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SCHISTOSOMIASIS IN THE AMERICAS

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SCHISTOSOMIASIS IN THE AMERICAS*

INTRODUCTION

In the preparation of this document, devoted to the problems of schistosomiasis in the Americas, an effort has been made to avoid repeating the description of the work done by five study groups of the World Health Organization reported in the following publications:

- 1) Scientific Group on Research in Bilharziasis:
Molluscicides, February, 1959.
- 2) Scientific Group on Research in Bilharziasis:
Chemotherapy, October, 1959.
- 3) Scientific Group on Research in Bilharziasis:
Assessment of Medical and Public Health
Importance, July, 1960.
- 4) Scientific Group on Research in Bilharziasis:
Immuno-Biological Diagnosis of Bilharziasis,
August, 1961.
- 5) Scientific Group on Research in Bilharziasis:
Pathobiology and Immunity, December, 1962.

The Pan American Health Organization, mainly interested in the past in the development of control and preventive measures, has nevertheless been aware of the major research needs in the field of schistosomiasis and has taken part in some of the fundamental research studies, such as:

*Prepared for the Second Meeting of the PAHO Advisory Committee on Medical Research, 17-21 June, 1963. The present document revises and completes RES 1/12 presented at the First Meeting of the PAHO/ACMR.

- 1) Field trials of new and potential molluscicides, and the development of application techniques for one of them (i.e. sodium pentachlorophenate - NaPCP - Brazil, 1950-1955.

These were conducted in collaboration with the United States Public Health Service (NIAID, NIH) and the National Ministry of Health of Brazil.

- 2) Snail ecology studies conducted in Brazil during 1952-1954 with the same collaboration as the above.
- 3) Research planning in the field of malacology as included in the activities of the PASB/WHO Working Group for the Development of Guidance for Identification of American Planorbidae Involved in Schistosomiasis, November, 1961. (B5 9/12 1961)

Any plans to extend the Organization's role in such research should depend upon an appraisal of the present situation of schistosomiasis in the Americas, and this calls for evaluation of the research needs which this appraisal reveals. As a first step in this direction, this document gathers and summarizes the data available in the technical literature and in the reports of the Organization. This has been prepared by Dr. Willard H. Wright with the help of a group comprised of Dr. N. Ansari, Dr. Ernest Carroll Faust, Dr. Emile A. Malek, Dr. Harry Most, Dr. Rafael Rodriguez-Molina with the secretariat services of Dr. E.C. Chamberlayne.

The text contains information on the distribution, the prevalence, the control programs, and the problems of schistosomiasis

in the Americas, with an indication of research needs, plus outlines of research projects to meet these needs. It is hoped that the document will call forth comments and suggestions from the many individuals who have had extensive experience in the field and a wide knowledge of the disease in the Americas. Comments and criticisms should be directed to the Communicable Disease Branch, PAHO.

PREVALENCE, DISTRIBUTION AND CONTROL OF SCHISTOSOMIASIS
IN THE AMERICAS

I. DEFINITION OF SCHISTOSOMIASIS

1. Schistosomiasis is a disease of man and domestic animals, primarily affecting the visceral organs of the victim, especially the intestines, liver, bladder and lungs. The infection is produced by blood flukes, trematodes belonging to the genus Schistosoma. Three of these species are important human parasites having extensive geographical distribution. Schistosoma japonicum is endemic in Japan, China, Celebes, Thailand and the Philippines, and involves an estimated 100,000,000 persons. 1/ The infection is found in certain domestic animals in Taiwan (Formosa) but autochthonous cases in man have not been recognized. Schistosoma haematobium occurs in a small focus in Maharashtra State in India and has been reported in Southwest Asia from Aden, Saudi Arabia, Yemen, Israel, Lebanon, Syria, Turkey, Iraq and Iran. In North Africa, the parasite is endemic in Morocco, Spanish Morocco, Algeria, Tunisia and Egypt. The species is widely distributed throughout the rest of Africa and occurs in Mauritius. A small focus exists in southern Portugal. It has been estimated that 40 million persons are infected. 1/ Schistosoma mansoni occurs in Israel, Yemen, Aden and Saudi Arabia and is widely distributed throughout Africa, although not to the same extent as S. haematobium. In the Western Hemisphere, S. mansoni is endemic in the Dominican Republic, Puerto Rico, Vieques, Antigua, Guadeloupe, Martinique and St. Lucia. It also occurs in Venezuela and Surinam and is extensively distributed in Brazil. This species is said to infect approximately 30 million individuals. 1/

2. For a clear conception of the epidemiology of schistosomiasis it is necessary to know that the agents of this disease require two hosts, viz., man or other susceptible mammals, in which the worms mature and discharge their eggs, and certain groups of aquatic molluscs (snails) in which the invading larva (miracidium), hatched from the egg in feces-contaminated water, undergoes development and multiplication; then the fork-tailed larval progeny (cercariae) erupt into the water and on contact with the skin of the definitive mammalian host penetrate and undertake migration through the blood stream and mature as they become localized in the mesenteric venules (Schistosoma mansoni, Schistosoma japonicum) or vesical plexus (Schistosoma haematobium); here they mate and the females discharge eggs over a period of many years. Thus, in all three types of schistosomiasis man on the one hand and the appropriate species of snails on the other must be reckoned with in any public health control program.

II. SCHISTOSOMIASIS MANSONI IN THE AMERICAS

Manson's schistosomiasis was probably introduced into the Americas with slaves brought from endemic foci in East, Central and West Africa in the 16th, 17th and 18th centuries (Scott 2/), and became established in those areas in the West Indies and South America where appropriate fresh water snails existed in water contaminated by infected human excreta. In this way, the disease became established in the New World. Although large numbers of infected African slaves were imported into other regions of the

Americas (viz., Continental U.S.A., Mexico, Central American countries, Cuba, etc.), the absence or lack of abundance of susceptible snails prevented development of Manson's schistosomiasis in those countries, just as vesical schistosomiasis in imported Africans failed to become established anywhere in the Americas, due to lack of snails utilized by Schistosoma haematobium.

1. Distribution and intensity of the infection. In the West Indies schistosomiasis mansoni occurs in only two small foci in the Dominican Republic, 3,4/ i.e., Las Palmillas and Hato Mayor, both near the south coast east of Santo Domingo City. In St. Kitts in 1932 approximately 25% of the 56,000 inhabitants were infected in highly endemic coastal areas, 5/ but by 1945 infection in man had practically abated and by 1959 was no longer present in the human population 6/. In Guadeloupe (with 275,000 inhabitants) and Martinique (with 277,000 inhabitants) somewhat less than 10% incidence is reported, 7,8/ but nearly 25% of the 100,000 individuals in St. Lucia are infected, in the many endemic foci, including mountain streams. 9/. Highest infection rates are in Ravine Poisson, Fond St. Jacques, Bexon and Desruisseaux. Spread of the disease in recent years has been attributed to population movements away from endemic areas, and to the increase in cultivation, especially of bananas. An approximate estimate of the total infection of these islands is 100,000 persons. In the Commonwealth of Puerto Rico the most recent survey of school children (White, Pimental and Garcia) 10/ indicates that the infection is widely established throughout the island, including all of the coastal areas except

the northwest, likewise some upland centers, with incidence figures varying from 0.6 to 29.9% and an overall average of 10.0% hence affecting nearly 235,000 persons. According to Maldonado and Oliver-González ^{11/} in 6 endemic foci investigated there was a decline from 22.2% to 11.3% between 1953 and 1955, but with continued high soil pollution.

The three countries in South America in which Manson's schistosomiasis is known to be indigenous are Venezuela, Surinam and Brazil. The very few infections diagnosed in French Guiana were no doubt imported and there is no good evidence that the disease is endemic in that country. ^{12/} A single fecal specimen of an individual from a relatively inaccessible mountain village in western Antioquia, Colombia, ^{13/} requires careful epidemiological study of the region to determine if the infection was locally acquired or was imported. In Venezuela, endemic areas exist in the States of Aragua, Carabobo, Miranda, Maracay, and the Federal District. The disease has been reported also from the State of Guarico. All the endemic areas are in the northcentral part of the country, with prevalence figures of 9.9 to 31.6%. The number of cases in Venezuela is estimated to be approximately 30,000. ^{14/} In Surinam there is intensive prevalence on the coastal strip. Of 100,000 individuals living in the endemic area, about 9,300 are infected, although more detailed surveys may disclose a larger number. ^{15/}

The most widely distributed region of Manson's schistosomiasis in the Americas is Brazil. Beginning in the State of Para,

two centers of endemicity have been discovered, one on the coast east around Belem, and one inland at Forlandia; there are possibly two or three other minor foci. There is no report of this infection in the State of Ampara, northeast of Pará. Only one small northern coastal area is known for the State of Maranhão. Reported infection in the State of Piauí is relatively insignificant. However, higher prevalence rates occur in the coastal and adjacent forested areas of the northeastern group of states, beginning with Ceará (0.93% incidence), with increasing intensity through Rio Grande do Norte (2.31%) and Paraíba (7.53%), to attain a maximum in Pernambuco (25.17%), Alagoas (20.48%) and Sergipe (30%), and in some foci reaching 60% intensity. The disease is widely disseminated throughout the coastal two-fifths of the large State of Bahia (16.55%), and is also reported as indigenous in the mid-San Francisco Valley and even in the western plateau. Minas Gerais, although an inland state, has rather widely disseminated infection throughout all but the western section, and has a moderately high overall percentage incidence (4.41) which in some localities reaches near saturation (93.9%). Proceeding down the coast the disease exists to a much lesser extent in isolated foci in the States of Espírito Santo (1.63%), Guanabara (0.10%), São Paulo (both on the coast and inland next to Paraná, in the north and in the central plateau), and in the north of Paraná (0.12%). Endemic foci occur in the State of Rio de Janeiro. The infection has not been reported as indigenous for the southernmost states of Sta. Catarina and Rio Grande do Sul. Only one center of doubtful endemicity has been reported for the State of Goiás, and it is questionable whether or not infection is

locally propagated in the State of Mato Grosso. The total cases in Brazil amount to an estimated 4 to 6 million. 16,17/

Thus, the amount of indigenous schistosomiasis presently known or estimated for South America is between 4,150,000 and 6,170,000 cases. Adding to this figure the 100,000 cases in the West Indies, one arrives at the total of 4,250,000 to 6,270,000 or 6.7 to 8% of the population of about 80 million persons in these endemic countries.

In continental United States of America there are no autochthonous foci. The infection rate among the many tens of thousands of persons of Puerto Rican birth living in New York City is about 10%. 18/ In Philadelphia a small sampling of Puerto Rican school children, based on a single fecal examination each, showed an incidence percentage of 3.0. 19/

2. Planorbid snails involved

Australorbis glabratus is the well-known and highly susceptible intermediate host of Schistosoma mansoni in several extensive areas of the West Indies and South America. A second species, A. tenagophilus (syn. A. nigricans), is widely distributed in central and southern Brazil. Although it is usually regarded as a poor host, hence of secondary importance, in areas of heavy fecal pollution of the water the infection rates in this snail may reach levels as high as those of A. glabratus under comparable conditions.

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Tropicorbis stramineus (syn. T. centimetralis) has extensive distribution in Brazil, from the Amazon region to the Central States,

while in certain areas of the northeastern part of the country it is the only known intermediate host.

Several species of Tropicorbis have been found experimentally to be potential hosts for S. mansoni. T. havanensis from Baton Rouge, Louisiana, has been shown to be moderately susceptible (17% with normal shedding of cercariae, compared with 95 to 100% for A. glabratus), ^{21,22/} whereas a different strain of the same species from lagoons in a New Orleans park was completely refractory. ^{23/} T. riisei from a limestone sink pond in Puerto Rico and T. albicans, also from Puerto Rico (Richards, 1963) ^{24/} T. chilensis from Rio Mapucho near Santiago, Chile (Barbosa and Barbosa, 1958), ^{25/} and T. philippianus (Barbosa and Barbosa, 1958) ^{26/} from Guayaquil, Ecuador, have all been demonstrated to be good experimental hosts. (Both T. chilensis and T. philippianus occur in habitats west of the Andes, where schistosomiasis has not been known to have become established up to the present time.)

The aquatic snail hosts of the schistosomes can live for long periods out of the water. Many observations have been made in tropical and subtropical areas in Africa and in the Western Hemisphere on the ability of these snails to withstand drought for several months (Greany, 1952 in the Sudan; ^{27/} Barlow, 1933 in Egypt; ^{28/} Oliver and Barbosa, 1955 ^{29/} Barbosa and Olivier, 1958 in Brazil ^{30/} and Malek, 1958 in the Sudan). ^{31/}

The snails that survive the dry period are not actually exposed to severe desiccation or to high temperatures but are usually covered and protected in the shade of vegetation and in a

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microhabitat which preserves a certain degree of humidity. The humidity of this microhabitat determines whether the snail will survive until the end of the dry period. The surviving snails are also protected in mud cracks. If they are found in the mud this does not mean that they have actively burrowed into the mud but had accidentally been buried.

The ability of these snails to survive drought periods makes clearance of canals of mud and vegetation an inefficient method of eradicating these watercourses of their snail fauna. A large number of the snail hosts in Egypt withstand a 40-day dry period in irrigation canals after these canals have been cleared of their mud and vegetation. A number of snails survive in the mud and among the vegetation dumped on the banks of these canals. This is an important aspect to be considered in mollusciciding programs. The few survivors on the banks are out of reach of the chemical and can repopulate the canal, if the mud is put back in the canal purposely or accidentally.

The most extensive studies on the ability of the snail vectors to withstand desiccation were carried out by Olivier and Barbosa^{29/} in northeastern Brazil. Australorbis glabratus and Tropicorbis stramineus survived in pools that remain dried up for 5-7 months every year. The reproductive potentials of snails that survive the dry season is apparently very pronounced, as these survivors can repopulate the habitat to maximum density in about 50 days after the flooding of the area. In northeastern Brazil it has been observed that a certain species of snail in several

localities exhibits various degrees of tolerance to desiccation. Moreover, snails from permanent bodies of water are less tolerant of drying than those from temporary pools.

Of epidemiological significance is the finding that partially developed infections of Schistosoma mansoni are arrested when the snail is out of the water but its development is resumed when the snail is put back in the water in the laboratory, or when the water returns to the habitat in the field. These immature infections are thus carried from one season to the other and thus are able to maintain endemicity in the area.

Infection, however, dies in the snails exposed to drought, if it is mature. Such an observation has been reported by workers in Brazil and others in Africa.

3. Molluscan habitats.

The planorbid hosts of Schistosoma mansoni usually live in shallow waters of streams or pools that are more or less permanent, with a moderate amount of organic pollution, moderate penetration of light, little turbidity, a muddy substratum rich in organic matter supporting growth of aquatic weeds and microflora, and further characterized by being stagnant or slow-flowing. However, these snails are able to accommodate themselves to a wide range of ecological conditions. For example, they also breed in large bodies of water such as lakes or reservoirs, in small ponds, and in the sheltered backwaters of torrential rivers; likewise in irrigation and drainage ditches (especially of sugar and banana plantations in the West Indies), swamps and burrow pits. In the

St. Lucia flooded stream embankments, where "dasheen" plants are grown, not infrequently harbor the snail host, Australorbis glabratus.

In Puerto Rico the alluvial areas have many locales favorable to A. glabratus and constitute the major foci for the transmission of the disease. Although this species also occurs in limestone sink ponds on the North Coast, this area is relatively free of the disease, possibly because of infrequent use by the population (Harry and Aldrich).^{32/}

The physico-chemical composition of the water probably plays an important role in the distribution of these snail hosts. For A. glabratus the maximum tolerated concentration of chlorides as NaCl was found experimentally to be 3641 ppm (Deschiens),^{33/} while in natural planorbid habitats in Brazil de Andrade^{34/} found that the maximum chloride content is 2562 ppm. Lime is essential for the formation of the snail's shell; the calcium ion is also important in the animal's metabolism and helps to regulate the permeability of the tissues. Although these snail hosts tolerate a wide range of water hardness, in very soft water they are scarce and their shells become relatively thin.

Harry and Aldrich^{32/} observed the absence of A. glabratus from most Puerto Rican waters containing only small amount of inorganic ions. Optimum snail habitats in this area usually have 150 to 500 ppm., but snails have been found in concentrations up to 3,000 ppm; only rarely are they found in Puerto Rican waters which have concentrations consistently lower than 150 ppm. It

seems likely that other factors are responsible for the rarity of the snails in such waters, since these snails can be reared experimentally in distilled water.

Development cycle of susceptible snails. In most endemic areas of schistosomiasis in the Americas the temperature and other environmental factors are very favorable for reproduction and growth, so that in permanent bodies of fresh water reproduction continues almost throughout the year unless interrupted by heavy rains. In temporary bodies of water reproduction is interrupted by the dry season but is resumed by the few survivors as soon as the water is replenished. In northeastern Brazil the snails may attain saturation density within 50 days if there are a few mature snails in the habitat (Barbosa and Olivier.^{30/}

In addition to the seasonal fluctuation in the population density of the snails there is also fluctuation in their infection with the schistosomes. Some techniques have been in use to estimate the snail population for ecological field studies, for studies on the transmission potentials of these snails, and for evaluation of mollusciciding operations. Choice of the sampling method depends on the objective of the study and on the area, since a method applicable for one area may not be suitable for another. These techniques were reviewed and evaluated by Hairston et al.^{35/} and in World Health Organization Tech. Rep. Ser. 214 (1961).^{36/} By the use of standard sieves, scoops, dredges and the like, the population density is estimated by recording the average number of snails collected in each dip. Counts per unit of time from

measured and marked areas in the habitat have been recommended by Olivier and Schneiderman.^{37/} The quadrat method used in many ecological surveys has been adapted to amphibious snails (Pesigan et al.)^{38/} and can also be used in dried-up habitats of the aquatic hosts. Palm leaf traps placed in the water at regular intervals along both banks of canals are very effective in survey work. The snails collect on these leaves to feed on the thin algal film.

