (86). Snails attain a diameter of about 18 millimeters in the first year and require about two years to reach their maximum diameter of 30 to 33 millimeters (32).

A variety of organic materials serve as food for the snails. They appear to prefer decomposed to fresh materials and seem to thrive on rotting vegetation. Biomphalaria does not demonstrate preference for specific aquatic plants(29).

If Biomphalaria is erradicated from a habitat by chemical treatment or by stream flooding and if a few snails are replaced by flooding or by other means, repopulation is rapid, and in about 90 days the colony will have returned to its normal size (32). It is rare to find a mixture of sizes of snails in a habitat; yet, colonies containing only small snails are rare. Colonization appears to be cyclical with no apparent stabilization. The finding of only large snails and few or no egg masses usually indicates the terminal decline of a colony (32). It has been found that crowding affects colonization by lowering the snails' egg-laying capacity.

Biomphalaria is known to be dispersed by transport from the normal movement of its aquatic environment (31). Dispersion also occurs from transport by other animals (32). Eggs have been observed attached to the skins of toads and to the surface of large water beetles. The most important factor, however, in the reestablishment of depleted colonies is probably the attachment of

young snails to the legs of birds and the feet of cattle (32).

Biomphalaria has been observed to survive for several weeks when buried in streamside mud, and laboratory studies show that it may survive burial under soil and plant debris for four months; thus, a portion of a snail colony can probably endure any short-term droughts. In regard to natural enemies, Biomphalaria is readily eaten by some species of fish, <u>Lepomis Microlophus</u> and <u>Lepomis auritus</u>. It may be affected by worm parasites, protozoa or bacteria, and it is commonly eaten by rats, which apparently fish them out of shallow or receding water. Biomphalaria may occur in association with a variety of other snails without apparent 111 effects. However, it has been demonstrated that it very rarely survives in association with <u>Marisa cornuarietis</u>, a predator snail which may be used for biological control (29, 30, 31, 32, 74, 75, 80, 87).

Location, number, size and type of bodies of water determine the presence and population intensity of snail colonization. Irrigation channels become ideal habitats depending upon stability of flows and amounts of submersed vegetation serving as food and protection. Stream gradients above about 2 percent appear to be harmful in the development of significant populations (75); however, still bodies of water such as ponds or swamps will support the vector snail.

The snail is difficult to control because: 1) it is adapted to a great variety of freshwater environments; 2) it may be transported to new sites of action by currents or streams or by attachment to animals; 3) time required for reestablishment of a snail colony

is short (probably about one month); 4) young snails of small diameter (2 to 3 millimeters) and older snails of larger size can become infected; 5) snail infections mature rapidly; 6) only a low percentage of infected snails in a colony associated with human habitation are necessary to maintain the disease; and 7) even in drought conditions, the snail can survive for several weeks.

The disease, schistosomiasis, is so complex that it is difficult to predict the consequences of proposed control programs. One method used in other areas involving complex processes is the use of mathematical models. The application of mathematical modeling techniques to the development of control programs for schistosomiasis has been relatively scarce until recent times. Most work has been done in attempts to describe the disease process in gross statistical terms (27, 52). This lack of detailed mathematical description has been due largely to the complex nature of the disease's natural history. There is still much about schistosomiasis which is not clearly understood, but a disease model is able to point to areas where our understanding is particularly lacking and where additional research needs to be done in order to clarify obscure details (1, 17).

In general, models of physical processes proceed from models based on minimal understanding of the detailed descriptions of fundamental actions within complex systems. Hairston (27, 28) has developed a model based upon actuarial methods which describes schistosomiasis in terms of probabilities and average characteristics. The model has been applied to two populations of <u>Schistosoma</u> japonicum in the Philippines (72). The model comes close to

describing the populations studied and points out that there is a discrepancy in the literature accounts of schistosomiasis which may possibly be attributed to lack of information about the contribution of other mammalian hosts such as rats, dogs, livestock, etc., to the epidemiology of the disease. Hairston's conclusions (27, 28) have been confirmed by a recent study in which rats were discovered to continue transmission of the parasite independently of the human population (72). This illustration of the predictive capabilities of disease modeling techniques points out their value as a tool in attacking other environmental health problems.

Hairston's model, while quite useful, considered only gross aspects of schistosomiasis. His model was based upon relative frequencies of infection, average death rates and gross estimates of probabilities. It ignored the more detailed solution of the problem in dynamic terms and concerned itself with only a broad statistical interpretation. Another model of this same nature but considering more detail has been proposed by MacDonald (52) in which the author considered the bisexual nature of the parasite in order to develop a descriptive probabilistic model. The model was particularly appropriate in populations with low levels of parasite prevalence but was difficult to apply under conditions of high prevalence where infection is widespread. The model pointed out qualitatively that, under the assumption there is only one host population, if the total number of parasites drops below a certain natural "break point," the disease becomes limited and goes to extinction without further control. The problem of reducing the parasite population to a point below the

natural break point still remains. To date actual programs have had little success in this undertaking and MacDonald's model has not yet been adequately verified. Assuming it is correct, however, one is encouraged to seek programs which will reduce schistosomiasis below the point at which the disease is able to sustain itself.

Goffman and Warren (25) have developed a dynamical representation of epidemic conditions for schistosomiasis based upon the classic Kermack-McKendrick (47) model of epidemic processes. The model attempted to describe the disease under conditions found in epidemic areas. The Goffman and Warren (25) model concentrated upon the snail as the most significant factor in the control of the parasite. Unfortunately the conclusions reached have not been verified; indeed significant evidence is available (9, 11, 45, 72) to refute the adequacy of snail control as a means of controlling schistosomiasis. The function of the model was primarily to suggest interrelations worthy of additional research.

Models of schistosomiasis have been proposed and have assisted in directing attention to areas where additional research has been desirable. Each model, as characteristic of all models, has been inadequate in many respects. One area where additional effort seems to be justified is in the study of dynamic descriptions of populations with high, endemic rates of prevalence. This is the condition that has been found most commonly in those parts of the world where schistosomiasis is present. If an adequate control program can be developed for these areas, one that will carry the

disease rates below a certain natural "break point," it may be possible to eradicate the disease completely from infected populations.

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#### CHAPTER III

#### PURPOSE AND SCOPE

Schistosomiasis has been one of the most costly diseases afflicting mankind both in terms of actual economic loss and in terms of human waste. Control programs have been attempted but few if any have succeeded in eliminating the problem. This lack of successful control has arisen from the complex nature of the disease and its interactions with its host populations. The successful design of control programs must involve an analysis of the complicated interactions of infected and uninfected populations of humans, snails and alternate mammalian hosts such as cattle, rodents or monkeys. Models have been developed to predict the course of the disease in small populations with low rates of infection. Unfortunately, the literature contains few attempts at developing models for the prediction of the course of the disease in populations with high endemic rates of infection and no reference has been found to models which consider economic aspects of alternate control programs.

This study was performed in an attempt to develop a mathematical model of the disease, schistosomiasis, which would provide a tool for the program designers of future schistosomiasis control programs by providing more adequate knowledge of the consequences

of alternative programs. The model includes provision for describing different initial population conditions and various control programs imposed upon specific conditions of infection and transition among populations of infected and uninfected humans, mollusks and other mammalian hosts. A simple comparison of program costs was developed and included in the model to allow comparison among alternate programs. An attempt was made to validate the model to assure that results obtained from it might be accepted as adequate representations of actual programs under field conditions. The model was used to describe "likely" control programs in order to illustrate its use and to provide guidance to those who may attempt to control the disease in the future. The model was developed in a manner to allow general applicability and to be flexible enough to incorporate future advances.

#### CHAPTER IV

#### DEVELOPMENT OF THE DISEASE MODEL

Schistosomiasis was observed to be a complex, cyclical disease involving two different categories of host (molluskan, mammalian), at least five different phases in the development of the parasite itself (egg, miracidium, mother spore, cercaria, adult) and two different periods of reproduction (within the mammal and within the snail). Indeed, so complicated is schistosomiasis that models of only certain aspects of the disease such as the bisexual reproductive period or the snail population, have been developed (40, 52). Any adequate model of the disease as a whole had to consider each aspect of its natural history. This necessity immediately introduced error into the model since it was impossible to consider all of the interactions of the actual process. Much of the inherent error in the model was anticipated however, and with carefully chosen assumptions a working model was developed.

Weir (102) pointed out that in those localities where schistosomiasis was found endemically, essentially 100 percent of the population was infected. MacDonald (52) developed a model which pointed out that below a natural "break point" the bisexual parasite would undergo eradication with essentially no control necessary.

The literature reported few modeling attempts concentrating on the description and the development of control programs for areas of endemic, high infection. Such control programs, by reducing the high rates of prevalence, could be expected to drive the disease to the point, predicted by MacDonald, where natural extinction would take place.

In small populations with low rates of infection, it has often been impossible to develop dynamical models based upon uniform interactions; instead stochastic models and simulations have been necessary. By restricting the model with the assumption that the populations considered are large with high, uniform reaction rates, it was possible to develop a dynamical interpretation of the disease. Conditions which led to disease reduction, with associated reductions in parasite populations and population interactions caused the model to cease to satisfy this basic assumption; however, as this occurred, MacDonald (52) predicted eradication would occur.

The human population was divided into four categories in relation to the disease. These were:

- 1) P1, Unexposed and uninfected,
- 2) P2, Exposed and uninfected,
- 3) P3, Exposed and infected,
- 4) P4, Unexposed and infected.

The population categories as defined were found to describe grossly the population breakdown by age group in endemic areas; thus, newborns and the very young were found to make up a considerable portion of population  $P_1$ , children of school age appeared to be a significant

part of population  $P_2$  and  $P_3$ , and edults constituted a major portion of population  $P_4$  (14, 34). This breakdown by age was certainly not exact but appeared to be close enough that a detailed cross classification of the human population by age group did not appear to be justified.

The snail population was divided into two classes:

1) P<sub>6</sub>, Exposed but uninfected,

2) P7, Exposed and infected.

It was assumed that all snails were exposed since contact with bodies of water containing miracidia constituted exposure.

The population of miracidia has been designated as  $P_5$ , and the population of cercariae as  $P_8$ . Both of these populations were considered as concentrations rather than as absolute numbers of organisms.

The population of animals other than humans that carried the adult schistosome was divided into two categories as follows:

1) P<sub>q</sub>, Animals exposed but uninfected,

2) P10, Animals exposed and infected.

As in the case of the snail population, it was assumed that each member of the susceptible animal population was exposed but not necessarily infected. If the susceptible animal population were uncontrolled with free access to sources of infection, then this assumption would approximate the natural condition. This would be the case with a large population of rodents in the environment. If the susceptible animal population were controlled with limited access to sources of infection, then the assumption of universal exposure would not be true. In this case, however, the assumption would lead to a "worst case," i.e., a case as difficult or more difficult to control than the worst natural condition. If a control program could be developed to control the disease in its worst case, it would necessarily be able to control the disease for any case. If indeed the susceptible animal population were not universally exposed, populations  $P_9$  and  $P_{10}$  were interpreted to be those members of the susceptible population that were exposed and it was assumed that there was a very low rate of transition between the exposed and the unexposed populations. Such a situation would exist if, for example, cattle might be considered to be a significant portion of the susceptible animal population. Pesigan, <u>et al</u>., (72) however in a study in the Philippines discovered that rats constituted a major portion of susceptible animals in the transmission of the disease and that they had relatively high rates of exposure.

Having defined the populations and subpopulations of interest, the interactions of these populations among one another were considered (see Figure 2). The set of differential equations developed to model the actual population interactions are as follows:

1) 
$$\frac{dP_1}{dt} = F_1(P_1 + P_2 + P_3 + P_4) - F_2P_1 - F_3P_1$$
  
+  $F_5P_2 + F_8P_3 + F_{12}P_4$ ,  
2)  $\frac{dP_2}{dt} = F_3P_1 - F_4P_2 - F_5P_2 - \frac{F_6P_2P_8}{D} + F_9P_3$ ,

3) 
$$\frac{dP_3}{dt} = \frac{F_6 P_2^2 P_8}{D} - F_7 P_3 - F_8 P_3 - F_9 P_3 - F_{10} P_3$$
  
+  $F_{13} P_4$ ,  
  
4)  $\frac{dP_4}{dt} = F_{10} P_3 - F_{11} P_4 - F_{12} P_4 - F_{13} P_4$ ,  
5)  $\frac{dP_5}{dt} = F_{14} P_3 + F_{15} P_4 + F_{16} P_{10} - F_{26} P_5$   
-  $F_{19} P_6$ ,  
  
6)  $\frac{dP_6}{dt} = F_{17} (P_6 + P_7) - F_{18} P_6 - F_{19} P_6 P_5$ ,  
  
7)  $\frac{dP_7}{dt} = F_{19} P_6 P_5 - F_{20} P_7$ ,  
  
8)  $\frac{dP_8}{dt} = F_{21} P_7 - F_6 (P_2 + P_3) - F_{24} (P_9 + P_{10})$   
-  $F_{27} P_8$ ,  
  
9)  $\frac{dP_9}{dt} = F_{22} (P_9 + P_{10}) - F_{23} P_9 - \frac{F_{24} P_9^2 P_8}{D}$ , and  
10)  $\frac{dP_{10}}{dt} = \frac{F_{24} P_9^2 P_8}{D} - F_{25} P_{10}$ ,

where, P's, represent population groupings,

dt, denotes incremental time,  $F_1$ , is the human birth rate coefficient,  $F_2$ ,  $F_4$ ,  $F_7$  and  $F_{11}$  are death rate coefficients for the human populations,  $P_1$ ,  $P_2$ ,  $P_3$  and  $P_4$  respectively,  $F_3$ , is the rate coefficient for humans moving from

P<sub>1</sub> to P<sub>2</sub>,

 $F_5$ , is the rate coefficient for humans moving from

 $P_2$  to  $P_1$ , F<sub>8</sub> and F<sub>12</sub> are the rate coefficients of cures taking place in infected populations P<sub>3</sub> and P<sub>4</sub>,

 $F_6$ , is the rate coefficient for infection of uninfected,

exposed humans, i.e., for transition from  $P_2$  to  $P_3$ ,  $F_9$ , is the rate coefficient for transition from  $P_3$  to  $P_2$ ,  $F_{10}$ , is the rate coefficient for transition from  $P_3$  to  $P_4$ ,  $F_{13}$ , is the rate coefficient for transition from  $P_4$  to  $P_3$ ,  $F_{14}$ ,  $F_{15}$  and  $F_{16}$  are the rate coefficients for production

of miracidia from infected host populations  $P_3$ ,  $P_4$ 

and P10'