4. Technics for determining the prevalence of schistosomiasis mansoni in man. (a) The usual method employed in an epidemiological survey is to make a fecal examination of the respective population groups. For convenience, the population sampling usually consists of school-age children, who represent a relatively uniform group and provide opportunity to assess changes which may occur in prevalence of the disease in a relatively short span of years. Clean cylinders of waxed cardboard with a close-fitting lid, such as half-pint ice cream containers, are particularly suited for distribution to the children the day before the fecal samples are to be obtained. For each pupil a record is made of sex, age, and residence in the area, whether urban or rural. On delivery of the specimens next morning the containers are taken to the diagnostic laboratory and if not examined immediately are refrigerated until they are to be processed. Since relatively few eggs are laid per female Schistosoma mansoni per day (only about one-sixth the number produced by S. japonicum), direct fecal films frequently fail to reveal the characteristic eggs unless the infection has just matured or the number of worms is consider-

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able. Concentration by approved sedimentation techniques is therefore indicated, utilizing a few grams of the feces thoroughly comminuted in tap water, poured through two layers of wetted cheesecloth and allowed to sediment in a 500 ml. urinalysis jar, with 2 or 3 decantations of the supernatant water to reduce the amount of sediment in which the eggs will be found. Adding 0.5% glycerine to the water will improve the technique (Faust and Hoffman),^{39/} while sodium sulfate-Triton detergent in the water will speed up the process (Faust and Ingalls;^{40/} Maldonado and Acosta-Matienzo).^{41/} Care must be taken not to pour off any of the bottom sediment during decantations. In case gross inspection of the feces shows that there is considerably fatty material, the formalin-ether technique of Ritchie^{42/} may be employed.

(b). In the clinic these same concentration techniques are recommended, but with older patients having more chronic infection the chances of recovering the eggs are fewer. Hence snipping a small sample of intestinal tissue from the level of the valve of Houston and pressing it between 2 microscope slides, often reveals characteristic eggs lodged in the tissues when the fecal sediment is negative.^{43,44/} The sodium sulfate-HCl-Triton-ether technic has also been employed with success in some endemic areas.

(c). Various immunological tests have been employed for the diagnosis of schistosomiasis. A critical evaluation of these tests has been provided by Kagan and Pellegrino.^{45/} The intradermal test is of value in adults but is less effective in children. It has a relatively high efficacy in disclosing chronic infections

but is of less value in determining recent acute infections. Positive reactions, however, do not necessarily indicate a current infection, since skin sensitivity may persist for years after the termination of infection, either spontaneously or by chemotherapy. Results vary somewhat with the type of antigen, the dilution employed and the method of reading the reaction.

Numerous serological methods have been utilized for the diagnosis of the disease. The complement fixation has proved to be very reliable, since it provides a high percentage of positives and few non-specific reactions. The precipitin test is not as effective as the CF and some other serological tests and tends to give a considerable percentage of non-specific reactions with crude antigens. The circumoval precipitin test is a sensitive method for detecting chronic schistosome infections. The "cercarien-hüllen reaktion" (CHR) of Vogel and Minning has proved to be useful in endemic areas where it is not difficult to secure large numbers of cercariae. The cercarial agglutination test is promising but needs further evaluation. The miracidial immobilization method of diagnosis has given good initial results but has not been applied on a practical scale. The flocculation and hemagglutination tests have both been employed in the diagnosis of schistosomiasis and offer considerable promise; further evaluation needs to be made. A more recent development in serological technique concerns the fluorescent antibody reaction of Sadun et al.^{46,47/} and Anderson et al.^{48/} This test shows great promise and apparently is highly specific. It can be carried out with finger blood dried on filter paper and

therefore would be valuable in epidemiological surveys.^{48/} The schistosome plasma charcoal test is a new development of great promise.^{265/}

At the time of fecal examination, rectal biopsy or serological test, it is highly important to ascertain whether a positive person has been resident for some years in the examination area or has recently immigrated into the area, in order to determine if he lives in a known endemic focus of the area or has come from another endemic region.

5. Epidemiological determinants of infection. (a). The most likely first evidence of an infection consists in the discovery of human cases. As indicated above, it is essential to determine if the discovery represents a previously undiagnosed endemic focus, or provides evidence of an immigrant from another focus who conceivably might initiate a new area of infection where the appropriate molluscan host is present.

A possible, as-yet undetermined source of S. mansoni eggs for infecting the snail is the non-human reservoir. A considerable number of mammals have been found naturally infected in schistosomiasis territory in the Americas, including opossums, rats, native mice and cavies in Brazil,^{49/} the rabbit in Venezuela^{50/} and the African green monkey in St. Kitts.^{51/} Even though these animals may be infected, it is necessary to determine which ones, if any, excrete viable S. mansoni eggs directly into the snail's habitats frequented by human beings.

(b). The second epidemiological determinant is the snail

host, its prevalence and local abundance. Australorbis glabratus is the most prevalent susceptible snail in the general area, but it may not be in the locale where it can be readily infected from human sources. Thus it is essential to discover what opportunities there are, if any, for the snail to be exposed. Moreover, different strains or races of the same species of snail exhibit different degrees of susceptibility to the same strain of the schistosome; and likewise different strains or races of S. mansoni have different degrees of infectiousness for the same species of snail. Hence the parasite can become established and maintain itself in a certain locality only if snail and parasite are mutually adaptable.

High prevalence rates in man may be associated with low rates in the snail hosts. This is especially the case when Tropicorbis stramineus is involved. In one endemic area in Pernambuco State, Brazil, where the incidence in man was 30.9%, that in T. stramineus was only 0.1%, while in another area in the same State human infection was 30.1% and 8.8% of Australorbis glabratus were infected. 52,53/

(c). The third determinant consists of the types of human activities favoring propagation of the disease. Among the determining factors are, on the one hand, the insanitary disposal of human excreta which directly or indirectly contaminates the water close to the snail's breeding grounds. Is egg-infested urban sewerage discharged into the water, or is the night pot (commode) rinsed out in the water? Is a latrine placed over the bank of the

water so that the feces fall directly into the water? Again, are the feces evacuated directly onto the ground above the water, so that they are washed down by the first rain? All of these human customs provide potential opportunity for infection of the snail host. Finally, to complete the cycle between the infected snail and the human host there must be human contact with the infected water containing the infective-stage schistosome larvae which have emerged from the snail and which during their infective period of several hours are in the top level of the water (in the case of S. mansoni). The opportunities for human exposure are multiple, although they vary somewhat in different endemic areas. Agricultural pursuits such as irrigation, rice- and sugar-cane cultivation and irrigated vegetable gardening constitute the principal hazards for adult males. Domestic use of infected water for laundry, bathing and drinking purposes provide another major source of infection. For children, walking barefooted through the water, swimming and fishing in the streams are frequent means of acquiring repeated infections. In perhaps a minority of instances reservoirs of unfiltered urban water supplies are inhabited by the snail host which has become infected.

III. CLINICAL ASPECTS OF SCHISTOSOMIASIS MANSONI

1. Introduction In discussing the clinical aspects or patterns in schistosomiasis mansoni, the following considerations must be borne in mind:

When the physician examines a patient suffering from this condition, (diagnosis having been established by finding of ova in the stools, by serologic tests or by finding of ova in a small piece of tissue removed from the rectal valves ("rectal biopsy"), he wants to know the following: What organs and to what extent are they involved by the disease? The tools that make this information available to the physician include the history offered by the patient, such as the number of exposures and duration of symptoms; analysis and evaluation of symptomatology; and a complete physical examination including recto-sigmoidoscopic examination. Does the patient have a large liver, a large spleen? Is he suffering from dysentery? Has he ever vomited blood or passed blood in the stools? Are the lungs and the heart in a normal condition? Are anemia, leukocytosis and eosinophilia present? Are the cephalin flocculation and excretion of bromsulphalein tests abnormal? Are there clinical evidences of pulmonary and portal hypertension?

The patient may appear to be asymptomatic in spite of the fact that schistosome ova are present in the stools and the circum-oval precipitin reaction is 44. After studying the case the physician cannot visualize the amount of disease in terms of number of living worms, and the number of ova in the host, because unlike bacteria, fungi, or viruses, schistosomes do not multiply in the human host.

So many cercariae penetrate the skin at a given exposure; so many attain maturity to (X) numbers of adult male and female worms, which after copulation produce large numbers of ova daily, of which an unknown number are carried by the circulating blood to the liver, lungs, and other organs of the body; and finally, (X) numbers of eggs are passed daily in the stools. The physician's armamentarium offers no method by which he may quantitate the number of worms harbored by his patient, nor can he estimate the number of cercariae that penetrated the skin during any single exposure.

Value of the egg count as an index of intensity of infection:

When a sample of stool contains 500 ova per gram, the finding does not necessarily mean that the infection is a heavy one, since egg counts vary considerably and the number of eggs on the following day might be considerably less.

In disease caused by schistosomes, tissue changes depend on the number of worms present in the host, and these vary according to the number of larvae (cercariae) that penetrated the skin. This characteristic of infections gives rise to variability and differences in the clinical response to the disease in different patients. To illustrate: Two individuals of the same sex and age are exposed at the same time to polluted water. One develops a severe, acute type of infection associated with involvement of the liver and spleen, while the other does not show any clinical evidence of the disease though they both have schistosomiasis, as demonstrated by ova in the stools. Presumably, they were exposed to the same number of cercariae in the water. It is logical to assume that one patient

became heavily infected while the other acquired but a light infection with the parasite.

Patients suffering from schistosomiasis frequently harbor intestinal helminths such as hookworm, Ascaris, Strongyloides, and Trichuris. The presence of these worms may add further confusion to evaluation of symptomatology in terms of S. mansoni infection.

Longevity of infection in man. Living ova have been observed in the stools of an adult who resided in New York City for over 25 years, where re-infection is not possible.

Pathogenesis of the disease in man. According to E. Koppish^{54/} schistosomiasis mansoni may be classified into three stages:

(a) An early stage of migration during which the cercariae are being carried by the blood to the liver, maturing into adult parasites within intrahepatic portal veins.

(b) An intermediate stage during which ova are accumulating in various organs: and

(c) A late stage characterized by serious, irreversible and permanent damage to organs mainly through fibrosis.

The organs most frequently affected as a result of infection with the parasite are the colon, liver, spleen, rectum, and lungs.

The greatest damage to the tissues is caused by the ova. Histologically the predominant lesion is the pseudotubercle, a lesion incited by the ova retained in the tissues.

CLINICAL MANIFESTATIONS OF SCHISTOSOMIASIS MANSONI

1. Initial manifestations. The earliest symptoms are asso-

ciated with the penetration of the skin and subcutaneous tissues by the cercariae. Pruritus, erythema and papular eruption may occur at the sites of penetration and may last from several hours to several days. Not all exposed individuals show local reactions. Some develop a pronounced sensitivity which results in intense reactions while others may be completely insensitive. Urticaria may appear and may be accompanied by mild pyrexia. Systematic manifestations which may accompany or follow cercarial penetration consist of anorexia, headache, generalized aches and pains and mild diarrhea with abdominal discomfort. These symptoms are probably associated in part with migration of the cercariae and may last for one to two weeks.

2. Early acute schistosomiasis. This stage may occur during the migration of the developing worms. It is usually mild and may go entirely unrecognized. The symptoms may be vague and consist of anorexia, headache, abdominal discomfort, low grade fever and transient urticarial eruptions. On the other hand, when the exposure is severe and the individual is extremely susceptible, the clinical manifestations may be marked.

The incubation period in the acute disease is extremely varied. The migratory phase may merge into the phase involving maturation of the worms and beginning oviposition.

Diaz-Rivera et al.^{55/} reported 12 cases occurring in young males who were studied over a period of 6 years, following initial and consecutive exposures and infection. It was assumed that the individuals became infected in heavily contaminated streams in

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bright daylight and mid-afternoon in Puerto Rico. The clinical picture was characterized by a sudden onset and by the explosiveness and severity of the constitutional manifestations, which comprised shaking chills, spiking temperature up to 104° and 105°F, profuse diaphoresis, non-productive cough, generalized body aches, pain in the extremities, weakness, lassitude, nausea and vomiting and watery and bloody diarrhea accompanied by tenesmus associated with generalized crampy abdominal pain. Along with these manifestations there occurred moist rales over the lungs, hepatosplenomegaly, high eosinophilic leukocytosis, anemia, and a high serum globulin with an increase of the gamma globulin fraction, as shown by electrophoretic analysis. A clinical manifestation rarely mentioned in the literature but present in all cases was generalized lymphadenopathy.

After a variable period of pyrexia that lasted over 74 days in one case, the symptomatology gradually subsided and improvement followed defervescence, which abated by lysis. No deaths occurred. Delayed signs of allergy were observed in some cases, including transitory puffiness of eyelids and face, urticaria and purpura.

The cases of acute schistosomiasis reported above received anthelmintic therapy (Stibophen). Transitory improvement particularly in appetite and disappearance of weakness was observed and gains in weight were registered within 2 to 7 weeks following treatment. However, three to five years following the acute stage and after repeated therapy most of the patients still had ova in the stools, associated with enlargement of the liver and spleen.

A few patients who were clinically well at this time still showed evidence of schistosomiasis such as liver fibrosis (needle biopsy), ova in the stools and positive biopsy specimens removed from the rectal mucosa.

According to Pons and Hoffman^{56/}, the febrile phenomena towards the end of the period of invasion are variable and may be preceded by some premonitory symptoms. As it happens in the infections with the other schistosome species, the symptoms of the first stage of the disease have not been adequately observed in most of the cases. This may be due to several reasons such as the patient's ignorance in some cases, mildness and short duration of the disease in others. Sometimes, mainly in the more severe forms of the disease, a wrong diagnosis is established, since a spontaneous remission of the acute manifestations is the rule.

In a swimming-pool outbreak of S. mansoni observed by Ferreira et al.^{57/} in Brazil, among the 12 exposed individuals, eight developed symptoms of the acute stage of the disease. These started as prodromic manifestations, about the thirtieth day after the initial exposure and consisted of general malaise, mild hyperthermia and anorexia. Antithermics and sedatives apparently brought about some improvement until the forty-sixth day after the initial exposure, when a more acute picture, consisting of high fever, generalized muscular pains, anorexia and enlargement of the liver, was observed. Among the four patients who did not complain of acute manifestations, only one was later found to be infected by the finding of S. Mansoni eggs in stools. Pulmonary symptoms occurred

only in one of the patients. No conspicuous digestive manifestations were observed even after eggs were found in stools. Among the most interesting laboratory findings in those cases, at the end of the toxemic stage, were the high degree of eosinophilia (from 28-72 per cent) and a constant serum protein electrophoretic pattern, with a significant increase in the alpha 2 and gamma globulin fractions.

Another interesting report on the acute stage of Manson's schistosomiasis was that given recently by Marques^{58/}. Among four young boys who had a more prolonged contact with infected water, in a group of eight, acute symptoms were observed in three cases. In two of them, in which clinical observation was more accurate, a febrile disease developed with diarrhea, generalized pains, headache and vomiting. These symptoms started within three days in one case, and in one week in the other. Chest X-rays of one patient showed shadows round the hilus of the right lung and micronodules on both bases about 23 days after the exposure. This patient had cough with bloody sputum, while the other had a non-productive cough.

Other interesting observations on the acute stage of Manson's schistosomiasis were those reported by Montestruc^{59/} in Martinique. Among 13 people collectively exposed, three local individuals already infected with the parasite for some years suffered only minor symptoms. A group of three who immersed for over 30 minutes developed increasing urticaria 8-10 days later. From the fifteenth to the twentieth day they were seriously ill with fever and muscular pains. Their symptoms developed into a more severe form with dysentery 45 days later. S. mansoni eggs were found in the stools

a few days later. Another group of seven people not previously infected and who were exposed for a shorter period, developed similar symptoms but with less intensity.

3. Chronic schistosomiasis. There is no sharp line of demarcation between the acute and chronic forms of schistosomiasis. The sub-acute and acute phases gradually merge into the chronic phase provided that infection is of a sufficient magnitude. On the other hand, chronic asymptomatic cases are frequently observed.

Usually, patients presenting symptoms, physical signs, and laboratory evidence of the chronic disease are cases where symptoms have been present for six months to several years. Some of these cases may not recall having had an illness that can be identified as the acute stage of the disease. Many individuals present a history of repeated exposures prior to the appearance of symptoms. This is common in endemic areas. A smaller group give a history of a single accidental exposure followed at an indefinite time after exposure, not by the acute stage, but by episodes of abdominal pain associated with mild diarrhea or dysentery.

Gastrointestinal manifestations include frequent generalized abdominal pain, associated with diarrhea, intermittent with constipation. Stools may be liquid, soft, or solid and are mixed with streaks of red blood or with mucus. Tenesmus may be present and severe. Loss of weight and anorexia occur. The colonic and rectal mucosa is congested and may show punctate hemorrhages that can be seen on proctoscopic examination. Small circumscribed yellowish spots that are made up of a conglomerate of eggs may be seen also

on the surface of the mucosa by proctoscopic examination. There is thickening of the intestinal wall due to edema and fibrosis of the submucosa. Occasionally pedunculated or sessile polypi are found in the rectum. Numerous ova may be present in sections of these polypi.

When hepatosplenomegaly appears, the late manifestations of the disease frequently give rise to a new and ominous clinical picture. The clinical manifestations are emaciation, hepatosplenomegaly, ascitis, evidence of cirrhosis of the liver, and of portal hypertension. Some cases develop hypersplenism associated with leukopenia, thrombocytopenia, and macrocytic anemia. However, the bone marrow is not megaloblastic. Bilirubinemia and jaundice are seen rarely even in the presence of advanced cirrhosis. Uncontrollable massive hematemesis from ruptured gastro-esophageal varices is a frequent cause of death. Ascites and hepatic insufficiency may occur.

When the above manifestations appear, certain alterations have taken place in the liver. Ova are retained in the portal spaces producing embolization. Pseudotubercles accompanied by eosinophils form around the eggs. The organ becomes enlarged but later it may contract as scarring ensues. On section of the liver the characteristic picture is a periportal fibrosis. The larger portal veins are surrounded by collars of fibrous tissue constituting the characteristic pipe-stem cirrhosis of Symmers. The spleen frequently becomes enlarged sometimes weighing more than 1,500 gms.

Pulmonary involvement is due to penetration of eggs into the lungs and the formation of pseudotubercles. In some cases the gross

appearance of the lung resembles miliary tuberculosis. Microscopically, there are pseudotubercles, patches of eosinophilic infiltration and occasional hemorrhages. The eggs arriving in the lungs as emboli obstruct the small arteries, and the intima becomes thickened by fibrosis. In time the right side of the heart undergoes hypertrophy and cardiac failure ensues. Farid et al. (60/) reported that in S. mansoni cases in Egypt pulmonary function tests showed evidence of mild ventilation insufficiency while right cardiac catheterization demonstrated an elevated pulmonary arterial pressure.

Other pathologic findings in the lungs are those of an obliterative endarteritis, the pathophysiologic abnormalities being increased pulmonary vascular resistance with subsequent pulmonary hypertension. The most important pathologic factor is egg embolization of the terminal arterioles and inflammation surrounding the ova. The mechanisms by which ova reach the lungs is not clear. As oviposition is known to occur in the portal system, the way by which the ova can reach the vena cava are, either, through portocaval anastomotic vessels or through venous shunts in the damaged liver. Egg embolization from the hemorrhoidal plexus of veins seems a more logical explanation of migration of eggs to the lungs.

As a rule patients who develop marked pulmonary impairment leading to chronic cor pulmonale, heart failure and death, also present extensive portal (liver) fibrosis associated with congestive splenomegaly. Hypertrophy of the right ventricle and pulmonary artery dilation are part of the postmortem findings in these cases.

Recent investigations by Tavares ^{61/} in Pernambuco, Brazil,

showed a significant incidence of S. mansoni pulmonary endarteritis. This has been considered the most common cause of chronic cor pulmonale in that area.

De Carvalho and Coelho^{62/} found 15.3 percent of pulmonary lesions produced by the eggs of S. mansoni in 799 autopsies at the School of Medicine, University of Recife.

Summary. Various clinical aspects or patterns of schistosomiasis mansoni have been discussed. In a general way, anatomical alterations are in agreement with clinical manifestations, symptomatology; physical examination; stool examination; rectal biopsy; complete blood count; serologic tests; liver function tests; liver biopsy).^{63/}

A considerable percentage of individuals showing ova in the stools are asymptomatic, particularly those well nourished individuals belonging to higher socio-economic strata.

The disease is most commonly encountered among the rural indigent and the poorly nourished. The factors of poverty and malnutrition may influence the course of the disease; and anemia, other parasitoses, surgery and tuberculosis may complicate or aggravate the clinical picture.

The massively infected previously unexposed individual frequently presents severe clinical manifestations from the onset of the disease (acute state), the severity of symptomatology being conditioned by organ hypersensitivity. Symptoms when present are referred to the gastrointestinal tract (colon and rectum), liver, spleen, and lungs. The degree of severity of the allergic state

is indicated by the marked eosinophilic response in the peripheral circulation during the acute stage. In some cases the persistence of marked eosinophilia seems to point to a prolonged allergic response, the adult parasites and ova being the source of allergens. Enlargement of the liver and spleen with general lymphadenopathy also may appear during the acute phase of the disease. If no further exposure occurs, the size of the liver and spleen may revert to normal, particularly if anthelmintic therapy is administered early, and if the general nutrition of the patient is improved.

In Puerto Rico, schistosomiasis is at present more commonly an intestinal disorder (symptomatic, chronic stage) and although liver and lungs are frequently involved, severe hepatic and pulmonary manifestations are rare. In other endemic areas in the Americas, more severe forms may be encountered. Gastrointestinal symptoms and signs are more commonly observed in chronic, long standing infections. These are referred to the colon and rectum and comprise bouts of diarrhea alternating with constipation. Diarrhea may be accompanied by blood, mucous or tenesmus, and is associated with congestion and edema of the colonic and rectal mucosa.

The late stage of the disease is associated with fibrosis (cirrhosis) of the liver, portal hypertension and marked splenic enlargement, resulting from intrahepatic vascular obstruction, and is more frequently observed in highly endemic areas. Repeated exposures to the parasite appears to be a common factor in this stage.

Pulmonary insufficiency leading to pulmonary hypertension associated with chronic cor pulmonale and heart failure generally

develops in individuals also presenting hepatosplenomegaly and portal hypertension. The pathogenesis of the pulmonary alterations is dependent on an extensive arterioclitis as a result of multiple and persistent egg embolization and subsequent proliferation of connective tissue leading to a reduction in the pulmonary vascular bed.

The late stages of the disease may give rise to chronic invalidism which may lead to death, caused either by massive and repeated hemorrhages, (hematemesis) resulting from ruptured gastroesophageal varices, or from cardiac failure secondary to pulmonary hypertension and insufficiency.

IV. THE ECONOMIC ASPECTS OF SCHISTOSOMIASIS

It is difficult, if not impossible, to measure the cost of schistosomiasis to the individual and to the community. This is indeed true for many, if not all, tropical diseases. Epidemiological services in many parts of the tropics have not been developed to point where the reporting of vital statistics can be regarded as satisfactory. Even for the Americas, where disease reporting is on a more efficient basis than in many other parts of the tropical world, it is only possible to estimate rather crudely the number of schistosomiasis cases in the endemic areas. In 1957, five countries in the Americas reported cases of schistosomiasis to the World Health Organization. In 1959 and 1960, only three countries reported cases to PAHO. The morbidity rates per 100,000 population in these countries in the latter year were as follows: Dominican Republic 1.4, Venezuela 24.7 and Virgin Islands (U.S.A.) 15.6.^{64/} Since schistosomiasis is not endemic in the Virgin Islands, the cases no doubt represented imported ones.

Even if reliable evidence were available concerning the number of infected individuals, the task of delineating the economic loss from the disease would be an imponderable one. There is little evidence concerning the overall incapacitation invoked by the disease. It is possible to evaluate total disability but much more difficult to estimate the extent of partial disability. Marked differences are noted in the degree of clinical involvement and such differences exist on an individual and on a community basis. Even in a community with high endemicity, certain persons will be

less severely affected than others. Certain areas are marked by a high percentage of severe infections while in other areas clinical involvement appears to be at a minimum. It is this latter situation which apparently has given rise to the concept that schistosomiasis for the most part is a disease of little public health significance and for this reason merits little attention on the part of health authorities. In Africa, especially, there are two schools of thought concerning the gravity of the disease. One view is that the condition in most of Africa is so mild that it can be discounted in contradistinction to the situation in Egypt where marked clinical manifestations are evident. The other view is that schistosomiasis in most of Africa is a serious condition which warrants concern on the part of health authorities. It is the opinion of Gelfand^{65/} that those who minimize the importance of the disease have had little autopsy experience and lack the benefit of adequate clinical observation. Gelfand's opinion concerned urinary schistosomiasis and is therefore more significant when considered in connection with schistosomiasis mansoni which generally produces more severe manifestations, because of greater egg output.

A few studies have been made on Puerto Rican components of the U.S. Army in non-endemic areas in Continental U.S., following rejection of many male Puerto Ricans of military age because of Schistosoma mansoni. Among such persons without complaints, Lyons and Benson^{66/} found that treatment produced remarkable improvement in their appearance, with increased appetite, gain in weight, more capacity for hard work, and healthier outlook on life. Observations

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on civilians of Puerto Rican birth in New York City and in Puerto Rico indicate that infection acquired there is presently no less severe than it was two decades ago.^{18,67/} Pessoa^{68/} compiled data on severe infections in children of pre-school and school age in the highly endemic areas of alagôas, Brazil, where 50 per cent of the severe hepatosplenic form of the disease was found in youths 15 years of age, and where 80 per cent of severely infected persons are in the age group 10-30 years. Similar data have been reported by Brener and Mourão^{69/} for the State of Minas Gerais. In Venezuela there are higher death and morbidity rates in the four political subdivisions endemic for schistosomiasis compared to the non-endemic areas (Curiel, Guzman and Ochôa).^{70/} The so-called inapparent infection has been demonstrated to represent a subnormal state of physical being. There is justification to conclude that "mild infections," even though moderately well tolerated, represent a medical and public health situation which needs to be controlled.

There are other factors which add difficulty to the task of evaluating the economic impact of schistosomiasis. In most endemic areas, concomitant conditions are prevalent and these conditions, such as malaria, filariasis, intestinal parasitic infections and malnutrition contribute to the ill health of the population. It is not possible to determine with any degree of exactitude the relative contribution of each of these concomitant conditions to the lowered health standards of the community.

Schistosomiasis is an insidious disease. Only in exceptional cases does it present acute alarming clinical manifestations and

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these instances only arise for the most part after heavy exposure of previously unexposed individuals. Since there is no multiplication of the etiological agent in the body of the infected person, the lesions of the disease build up slowly and the damage to the host is compounded over a long period of time. If the body exerts a sufficient immunological response to the infection, the disease may be arrested in time; if not, and exposure is repetitious, the disease may reach the stage in which the individual is totally incapacitated. In any event, however, there is little doubt that the resistance of the infected person is lowered and that as a result he becomes more susceptible to intercurrent infections.

If schistosomiasis were an acutely fatal disease, some overall estimate might be made of the damage which it causes. However, few deaths are ever attributed to the disease and mortality figures are extremely low.

With the above facts in mind, it is not difficult to understand that the problem of evaluating the economic consequences of the disease is at present an unsolvable one. There are no accurate standards for measuring the extent of clinical involvement and consequently no precise method of estimating the amount of damage which the disease has caused to the individual or the community.

1. Estimated costs of physical incapacity from schistosomiasis.

Certain data are available concerning the economic loss from the disease. Most of the data represent estimates which would fail to satisfy an economist but in a few cases the information is of a more precise nature.

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In Japan the economic loss, plus the cost of treatment for an area of 90 square miles, was reckoned at \$3 million per annum, and the loss for the Island of Kyushu at \$2,500,000. In Egypt, where the disease is hyperendemic, the reduction in total economic productivity is estimated to be some 30 per cent and the financial loss \$57 million annually. Medical treatment of some 1,700 American soldiers infected on Leyte during World War II was estimated to have cost \$3 million, and it was calculated that 300,000 working days were lost.^{71/}

The economic cost of illness can be divided into three categories, viz: Resource use, resource transfer and resource loss.^{72/} These concern the nation as well as the individual.

Resource use includes the cost of public health and medical care programs. It also embraces the payments of the individual to the persons and the institutions ministering to him during his illness. In the countries which are highly developed economically, the ill person pays the physician, the nurse, the pharmacist, the hospital and the private laboratory. In many areas, sick persons cannot command all of these services. Regardless of the type of ministrations, however, in most instances he still pays something for medical care even though such care may be woefully inadequate.

Resource transfer refers to the cash payments for the time loss occasioned by illness. In the highly developed countries it is convenient to measure the magnitude of this transaction by having recourse to the records of social security programs. However, in many tropical areas, there is little or no form of monetary recompensation for illness and it is therefore difficult to arrive at

any valid figure of the magnitude of resource transfer.

Resource loss is also of importance and includes the economic consequences of work days lost and decrease in productivity. In countries with well developed social security and other systems of health insurance, factual data can be produced to indicate the extent of resource loss. In other countries with no such systems or only partially inclusive systems, the loss in terms of productivity cannot be calculated with any degree of accuracy.

There are, however, data to indicate that the percentage of economically active males is lower in some tropical areas than in the highly industrialized countries of North America and Western Europe. The working population may be roughly equated with that between the ages of 15 and 65. MacDonald ^{23/} has indicated that the expectation of life of the average male inhabitant of England and Wales at 15 years is 55.0 years, and for the similar inhabitant of the former Belgian Congo for example is 37.8 years, a difference of 17.2 years. If allowance is made for the probability of some persons surviving long past 65 and others dying earlier, the expectations of life in the age period 15 to 65 are reduced to 46.7 and 35.3. The difference between these two figures represents the cost of premature death to the Congo in comparison with England and Wales. It amounts to about 24 per cent of the potential annual wealth of the country, and is additional to loss due to ill-health, of which no account is taken in the life tables. The economic significance of either death or disablement varies with the age of the individual when it occurs. A Congolese aged 15 years has an expectation

of about 35 working years, but this declines with advancing age to 25, 18, 11 and 4 years of expectation at 30, 40, 50, and 60 years of age, and his potential value to the community sinks accordingly.

This illustration concerns productivity in general and, as indicated, does not consider loss due to ill health. It is given as an example of the complexity of endeavoring to evaluate the economic cost of the disease in general. When one attempts to confine his estimation to a particular disease, such as schistosomiasis, the variables are even more imposing and the task more difficult.

2. The economic burden of schistosomiasis on the community.

Data are available from at least one carefully planned and controlled study on the economic impact of schistosomiasis. This study was part of a WHO cooperative project on the Island of Leyte, Republic of the Philippines.^{74,75/}

The study involved a measurement of the disability due to schistosomiasis. After a preliminary sampling, a group of 278 individuals was selected for interviews, case histories, clinical gradient estimations, and follow-up for more than two years. As a result of the findings, it was estimated that approximately 38 per cent of a quarter million infected individuals in the Philippines manifested symptoms of schistosomiasis. Of the 100,000 cases, 57 per cent were classified as mild, 39 per cent as moderate and 4 per cent as severe and very severe. Careful inquiry was made into the amount of illness and the number of days lost from work. Four categories were established as a result of the survey. Class I involved non-disabling sickness in which there was no absence from

work but with an assumed loss of working capacity of 25 per cent. Of the disabling illnesses, Class II concerning absence from work but no confinement with an assumed loss of working capacity of 50 per cent. Class III involved patients confined to the house with a loss of working capacity of 75 per cent and Class IV comprised individuals confined to bed by their schistosome infection with total loss of working capacity.

The final calculations from the survey indicated for the Philippines as a whole an annual loss of working capacity from schistosomiasis amounting to \$1,350,000 with an additional cost for medical expenditures of \$5,282,500. It was calculated that the economic loss from schistosomiasis in the Philippines imposed a heavier economic burden than did malaria and was several times greater than the estimated cost of controlling the disease in that country.

With this in mind, it may be of interest to cite data concerning the economic benefits which followed malaria control programs in the same country. School absenteeism was reduced from 40 to 50 per cent daily to 3 per cent daily in 3 years from 1946 to 1949, in which intensive malaria control measures were in force. During the same time, daily time loss among workers in industrial enterprises was reduced from 35 per cent to 2 to 4 per cent. The same amount of output was possible in 1949 with only 75 to 80 per cent of the 1946 labor force.^{75/}

V. METHODS OF CONTROL OF SCHISTOSOMIASIS MANSONI

In so far as is presently known, maintenance of this disease in the Americas involves only two alternate hosts, man and the susceptible snail. Interruption of the cycle can be effected theoretically by preventing human exposure, by sanitary disposal of human excreta, by measures directed against the snail host, by safeguarding against non-human reservoirs which may play a role in perpetuating the cycle, by chemotherapeutic treatment of human carriers, and by widespread educational propaganda concerning the dangers of the disease and how to avoid exposure. All of these methods are related in some measure to the aquatic habitants of the snails. From a practical viewpoint it is necessary to consider which of these procedures will be most effective in each country, considering the various endemic areas, the habits and cultural levels of the exposed population, the number of available trained personnel, the funds available for conducting the control program, and the probably effectiveness of each available procedure over short and long periods of operation. These several methods of control will be considered in this section and will be evaluated in Section VI.

1. Safe domestic water supply. This constitutes one of the cooperative projects which has been under way in Latin America for approximately two decades. Primary emphasis has been placed on urban centers to assure potable water for members of the community in their homes, for drinking, bathing, and washing of clothes. Safe laundry facilities have been installed for community use near

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the homes, to prevent use of infested water in nearby streams and canals. Turbidity in the urban water supply is eliminated by settling of water in reservoirs and by filtration; chlorination with 1-3 parts per million of nascent chlorine for 30 minutes kills the viable infective-stage schistosome larvae present in water derived from contaminated sources. In addition, where a single urban water supply has not been practical, dug wells from safe underground sources, with concrete curbs, have been installed to provide uncontaminated water for domestic use.

If bath water is allowed to stand for 60 hours after being drawn from infested streams, it is safe for use. Copper sulphate at a concentration of 50 parts per million or more will destroy all or nearly all cercariae or infective larvae after exposures of 1 hour or more. Water for bathing purposes is also safe if heated at 50°C. (122°F.) for 3 minutes.

2. Sanitary disposal of human excreta. Hand-in-hand with the installation of safe domestic water supplies is the necessity for sanitary disposal of human excreta. For the urban centers community disposal plants are required, planned and constructed under the supervision of experienced sanitary engineers, and including sanitary flush toilets for each home. This type of facility requires that the sewerage discharged from the system be settled satisfactorily so that it will not contaminate the body of water into which it is emptied.

Not all sewage treatment processes are effective for the destruction of schistosome ova.^{76/} At low temperatures of 44° to

65°F. digestion or digestion and storage periods of 2 to 3 months are required to render schistosome ova non-viable. Higher temperatures facilitate destruction. In drying sludge a survival period of 3 weeks for the ova can be expected at temperatures of 60° to 75°F. A reduction of the moisture content of the sludge apparently has no deleterious effect upon the ova until the moisture drops well below (less than 20 per cent) the spadeability content (60 to 70 per cent) commonly used as the criterion for disposal. In sludge dried at very warm temperatures, 85° to 90°F., the ova become non-viable within 9 to 10 days. Considerable attention must be paid to prevailing temperatures in determining the retention periods for drying sludge. Intermittent sand filtration is very effective for removing schistosome ova from sewage. Trickling filters are not effective for removing schistosome miracidia from sewage. Septic tank processing with moderate temperatures of 60° to 75° F. renders schistosome ova non-viable in 2 to 3 weeks. Care needs to be exercised to obviate incoming ova escaping with the effluent.

In villages and rural areas where community sewage disposal is not practical, sanitary latrines are required; they need to be placed so that the human excreta will not be discharged directly into bodies of water or indirectly through ground water so as to contaminate dug wells supplying water for domestic use.

3. Control of the snail intermediate host. Since the susceptible snail is a sine qua non for continuation of the life cycle of the parasite, it is logical to direct control efforts against

this important facet of transmission. Various methods have been utilized toward this end. These measures include the application of molluscicidal chemicals, the physical clearing of vegetation in the aquatic habitats of the snail, the employment of engineering procedures to eliminate or assist in eliminating areas providing favorable harborage for the snail, and biological control.