F<sub>26</sub>, is the death rate coefficient for the miracidia population,

 $F_{19}$ , is the rate coefficient for infection of uninfected snails, i.e., for transitions from  $P_6$  to  $P_7$ , F<sub>17</sub>, is the snail birth rate coefficient,

 $F_{18}$  and  $F_{20}$ , are the snail population death rates,  $F_{21}$ , is the rate coefficient for production of cercariae,  $F_{24}$ , is the rate coefficient for infection of the alternate host population,

F<sub>27</sub>, is the cercariae death rate coefficient,

 $F_{22}$ , is the alternate host birth rate coefficient,

 $F_{23}$  and  $F_{25}$ , are death rate coefficients for the alternate

host, and  $D = P_2 + P_3 + P_9 + P_{10}$ , is the exposed population of

potential hosts capable of removing cercariae from P<sub>8</sub>. The units of each of the terms are given as follows:

1)  $P_1$ ,  $P_2$ ,  $P_3$  and  $P_4$  as numbers of people,

2)  $P_5$  as the number of miracidia per unit volume of water,

- 3)  $P_8$  as the number of cercariae per unit volume of water,
- 4)  $P_6$  and  $P_7$  as numbers of snails,
- 5)  $P_9$  and  $P_{10}$  as numbers of alternate hosts,

- 12)  $F_{27}$  as cercariae per cercaria per unit time,
- 13)  $F_{22}$ ,  $F_{23}$ , and  $F_{25}$  as numbers of alternate host per alternate host per unit time,
- 14) F<sub>6</sub> as number of people per cercariae-person per unit time,
- 15) F<sub>19</sub> as number of snails per miracidia-snail per unit time,
- 16) F<sub>24</sub> as number of alternate hosts per cercariae-alternate host per unit time.


Figure 2 - Schistosomiasis model.

Births and deaths were considered to be proportionate to population size. This assumption was not strictly true but was assumed accurate for steady state populations. Births in each population group (human, snail and alternate host) were allowed to enter only the uninfected populations. Deaths were allowed in each population proportionate to the population size. In the human population transfer from unexposed to exposed was assumed proportionate to the size of the unexrosed population. Similarly transfer from the exposed to the unexposed population was taken as proportionate to the size of the exposed population. The rate of cure in the uncontrolled state was considered to vary as the size of the infected population. This assumption might not be true with control programs in effect, but in the endemic state this assumption appeared valid. It was assumed that no cures took place in the snail and animal populations. This may be seen to be correct approximately since neither the snail nor the rat (presumed to be the most significant host animal other than human beings) have long lifetimes in relation to the disease. This assumption led to a worst case restriction and was accepted as having no adverse effect on the model. Transfer from the uninfected to infected populations in both the human and rat populations was presumed to be proportionate to the size of the uninfected, exposed populations and to the size of the portion of the cercariae population available to cause infection in each of the exposed, uninfected populations. In order to determine the portion of cercariae available for infecting uninfected populations, it was assumed that both the human and rat populations could receive multiple infections.

Symbolically this is given by,

$$(F_{6}P_{2}P_{8})(\frac{P_{2}}{P_{2} + P_{3} + P_{9} + P_{10}}), \text{ or}$$

$$(\frac{F_{6}P_{2}^{2}P_{8}}{P_{2} + P_{3} + P_{9} + P_{10}}) \text{ for humans and by,}$$

$$F_{2}P_{2}$$

$$\left(\frac{P_2 + P_3 + P_9 + P_1}{P_2 + P_3 + P_9 + P_{10}}\right)$$
 for the alternate host population.

Miracidia arose from infected humans and rats and were removed from the population by death or by infecting a snail host. It was assumed that snails could not contain multiple infections; thus only uninfected snails were available to remove miracidia. This was not the case for cercariae which could be removed from their population group by either uninfected or infected humans and rats or by death. Cercariae arose from the infected snail population. Infection of the uninfected snails varied as the population of uninfected snails and as the population of miracidia available for infection.

It may be seen that the system of equations is nonlinear; hence the powerful methods used to study linear systems were not readily applicable. Rather than attempt to solve the equations directly, the model was programmed on a Control Data Corporation 3170 computer for numerical integration of varying control programs. The model developed was a discrete time model simulating a period of twenty years. Each time period was taken to be three months. This time increment was found to adequately represent all populations except those for the miracidia and cercariae with their relatively

short lifetimes. Rather than attempt to use a very small time increment to model the population transitions in the miracidia and cercariae populations, it was decided to interpret populations P5 and  $P_8$  as the average daily production of miracidia or cercariae per unit volume of water and to assume that the actual populations of miracidia and cercariae were directly proportional to the production of new members of those populations. This interpretation in a declining population caused the model to overestimate the average population of the parasite but again this was a worst case situation, which if shown to decrease the overall infection and parasite numbers necessarily led to a reduction in any actual control program. In order to model the derived differential equations on a digital computer, it was necessary to change the form of the equations from differential to difference equations. The difference equations used are given as follows:

1) 
$$P_{1,n+1} = P_{1,n} + F_1(P_{1,n} + P_{2,n} + P_{3,n} + P_{4,n})$$
  
 $- F_2P_{1,n} - F_3P_{1,n} + F_5P_{2,n} + F_8P_{3,n}$   
 $+ F_{12}P_{4,n}$   
2)  $P_{2,n+1} = P_{2,n} + F_3P_{1,n} - F_4P_{2,n} - F_5P_{2,n}$   
 $- \frac{F_6P_{2,n}^2 R_{8,n}}{D_n} + F_9P_{3,n}$   
3)  $P_{3,n+1} = P_{3,n} + \frac{F_6P_{2,n}^2 R_{8,n}}{D_n} - F_7P_{3,n} - F_8P_{3,n}$ 

--

$$F_{9}P_{3,n} - F_{10}P_{3,n} + F_{13}P_{4,n}$$
4)  $P_{4,n+1} = P_{4,n} + F_{10}P_{3,n} - F_{11}P_{4,n} - F_{12}P_{4,n}$   

$$- F_{13}P_{4,n}$$
5)  $P_{5,n+1} = F_{14}P_{3,n} + F_{15}P_{4,n} + F_{16}P_{10,n}$ 
6)  $P_{6,n+1} = P_{6,n} + F_{17}(P_{6,n} + P_{7,n}) - F_{18}P_{6,n}$   

$$- F_{19}P_{6,n}P_{5,n}$$
7)  $P_{7,n+1} = P_{7,n} + F_{19}P_{6,n}P_{5,n} - F_{20}P_{7,n}$ 
8)  $P_{8,n+1} = F_{21}P_{7,n}$ 
9)  $P_{9,n+1} = P_{9,n} + F_{22}(P_{9,n} + P_{10,n}) - F_{23}P_{9,n}$   

$$- \frac{F_{24}P_{9,n}^{2}P_{8,n}}{D_{n}} \text{ and}$$
10)  $P_{10,n+1} = \frac{F_{24}P_{9,n}^{2}P_{8,n}}{D_{n}} - F_{25}P_{10,n}$  where

 $n = 0, 1, 2, 3, \ldots$ 

and P, F and D are population and three-month rate coefficients as defined above.