(a) Molluscicides. For the molluscicide operation to be successful, it has to be well planned and preceded with at least a year of preliminary studies in the area to be treated. Objectives of these studies are to develop the best strategy in applying the molluscicide, to give a maximum decrease in transmission at a low cost. In this way, the choice of the molluscicide most suitable for the local conditions, the timing of the operation and base line data to be used in the post-control evaluation are among the important goals of the preliminary studies. Information should be gathered during this period as to the hydrography of the area, the molluscan fauna in general, and the species which are recognized hosts in other places. The latter species of snails should be accepted provisionally to act in this capacity until laboratory and field studies are conducted.

The distribution of all snails in the area, the seasonal fluctuation in their life cycle and in the trematode infection rates should be determined.

Preliminary studies should be carried out in the laboratory and in the field.

A study of the ecology of the snail hosts during the pre-

control period is essential for the success of the mollusciciding program. The following data have to be gathered on those species that were proved to be hosts: Distribution throughout the scheme; the areas where they are abundant and others in which they are scarce or absent; the distribution of the vegetation in the water courses; the seasonal fluctuation in the population density of the snails throughout the area for at least one year before the application of the molluscicide; and the peak or peaks in egg laying.

Data on the seasonal fluctuation in the population density is important in the timing of the operation. It is usually beneficial to apply the molluscicide when reproduction is at its highest, as young snails are more susceptible to the molluscicide than adult snails.

Of importance also is the determination of infection rates among the snails and their seasonal fluctuation. Reduction in transmission is affected if the water is treated when it is most infective.

Water analyses have to be carried out periodically with emphasis on the hardness and hydrogen ion concentration. A knowledge of the chemistry of the water is essential in the choice of a molluscicide which would be effective in the particular type of water in the area to be treated.

Copper sulphate. Copper sulphate has been employed as a molluscicide for several decades with a certain amount of success in some areas.^{27/} It has been applied both periodically and by continuous application of low concentrations. The latter method

has apparently been of value in controlling the molluscan intermediate hosts in the Gezira area of the Sudan. The chemical tends to be precipitated out of water with a high alkalinity. It combines with organic matter and its activity may be rapidly dissipated; for this reason, it is necessary to clear vegetation before its use, a requirement which adds greatly to the cost of control campaigns. The compound is slightly ovicidal but has little or no effect on cercariae. At usual rates of application, it is less toxic to fish than some other compounds. It has no practical toxicity to man or animals. However, it is highly corrosive to containers, pumps, etc. which must be rinsed thoroughly after use. In order to achieve molluscicidal effect in periodic applications concentrations of 20 to 30 ppm must be employed. The compound is still useful for snail control under certain conditions.

Sodium pentachlorophenate. Sodium pentachlorophenate (NaPCP) has been developed within the past decade and has been used successfully for snail control in Japan and Venezuela, and in one area in Egypt.^{78,79,80/} It has not proved effective under certain conditions in Brazil and in the Transvaal. It is toxic to snail eggs and cercariae at the same concentrations used to kill snails. In the recommended concentrations for molluscicidal operations, it is not dangerous to human beings or domestic animals. Cases of poisoning in man have resulted from gross negligence, failure to properly instruct laborers in the safe handling of the compound, or exposure to concentrations far greater than those employed in snail control.^{81,82/} The chemical dust is very irritating to the mucosa of

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the respiratory tract. Although highly toxic to certain fish, amphibians and invertebrates, the effect on the aquatic environment is probably less lasting than that of copper sulphate. In flowing water, NaPCP has usually been applied at concentrations of 10 ppm for 8 hours. In still waters, good results have been obtained at 5 ppm. In irrigation canals and in streams with unobstructed flow, NaPCP has been carried for long distances and has retained its initial lethal concentration. The chemical has certain herbicidal properties. It has a serious disadvantage in being broken down by exposure to direct sunlight, especially in waters which are clear and free from suspended solids. Turbidity did not reduce its efficacy in Egypt. Under conditions with strong exposure to ultra-violet light, it should be applied in the late afternoon or on cloudy days. NaPCP is non-corrosive.

Copper pentachlorophenate. This compound is a highly effective molluscicide. It is non-irritating to snails and does not cause them to escape from the aquatic environment, a thing which has been reported in some areas following the application of NaPCP. The compound is insoluble in water and can be prepared in the field by independently dispensing copper sulphate and NaPCP and mixing the two solutions in the snail habitat. CuPCP has a long residual effect, especially in still waters. However, it has been used with success in other types of habitats in Venezuela.^{79/}

Bayer 73. Bayer 73 (5-chlorosalicylic acid (2-chloro-4 nitro-anilide) is a recent development which shows great promise as a molluscicide.^{83/} It is sparingly soluble in water but is formulated

as a wettable powder, miscible with water as a stable suspension. The chemical is non-irritating and has a low level of toxicity to mammals. It is effective against snails in concentrations as low as 1 ppm. The snails are not irritated by the compound and make no effort to leave the aquatic environment. The chemical is affected adversely by strong sunlight but to a lesser extent than NaPCP. It loses much of its effectiveness in highly alkaline waters. Concentrations lethal for snails kill schistosome eggs and cercariae. It may scorch aquatic vegetation and destroy algae but this effect is short-lived. It is toxic to fish at concentrations employed against snails in the field. It would appear that the chemical can be marketed at a price to compete with NaPCP.

Aqualin. This compound has been employed as an herbicide; the active agent is acrolein ($\text{CH}_2\text{:CH-CHO}$). It is effective against snails, ova and cercariae at concentrations of 3 ppm and is carried for long distances in flowing water.^{84,85/} The compound would appear to be most effective in fast flowing streams. It vaporizes rapidly and cannot be employed as a spray. It is usually introduced directly into the discharge side of a circulating pump under water. The material is highly inflammable and should be handled and used under adequate precautionary measures.

Other molluscicides. Many other chemicals have been used for snail destruction, including I.C.I. 24223 (iso-butyl-triphenyl-methylamine), copper carbonate, Rhodiacid, dinitro-ortho-cyclohexyl phenol, calcium arsenate, calcium cyanamide, etc. Some of these are

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effective under some circumstances and need further evaluation. Others have been superseded by more effective chemicals. Many other compounds have been laboratory and field tested. Some have evidenced high efficiency but are too expensive or are not readily available for control purposes.

Application of molluscicides. There is evidence that many of the disappointing results secured with molluscicides of recognized value have arisen because of a lack of understanding of the technical requirements for their use. Highly trained personnel are required. Due reconnaissance should be made of the area to be treated and a critical appraisal arrived at concerning the nature of the aquatic environment and the molluscicide and the method of application likely to produce the desired results. In the case of streams and irrigation canals, it is essential to estimate the rate of flow in order to gauge accurately the amount of molluscicide required. In standing water, the average volume needs to be determined for the same purpose.

There are many ways of applying molluscicides; the selection of the most suitable method for any given site depends on the environmental conditions and the ecology of the molluscan intermediate host in the area. Molluscicides have been employed by means of sprays, by allowing the chemical to dissolve directly in flowing water, by the employment of apparatus which affords a constant output of the chemical for a given period of time, by broadcasting the chemical in powder form with a suitable vehicle, by applying the molluscicide along the shores of streams and irrigation canals, by

the use of emulsifying agents, and other means.

Evaluation of molluscicide treatment. Once applied, it is essential to determine the concentration of the molluscicide in the water, whether stationary or flowing. If applied to streams or irrigation canals, the operator will wish to know how far the chemical is carried in lethal concentrations. Various means are available for such determination. In the case of sodium pentachlorophenate and Bayer 73, colorimetric methods are available. The dispersion of Aqualin can be followed by the yellow color of the product in solution.

It is assumed that the operator has, as a preliminary measure, made some determination of the snail population in the area to which the molluscicide is to be applied. With this determination as a base line, it is necessary after chemical treatment of the water to arrive at some estimation of the relative efficacy of the application. This can be accomplished in two ways. The first consists in carrying out a careful search and surveillance for living snails after the application of the molluscicide, employing the same techniques that were utilized in conducting the pre-treatment estimation of the snail population. The second method of appraisal will usually make itself evident by a repopulation of the area in event that the mollusciciding has not been successful, or all snail eggs have not been killed, or there are opportunities for reinfestation from areas outside of the mollusciciding scheme. Even with the most efficient molluscicides, applied in the most effective manner, is it seldom that the total snail population is eradicated by one application. In most instances, repeated treatment is needed.

(b) Clearing of aquatic vegetation. This measure is essential when copper sulphate is employed as a molluscicide and is also advantageous in some circumstances prior to the use of other molluscicides. However, those chemicals with herbicidal properties can usually be utilized without the expense of prior clearing.

(c) Engineering practices and water management. There is no doubt that the engineering control of the molluscan intermediate hosts of the human schistosomes has not been adequately exploited. Engineering practices conducive to control consist in filling or draining small bodies of water providing good habitats for snails, straightening stream beds to increase water flow, lining of irrigation ditches to increase water velocity, the employment of fluctuating water levels, and other water management procedures which tend to render the aquatic environment unsuitable for the snail hosts. In some areas primitive agricultural practices and poor irrigation methods contribute materially to the spread of schistosomiasis. Inadequate provision for drainage causes the land eventually to become water logged and salted. Good water management in irrigated areas will frequently obviate snail harborage and prevent the introduction and dissemination of the disease. On the other hand, where little attention has been paid to such a remedy, irrigation systems have provided ideal conditions for the dissemination of schistosomiasis.

(d) Biological control. In economic entomology considerable progress has been made and success achieved by the introduction of insect enemies of other insects injurious to garden and field crops.

In Brazil a micro-organism, Bacillus pinotti, has been found to be damaging to the snail hosts but apparently its use as a biological control agent has not been widely promoted. In Puerto Rico small colonies of the ampullarid snail Marisa cornuarietis were introduced into Australorbis glabratus habitats and the relative numbers of A. glabratus studied over an 81-week period. It was observed that while Marisa was devouring the aquatic vegetation it also ate the egg masses and young snails of Australorbis, so that with the multiplication of the predator the Schistosoma host snail was reduced almost to extinction. The experimental ponds remained free of vegetation and Australorbis has failed to recover at the end of the observation period (Radke, Ritchie and Ferguson).^{86/} It remains to be demonstrated if similar results will be obtained in case the predator should be introduced into A. glabratus habitats in other endemic areas. Moreover, precaution must be taken that the predator snail does not overrun streams and ponds into which it is introduced and thus produce more harm than good.

4. Safeguarding against non-human reservoirs. In the endemic foci of schistosomiasis in the Americas a rather impressive number of mammals have been found to be naturally infected. With the exception of the African green monkey (Cercopithecus sabaesus) in the central mountain forests of St. Kitts,^{51/} these reservoirs have all been discovered in the heavily endemic foci of the northeastern states of Brazil and in the States of Bahia and Minas Gerais,^{49/} and in Venezuela.^{50/} The list includes three species of opossum, the black rat, the Norway rat, the white-bellied rat, two species of

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rice rat, several species of native mice, and the native guinea pig from Brazil, and the rabbit from Venezuela. Of this group the only species which habitually frequents water is the rice rat (Oryzomys spp.). This rodent, reported to be a natural reservoir in two Brazilian states with high endemicity, is known to discharge viable Schistosoma mansoni eggs in its feces, and is therefore the most likely non-human carrier of the infection. It will be necessary to determine the significance of this reservoir and the others found naturally infected in Brazil or elsewhere before an evaluation can be placed on their relative importance in the propagation of schistosomiasis in endemic countries.

5. Treatment of human carriers. The individual who is daily evacuating viable eggs of Schistosoma mansoni in his feces constitutes a public health menace. As a carrier of the parasite he is the most likely agent for reinfection of the susceptible snail host. Even though it may not be feasible to treat all carriers with curative anti-schistosomal drugs, it may be of practical value to administer certain drugs (antimonials intramuscularly or lucanthone Miracil D by mouth in coated tablets) in short courses periodically in outpatient clinics, to reduce temporarily the excretion of viable eggs.^{87/} This program should be conceived primarily as a public health measure.

6. Public health education. In connection with education of the community concerning parasitic and other infectious diseases, persons residing in endemic schistosomiasis areas require simple

explanations of the seriousness of schistosomiasis for the infected individual and for his associates, how the disease is perpetuated from man to snail and back again to man through the contaminated water in which the snail lives, and the measures which will insure against infection of the snail and against human exposure. Not only should such public health education be directed towards the individual but to an even greater degree towards the community as an integral socio-economic unit.^{88,89/} Practical acceptance of the reasons for combating schistosomiasis must be accompanied by active cooperation of the community with the local public health authorities in charge of the program. This cooperative effort will require changes in the habits, customs, and even cultural standards of the community; since the effectiveness of the control program can not be measured in terms of two or three years, but rather over longer periods of time, it will not be expected that low standards of personal and group hygiene and environmental sanitation which have been practiced for generations will be changed overnight, but only gradually.

7. Central administrative control and direction. In each country in which endemic areas of schistosomiasis exist, a problem as serious and many-faceted as the control and eradication of schistosomiasis must have central administrative control and direction. In Brazil there is constitutional requirement that the Federal Ministry of Public Health be responsible for all health programs in the States and their political subdivisions. To this end in Brazil and other countries where schistosomiasis exists there

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should be first of all close cooperation between the Ministry of Public Health and the other national ministries, to assure uniform and concerted effort in combating the disease, and a single experienced public health administrator should be assigned full-time responsibility for this program. Furthermore, there is need for constant communication between the national organization and local health units, to provide both information and services, so that consistent plans will be organized and programs conducted on the basis of the best scientific knowledge, along the most efficient and economical pathways.

VI. EVALUATION OF CONTROL PROGRAMS IN SCHISTOSOMIASIS MANSONI

In order to have a basis for evaluation of the effectiveness or ineffectiveness of control methods and programs, it is necessary to have considerable information to compare with the results to be obtained as the program proceeds.

(1) In the first place, there should be substantial data on the geographical extent and intensity of the disease in each endemic area. In some regions, as the coastal and adjacent forest zones of the northeastern states of Brazil and in north central Venezuela, the endemic foci are more or less contiguous, whereas in other regions of endemicity they may be separated from one another by natural physiographic or climatic barriers; or they may be distributed widely but in multiple locales throughout an extensive terrain, as in the State of Minas Gerais, Brazil.

(2) In the second place, competent workers should have provided overall and location spot maps of the snails responsible as intermediate hosts of the disease. Such maps should include, if possible, not only those areas known to be endemic foci with demonstrated human infections but also adjacent regions or non-contiguous ones where the susceptible snails are present but as yet are not known to be infected. These data are essential before any type of molluscicidal procedures are undertaken.

A further requirement concerns intimate knowledge of the ecology of the molluscan intermediate host or hosts within the area. While the acquisition of such knowledge may require some time and

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effort, it is advisable to make such observations prior to any program aimed at snail destruction.

Assuming that data on the extent and intensity of the disease in man are provided for such endemic foci, that there is relatively accurate mapping of the habitats of the snail hosts and some information concerning their ecology, it will probably be desirable to test the control measures which have been decided upon in a relatively modest pilot project, to discover the pitfalls and inadequacies as well as the most practical and effective methods of conducting a more pretentious program. Field testing of the project on a small scale is particularly important if the funds manpower available are meager, since a well-planned and satisfactorily conducted pilot test which shows potential practical value of the control measures employed should stimulate the allocation of larger appropriations and more trained personnel for the project.

In setting up the project, each of the following items of control should be considered and evaluated from the standpoint of the nature and extent of the problem, the available facilities, the amount of funds, and the number and type of trained personnel: (1) safe water supplies for domestic use and sanitary disposal of human excreta; (2) molluscicidal control measures; (3) biological control of snail hosts; (4) engineering methods of control; (5) the influence of potential mammalian reservoirs of infection; (6) treatment of human carriers; and (7) public health education. Each of these aspects will now be considered.

It is difficult to place relative values on various methods of schistosomiasis control for the reason that nearly all available procedures have been employed in the endemic areas in which control has been attempted. This has necessarily followed because no one method of control is singularly effective from a practical standpoint.

1. Control by sanitary measures. The installation of sanitary facilities, including safe water supplies, properly constructed latrines or sewage systems, and bathing and laundering facilities represents a capital expenditure not only of benefit in the control of schistosomiasis but of other water-borne and fecal-borne diseases as well. Such a program should be tied to general health improvement schemes and not carried out for a single disease. The installation of such facilities will need to be accompanied by an intensive health education program so that the populations will realize the importance of using them. Populations in many areas are slow to alter age-old habits and benefits from new installations cannot be expected to materialize rapidly. In some cases salutary results are only of a temporary nature and the installation remains as a monument to another lost cause. For instance, in the WHO assisted pilot project in Leyte, an environmental sanitation campaign proved to be ineffective as a control measure.^{90/} Nevertheless, sanitary control of schistosomiasis is a sine qua non and the ultimate goal to be kept constantly in mind.

2. Molluscicidal control measures. The successful applica-

tion of molluscicides results in a rapid interruption of the transmission of infection. If the chemical is effective also against snail eggs, the cycle of transmission continues to be interrupted until reinvasion of the treated area. Certain herbicidal effects possessed by certain molluscicides may in some places obviate expensive weed control and clearing of irrigation canals. All of these advantages accrue without the active cooperation of the exposed population, a cooperation which is essential and sometimes difficult to secure in the application of other control measures. In many endemic areas, mollusciciding will aid in the control of certain trematode diseases of domestic animals.

On the disadvantageous side, the employment of molluscicides is relatively costly since applications must usually be repeated over a period of time; in fact in the past it has required a period of years before substantial control has been achieved. The problem of reinfestation has not been solved and it is not always possible to ascertain the means by which repopulation occurs, assuming that the molluscicide has been effective in destroying all snails and eggs. Consideration must be given to the relative values to be placed on the long-term use of molluscicides versus the benefits to be derived from capital expenditures for permanent sanitary improvements or engineering works to obviate snail harborage. Under some circumstances, it may be found that the latter offer the best investment. A mollusciciding campaign will lack permanent value unless snail eradication can be accomplished. At present, such a goal is difficult to achieve. However, in nearly every area in which progress has been made in the control of the disease,

molluscicides have played a prominent role. No doubt more effective compounds will be developed and better methods will be devised for their use.

3. Biological control of snail hosts. Biological methods of control have been tried in certain localized foci. The most promising has consisted in the introduction of the ampullarid snail Marisa cornuarietis in certain areas in Puerto Rico, with resulting control of the molluscan intermediate host, A. glabratus. Other biological methods have been less successful. However, before the introduction of M. cornuarietis into any endemic area, it would be necessary to evaluate the potential danger of placing the predator snail in unrestricted locales, where its demonstrated propensity to consume vegetation may damage irrigated rice fields or vegetable truck farms, and thus produce a greater menace than help to the economy of the area.