•

Note that the populations of miracidia  $(P_5)$  and of cercariae  $(P_8)$  were altered to reflect their interpretation as average daily parasite production. With this interpretation it was no longer necessary to account for the removal of parasites from the  $P_5$  and  $P_8$ 

populations. It was still necessary, however, to appropriately divide the populations P<sub>5</sub> and P<sub>8</sub> into portions available for infection of the snail, human and rat populations. The model did not attempt to utilize second order approximation methods since in most cases the necessary parameters and initial conditions necessary to accurately calibrate the model did not exist. Indeed the data available in the literature was sufficiently unreliable that an attempt to do a high order approximation would not have revealed any additional information; hence the present model was restricted to a first order nonlinear approximation of the differential equations describing the schistosomiasis cycle.

Once the model was developed and errors in the programming language were eliminated, it was necessary to validate the model utilizing actual data. This validation was made difficult by the lack of available data of the detail necessary to establish the appropriate initial conditions for the model. It was possible to obtain general descriptions of control programs which were used to estimate population parameters for the model. The same program descriptions were used to establish whether the model did indeed "act" as natural populations acted under the influence of control programs.

### CHAPTER V

### VERIFICATION OF THE MODEL

Unfortunately there was no way a priori to insure that the model was valid; thus the more experimental evidence that could be used in its validation, the more confidence that could be placed in its ability to predict programs that had never before been tried. Before the model was used to predict the outcome of specific control programs, an attempt to verify it was undertaken. Unfortunately a quantitative verification was impossible because of the lack of reliable data necessary to establish the initial conditions of the model and to compare with the model as it was used to simulate real populations. However, it was possible to perform a qualitative verification wherein the necessary initial conditions were estimated for a population and the model was used to simulate a control program. The model results were compared against the reported results of a similar control program that had been carried out and reported. The qualitative verification was made by using the population statistics estimated from data reported by Hairston (28) from a Philippine study. As in other reports, not all the necessary data was given and it was necessary to estimate some part of the initial parameters from experience with other studies, in particular with data from Puerto Rico.

In order to establish a baseline from which the efficiency of various control programs could be compared, it was assumed that in endemic populations the disease would have reached a steady state with little or no change in disease rates from year to year. This assumption led to a system of equations derived by setting the derivatives representing the rates of change for each identified population group to zero. This series of equations was useful in estimating initial population parameters since not all of the variables in the system of equations were independent; thus the number of variables that had to be estimated was reduced. Before solving the set of equations for dependent variables in terms of estimated variables, further assumptions were made. It was assumed that the birth rate of each population group was equal to the death rate in that population at steady state; thus there would be no net growth in the human, snail or rodent populations. Further it was assumed that no human being infected and exposed could undergo spontaneous cure and that there were no control programs in operation. It was assumed that the rates of transition between the unexposed and exposed populations were the same irrespective of whether or not a person was infected. With these assumptions the set of difference equations was solved to yield the following set of equations for use in estimating endemic parameters:

1) 
$$F_3 = \frac{F_{12}P_4(P_2 + P_3)}{E} + \frac{F_1(P_2 + P_3)(P_3 + P_4)}{E}$$
,  
2)  $F_5 = \frac{F_{12}P_4(P_1 + P_4)}{E} + \frac{F_1P_4(P_1 + P_2 + P_3 + P_4)}{E}$ ,

3) 
$$F_6 = \frac{F_{12}P_4 + F_1(P_3 + P_4) - P_2 + P_3 + P_9 + P_{10}}{P_8P_2}$$
  
4)  $F_{16} = \frac{P_5 - F_{14}P_3 - F_{15}P_4}{P_{10}}$ ,  
5)  $F_{19} = \frac{F_{17}P_7}{P_5P_6}$ ,  
6)  $F_{21} = \frac{P_8}{P_7}$ ,  
7)  $F_{24} = \frac{F_{22}P_{10}(P_2 + P_3 + P_9 + P_{10})}{P_8P_9}$ , where  
 $E = P_1P_3 - P_2P_4$ ,

P stands for the appropriate population and F represents rate coefficients as defined above. These equations yielded necessary values for the unknowns  $F_3$ ,  $F_5$ ,  $F_6$ ,  $F_{16}$ ,  $F_{19}$ ,  $F_{21}$  and  $F_{24}$  in terms of the estimated coefficients  $F_1$ ,  $F_{12}$ ,  $F_{14}$ ,  $F_{15}$ ,  $F_{17}$  and  $F_{22}$ .

From the work of Hairston (28) it was possible to estimate the population parameters given in Table 1. The value associated with  $P_5$  and  $P_8$  was established by assuming that a quantity of water necessary to contain 10,000 miracidia or cercariae was considered. The birth rate for the human population was taken as 200/10,000 or  $0.5 \times 10^{-2}$  per quarter. The birth rate for snails was taken as 0.373 per quarter. This rate was taken as the normal rate of viable reproduction in a population at steady state. It should be noted

,

Population Number	Number of Members	Factor Number	Value	Factor Number	Value
1	16,200	1	$0.5000 \times 10^{-2}$	13	0.5100 x 10
2	3,300	2	$0.5000 \times 10^{-2}$	14	0.3252
3	6,700	3	$0.5100 \times 10^{-2}$	15	$0.5070 \times 10^{-1}$
4	23,800	4	$0.5000 \times 10^{-2}$	16	$0.3180 \times 10^{-1}$
5	10,000	5	0.1990	17	0.3730
6	5,087,873	6	$0.3793 \times 10^{-3}$	18	0.3730
7	565,319	7	$0.5000 \times 10^{-2}$	19	$0.4144 \times 10^{-5}$
8	10,000	8	0.0000	20	0.3730
9	52,000	9	0.0000	21	$0.1769 \times 10^{-1}$
10	208,000	10	0.1990	22	$0.8333 \times 10^{-1}$
		11	$0.5000 \times 10^{-2}$	23	$0.8333 \times 10^{-1}$
		12	$0.2100 \times 10^{-4}$	24	$0.1731 \times 10^{-3}$
				25	$0.8333 \times 10^{-1}$

POPULATION SIZE AND TRANSITION RATES FOR POPULATIONS WITH ENDEMIC DISEASE<sup>a</sup>

<sup>a</sup>Estimated from data given by Hairston (28).

that this birth rate may be many times higher in uncrowded conditions (13, 41). It was estimated that the rate of spontaneous cure in a human population of infected, unexposed humans is approximately  $0.21 \times 10^{-4}$  per quarter. This is substantiated by the lifetime of schistosomiasis in man which has been observed to be twenty to thirty years. The rate of production of miracidia coming from the infected, exposed human population was estimated to be approximately 0.33 per day per unit of water (28). For humans infected but not exposed this rate was taken as 0.507 per day. The birth rate for the host animal other than human beings was taken as  $0.833 \times 10^{-1}$  per quarter. This rate was assumed to represent closely that of a rat population in its natural setting (28). From these estimated proportionality constants and the assumptions made above, it was possible to calculate the dependent proportionality constants necessary to produce a steady state population. When these constants were used in the model program the populations were indeed constant for a period of twenty years. Once the steady state solution had been derived it was possible to introduce changes simulating control programs and to see if the model could be used to predict the results of control programs that had actually been tried.

In Egypt a control program was attempted by eliminating the transmission of miracidia from the human to the snail population by introducing improved waste disposal (98). The first attempt made to verify the model with an actual control program was based on this study. The model was made to represent a 100 percent efficiency of removal of eggs from human waste by setting the transition constants representing the transmission of miracidia from the human population to the snail population equal to  $0.1 \times 10^{-30}$  miracidia per person per day reaching the snail population; thus the rate of miracidia production from human beings was effectively zero. Curve "B" of Figure 3 illustrates the predicted twenty year history of the disease in the human population. It may be seen that the disease decreases but the decrease is surprisingly slow. This relatively slow decrease was observed in the Egyptian project. Indeed the level of efficiency of the waste disposal program in the Egyptian project was far below 100 percent and no statistically significant reduction in disease levels could be detected. Scott, et al., (98) stated, "The inescapable conclusion from these experiements is that the sanitation produced no measurable effect on infection .... " The qualitative validation of the model with an actual control program had thus been shown in one case. In order to further validate the model, additional examples were sought.

One of the most commonly suggested control programs is that of elimination of the snail vector. It is obvious that elimination of the intermediate vector will eventually lead to complete eradication of schistosomiasis. In order to test the efficiency of this control program the model was made to represent a program that eliminated 99.9 percent of the remaining snail population each quarter; thus in six months the snail population was effectively reduced to zero. Curve "C" of Figure 3 illustrates the results of this control program over a twenty year period. Again the level of disease was reduced but in twenty years approximately two-thirds of



Figure 3 - Effect of complete waste and snail control.

the total incidence remained. This long period of only slight reduction is a consequence of the long lifetime of the parasite in the human population. Ferguson, <u>et al.</u>, (18) stated that in a program in Vieques, Puerto Rico, the snail population was never completely eliminated and that if control of the snail population should lapse for even one month, the population size would return to normal levels; thus expectations of eliminating schistosomiasis by control of the snail population alone appear to be hopeless. Indeed no reference could be found to snail control being used as a successful schistosomias control program.

The last attempt at validation of the model was taken from a study in Puerto Rico involving both snail control and treatment of the infected population. In 1954 the Puerto Rico Health Department initiated a project for the reduction of schistosomiasis on Vieques Island, Puerto Rico, (18). The project involved both treatment of infected individuals and chemical control of the snail population. After five years no infections were found in children in the first grades, a reduction from 7.1 percent five years earlier. The model was made to represent a program involving treatment of 90 percent of infected humans every three months and a reduction of 90 percent of the normal snail population. Curve "C" of Figure 4 illustrates the simulated results of such a control program. In five years of the program activity, the model predicted a drop in the portion of infected humans (for the given population) from 61 percent of the entire population to less than 1 percent of the population. Again the model accurately predicted the qualitative outcome of an actual



Figure 4 - Effect of human treatment programs.

### CHAPTER VI

#### PROGRAM MODELS

Having been qualitatively validated, the model was used to investigate new control programs. One control program that had never before been studied was the control of the alternate host population. In the Philippines Pesigan, et al., (72) showed that the rat was the most significant alternant host. A rat control program would impact not only on schistosomiasis but also on other important public health problems. The model was used to simulate a reduction of 99.9 percent of the total rat population every three months. The results for a twenty year period are shown as Curve "A" of Figure 5. Note that the number of infected humans increased instead of decreasing as expected. This increase was caused by the increase of cercariae available to infect humans instead of rats and the steady state saturation of the snail population with infection such that a reduction of the miracidia population did not significantly reduce the number of infected snails. It may be seen that this need not always be the case. Given a population wherein the alternate host accounts for a significant part of miracidia production, yet does not remove a large number of cercariae, then the reduction of the alternate host population would result in a reduction in the amount of human infection. Using data



Figure 5 - Effect of alternate host control and reduction of human exposure.

in the model based upon a study by Hairston (28), however, it appeared that reduction of the alternate host population would lead to an actual increase in the number of humans infected.

Another control program that had not been reported was one to reduce human exposure. Jobin and Ruiz (34) reported that in Puerto Rico approximately 50 percent of exposure could be reduced by the provision of safe areas for recreation. Curve "C" of Figure 5 illustrates the predicted twenty year outcome of a 90 percent reduction in human exposure. Note that the total number of infected humans was reduced gradually. It appeared that a control program based on the reduction of human exposure alone would not be rapid enough to have immediate impact on the disease; however, the inclusion of a reduction of human exposure as part of a more comprehensive program of control may reduce the potential for reestablishment of the disease if it were once eradicated from a locality.

Curve "C" of Figure 3 illustrates the reduction of the number of infected humans over a twenty year period given that the snail population could be completely controlled. The literature indicated that the complete control of the snail population is a virtual impossibility; yet if it were possible, then the model showed that after twenty years only about one-third of the infected human population would have undergone spontaneous cure. This curve represents the most efficient rate of reduction of the disease from the human population if no treatment of infected individuals were undertaken. In order to rid the human population of the disease at a faster rate it was found necessary to establish a treatment program.

Curve "B" of Figure 4 illustrates the result of a program of 99 percent treatment of infected humans each quarter. It may be seen that the incidence of infection in human beings dropped rapidly then gradually rose as the exposed population increased. The potential for infection, as measured by the number of cercariae available for infection, should the treatment program ever be stopped, remained high since the alternate host continued to propagate the disease (see Figure 6); hence even though the treatment program showed rapid reduction in the incidence of the disease in human populations, it could hardly be called successful since it could never be stopped without incurring an immediate rise in the rate of infection leading rapidly to endemic rates of infection. In order to reduce the potential for reinfection alternate procedures had to be considered. One such method of reduction of total number of infections with an associated reduction in the potential for reinfection was given in the Vieques control program already discussed. Another possible method considered was one of the combination of human treatment with a program to reduce the population of the alternate host.

Curve "A" in Figure 4 illustrates the results obtained when a program to treat 70 percent of infected humans was combined with a program of rat control resulting in the elimination of 50 percent of the rodent population. The program did not produce complete control but the potential for reinfection was greatly reduced. The potential for reinfection is illustrated in Curve "E" of Figure 6.

The only methods of disease reduction that were capable of eliminating the disease were those which involved treatment of



Figure 6 - Effect of control programs on cercariae populations.

infected individuals in conjunction with a program to reduce the number of cercariae available to infect humans. The number of available cercariae were reduced (see Figure 6) by reducing human exposure as illustrated in Curve "C" of Figure 5, or by reducing the number of snails available to produce cercariae as illustrated in Curve "C" of Figure 3 or by reducing the number of infected snails by decreasing the number of miracidia available for infection as illustrated in Curve "A" of Figure 5. This reduction of the number of miracidia available for infection was produced by reducing the alternate host population; thus decreasing the number of available miracidia.

In order to assist in the decision of which control program to use, the cost of each program was considered, and the model was modified to include a simple analysis of program costs.

### CHAPTER VII

#### PROGRAM COST CONSIDERATIONS

In order to make logical decisions among alternate control programs it was necessary to consider program costs relative to the effect produced by each program. This chapter explains how program costs were incorporated into the general schistosomiasis model and, using the cost model, how comparisons were made among alternative schistosomiasis control programs.