4. Engineering methods as applied to control. Engineering techniques such as drainage and filling, alteration of agricultural practices, lining of ditches and canals, straightening of channels, weed removal to increase water velocity, damming and ponding, fluctuation in water levels and other practices have been utilized locally, frequently in conjunction with other control methods. Their usefulness is tied to the type of topography, the nature of the snail harborage, the conformation of infested waters and agricultural practices. Such procedures are capital expenditures from which long-term benefits can be expected in many cases. The degree

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of effectiveness and the relative permanence of the procedure will indicate whether the capital expenditure is warranted. In some cases the cost will not exceed that of prolonged mollusciciding; given comparable results in control, the advantage would lie in the adoption of the engineering methods.

5. The influence on control of potential mammalian reservoirs of infection. As previously indicated, many lower animals in some endemic areas have been found to harbor S. mansoni. The potential importance of these reservoir hosts needs to be more thoroughly evaluated before any extensive control campaign is launched. The present evidence would not indicate that lower animals constitute a serious threat or play a significant role in the transmission of the disease. Perhaps in localized areas, however, they may be sufficiently important in this regard that control measures should provide for such contingency.

6. Treatment of human carriers. Experience has demonstrated that the largest proportion of viable eggs produced by Schistosoma mansoni in the smaller intestinal veins of man are evacuated in the feces during the active stage of the infection. In chronic cases the eggs tend to remain in the intestinal wall or are carried into the liver. Repeated exposure tends to reactivate the infection as newly matured worms produce new batches of eggs. Therefore, in a practical sense, the active cases constitute the important source of eggs for reinfesting the snails. In countries in which large scale treatment campaigns have been carried out,

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there is some question as to the net benefits. It is difficult, if not impossible, to carry out treatment on a large segment of the population. Present drugs lack desired efficacy and side reactions are frequently so disagreeable that a relatively small percentage of individuals consents to complete the treatment. It is the consensus of opinion that large scale chemotherapy has not contributed materially to the control of the disease, although it has been of benefit in reducing the intensity of the infection and thereby has obviated some of the complications. Its employment will depend largely on the characteristics of the endemic area and on the willingness of the population to cooperate.

7. Public health education. Any campaign for the control of schistosomiasis should be fortified by an earnest effort to acquaint the population of the endemic areas with the nature of the disease, the manner in which it is transmitted, and the purposes of measures which are being taken to alleviate the situation. Effort should be made to stimulate the interest in the local inhabitants of the area and, where possible and feasible, endeavor to have them take an active role in helping to promote the control efforts. In nearly every country in which some progress has been made in arresting the disease, public health education has played an important role, even though it may have taken considerable time to awake and maintain the necessary interest on the part of the local citizenry.

The task is one in which the public health educator has the important role. Other individuals, such as the sanitarian, public

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health nurse, etc., must have had training in this phase of the program; and he (or she) must have a sympathetic understanding of the background, the education, mores, habits and superstitions of the people of each endemic community. Without the cooperation of the community the entire program may fail. This part of the campaign will not be easy and will require effort and much time to accomplish. Hence evaluation of failure or success of control will need to include progress in community education.

VII. ACTUAL AND POTENTIAL EXTENSION OF SCHISTOSOMIASIS
IN THE AMERICAS

As previously indicated, establishment of the disease in the Americas was actually an extension from its African habitat. There are relatively few recent records of its introduction from one to another completely different focus in the Western World; of these the development of an endemic center at Fordlandia, State of Pará, Brazil^{91/}, following introduction of laborers from coastal Brazil, is an outstanding example. Yet today there are known extensions of the disease within the past quarter of a century in Puerto Rico^{92,10/}, Venezuela^{14/}, and particularly in Brazil, where it has become endemic in new centers to the south, and southwest of the hyperendemic coastal areas in the northeastern States^{17/}. With increasing migration of inhabitants from this relatively dry, agriculturally unproductive region to the fertile, as yet sparsely settled regions of the States of Goiás, Pará, Mato Grosso and inland São Paulo, there is every likelihood that infected newcomers will "seed" the previously uninfected territory wherever the carriers of the disease provide the inoculum for the susceptible snails, which will, in turn, provide opportunity for exposure of other settlers in the new territories. Similarly the present concentration of schistosomiasis in Venezuela and Surinam along heavily populated coastal areas will unquestionably work inland if any "population explosion" causes individuals and families to seek relief from the overpopulated districts. Wherever the appropriate snails are established these inland regions will be subject to the disease. Moreover, in British Guiana and parts of

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Chile, where susceptible snails are present, there is the liability that the infection may become established. French Guiana may also be a favorable territory, although thus far the snails tested have proved to be refractory. In Puerto Rico essentially all of the island where Australorbis glabratus breeds is already schistosomiasis endemic territory.

The proposed reclamation of agricultural lands in northeastern Brazil through the extension of existing irrigation systems and the establishment of new systems will increase the possibilities for spread of schistosomiasis in an area in which the disease is already a major health problem. Any plans for the rehabilitation of the area should undoubtedly take into consideration the potentialities for the spread of infection.

In addition to the extension of the disease into previously non-endemic regions, the rapid increase of population since 1940 in Brazil, Venezuela, Surinam and the Dominican Republic indicates that, at the present growth trend, by the year 2000 there will be nearly a five-fold increase over 1960 (viz., in Brazil from 66.3 to 400.0 million, in Venezuela from 7.36 to 37.5 million, in Surinam from 0.295 to 3.3 million and in the Dominican Republic from 3.0 to 14.2 million.) With increased migration of workers from congested to sparsely settled areas in each of these countries there is a possibility that the calculated Schistosoma-infected persons will increase respectively from the 1960 estimates of 5 million to 28.5 million in the year 2000 (Brazil), from about 30 thousand to 150 thousand (Venezuela), and from 9,300 to 75 thousand (Surinam).

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In view of lack of sufficient information concerning the extent of the disease in the Dominican Republic, it is impossible to provide an estimate of the present or a forecast for the future of this disease in this country.

The above extrapolation is based on the concept that the increased populations will be exposed to schistosomiasis and become infected to the same degree as at present; that there will be no extension of control measures; or that control measures, if applied, will be totally ineffectual. At present, there is no indication that such a concept may prove to have any validity. However, the data do indicate the grave future potentialities of the disease unless effort is made to curb it.

VIII. REPORTING OF SCHISTOSOMIASIS

Nowhere in the Americas is schistosomiasis a reportable disease. Yet in some regions of the hemisphere it constitutes one of the major baffling medical and public health problems of our time. Even in New York City, the City Health Department is able to tabulate annually only 5 per cent of the estimated infected Puerto Rican population living in the City; and in Puerto Rico itself only 5.8 per cent of the positives were reported in 1958. In Venezuela 13.4 per cent of the cases were listed in the same year, while in the Dominican Republic 49 cases were recorded for that year.

In view of the seriousness of the situation in endemic areas and potentially serious development of the disease in other areas, it would be advantageous to include schistosomiasis in the list of reportable diseases in countries with known endemic foci. Inclusion of schistosomiasis among the notifiable diseases in these countries:

- (a) Will make it easier to define its present prevalence and geographic confines.
- (b) Will provide a better basis for the health authorities of the countries to evaluate progress or failure in the attack on the disease within the country, and
- (c) Will make surveillance and evaluation of its present and prospective status a simpler task for PAHO.

IX. RESEARCH AND TRAINING NEEDS IN SCHISTOSOMIASIS
IN THE AMERICAS

Present inability to control schistosomiasis is linked largely with a past dearth of research effort which has been distinctly limited, for instance, when compared to the vast amount of investigation which has taken place in the field of malaria and many other infectious diseases. As a consequence, answers are lacking for many of the vital questions which pertain to control.

Much of the pioneer research in schistosomiasis was conducted in the Americas and this traditional interest has been maintained over a long period of years. Currently, institutions concerned with such research at a national level are located in Brazil, Venezuela and Puerto Rico. In Brazil the major center of such activity is at the Instituto Nacional de Endemias Rurais at Belo Horizonte, Minas Gerais, and its branch laboratory at Recife, Pernambuco. In Venezuela, most of the investigations are under the aegis of the Ministry of Public Health and Social Assistance, including its Institute of Hygiene and the Department of Tropical Medicine in the Medical School of the Central University in Caracas. In Puerto Rico, early investigations on schistosomiasis were conducted in the School of Tropical Medicine. After the incorporation of that institution into the Medical School of the University of Puerto Rico, the work has been continued in the latter institution. In recent years, collaborative research in Puerto Rico has been fostered by the School of Medicine, the U.S. Army Tropical Research Medical Laboratory and the Puerto Rico Field Station of the U.S. Public Health

Service. All of the above-mentioned laboratories are capably staffed and can be expected to continue their significant contributions to the schistosomiasis problem.

It is obvious, however, that present research endeavors need to be fortified and extended if more material progress is to be made in the control of the disease. This effort will require additional facilities, equipment and personnel.

Patterns of research in schistosomiasis. While the ultimate aim of research is to augment knowledge needed for the control of the disease in the Americas, there is no dogmatic definition of what constitutes such research. Fundamental studies, frequently referred to as "basic research", may have as an objective a goal far removed from any thought of practical application. Yet studies of this type may unexpectedly elucidate some key factor, ignorance of which has long stymied some particular phase of control. Thus, it is not possible on an a priori basis to specify the kind of research which will be most productive in contributing to the final conquest of the disease. Rather schistosomiasis research should have a broad basis and any investigative program should be sprinkled liberally with attempts to throw additional light on the fundamental physiological and biochemical mechanisms of the parasite and its molluscan intermediate host. At the same time, information is vitally needed on new methods of attack against both of these vital factors in the disease picture. This knowledge may be supplied by fundamental studies but possibly can be gained more speedily in some instances by a more direct and prosaic approach.

Disciplines involved in schistosomiasis research. Needless to say, schistosomiasis research must be conducted in many varied situations, including the laboratory, the hospital and clinic, and the field. The complexity of the problem, the bizarre epidemiological pattern of the disease, and the difficulty of treatment and control call for the collaboration of specialists in many different disciplines. Such include clinicians, epidemiologists, immunologists, parasitologists, biologists, malacologists, physiologists, biochemists, chemists, engineers and others.

The clinician represents an important cog in any effort to combat schistosomiasis. He is usually the first to observe clinical cases and the first to become aware of sub-clinical cases which may represent new foci of infection. It has already been noted that present day treatments for schistosomiasis lack desired efficacy and have annoying side reactions. This situation obviates to a considerable extent the employment of mass therapy in the control of the disease. Vigorously pursued research is needed for the development of new and more effective methods of chemotherapy. It is here that the clinician can play a major role.

The epidemiologist is an integral part of any control campaign for it is his function to investigate and evaluate the factors responsible for the spread of the disease in the community and on the basis of his evaluation to recommend measures most applicable to control.

The immunologist can contribute to research on immunological methods of diagnosis. He has a broad field before him in studying

the development of resistance to infection and it is hoped that he may be able to devise methods for immunizing against the disease.

The parasitologist and the biologist are needed in studies on methods of diagnosis, for identification of parasites, for studies on the environmental factors affecting the distribution of the molluscan intermediate host, for detecting reservoir hosts, and for assisting the epidemiologist in appraising the disease situation in the community.

The malacologist is concerned with snail identification and the factors bearing on snail ecology.

The physiologist and the biochemist are capable of bringing their talents to bear on the elucidation of the life processes of both the parasite and the molluscan intermediate host. It is here that we may look for the key to unlock some of the mysteries surrounding the problem of control.

The chemist can fulfill a vital role in the development of new chemotherapeutic compounds for the treatment of the disease and new molluscicides for attack on the snail host.

The engineer is needed to assist in the many problems of snail control and can furnish essential aid in water management, an extremely important factor in many endemic areas of the disease.

Needs for training in schistosomiasis in the Americas. Additional undertakings in the research and control of schistosomiasis in the Americas will create a need for cooperative effort. As research is expanded, facilities should be provided for training additional research personnel. Opportunities should be created also

for exchange of workers between different laboratories and for gaining experience in other endemic areas. It may be found advantageous for PASB/WHO to sponsor a fellowship program. At the same time, consideration should be given to supporting annual or biennial "workshops", where research investigators from various laboratories could have the opportunity of exchanging views and correlating research efforts.

As control measures are extended and efforts intensified, it will be essential to train additional workers in the many techniques which enter into the conduct of a control campaign. This increased personnel will include individuals in both professional and sub-professional categories.

International technical and training centers for the Americas.

The reactivation of interest in schistosomiasis in the Americas and the establishment of additional control campaigns will, it is believed, render it desirable to provide certain cooperative facilities designed to expedite training of personnel and to offer essential services which do not necessarily require duplication in every endemic area. Such a center or centers should be peculiarly adapted to supply the services for which demand arises. The facilities should be located in a highly endemic area of schistosomiasis where clinical cases are readily available, where supplies of molluscan intermediate hosts are plentiful, where laboratory space and equipment are adequate to care for visiting workers, and where the professional staff is composed of outstanding scientists representing the many disciplines which have been enumerated above as constituting

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the most effective research team. The sponsorship of such a center or centers is the concern of PASB/WHO.

In addition to serving as a training center, the technical facility could perform functions such as the following.

The PASB/WHO Working Group for the Development of Guidance for Identification of American Planorbidae Involved in Schistosomiasis at its meeting on 6-9 November 1961 recommended the preparation of a guide for the neotropical planorbids for use by public health workers involved in survey work and control programs of schistosomiasis in the Americas. This guide will be of great value but it should be supplemented by a permanent central snail identification center, which could serve all the Americas.

The need for simple procedures for the diagnosis of the disease and the detection in control campaigns of asymptomatic carriers of infection has long been felt. While a positive stool examination provides a definitive diagnosis, a negative result only leaves doubt concerning the presence or absence of infection. In the clinic or hospital repeated stool examinations may eventually provide the desired information but multiple examinations are too costly and too time consuming for utilization in epidemiological surveys and in checking the results of mass treatment and control campaigns. Effort has long been directed toward the development of immunological procedures to detect infection with greater simplification and greater reliability than provided by the stool examination. Various methods of immunological diagnosis have been reviewed in Section II. As indicated, certain of these appear to be of consider-

able promise and to be adapted to field use. If and when such tests come into use for large scale surveys, it would be of distinct advantage to have available an antigen reference center for the Americas for the purpose of antigen standardization, if not production. Such a facility could be utilized by all countries engaged in control campaigns.

While methods for the control of schistosomiasis at present lack desired efficacy, there appears to be little doubt that the employment of molluscicides will constitute one of the most dependable weapons in most areas in which control is attempted. If such proves to be the case, it will no doubt be highly desirable to have a centralized molluscicide testing center which could serve as a reference laboratory. Such a laboratory could formulate chemical and physical standards for effective products and carry out reference tests on samples of molluscicides submitted by various countries engaged in the control of the disease to insure quality control.

In applying molluscicides it is essential to have accurate information on the dilution of the chemical in order that an adequate lethal concentration may be maintained over the length of stream in which it is designed to kill snails. Tests have been developed for measuring such molluscicide concentration. The molluscicide testing center might also prepare the test kits and maintain standards of accuracy by check testing the kits at intervals.

X. SOME RESEARCH PROBLEMS IN SCHISTOSOMIASIS IN THE AMERICAS

The need for research in schistosomiasis in the Americas is indicated in the previous Section and it is intended here to outline in some detail problems which seem to be of special importance. There are, of course, many others which could and no doubt will receive attention as time goes on. However, those projects listed below are believed to be some of the ones whose solution will contribute significantly to the control of the disease.

It has already been mentioned that there is needed for three types of research. These are: (1) Fundamental research which is directed at elucidating some of the basic physiological and biochemical mechanisms of both the parasite and its intermediate host; (2) developmental research which is concerned mainly with those problems having to do with the diagnosis, treatment and control of the disease; and (3) applied research which deals with the field testing and perfection of methods for practical application. As stated, any research program must be kept flexible and in keeping with the abilities and talents of the staff. If facilities and personnel permit, a versatile program is usually the most productive.

1. Research on the Molluscan Intermediate Hosts

(a) Snail identification guide. The PASB/WHO Working Group for the Development of Guidance for Identification of American Planorbidae Involved in Schistosomiasis at its meeting on 6-9 November 1961 made considerable progress in dispelling some of the confusion which

surrounds the nomenclature of the molluscan intermediate hosts of Schistosoma mansoni in the Americas. It was the recommendation of the group that an identification guide for these molluscs be prepared in order that specific information on the subject might be available for field workers and others. Such a guide is urgently needed and it is the intention to produce and distribute it as soon as possible.

(b) Distribution of intermediate hosts and potential intermediate hosts. Once uniform criteria are set up for snail identification, attention should be given to mapping the distribution of known molluscan intermediate hosts and those which are suspected of carrying schistosome infection. This program is particularly pertinent for Brazil, where the disease is widely distributed and where it is entirely possible that intermediate hosts other than Australorbis glabratus, A. tenagophilus and Tropicorbis stramineus may exist. This may be especially true in areas which have not been surveyed for the disease.

(c) Genetic constitution and susceptibility to infection. Not all planorbid intermediate hosts of Schistosoma mansoni demonstrate equal efficiency in transmitting infection. A. glabratus is usually highly susceptible to infection and the parasite is seldom inhibited in its development in this species. However, Files^{93/} demonstrated resistance of a strain of A. glabratus from Salvador, Bahia, Brazil to infection with exotic strains of S. mansoni. Newton^{94/} exposed this strain of snail and a strain of A. glabratus from Puerto Rico

to a Puerto Rican strain of S. mansoni. The parasite developed without any effective interference on the part of the Puerto Rican snail. On the contrary, in the Brazilian snail the parasite was destroyed and removed, usually within 24 to 48 hours after penetration. Later Newton^{95/} demonstrated that susceptibility to S. mansoni infection in A. glabratus is a heritable character, and that several genetic factors are probably involved. Barbosa^{96/} showed that the Bahia snail was a very poor host even for a Brazilian strain of the parasite. A. tenagophilus has been considered a poor host but recent work^{20/} would indicate that it can be an important factor in transmission when pollution of streams is at a high level. T. stramineus is a less favorable host than is A. glabratus^{97/}.

In more recent studies, Paraense and Corrêa^{98/} sampled 23 populations of A. glabratus scattered over the range of the species. These were exposed to 10 miracidia per snail of a strain of S. mansoni from Belo Horizonte, Brazil. A great majority of populations were highly susceptible, showing infection rates above 50 percent. Six populations, however, were less susceptible or even highly resistant to infection with rates of 48, 24.1 and 0 percent. Strains from Salvador, Bahia were entirely resistant when exposed to as many as 1,000 miracidia. The same authors found that A. tenagophilus from Pindamonhangaba, São Paulo, Brazil was insusceptible to infection with S. mansoni from Belo Horizonte when exposed to 50 miracidia. Exposure to 1,000 miracidia resulted in infection in 1 of 54 specimens. On the other hand, A. tenagophilus from São José dos Campos, São Paulo, which was insusceptible to infection, was easily

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infected with a local strain of S. mansoni. The latter strain, however, failed to infect A. glabratus from Belo Horizonte which is highly susceptible to local S. mansoni.

Coelho^{99/} has studied the resistance of A. tenagophilus to schistosome infection. He exposed 1,433 specimens of this species from 14 districts of the States of São Paulo, Guanabara, Rio de Janeiro, Minas Gerais and Rio Grande do Sul to S. mansoni miracidia. After 35 days cercariae and secondary sporocysts could be found in only 0.5 per cent of the 1,019 surviving specimens. The percentage of infection among 195 A. glabratus and 50 A. stramineus used as controls was 80 per cent and 5.5 per cent, respectively. Histological preparations from the cephalo-podal region of 49 A. tenagophilus from 7 districts of São Paulo killed 36 and 74 hours after exposure revealed granuloma formation around 88.7 and 93 per cent of the primary sporocysts, which were undergoing resorption.

Additional studies are needed on the relative susceptibility to infection of strains of the known intermediate hosts, since this may be of considerable importance in the epidemiology of the disease, especially in Brazil. It would be interesting to investigate further the role of the genetic constitution in relation to susceptibility to infection.

(d) Development of strains of snails resistant to schistosome infection. Since it has been demonstrated that certain strains of known snail vectors are wholly or partially resistant to certain strains of S. mansoni, it might be profitable to direct research toward the development of strains of vectors which would be com-

pletely and permanently resistant. Beginning with strains which are known to be at least somewhat resistant and reconstructing the genetic pattern, it might be possible to develop resistant strains which could be substituted for susceptible snail populations in an effort to achieve biological control of the disease.

(e) Experiments with X-ray and radioactive substances on gonadal activity of molluscan intermediate hosts. As far as information is available, it would appear that little research has been conducted on the effect of radioactivity on the gonads of the snail vectors of schistosomiasis. Azevedo and Gomez^{100/} found a considerable variation in the susceptibility of various molluscs to gamma radiation. When exposed in aquaria, marked cellular alterations were noted in the penial complex as well as in the prostate and ovotestis. Later, Azevedo et al.^{101/} exposed a number of species of snails, including Australorbis glabratus, under the same relative conditions in aquaria, to P^{32} , I^{131} and Cu^{64} and noted certain histological changes in various tissues including the gonads. However, in the above experiments the exposed snails were destroyed and no observations were made on sexual activity following the irradiation. Webbe and Read^{102/} used cobalt⁶⁰ for labelling snails in a study of field populations. An initial mortality occurred in Bulinus (Ph.) nasutus productus due in part to radiation and in part to handling in the laboratory. There were no changes in growth or reproduction of marked snails. Johnson et al.^{103/} studied the uptake of Sr^{85} , Fe^{59} , Rb^{86} and Na^{22} by A. glabratus. The radioactive iron was the only compound transferred to the egg.

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Further studies along these lines would be interesting, as would observations on the effect of irradiation on reproduction and growth.

(f) Metabolic pathways and biochemical mechanisms in molluscan intermediate hosts. While the intermediate metabolism of the parasite, S. mansoni, has been studied to a considerable extent, less attention has been paid to similar phenomena in the molluscan hosts. Von Brand and his co-workers 104,105,106/ have contributed to knowledge of the physiology of certain of these snails under both aerobic and anaerobic conditions. Martin 107/ summarized the present status of the carbohydrate metabolism of the members of the Phylum Mollusca and included data concerning certain species of snails. As indicated below, limited information is available on intermediate carbohydrate metabolism but no observations have been made on protein and lipid metabolism in schistosome vectors.

In studies on the influence of some potential molluscicides on the oxygen consumption of A. glabratus, von Brand et al. 108/ suggested that one of their possible functions is the coupling of phosphorylation to oxidation. However, probably because of technical difficulties, Rees 109/ was unable to demonstrate such coupling in Helix pomatia or Weinbach 110/ in the hepatopancreas of Lymnaea stagnalis. Later, however, Weinbach 111/ was able to demonstrate oxidative phosphorylation in the albumin gland of this snail. Previously, he had noted 112/ that the molluscicidal action of pentachlorophenol was probably linked with an inhibition of oxidative phosphorylation. Somewhat later, Michejda et al. 113/ demonstrated

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a high P/O ratio in sarcosomes from the heart muscle of Helix pomatia. Another interesting observation on snail metabolism was made by Polster^{114/}, who employed P³² in demonstrating that phosphorus is the agent concerned in the transfer of calcium to the shell.

Further studies on the intermediate metabolism of the molluscan intermediate hosts would no doubt contribute basic information which might be of great practical value in snail control.

(g) The physiologic constitution of various strains of molluscan intermediate hosts in relation to their susceptibility to schistosome infection. It has been noted that differences in susceptibility to schistosome infection have been demonstrated in certain strains of A. glabratus. Relatively few studies have been conducted on the physiology of various strains of schistosome vectors but indications are that physiologic differences exist between strains of the same vector snail. Olivier et al.^{115/} found, for instance, that a Dominican strain of A. glabratus had a significantly higher polysaccharide content and anaerobic carbon dioxide output than did a Puerto Rican strain of the same snail. Newton and von Brand^{116/} conducted comparative physiologic studies on the non-susceptible strain of A. glabratus from Salvador, Bahia, Brazil and a susceptible strain of the same snail from the Lake Valencia area of Venezuela. The two snails showed no difference in organic substances, ether extract and nitrogen content. The shells of the Venezuelan strain were significantly heavier than those of the Brazilian one, and the former stores about twice as much polysaccharide as did the latter. Neither strain was capable of using

inulin or a dextran from Leuconostoc to synthesize polysaccharide. The feeding of cornstarch, or cornstarch fraction A, led to a pronounced and equal synthesis of polysaccharide in the two strains, indicating that the difference in polysaccharide levels maintained on the normal diet was not due to differences in synthesizing or storage capacity. Both strains had an identical rate of oxygen consumption, but the Brazilian strain produced significantly less anaerobic carbon dioxide than the Venezuelan snail. The Brazilian snail tolerated anaerobiosis for shorter periods than did the Venezuelan one. The difference appeared to be due to the lower polysaccharide levels maintained by the Brazilian snail on the normal diet. When the polysaccharide level was increased, there was no change in the anaerobic survival time of the Venezuelan strain. However, such time in the Brazilian strain was increased to approximately the same period as in the former snail. In addition to these differences, Newton and Haskins^{117/} found that the two strains differed in susceptibility to the molluscicide, sodium pentachlorophenate.

It appears doubtful that the above-mentioned results were due to climatic adaptation, since Olivier et al.^{115/} worked with strains coming from the same climatic zone. Rather the differences seemed to be basic in character and induced by unknown causes which became genetically fixed through geographic segregation and other factors.

It is apparent that the phenomenon considered here is worthy of further investigation and that additional experiments on the physiology of various strains of schistosome vectors may throw some

light on the fundamental mechanisms of resistance to schistosome infection. Such studies would seem to be an essential prelude for investigations at the cellular level.

(h) Differences in susceptibility to desiccation -- mechanisms of adaptability. It has been demonstrated that a number of species of schistosome vectors have the capacity under certain circumstances of resisting desiccation to a remarkable degree. Such was found by Olivier and Barbosa^{118/} to be true for A. glabratus and T. stramineus in Northeastern Brazil. Olivier^{119/} was of the opinion that there was some evidence to indicate strain differences in this regard. Kloetzel^{120/} studied the resistance of two strains of A. glabratus, one from Olinda (Brazil), a locality which dries every year, and the other from a permanent lake (Dique do Tororó, State of Bahia). The Olinda snails were able to survive well under conditions in which there was a gradual reduction in the atmospheric humidity. Under these conditions, the mortality rate was proportional to the loss of weight up to the 7⁴th day; after that the death rate increased rapidly. On the other hand, snails from Dique do Tororó showed little resistance to drying. The same investigator^{121/} found that A. nigricans (syn. A. tenagophilus) from Reprêsa Billings (São Paulo) was much less resistant to desiccation than A. glabratus from Pernambuco and of the same order as that of A. glabratus from Dique do Tororó. Megalhães Neto^{122/} carried out experiments on the physiology of desiccation and showed that in A. glabratus the oxygen consumption decreased to a very low level when the snails were subjected both to desiccation and starvation. The glycogen content of the digestive gland, stomach and ovotestis

dropped to less than 50 per cent after drying of the snails for 15 days and at 75 days reached a level of only 10 to 15 per cent. However, glycogen depletion in the foot of the snail was less pronounced as shown by Magalhães Neto and Almeida^{123/}. Later, von Brand et al.^{124/} observed the effect of starvation and desiccation on A. glabratus. Starvation is involved since the animal retracts in its shell during periods of drying and is unable to feed. Decreasing humidity led to a progressively greater rapid decline of survival time, body weight and rate of oxygen consumption. Lactic acid disappeared from the tissues during desiccation and volatile acids were diminished. The decrease in oxygen consumption was due largely to the desiccation proper.

Richards^{125/} studied the occurrence of apertural lamellae in A. glabratus and in three species of Tropicorbis. He found that lamellate A. glabratus were not uncommon. Lamellate snails showed a tendency to climb out of the water and suspend feeding and growth. Most of the A. glabratus found aestivating in nature were small, lamellate and with froth epiphragms. Such snails survived up to 4 months out of water. Richards pointed out that the tendency of certain A. glabratus to form lamellae, leave the water, produce epiphragms and aestivate may be of concern in the employment of molluscicide control.

It would appear that additional studies would be of value in comparing physiological patterns in resistant and non-resistant strains of vector snails, as well as in endeavoring to elucidate the underlying mechanisms involved in the development of the resistance complex.

(i) Effect of schistosome infection on the physiology and chemistry of Australorbis glabratus. While some trematode parasites apparently do little damage to their molluscan hosts, it has been observed by many investigators that certain parasites are responsible for considerable pathological alterations, which in many cases may lead to premature death. Cort^{126/} noted that Oncomelania nosophora infected with Schistosoma japonicum were less resistant to desiccation than uninfected snails. Gordon et al.^{127/} observed that Planorbis pfeifferi infected with S. mansoni had a higher death rate than did uninfected snails maintained under the same conditions. Barlow^{128/} found evidence to indicate that the drying of snails during the winter closure of irrigation canals in Egypt resulted in a marked decrease in the snail populations. Brumpt^{129/} noted that A. glabratus infected with S. mansoni was less hardy when subjected to dry conditions. In Northeastern Brazil the investigations of Olivier et al.^{130/} indicated that A. glabratus infected with S. mansoni die in much greater numbers than do non-infected snails when removed from the water. The greatest number of deaths occurred during the first 20 to 30 days, after which there was no marked difference between the two groups. Those infected snails which survived drying for 20 days or more lost their schistosome infection. However, evidence indicates that immature schistosome infections are retained during prolonged drying, the mature infections being the ones which are lost.

There are other effects of schistosome infection on the physiology of the snail. Brumpt^{129/} found that infected snails laid

fewer eggs. Coelho^{131/} observed that, although complete castration did not occur following infection, there was a significant reduction in the number of egg masses and in the number of eggs produced. Most of the eggs from infected snails failed to develop and the mortality of young hatched from surviving eggs was at a high level during the first 10 days. However, after 30 days progeny from infected and uninfected snails were of normal size indicating that deleterious effects of the schistosome infection are exercised on the off-spring only during a relatively short time. Najarian^{132/} noted a significant reduction in the average number of eggs laid per day by Bulinus truncatus infected with S. haematobium as compared with non-infected snails. The schistosome infection had a greater effect on the average numbers of eggs laid per clutch than on the rate of oviposition. The experiments support the view that fully developed schistosome infections reduce the reproductive capacity of the snail hosts.

Very few observations are on record concerning the basic nature of the physiological alterations in various species of snails following schistosome or other trematode infections. Von Brand and Files^{133/} studied the chemical and histological alterations of S. mansoni infection in A. glabratus. Storage of fat was not seriously impeded and oxygen consumption of the snail remained normal. However, the infected snails had a reduced polysaccharide content which appeared to result from diminished storage both in parasitized and non-parasitized organs. It was not evident whether such decreased storage was due to an impaired carbohydrate digestion and

resorption, or to a toxic action by the parasites. Food consumption by the parasite was apparently not a factor.

This seems to be a fertile field for additional research. It would be of great interest to know whether the schistosome infection materially alters the basic metabolism of the snail and, if so, by what means and in what manner.

(j) Studies on the biology and chemistry of the aquatic environment. This is a field which has been investigated rather extensively but with results which leave much to be desired. It would be reasonable to assume that the molluscan intermediate hosts of the human schistosomes would have to have an optimum range of biological and chemical requirements for their well being and for their continued reproduction and growth. One might also assume that it would be possible to define within reasonable limits the specific nature of these requirements and be able to identify the necessary biota and the chemical elements which are essential, either singly or in combination, to satisfy the needs of the snail. The investigations thus far have not succeeded in providing definitive answers to these questions. Certain physical factors exert some influence, the most important of these being the stream gradient which will be discussed later. The following is a review of some of the observations which have been made on the biology and chemistry of the environment.

Pollution. The degree of pollution undoubtedly plays a certain role in the well being of the snail. Harry and Aldrich^{134/}

stated that A. glabratus is favored by mild pollution but inhibited by heavy pollution. Alves^{135/} believed that pollution is of considerable significance. Malek^{136/} noted that in Egypt the schistosome vectors thrive in polluted areas yet excessive pollution is inimical. At the same time, instances were cited in which the snails were abundant in places where pollution was absent. De Meillon et al.^{137/} in South Africa found striking biological differences between heavily polluted and lightly polluted streams and noted the absence of schistosome vectors from heavily polluted areas. These authors pointed out differences in the diatom populations in the two types of streams, which suggested that pollution per se is not the determining factor but that the resulting chemical and biological changes are important. Certainly, such features need further investigation. Watson^{138/} reported that Bulinus truncatus in Iraq definitely prefers polluted waters but that excessive pollution creates an unfavorable habitat for the snail. Watson suggested that the favorable influence of pollution may be associated with one or more of the following factors:

1. The use of human feces as food for the snail.
2. The contribution of human feces to a soft substratum rich in decaying organic matter.
3. The possible fertilizing effect of human urine and feces on unicellular algae which constitute the essential diet of the young snails.
4. The possibility that pollution may discourage snail enemies or competing fauna.

5. The possibility that human urine or feces supply some growth factor which stimulates reproduction of the snails.

Flora of the Environment. Water plants form a desirable but not an entirely essential factor in the ecology of vector snails. Bulinids appear to be more slightly dependent than planorbids on the presence of vegetation. In Egypt, B. truncatus favors Potamogeton, Nymphaea and Pistia, while B. boissyi prefers a habitat containing Eichornia, Typha and Panicum. Watson^{138/} pointed out that B. truncatus is not especially attracted to Potamogeton in Iraq but there is some favorable relationship between this snail and willow trees. Oncomelania spp. require emergent vegetation or vegetation growing closely along the bank near the water's edge on account of their amphibious habits. Malek^{136/} noted that the microflora (periphyton) forms the main food source for the snails and named certain species collected in snail habitats in the White Nile. It was his opinion that schistosome vectors (at least in the Sudan) show no preference for any particular species of microflora. De Meillon et al.^{137/} in South Africa observed that filamentous algae mats, composed mainly of Spirogyra, were unfavorable for Physopsis africana but that Planorbis sp. increased in number with the development of the mats. Standen^{139/} thought that an abundant growth of unicellular algae is essential for the nutrition of young snails.

Fauna of the Environment. While there are certain faunistic enemies of schistosome vectors, there seems to be little evidence to

indicate that any special combinations of the fauna produce a favorable environment. Harry and Aldrich^{134/} were of the opinion that no single species seemed to affect appreciably the distribution of A. glabratus in Puerto Rico. De Meillon et al.^{137/} believed that vector snails are entirely independent of all other macrofauna. However, they did note that the presence of certain species of Ephemeroptera provided a good indication of current speed of the water and were a useful indicator of various types of snail habitats.

Chemistry of the Water. It might be reasonably anticipated that the chemistry of the aquatic environment would be the most important clue as to its suitability for snails. However, observations to date have failed to indicate that there is any definite relationship between the chemistry of the water and its attractiveness for vector snails. Alves^{135/} could draw no definite conclusions in this regard as the result of his water analyses in Southern Rhodesia. Marill^{140/} could not demonstrate any correlation between chemical constitution of the water and the presence of Bulinus in certain localities in Algeria. In no observation has it been indicated that the hydrogen ion concentration has any relation to the presence or absence of schistosome vectors. Harry et al.^{141/} determined the concentration of dissolved solids in the aquatic environments in Puerto Rico. It was evident that the higher concentrations of bicarbonate, carbonate, sulfate, chloride, magnesium and calcium ions did not exclude A. glabratus. Deschiens et al.^{142/} calculated the lethal concentration of these major ions for A. glabratus and Bulinus contortus. These limits were far above

those encountered in Puerto Rico. Harry et al.^{141/} pointed out that possibly the ratio between the weak acids and the strong acids might be a significant factor in limiting the distribution of A. glabratus. Vector snails vary in their tolerance to total salinity but a high salt content is generally lethal. However, a gradual increase in salinity, especially in coastal areas, is tolerated to a certain extent as pointed out by Malek^{136/} in the case of marshy areas along the Mediterranean Coast in Egypt and in drains leading to the coastal lakes. Watson^{138/} has discussed the distribution of B. truncatus in Iraq from the standpoint of salinity.