The costs associated with control activities were classified into three groups: 1) start-up costs, 2) fixed program costs and 3) variable costs proportionate to some level of effort within the activity. Start-up costs were taken as those costs associated with the initiation of a program. For example consider a program involving control of the snail population in a lake. The initiation of such a project would involve certain one time purchases such as the purchase of a boat, spraying equipment and sampling equipment. These costs are not expected to recur; hence they would be classified as start-up costs. Fixed program costs were taken as those costs occurring at a fixed rate throughout the lifetime of a project regardless of the level of effort involved. As an example consider personnel costs, costs of supplies used at constant rates and maintenance costs. Variable costs were taken to be those costs which occurred in response to some level of program effort. For example consider the cost of patient treatment. Initially this cost might be quite high but as the control program begins to work, the number of patients treated would be expected to decline, and with this decline the patient treatment cost would also decline. Each group of costs was further divided into three classes: 1) lowest program cost, 2) most probable program cost and 3) highest program cost. For this paper the most probable cost was taken as the midvalue between the lowest and highest program cost.

Having classified the expenses of undertaking alternative control programs, it was a simple matter to account for the start-up and fixed program costs. The variable costs, however, required the computation of program costs for levels of effort above the natural steady state, i.e., computation of the cost of reducing infection had to take into account any natural reductions of infection which would have occurred without intervention. Figure 7 illustrates the relationship of the number of infected humans cured naturally to the number of infected humans cured as a result of some control program. The program costs were computed from the number of cures attributable to the program and not from the total number of cures that took place. In order to compute the variable program costs from the model, the transitions between each population group were computed twice for each three month period, once using the factors of the steady state solution, and once using the control factors,



Figure 7 - Number of humans cured as a consequence of program effort.

The difference between these two computations determined the variable program costs for that period.

Earlier it was seen that any program neglecting the medical treatment of infected humans was almost certainly doomed to failure (the most effective program reducing human infection by only one-third in twenty years). Reduction of human infection by treatment without additional program effort was seen to be essentially a treatment of the "symptoms" of the disease without affecting the underlying reservoir of potential infection remaining in the environment. It was concluded that any program, to be effective, must include both human treatment and some control of either the snail population, the alternate host population or the exposure of humans to infected waters. Based upon these conclusions, the model was used to simulate the course of disease involving the treatment programs as follows:

- 1) treatment of 70 percent of infected humans every three months and reduction of the alternant host population by 50 percent,
- 2) treatment of 70 percent of the infected human population and reduction of the snail population by 90 percent,
- 3) treatment of 70 percent of the infected human population every 3 months and reduction of human exposure by 50 percent,
- 4) treatment of 70 percent of the infected human population, reduction of the alternate host population by 50 percent and reduction of the snail population by 90 percent,
- 5) treatment of 70 percent of infected humans every three months, reduction of the alternate host population by 50 percent and reduction of human exposure by 50 percent,
- 6) treatment of 70 percent of infected humans every three months, reduction of the snail population by 90 percent and reduction of human exposure by 50 percent, and

7) treatment of 70 percent of infected humans every three months, reduction of the alternate host population by 50 percent, reduction of the snail population by 90 percent and reduction of human exposure by 50 percent.

Seventy percent was taken as a reasonable case finding and Similarly, a 90 percent reduction in the snail cure rate for humans. population appeared to be a reasonable reduction considering the rapid rate in which regeneration of suppressed snail populations occur. Jobin and Ruiz (34) indicated that a 50 percent reduction in human exposure might be achieved with the provision of adequate recreational areas, and the control of alternate host populations was expected to be at least 50 percent in areas where there had been little attention to this important public health measure. Using these data, hypothetical program costs were estimated. All programs were designed for human population of 50,000 with distributions among population classes estimated from the data given by Hairston (28). Table 2 gives the estimated program costs for treatment of 70 percent of the infected humans every three months. It was assumed that each person treated did not immediately return to an exposed state, but returned rather to the unexposed, uninfected population. The program assumed that the entire population was screened for schistosomiasis every period and that only those infected were treated. Fecal exams were used for identification of the infected population. It was noted that one exam was not sufficient to identify an uninfected person, but since the entire population was examined four times each year, it was assumed that infections which were not detected immediately would be picked up subsequently. The hypothetical treatment

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### ESTIMATED COSTS TO TREAT 70 PERCENT OF INFECTED HUMAN POPULATION EVERY THREE MONTHS

Start-up	Cost	<u>Low</u> \$0	<u>High</u> \$ 1,000
			-
Fixed Co	st/3 Month Period		
1.	Laboratory Technician (2-4)	\$ 3 <b>,500</b>	\$ 7,000
2.	Nurses (2-6	\$ 5,000	\$15 <b>,000</b>
3.	Physician (1-2)	\$ 3 <b>,250</b>	\$ 6,500
4.	Miscellaneous	<u>\$ 1,500</u>	<u>\$ 1,500</u>
	Total	\$13,250	\$30,000
Variable	Cost		
1.	Patient Treatment	\$1/patient	\$10/patient

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program employed fecal examiners, nurses and physicians. Each employee was assumed to have available 220 man days per year. Treatment was assumed to cost up to 10 dollars per person treated. Note that in none of the proposed models was any attempt made to account for the cost of having the disease, nor was any attempt made to account for the time value of money.

Table 3 gives the estimated cost for a typical snail control program (18). It was assumed that control was established solely by the use of poisons rather than by using biological controls. No attempt was made to account for damage to the environment resulting from the use of molluscicides; although a program designer would certainly take this into consideration.

Table 4 gives the estimated costs for a program which reduced the exposure of human beings to infected water sources. Two alternatives were combined: 1) reduction of exposure by building and maintaining recreational areas such as public swimming pools or 2) reduction of exposure by fencing and patrolling areas of potential infection. It was assumed that either or both or neither of these programs would be used in conjunction with an advertising campaign to inform the public; thus, the lowest costs would be those associated with the advertising campaign alone and the highest costs expected would be those associated with a combined program involving all three.

Table 5 gives estimated costs for a campaign which was expected to reduce the alternate host (rat) population to 50 percent of the steady state population levels. Costs from each of the

## ESTIMATED COSTS TO CONTROL SNAIL POPULATION AT 10 PERCENT OF STEADY STATE SIZE

		Low	High
Start-up	Cost		
1.	Equipment and Miscellaneous Expense	\$1 <b>,0</b> 00	\$2,000
Fixed Co	st/3 Month Period		
1.	Two man team	\$4,000	\$4 <b>,000</b>
2.	Poison	\$ 150	\$ 200
3.	Miscellaneous	<u>\$ 50</u>	<u>\$ 50</u>
	Total	\$4,200	\$4,250
<u>Variable</u>	Cost	\$0	\$0

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### ESTIMATED COSTS TO REDUCE HUMAN EXPOSURE BY 50 PERCENT

		Low	High
<u>Start-up</u>	Cost		
1.	Fencing	<b>\$0</b>	\$10,000
2.	Recreation Areas (0-2)	<u>\$0</u>	<u>\$20,000</u>
	Total	<b>\$0</b>	\$30,000
Fixed Co:	st/3 Month Period		
1.	Maintenance	\$0	\$ <b>7</b> 5
2.	Life Guards (2)	\$2,000	\$ 2,000
3.	Health Education	\$    500	\$ 1,000
4.	Miscellaneous	<u>\$ 625</u>	\$ 1,000
	Total	\$3,125	\$ 4,175
<u>Variable</u>	Cost	\$0	\$ <b>0</b>

### ESTIMATED COSTS TO REDUCE ALTERNATE HOST POPULATION 50 PERCENT

Start-up	Cost	<u>Low</u> \$0	<u>High</u> \$ 100
Fixed Cost/3 Month Period			
1.	Control Team (2 men)	\$4,000	\$4,000
2.	Equipment and Supplies (poison, traps, etc.)	\$ 100	\$ 100
3.	Miscellane <b>o</b> us	<u>\$1,050</u>	<u>\$1,100</u>
	Total	\$5 <b>,15</b> 0	\$5 <b>,20</b> 0
<u>Variable</u>	Cost	\$ <b>0</b>	\$0

individual programs were combined appropriately for obtaining cost estimates for combined campaigns. Appendix A contains Tables 6 through 13 giving the high and low costs for each program along with its results in reducing the level of human infection and the potential for infection as measured by the number of cercariae per unit volume of water. It also contains tables 14 through 18 giving program results for programs involving only one program activity. Figure 8 compares each of the alternative programs after ten years of operation. Figure 8 allows one to visualize the relative results of each of the programs and to compare the costs of achieving those results. The positions of the letters "A" through "H" give the midvalues of the high and low program cost for each of their respective programs. The figure allows the decision maker to see the potential results of decisions before they would be carried out at considerable expense. It would still be necessary to weigh the cost of the disease to the population and the possible cost of the control program to the environment.

From Figure 8, it may be seen that all of the programs proposed in this study appear to cost about the same. If this were indeed the case, one would then choose the program which reduced the disease at the fastest rate. It should be noted that while the data in this report were estimated from actual data, they do not reflect the "true" parameters at any single location. The results have, however, been qualitatively verified and are expected to reflect closely the actual results.

a--Human treatment; b--Snail control; c--Alternate host control; d--Human exposure reduced



Figure 8 - Ten year program results and costs

### CHAPTER VIII

#### SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Based upon a study of the natural history of the disease schistosomiasis, a deterministic mathematical model was developed to describe the disease in large populations with high rates of infection. The model was programmed on a digital computer in order to simulate the results of alternate control programs. The model was qualitatively validated by simulating programs similar to actual control efforts that had been attempted in the past. Having been validated, the model was used to narrow the choice of alternative programs for controlling the disease. Program costs were included as part of the model in order to assist in choosing among the alternative programs. Based upon the results of the simulations performed using estimated parameters from actual populations, the following conclusions were drawn:

- 1) Control of the disease is extremely difficult, even impossible, with programs that do not include treatment of infected humans.
- Control of the alternate host population may not lead to reductions in the number of infected humans, but may actually cause an increase in the number of infections.
- 3) The most effective program relying on a single activity to reduce human infaction was found to be treatment of

those infected. The next most effective single treatment program was one of control of the vector snail.

- 4) Measures of program effectiveness should involve not only a measure of the number of infected humans but also a measure of the potential for infection remaining in infected water.
- 5) The most effective programs involve mass treatment of the infected populations.
- 6) Long after the disease may appear to be eradicated, there remains a potential for its return. Hopefully, however, the stochastic model developed by MacDonald (52) will be valid and the disease will undergo a catastrophic decline.
- 7) If the chain of transmission is not broken, the chance for reestablishment of the disease from outside areas will remain high, and it may be that no isolated attempt to eliminate the disease can ever succeed.

The fullest use of the model will come when it has been used to design a schistosomiasis control program; it is recommended, therefore, that the model be tested by use in the analysis of proposed programs. It is further recommended that international programs be developed to attack the disease widely, thus reducing the potential for reestablishment of the disease from outside sources. The use of mathematical models to "try out" disease control programs is highly desirable and may result in considerable cost savings and significant reductions of disease levels in relatively short times; therefore, it is recommended that mathematical modeling should be attempted to provide insights into all major disease control programs before they are initiated.
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### APPENDIX

DATA FROM SCHISTOSOMIASIS MODEL

# HUMAN TREATMENT ONLY<sup>a</sup>

End of Year	Infected Humans	Cercariae Per Unit Volume	Cumulative (Thousands Low	Program Costs of Dollars) High
0	30500	10000	0	0
1	745	9116	83	342
2	757	7293	138	428
3	788	6914	193	514
4	792	6805	248	601
5	793	6772	304	688
6	793	6762	35 <b>9</b>	775
7	793	6559	414	862
8	793	6758	470	949
9	793	6758	525	1036
10	793	6758	580	1123
11	793	6758	635	1210
12	793	6758	691	12 <b>97</b>
13	<b>79</b> 3	6758	745	1384
14	<b>79</b> 3	6758	801	1471
15	<b>79</b> 3	6758	856	1558
16	793	6758	911	1645
17	793	6758	966	1737
18	793	6758	1022	1819
19	793	6758	1077	1906
20	<b>79</b> 3	6758	1132	1993

<sup>a</sup>Treatment of 70 percent of infected humans every three months.

End of Year	Infected Humans	Cercariae Per Unit Volume	Cumulative (Thousands Low	Program Costs of Dollars) High
0	30500	10000	0	0
1	1019	7145	104	897
2	<b>8</b> 13	4234	129	936
3	781	3585	148	972
4	766	3362	158	1014
5	759	3272	177	1058
6	755	3235	195	1092
7	<b>7</b> 54	321 <b>8</b>	215	1131
8	753	3211	234	11 <b>70</b>
9	753	3208	253	1208
10	753	3207	272	1248
11	752	3206	291	12 <b>87</b>
12	752	3206	312	1325
13	752	3206	329	1363
14	752	3206	348	1401
15	752	3206	363	143 <b>8</b>
16	752	3206	386	14 <b>76</b>
17	752	3206	405	1514
18	752	3206	423	1552
19	752	3206	443	1591
20	752	3206	462	1630

HUMAN TREATMENT AND ALTERNATE HOST CONTROL<sup>a</sup>

<sup>a</sup>Treatment of 70 percent of infected humans every three months, reduction of alternate host population by 50 percent.

End of Year	Infected Humans	Cercariae Per Unit Volume	Cumulative (Thousands Low	Program Costs of Dollars) High
0	30500	10000	0	0
1	292	912	101	863
2	97	615	119	907
3	90	487	137	946
4	81	416	154	982
5	73	370	172	101 <b>8</b>
6	67	339	190	1053
7	62	316	207	1089
8	59	299	225	1125
9	56	286	243	1160
10	54	275	260	1196
11	52	267	278	1232
12	51	261	296	1267
13	50	256	313	1303
14	49	251	331	1339
15	48	248	359	1374
16	48	245	376	1409
17	47	243	394	1445
18	47	241	412	1481
19	47	239	429	1516
20	46	238	447	1552

## HUMAN TREATMENT AND SNAIL CONTROL<sup>a</sup>

<sup>a</sup>Treatment of 70 percent of infected humans every three months, reduction of snail population by 90 percent.

End of Year	Infected Humans	Cercariae Per Unit Volume	Cumulative (Thousands Low	Program Costs of Dollars) High
0	30500	10000	0	0
1	34 <b>7</b>	8917	95	859
2	115	7157	114	899
3	108	6747	131	939
4	106	6624	148	980
5	105	6586	164	1018
6	105	6573	181	1056
7	105	6569	199	1095
8	105	6568	215	1133
9	105	6568	231	1172
10	105	6568	248	1210
11	105	6568	264	1249
12	105	6568	280	1289
13	105	6568	297	1327
14	105	6568	313	1365
15	1 <b>05</b>	6568	340	1403
16	105	6568	356	1442
17	105	6568	374	1480
18	105	6568	390	1518
19	105	6568	418	1557
20	1 <b>05</b>	6568	436	1596

HUMAN TREATMENT AND EXPOSURE CONTROL<sup>a</sup>

<sup>a</sup>Treatment of 70 percent of infected humans every three months, reduction of human exposure by 50 percent.