It appears that schistosome vectors are tolerant of a wide range of water hardness, as expressed as CaCO_3 . In waters on the low side, the shell of the snail may be relatively thin. Small quantities of magnesium are essential for snails. Sodium may be detrimental if the concentration is high compared to other cations^{138/}. The iron content of inland waters is usually below the lethal limit for snails.

De Meillon et al.^{137/} conducted chemical analysis of waters in certain endemic areas of schistosomiasis in South Africa. They concluded that there was no significant qualitative or quantitative difference in the chemical composition (excluding trace elements) of waters which harbored vectors and those which did not.

The influence of dissolved oxygen has been observed by a number of investigators. Malek^{136/} found that in some snail habitats in the Sudan dissolved oxygen averaged 4.7-7.0 p.p.m. However, where algae and aquatic weeds were abundant, supersaturation of the

habitat, due to photo-synthesis, was noted. Van Someren^{143/} considered a low oxygen tension as being a major adverse factor for fresh-water snails. He noted that Lymnaea caillaudi, which occurs in the Nile along with B. truncatus, dies of suffocation below 10 per cent saturation. Zakaria^{144/} reported the same sort of susceptibility for B. truncatus, an observation concerning which there is some doubt. As previously noted, von Brand et al.^{104/} found that A. glabratus was able to maintain a steady rate of oxygen consumption over a wide range of oxygen tension.

Harry and Aldrich^{134/} were impressed by the correlation between small amounts of dissolved solids in certain Puerto Rican waters and the absence of A. glabratus. The concentration of dissolved solids in fresh waters on the island ranged from 50 to 3000 p.p.m. Optimum snail habitats usually had 150 to 500 p.p.m. but snails were found in concentration up to 3000 p.p.m. However, only rarely were they encountered in waters with concentrations consistently lower than 150 p.p.m. The lack of dissolved solids per se may not be the responsible factor. The above-mentioned workers thought that possibly the ionic balance, or "something varying with it", might be responsible. It was thought also that the presence of copper or zinc might constitute a limiting factor in the distribution of A. glabratus.

While much of the research which has been conducted on the biology and chemistry in relation to the occurrence of schistosome vectors has provided only negative results, it cannot be overlooked that the physico-biotic-chemical composition of the aquatic habitat

may play an important role. There is no doubt that much additional investigation is needed on this problem.

(k) Further experiments on the effect of stream gradients and water velocity on vector snails especially Australorbis tenagophilus and Tropicorbis stramineus. It has long been known that the molluscan intermediate hosts of the human schistosomes favor slow moving streams, collateral pools, marshy areas and small seepage tributaries. The stream gradient, one of the main factors governing the speed of the current, therefore, has a marked influence on snail populations. A number of investigations have been the means of defining certain limits as related to snail harborage and the results of these studies are summarized here.

Since snails are not always confined to the main channel, judgement must be exercised by the investigator in evaluating the snail population in terms of water velocity. Certain streams may have an overall channel velocity unfavorable to the snails which may, however, find shelter in pools or back waters of the stream. Furthermore, in the total length of a high gradient stream there may be reaches having a low water velocity. Harry and Cumbis^{145/} in Puerto Rico selected for their measurements of stream gradients a length of 1,000 meters and considered only snails in the main channel without reference to those in the collateral pools. In the examination of more than 350 collecting stations on various streams, it was observed that populations of A. glabratus were not maintained in reaches of streams steeper than 20 meters fall per 1,000 meters of length. Water quality and other factors apparently governed

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the spotty distribution observed in reaches with suitable gradients. Scorza et al.^{146/} in Venezuela checked several factors (pH, dissolved oxygen, temperature and depth and velocity of the water) for their effect on the distribution of A. glabratus. There was no apparent connection between any of these factors and the occurrence of the snail except water velocity. These workers found that velocities of 25-30 cm. per second represented the upper limits of tolerance for several species of planorbid snails. De Meillon et al.^{137/} noted in the highveld in South Africa that schistosome vector snails were not found in waters where the current speed exceeded one foot per second (30.48 cm. per second). Watson^{147/} and Zakaria^{144/} observed that in Iraq a flow rate of 15 meters per minute (25 cm. per second) was not unfavorable for Bulinus truncatus. It was shown that breeding colonies could be established up to a maximum continuous flow rate of 20 meters per minute (33.3 cm. per second). Lanoix^{148/} has discussed water velocity as it concerns the design of irrigation canals which frequently offer very favorable habitats for schistosome vectors. He has also stressed a fact of importance to the effect that the speed of the current is not uniform throughout the water prism but varies with the location. For instance, marginal velocity is considerably less than the velocity in the middle of the stream.

The ability of the snail to maintain its position in the face of swift water movement is governed somewhat by the contour of the channel and the availability of firmly rooted water plants to which the animal can cling. However, flooding almost invariably results in changes in snail distribution since flood water washes the

snails out of their customary habitats.

The stream gradient is not only of importance from the standpoint of snail harborage but presents interesting aspects with regard to schistosome exposure from cercariae of Schistosoma mansoni was reduced when water velocities attained 2.7 miles per hour (approximately 12.07 cm. per second). The worm burden was inversely proportional to the distance the cercariae were carried down stream. Somewhat unexpected results had been obtained by Rowan and Gram^{151/}, who exposed mice to infection in water with velocities of 2.7 to 50 cm. per second. While infections developed in mice at every velocity studied, the percentage of recovery of cercariae in terms of adult worms increased with the increased velocity of the water. The observations are surprising because it might be anticipated that in rapidly moving waters the cercariae would have less opportunity for attachment to and penetration of the vertebrate host. Additional observations should be made.

Further studies are needed on the effect of water velocity on snail harborage and it would be well if these could be carried out with the collaboration of a hydraulic engineer. Previous observations have not been entirely satisfying. Information should be gathered also on the distribution of A. tenagophilus and T. stramineus in relation to stream gradients.

(1) Experiments on chemical sterilization of molluscan intermediate hosts. Insofar as is known this is a field which remains unexplored but which should be investigated. It does not seem to be beyond the bounds of probability that something of promise

might develop from such research. The discovery of a chemical which would interfere with reproduction in the snail would represent a new approach to the problem of control. In this same connection, the possibility of developing "antifeeding compounds" should be explored.

(m) Development of chemical attractants for trapping vector snails. Sex attractants have been developed for certain insects and in at least one case have been found to be effective in control of the species. Because pulmonate vector snails are hermaphroditic, sex attractants would probably be of no practical value. However, little or no research has been conducted on chemical attractants for snails. An effective attractant might be of considerable value as a control device under certain circumstances, especially among the operculate vectors.

2. Research on Control of Molluscan Intermediate Hosts.

The present status of available control procedures for schistosomiasis is summarized in Section V with an evaluation of these methods in Section VI. The fact that relatively little progress has been achieved in curbing the disease is in itself an indication of the need for additional research to develop more effective procedures. Some of the problems which require additional investigation are enumerated below.

(a) Development of more efficient and cheaper molluscicides with special attention to chemicals which are not toxic to other aquatic fauna. The chemicals currently available for snail destruc-

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tion leave much to be desired. Paulini^{152/} reviewed the status of molluscicide control up to 1958 and Hoffman^{153/} the molluscicidal activity in relation to chemical structure. Since then a promising new compound, Bayer 73 (Bayluscid), has been introduced^{84,85/} and some others listed in Section V no doubt should be investigated further. More recently, Gretillat^{155/} field tested dimethyl-dithiocarbamate of zinc which had been shown by Nolan and Bond^{156/} to possess molluscicidal properties in laboratory tests. Investigations of other chemicals (ICI 24223, Organotins, Copper protoxide, etc.) are in progress.

The three most effective compounds presently available in order of preference are Bayer 73 (Bayluscid), sodium pentachlorophenate (NaPCP) and copper sulphate (CuSO_4). However, each of these has certain deficiencies and the relative effectiveness of each is reduced under certain circumstances. It was early noted by Dobrovolny and Haskins^{157/} that sunlight exerted a deleterious effect on NaPCP and Hiatt et al.,^{158/} showed that the velocity constant of activity loss is directly proportional to light intensity. There is, however, less loss of activity in waters high in suspended solids. It was early observed that the molluscicidal activity of Bayer 73 was also reduced by exposure to sunlight. GÖnnert and Strufe^{159/} showed that disintegration of the compound was mainly due to ultraviolet radiation as is the case with NaPCP. These investigators reported also that the amount of calcium and magnesium ions had little influence on the photochemical inactivation of the compound. High concentrations of silicic acid reduced the photo-

stability, whereas low concentrations increased it. The pH had little influence on the photochemical stability of either chemical. The influence of water temperature was the same for both compounds. Hoffman and Zakhary^{160/} had shown that relatively high temperatures increase the efficacy of CuSO_4 .

The adsorption on mud and colloidal particles may reduce considerably the efficiency of molluscicides. This is particularly true of CuSO_4 but applies also to NaPCP and Bayer 73 ^{157,159/}. When combined with mud, NaPCP was found to have a longer residual effect than CuSO_4 ^{161/}.

High alkalinity and high water hardness reduce the efficacy of CuSO_4 while NaPCP is also adversely affected by high alkalinity ^{162/}. High water hardness lowers the efficacy of Bayer 73 ^{163/}.

The question of toxicity is an important one both for human contacts and aquatic fauna. With proper precautions any of the currently available molluscicides can be employed safely and without toxicity to humans or domestic animals. However, all are toxic for much of the aquatic fauna. Shiff and Garnett^{164/} noted that the invertebrate fauna returned to normal much more rapidly after NaPCP application than it did after CuSO_4 . Nearly all of the currently employed compounds are toxic to fish, although CuSO_4 is less so than others.

In certain situations great advantage accrues when a molluscicide also exerts pronounced herbicidal effects. In this connection, Aqualin would appear to be particularly advantageous. At the same time, any chemical employed for snail control must be innocuous to field crops.

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Molluscicide screening. The need for more efficient molluscicides will entail an extensive program for the laboratory screening of new compounds and the field testing of those showing promise. The initial routine screening of chemicals is a fairly costly procedure and not one in which many research laboratories can afford a material investment of resources. Routine screening by commercial laboratories should be encouraged, although the profit potential from the discovery of a better molluscicide cannot be estimated at the present time. In order to avoid duplication of effort, screening results should be reported to WHO. Procedures for molluscicide testing were laid down by the WHO Expert Committee on Bilharziasis (Molluscicides) at its 1960 meeting^{165/}. Procedures for calculating and reporting data should follow the recommendations of Hairston (WHO/Mol/Inf/5, 28 June 1962). The possible advantage in using snail eggs instead of adult snails for laboratory screening have been pointed out by Olivier et al.^{166/}. Initial field trials should conform to procedures indicated in^{165/}. It is important to recognize that infected snails are much more susceptible to the toxic action of molluscicides than are non-infected snails^{167/}.

Summary. It will be seen that many factors are to be considered in the development of molluscicides. An ideal molluscicide would possess the following attributes:

Low cost

Easily transportable

Stable when stored under tropical conditions

Non-toxic to man and domestic animals

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Low toxicity or total lack of toxicity for aquatic fauna.

Possess herbicidal properties

Inocuous for field crops

Easily applied with a minimum of labor

Possess effective spreading action in flowing water

Capable of exerting favorable time/concentration ratios in flowing water.

Retain long residual activity

Incapable of provoking resistance

Unaffected by pH or chemical composition of the water

Chemically photostable under all conditions

Incapable of combining with organic material and/or mud

Effective for the destruction of snail eggs and schistosome cercariae in the same concentration as employed against snails.

Effective against all ages and sizes of molluscan intermediate hosts in low concentrations.

(b) Develop new formulations of known effective molluscicides with synergists, resins, inert carriers, surfactants, spreading or emulsifying agents or other physical or chemical mechanisms to provide for more effective distribution and to promote residual activity.

Compared to the enormous amount of research which has gone into the formulation of pesticides and insecticides, little has been done in this regard with molluscicides. Freytag et al.^{168/} devised a rapid method for screening surfactants adapted to molluscicides and evalua-

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ted the characteristics of 11 emulsions with 6 different molluscicidal compounds. Hunter et al.^{169/} had previously tested a number of dispersants and emulsifying agents. Ferguson^{170/} discussed the possible advantage of employing oil mists, emulsions and aerosols in dispensing molluscicides. Barbosa et al.^{171/} tried a combination of saponin from Sapindus saponaria with NaPCP and noted some synergistic action. Pereira and Mendonça^{172/} employed a mixture of resin soap with NaPCP without enhancing the molluscicidal activity.

With such limited observations, the need for additional studies is apparent. There is reason to believe that more effective formulations would not only increase the efficacy of molluscicides but might materially enhance residual activity. Perhaps the inhibiting effects of water hardness and photoinstability could also be obviated.

(c) Studies on the efficacy of continuous or intermittent application of low concentrations of molluscicides in various types of aquatic environments. The employment of low concentrations of molluscicides in snail control was first tried in the Gezira area of the Sudan. CuSO_4 at the approximate rate of 0.125 ppm. was continuously applied to irrigation canals in a pilot project between 1950 and 1955^{173,174/}. In addition, mechanical barriers, consisting of wire mesh screens, were placed at points on the main canals to trap snails and snail eggs on floating vegetation. Insofar as data are available, the results of the program in the Gezira have been good.

Freeman et al.^{175/} laboratory tested both CuSO_4 and NaPCP against Bulinus truncatus and Biomphalaria boissyi. Exposure periods varied between 5 and 7 days with concentrations of each chemical between 0.1 and 1.0 ppm. It was estimated that either chemical would have to be applied at a concentration of 0.4 ppm. to be effective against these snails.

In a developing irrigation scheme in Kenya, Teesdale et al.^{176/} employed CuSO_4 continuously in concentrations of 0.125 and 0.25 ppm. The chemical was introduced as soon as water started flowing into the canals. No pre-sulphation with higher concentrations of the chemical was used and mechanical barriers were not employed. Concentrations of 0.125 ppm. provided indeterminate results but 0.25 ppm. created a barrier which was lethal to snails passing through it.

Chemical barriers of CuSO_4 plus mechanical devices have been employed in Egypt in order to prevent infestation of newly created irrigation systems in Tahrir Province^{177/}. Because of logistic difficulties, a fair appraisal could not be made, although the method probably restricted to a certain extent entrance of snail hosts into the area.

Malek^{178/} evaluated chemical and mechanical barriers in pump irrigation schemes near Khartoum, Sudan. The experiments were not successful in demonstrating efficacy of these methods. Snails continued to survive and in some cases reproduced in treated canals. However, the studies did help to emphasize the complexity of the problem of evaluation and pointed to the need of additional observations.

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Insofar as is known, the method in question has been applied only to irrigation systems and has not been utilized for snail control in natural water courses. There are not many areas in the Western Hemisphere in which irrigation is practiced on a scale comparable to certain projects in Africa and in some other areas. However, plans for the agricultural rehabilitation of Northeastern Brazil, if fulfilled, will create extensive irrigation, which in nearly all endemic areas of schistosomiasis has led to an increase in the disease. The method should be tried under experimental conditions in certain natural water courses which lend themselves to this type of snail control.

Some of the factors which should be investigated in connection with the continuous application of molluscicides are the following:

1. The minimum effective dosage
2. Length of carriage of the molluscicide from point of application.
3. Residual effect, if any, through combination with mud or aquatic flora.
4. Ovicidal effect
5. Effect on snail reproduction
6. Relation of efficacy to water velocity and chemical composition of the water.
7. Photostability of the molluscicide
8. Relation of efficacy to amount of aquatic vegetation
9. Effect of water fluctuation

10. Relation of efficacy to presence or absence of mechanical barriers.
11. Value of interim application versus continuous application.
12. Relative efficacy of various methods of molluscicide application.
13. An evaluation of the necessity for application of full strength molluscicidal treatment prior to the employment of low concentrations for extensive periods.

(d) Biochemical and physiological studies to determine the mode of action of molluscicides. In spite of the fact that chemicals have been utilized in snail control for several decades, there is a definite lack of knowledge concerning the manner in which they act on the snail.

Hoffman and Kirdani (cited by Kirdani and Evans) ^{179/} conceived that the copper ion might act in the snail through the inactivation of vitally important sulfhydryl enzymes and that perhaps other effective molluscicides might have a similar mode of action. In their tests, copper and mercury compounds caused the disappearance of sulfhydryl groups in mixtures with cysteine hydrochloride, glutathione and BAL. However, other powerful molluscicides had no effect on SH compounds.

Kirdani and Evans ^{179/} studied the effect of CuSO_4 , 2-cyclohexyl-4, 6-dinitrophenol (DCHP) and NaPCP on succinoxidase activity of isolated mitochondria of snails. CuSO_4 inhibited this enzyme

at levels consistent with observations of other workers, but only at a concentration which greatly exceeds the lethal concentration for the entire animal. DCHP had a similar effect but at the same level, although it is a more powerful molluscicide. NaPCP produced less enzymatic inhibition than did CuSO_4 .

Weinbach and Nolan ^{180/} noted that aerobic exposure of living snails to low concentrations of pentachlorophenol (PCP) resulted in the accumulation of acetate, lactate, pyruvate and inorganic phosphate in their tissues. Low concentrations of the chemical stimulated the respiration but higher concentrations were inhibitory. The findings suggested that the molluscicidal property of PCP is due, at least partially, to its ability to uncouple oxidative phosphorylation, a phenomenon which was later demonstrated by Weinbach ^{111/}

Gönnert and Schraufstätter ^{154/} reported that Bayer 73 had the same effect on snail respiration as PCP but that the action of the former was much more pronounced. Gönnert ^{83/} has stated that the blocking of the respiration is reversible with NaPCP but is irreversible with Bayer 73.

Barbosa ^{181/} has reported on the long residual effect of copper carbonate and has suggested that it may act through its soluble fraction or as a stomach poison.

It is evident that much more needs to be learned concerning the mechanisms responsible for the deleterious effects of molluscicides on intermediate hosts of the human schistosomes and other trematode parasites. An elucidation of some of the factors involved may aid in the search for more effective compounds.