End of Year	Infected Humans	Cercariae Per Unit Volume	Cumulative (Thousands Low	Program Costs s of Dollars) High
0	30500	10000	0	0
1	334	714	122	1024
2	115	355	148	1075
3	91	248	172	1120
4	74	195	195	1164
5	62	160	219	1208
6	53	153	243	1251
7	45	116	266	1295
8	40	102	289	1339
9	35	90	311	1382
10	31	81	334	1426
11	28	73	357	1470
12	26	66	380	1514
13	23	61	402	1557
14	22	56	425	1601
15	20	52	448	1645
16	18	48	470	1688
17	17	45	493	1732
18	16	42	516	1776
19	15	39	538	1819
20	14	36	561	1863

## HUMAN TREATMENT, ALTERNATE HOST CONTROL AND SNAIL CONTROL<sup>a</sup>

<sup>a</sup>Treatment of 70 percent of infected humans every three months, reduction of alternate host population by 50 percent, reduction of snail population by 90 percent.

End of Year	Infected Humans	Cercariae Per Unit Volume	Cumulative (Thousands Low	Program Costs of Dollars) High
0	30500	10000	0	0
1	417	6943	116	1020
2	132	4048	139	1071
3	10 <b>9</b>	3391	161	1119
4	101	3164	183	1165
5	<b>98</b>	3073	204	1212
6	97	3034	226	1258
7	96	3017	248	1304
8	96	3010	270	1351
9	96	3006	291	1397
10	96	3005	313	1442
11	96	3004	335	1488
12	96	3004	356	1534
13	96	3004	378	1579
14	96	3004	400	1625
15	96	3004	422	1671
16	96	3004	443	1717
17	96	3004	465	1762
18	96	3004	487	1809
19	96	3004	509	1855
20	96	3004	531	1901

## HUMAN TREATMENT, ALTERNATE HOST CONTROL AND EXPOSURE CONTROL

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<sup>a</sup>Treatment of 70 percent of infected humans every three months, reduction of alternate host population by 50 percent, reduction of human exposure by 50 percent

End of Year	Infected Humans	Cercariae Per Unit Volume	Cumulative 1 (Thousands Low	Program Costs of Dollars) High
0	30500	10000	0	0
1	246	891	114	990
2	13	609	136	1020
3	9	485	157	1067
4	7	415	178	1105
5	6	370	199	1143
6	6	339	219	1182
7	5	317	240	1220
8	5	300	261	1258
9	5	288	282	1296
10	5	278	302	1335
11	4	270	323	1373
12	4	264	344	1411
13	4	259	365	1449
14	4	255	385	1488
15	4	252	406	1527
16	4	249	427	1565
17	4	247	447	1603
18	4	245	468	1641
19	4	243	489	1680
20	4	242	510	1718

## HUMAN TREATMENT, SNAIL CONTROL AND EXPOSURE CONTROL<sup>a</sup>

<sup>a</sup>Treatment of 70 percent of infected humans every three months, reduction of snail population by 90 percent, reduction of human exposure by 50 percent.

End of Year	Infected Humans	Cercariae Per Unit Volume	Cumulative (Thousands Low	Program Costs of Dollars) High
0	30500	10000	0	0
1	258	694	134	1150
2	16	349	160	1201
3	9	245	186	1245
4	7	193	211	1 <b>288</b>
5	6	159	237	1332
6	5	135	262	1375
7	4	117	288	1419
8	3	103	313	1462
9	3	92	338	1506
10	3	82	364	1549
11	2	75	389	1593
12	2	68	415	16 <b>36</b>
13	2	63	440	1680
14	2	58	<b>46</b> 5	1723
15	1	54	491	1767
16	1	50	516	1810
17	1	47	542	1854
18	1	44	567	1897
19	1	41	593	1941
20	1	39	618	1984

## HUMAN TREATMENT, ALTERNATE HOST CONTROL, SNAIL CONTROL AND EXPOSURE CONTROL<sup>a</sup>

<sup>a</sup>Treatment of 70 percent of infected humans every three months, reduction of alternate host populations by 50 percent, reduction of snail population by 90 percent, reduction of human exposure by 50 percent.

End of Year	Infected Humans	Cercariae Per Unit Volume
0	30500	10000
1	30480	7980
2	30341	6923
3	30186	6642
4	30033	6556
5	29889	6528
6	29754	6520
7	29627	651 <b>7</b>
8	29507	6516
9	29396	6516
10	29291	6516
11	<b>2919</b> 3	6515
12	29101	6515
13	29015	6515
14	<b>28</b> 934	6515
15	28859	6515
16	28788	6515
17	28722	6515
18	28660	6515
19	28602	6515
20	28548	6515

### SEWAGE TREATMENT ELIMINATING 100 PERCENT OF MIRACIDIA FROM HUMAN WASTE

End of Year	Infected Humans	Cercariae Per Unit Volume
0	30500	10000
1	30274	523
2	29685	9
3	29094	0
4	28515	0
5	27947	0
6	27390	0
7	26845	0
8	26310	0
9	25786	0
10	25273	0
11	24769	0
12	24276	0
13	23792	0
14	23318	0
15	22854	0
16	22399	0
17	21953	0
18	21516	0
19	21087	0
20	20667	0

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#### ELIMINATION OF 99.9 PERCENT OF SNAIL POPULATION EVERY THREE MONTHS--100 PERCENT CONTROL

End of Year	Infected Humans	Cercariae Per Unit Volume
0	30500	10000
1	33222	7740
2	34249	4792
3	35139	4394
4	35916	4373
5	36585	4415
6	37160	4463
7	37653	<b>4506</b>
8	38077	4544
9	38440	- 4576
10	38753	4604
11	39021	462 <b>8</b>
12	39252	4649
13	39451	4667
14	39622	4682
15	39770	4695
16	39897	4707
17	40006	4717
18	40100	4725
19	40181	4732
20	40252	4739

# ELIMINATION OF ALTERNATE HOST POPULATION<sup>a</sup>

<sup>a</sup>Elimination of 99.9 percent of alternate host population every three months--100 percent control of alternate host.

End of Year	Infected Humans	Cercariae Per Unit Volume
0	30500	10000
1	482	8749
2	548	7180
3	561	6842
4	563	6742
5	563	6712
6	563	6702
7	563	6699
8	563	6698
9	563	6698
10	563	6698
11	563	6698
12	563	66 <b>98</b>
13	563	6698
14	563	6698
15	563	66 <b>98</b>
16	563	6698
17	563	66 <b>98</b>
18	563	6698
19	563	6698
20	563	6698

## TREATMENT OF 99 PERCENT OF INFECTED HUMANS EVERY THREE MONTHS

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End of Year	Infected Humans	Cercariae Per Unit Volume
0	30500	10000
1	30166	9819
2	29590	8958
3	29008	8519
4	28436	8337
5	27875	8255
6	27325	8208
7	26788	8172
8	26260	8140
9	25744	8110
10	25237	8080
11	24742	8051
12	24256	8023
13	23781	7995
14	23315	7967
15	22859	7941
16	22412	<b>791</b> 4
17	21975	7889
18	21546	7863
19	21126	7838
20	20714	7814

## **REDUCTION OF HUMAN EXPOSURE BY 90 PERCENT**