(e) Development of more reliable methods for the automatic dispensing of molluscicides. Snail habitats vary so greatly that no single method of applying molluscicides can be employed in all types of aquatic environments. The labor involved in certain methods represents an important cost factor that might be reduced to some extent if better semi-automatic or automatic devices could be developed for dispensing chemicals in flowing waters.

It is not anticipated that mechanical distribution is applicable to all types of streams. Small seepage areas from which rivulets arise provide harborage for certain snail hosts and need to be treated by other means. In general, small water courses, limited in breadth and velocity, are amenable to treatment by more conventional methods.

The type of stream undoubtedly affects to a considerable extent the efficiency of any automatic dispensing device. For instance, Dobrovolny and Barbosa ^{182/} found that the apparatus devised by Haskins and Dobrovolny ^{183/} provided variable results. When NaPCP was applied in the form of briquettes, the concentrations downstream were much higher than calculated because of the rapid dissolution of the chemical. On the other hand, the drip method provided more sustained concentrations over a given period of time. Apparently, the rate of concentration decrease depended more on the velocity of the stream than on the amount of chemical employed.

A single piece of equipment can only treat a limited length of water course, the efficacy being governed by the distance to

which a lethal concentration is carried downstream. Consequently, automatic dispensing of molluscicides requires the same attention to chemical and physical conditions of the aquatic environment as is demanded by other means of application. A considerable number of dispensers might be required in some situations, thus offsetting to some extent the savings accruing from a smaller labor force.

Various types of equipment have been employed in an effort to eliminate manpower distribution. The relatively crude method of dripping a solution or suspension of the chemical from a container has been used with variable results.

Jove ^{184/} described a constant orifice box which has been utilized in Venezuela. This is a two-compartment container provided with copper floats and an inlet valve which governs inflow of the solution from the storage cask. The device is used to dispense CuSO_4 and tartaric acid, as well as NaPCP and copper pentachlorophenate (CuPCP). As described, the apparatus had certain disadvantages which it was anticipated could be corrected.

An automatic dispensing apparatus was developed by Klock ^{185/} and has been used extensively in Puerto Rico. It consists of a proportional head siphon-activated unit operating through a specially constructed weir. The weir will accommodate stream flows up to 1.5 cubic feet per second. As the stream level changes, such changes are communicated through a float to a siphon, which releases the chemical in solution continuously. The dosage can be set for any given period.

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Gram 186/ has developed a device which is considered an improvement over the Klock apparatus. It can accommodate medium sized streams with flows up to 3.0 cubic feet per second; it is simple and inexpensive to construct and has only one moving part.

While improvements have been effected for the automatic application of molluscicides, undoubtedly too little attention has been paid to this important phase of snail control. Development of multi-purpose equipment, applicable to all types of aquatic environments involving flowing water would help simplify the problem of chemical utilization and probably lower costs.

(f) Development of effective tests for detection of low dilutions of molluscicides. In the continuous application of molluscicides, it has not been possible to measure concentrations of the chemical and to estimate the extent of carriage or of residual activity. Certain methods for determining concentrations are given in (36). In addition, a number of other techniques have been devised.

Clark and Goodliffe 187/ developed a copper colordensitometer for field use which could measure concentrations as low as 3 ppm. Magalhães et al. 188/ described a photo-electric colorimetric test for copper which, however, would not detect low concentrations. Paulini 189/ developed a "Pridin-thiocyanate" test for field use which could measure copper in dilutions as low as 2 ppm. The tests described in (36) for CuSO_4 , NaPCP and Bayer 73 would not be applicable for detecting the small amounts of these chemicals which would be employed as chemical barriers.

Biological methods have been utilized in estimating concentrations effective for snail destruction. Klock ^{190/} described a technique for estimating NaPCP dosage by mortality rates in the common guppy, Lebistes reticulatus. Malek ^{178/} planted snails in plastic cages downstream in studying the efficacy of chemical barriers in pump schemes in the Sudan. Crossland ^{191/} employed a mud-sampling method for determining molluscicide efficacy. A series of mud samples were collected at 18 meter intervals and the results expressed as the number of snails per sample or as the arithmetic mean number per square meter of habitat.

All of these methods appear to lack the necessary delicacy for measuring very low molluscicide levels. Research is needed on this problem.

(g) Research on biological methods for controlling snail vectors. The literature contains numerous references to various parasites and predators which attack mollusks and which have been suggested as a means of biological control. Unfortunately, most of these reports are based solely on casual observation and are not substantiated by experimental investigation. Michelson ^{192/} has presented a thorough review of the subject literature. Only some of the more significant work will be cited here.

Many of the following studies have been conducted in the laboratory under conditions which were extremely favorable for the parasite or predator. There is no assurance that similar results could be obtained in the field. A natural environment favorable for the snail vector may not be equally advantageous for the attacking

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organism. Furthermore, the face of nature is constantly changing physically, chemically and biotically. Effective biological control would demand that the parasite or predator possess the capability of meeting and responding favorably to all of these varying influences, some of which might well be exceedingly deleterious to it. In microbiological attack, consideration must be given to the possibility that the snail may develop resistance to a degree that the offending organism would no longer be harmful.

Another aspect which deserves more than casual attention concerns the potential dangers of introducing a parasite or predator foreign to the area of contemplated biological control. There is always a degree of risk associated with such ventures. The control agent may thrive to a degree far beyond the comprehension of the introducer and may wreck collateral damage exceeding the benefits anticipated from control.

The reports in the literature cover a wide range of plant and animal enemies ranging from algae and bacteria to reptiles, fish, birds and mammals. Practically no mention has been made of viruses which might attack snails and this would seem to be a fertile field for investigation.

Dias 193,194/ isolated several species of bacteria from snails and found that one, Bacillus pinottii, had some lethal action. In field trials the mortality in certain foci was as high as 100 per cent. Maximum effect was not noted until 2-3 weeks after introduction of the bacillus. In most cases, reinfestation occurred after a lapse of time. Texera and Scorza 195/ discovered a focus

in the State of Aragua, Venezuela, in which Australorbis glabratus showed symptoms of epidemic hemorrhage described by Dias. Mass cultures of spore-forming bacteria obtained from these snails passed serially into other snails caused a mortality ranging from 20 per cent in the first passage to a peak of 80 per cent in the fifth, thereafter declining to 35 per cent in the ninth passage. Thus while initial results in both investigations seemed promising, this method of control apparently has definite limitations. Michelson ^{196/} isolated a pathogenic acid fast bacillus from Helisoma anceps. However, the disease produced by this organism was of a chronic nature and its value in biological control would not be promising.

Various reports indicate that certain annelids attack snails. Chernin et al. ^{197/} found that under laboratory conditions the leech, Helobdella fusca, effectively controlled growth of A. glabratus. All sizes of snails were killed but the young were especially susceptible.

Possibly the most promising agent for biological control is the snail Marisa cornuarietis, which was apparently introduced accidentally into Puerto Rico. Observations seemed to indicate that A. glabratus had disappeared from parts of streams where Marisa had flourished. Oliver-González et al. ^{198/} found that A. glabratus also disappeared from areas in which Marisa was artificially planted. Chernin et al. ^{199/} studied the activity of Marisa in the laboratory and observed that it was a voracious herbivore and capable of destroying young snails probably by ingesting them. Michelson and Augustine ^{200/} reported that Marisa showed similar activity in the

case of Biomphalaria pfeifferi in the laboratory. Ferguson et al. ^{201/} reported that Marisa purposely introduced into 8 farm ponds eliminated A. glabratus in an average time of 8 months. Widespread planting of Marisa in one endemic watershed practically eliminated A. glabratus in less than two years. Radke et al. ^{86/} have also reported good results with Marisa.

A considerable number of arthropods have been reported as attacking snails. Berg ^{202/} worked with a number of Sciomyzidae larvae and reported that larvae in 10 genera apparently feed on snails. The larvae apparently live within the snail shell and feed on the tissues for several days before death of the snail results. Simmonds ^{203/} reported that Sciomyzid predators, Sepedon macropus and Dictya sp., have been imported into Hawaii for the control of the molluscan intermediate hosts of Fasciola gigantica. Pringle ^{204/} observed that the larvae of 4 species of chironomid midges invade and destroy the contents of the egg masses of Bulinus (Physopsis) globosus in Amani Lake, Tanganyika. However, there seemed to be no evidence that the snail population was materially inhibited by these predators. Deschiens ^{205/} noted that Cypridopsis hartwigi, a small ostracod, attacks Bulinus and Australorbis; death of the snails is due to inanition caused by contusions and lacerations. Deschiens and Lamy ^{206/} reported that certain crayfish of the genera Astacus and Cambarus are predatory on planorbid schistosome vectors. Cambarus affinus, a tropical America species, crushes snails rapidly, especially if starved for 24 to 48 hours. Lagrange and Fain ^{207/} found that the crab, Potamon didieri, will devour snails.

A number of reports have dealt with fish predators of snails. Lagrange ^{208/} experimented in an aquaria with a number of species including Umbra pygmaea, Cichlasoma biocellatum, Tetraodon schoutedeni and Pelmatochromis kribensis. All of these species fed on young snails but C. biocellatum and T. schoutedeni were observed to devour large specimens. Oliver-González ^{209/} observed that in certain areas in Puerto Rico where A. glabratus could no longer be found, there was an abundance of guppies of the species Labistes reticulatus. Brought into the laboratory, the guppies fed actively on egg masses of snails.

De Bondt ^{210/} experimented with fish, Haplochromis mellandi, in the former Belgian Congo. The introduction of the fish into ponds, rice fields and low gradient canals effectively eliminated snails, the species of which were not stated.

In view of the success attained in the biological control of certain other pests, this would seem to be a fertile field for further study. However, other than the local success achieved in Puerto Rico with M. cornuarietis, there is no convincing evidence that biological control of snails has actually produced results. Additional research is no doubt warranted but at present there are no well defined leads as to the direction such research should take.

(h) Research on engineering measures and agricultural practices applicable to the reduction or elimination of snail vectors. Inadequate attention has been paid to ecological control of schistosome intermediate hosts. Such control concerns a number of factors which have to do with the immediate environment of the snails. The

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objectives of ecological control are aimed initially at changing the environment in a manner which will render it no longer tenable. Among the methods available are drainage, earth filling, straightening water courses, flooding, ponding and general land reclamation. In irrigated areas, proper water management may aid in snail control. In some endemic areas, it may be possible to effect changes in land utilization which would have a material bearing on snail ecology. The problem is essentially a local one and the methods to be applied can only be selected after careful ecological and engineering surveys.

Ecological control has received little attention in the Americas. The only sustained research on such control has been conducted in the Philippines where Oncomelania quadrasi, an amphibious species, is the intermediate host of Schistosoma japonicum. Similar measures against purely aquatic species may not be equally applicable or effective.

The results of the Philippine studies carried out in the Palo area on the Island of Leyte have been reviewed by Pesigan and Hairston ^{211/}. They indicated that ecological measures have reduced the vector population in the area by 95 percent in two years. The human prevalence of schistosomiasis showed a significant concomitant decrease. Hairston and Santos ^{212/} discussed the experiments in greater detail. Not all of the selected areas lent themselves to ecological control but in general the results were most promising. The methods employed proved to be very expensive but the latter authors were of the opinion that the dividends from land reclama-

tion and increased agricultural production offset to a considerable extent the cost of the control procedures. Ecological control has the advantage of being permanent or semi-permanent depending on the nature of the environment and the methods utilized.

The question of water management in irrigated areas presents many intricate problems, some of which have been reviewed by McMullen et al. 213/.

The possible advantages of ecological control in endemic areas in the Americas cannot be predicted. However, it does seem that some attention should be paid to this method. There are undoubtedly localized areas which would lend themselves to an experimental approach and information of considerable value might be derived from such studies.

(i) Investigation of the chemical and physical constitution of aquatic habitats in relation to the efficacy of molluscicides.

A review of the limited amount of research which has been conducted on the favorable and unfavorable features of the aquatic environment of molluscan intermediate hosts has been presented in Section 1 (j). Some of the physical and chemical factors influencing the efficacy of the more widely employed molluscicides are mentioned in Section 2 (a). Studies of this sort, however, have been initiated largely on a pro re nata basis. In other words when a molluscicide fails to work, some effort has been expended in certain instances to determine the reasons for such failure. Most of the studies have been limited in nature. Since considerable dependence must be

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placed on the employment of molluscicides in present control campaigns, it would seem that additional effort should be expended on learning more about the factors in the aquatic environment which may have some influence on molluscicidal efficacy. The need is especially applicable to those new chemicals which are still in the experimental stage and which may prove to be valuable additions to our armamentarium.

There are probably many factors involved in molluscicidal efficacy. These factors would no doubt vary from place to place and from chemical to chemical. Regardless of this, it would be advantageous to have knowledge of some basic patterns which would serve as a fundamental guide for selecting a molluscicide for any given area after the necessary preliminary surveys have been made. The need for such information will probably grow as control projects are launched in new areas and as the general attack on the disease is intensified.

Research along these lines could well be tied in with that proposed in Section 1 (j).

(j) Studies on the development of resistance to molluscicides.

The development of resistance of certain arthropods to some chlorinated hydrocarbon insecticides has raised the suspicion that snails may acquire a similar resistance to chemicals designed for their destruction. Although CuSO_4 has been employed for many years for snail control in some endemic areas, insofar as is known there have been no recorded data which would indicate that this chemical has induced resistance.

While NaPCP has come into use as a molluscicide more recently, there are several observations on its effect in this regard. Okabe et al.^{214/} reported that Oncomelania nosophora collected from areas in Saga and Fukuoka Prefectures in Japan, where NaPCP had been applied, were highly resistant. On the contrary, snails from Okayama Prefecture, where the chemical had never been used, were susceptible. Ota et al. (cited by Komiya et al.,^{215/}) exposed snails to NaPCP in successive concentrations of 1:100,000, 1:90,000, 1:20,000 and 1:10,000 for 1-6 hours at intervals of one week. O. nosophora so exposed developed resistance to the chemical. Gancarz^{216/} used substantially the same methods in exposing O. hupensis to NaPCP. The susceptibility of the snails to dosages of LD₃₀, LD₅₀, LD₇₀ and LD₉₀ was only slightly lowered. Komiya et al.^{215/} concluded that resistance had not developed in O. nosophora in two areas which had been treated with NaPCP twice a year for 4 years. Snails in areas treated for 7 years showed a small difference in susceptibility. In laboratory experiments, no resistance resulted from higher selection pressures. These workers failed to detect any strain of O. nosophora which exhibited a high resistance to NaPCP. Walton et al.^{217/} could not demonstrate resistance in O. nosophora from areas in which NaPCP had been applied for 4 and 7 years, respectively. However resistance of a marked degree to dinitro-o-cyclohexylphenol was encountered in snails from areas which had been treated with DN-1 for 6 years. Komiya et al.^{218/} have cited the work of Tsuda who found that susceptibility to molluscicides varies with the season of the year, a point to be kept in mind in any future investigations.

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Newton ^{219/} used two strains of A. glabratus, one from Brazil and the other from Venezuela, in an effort to develop lines resistant to NaPCP. After preliminary trials, two lines were selected for the tests which were carried through 10 generations. The dose-mortality curves of the selected lines were compared with those of the original colonies after consecutive exposures of 0.25 ppm. each. The selected Brazilian line showed a mortality of 20 per cent at 1 ppm., whereas 90 per cent of the original stock were destroyed at this concentration. The selected Venezuelan line required a concentration of 2.5 ppm. for 90 percent mortality versus 1.5 ppm. for the original colony. While some resistance was thus exhibited, it is doubtful that it was of a magnitude under the conditions in question to retard seriously the activity of the molluscicide with the dosages ordinarily employed.

The evidence at present indicates that CuSO_4 and NaPCP, the most widely employed molluscicides to date, have thus far not provoked significant resistance in any schistosome vector under observation. However, continued surveillance should be maintained, since longer periods of exposure may provoke greater alterations. Long term laboratory studies are needed on new compounds to determine their influence in this regard. In the meantime, field workers in areas in which these compounds are being employed should be on watch for any signs of resistance.

3. Research on the Parasite

(a) Development of in vitro cultures of S. mansoni to determine biochemical, physiological and nutritional patterns especially as related to growth and egg production. It has never been possible to maintain the human schistosomes in artificial media for any significant length of time. Senft and Senft ^{220/} employed a chemically defined medium and were able to keep adult worms alive for periods up to 45 days. Clegg ^{221/} was able to raise S. mansoni in vitro from an early larval stage to more mature forms. The males contained spermatozoa but the females failed to produce eggs. The rate of growth was slower than normal. More recently, Clegg ^{222/} devised a simple continuous flow apparatus which it is hoped will solve the problem of metabolite removal and simulate the conditions under which the trematode grows in the portal blood vessels of the host.

The entire life cycle of certain nematodes has been accomplished in vitro and Berntzen ^{223/} has recently succeeded in growing the tapeworm, Hymenolepis nana in vitro from the cysticeroid stage in beetles to adults containing infective eggs. With these advances, it would seem probably that early success may be attained in the artificial cultivation of the human schistosomes. Such an accomplishment would enable precise studies to be made on the physiology and nutritional requirements of the parasites. Such information would no doubt prove of great value in developing more effective drugs, aid in elucidating immunological problems and

contribute to a better understanding of the pathological effects of the parasite on the host.

(b) Determination of the relative importance of various lower animals in the epidemiology of schistosomiasis. Numerous species of lower vertebrate animals have been found to be susceptible to infection with S. japonicum and S. mansoni. On the other hand, only a few such animals are capable of being infected with S. haematobium.

Wright ^{224/} reported on natural infections with S. japonicum in certain animals in Japan. Cattle, dogs and rodents were most frequently infected. Pesigan et al. ^{74/} studied the relative importance of various lower animal hosts in the Philippines and concluded that the cow and dog showed the highest indices of transmission. Schwetz ^{225/} examined rodents from four endemic areas of S. mansoni in the former Belgian Congo and concluded that natural infections in such animals were very rare. (Schwetz had designated the rodent schistosome as S. mansoni var. rodentorum). Kuntz ^{226/} discovered a natural infection of S. mansoni in an Egyptian gerbil, Gerbillus pyramidum pyramidum, after having failed to find such infections in approximately 200 small mammals secured in the vicinity of villages with a high incidence of schistosomiasis. Kuntz and Malakatis ^{227/} attempted to experimentally infect 9 species of wild rodents, 3 carnivores and an insectivore from lower Egypt with S. mansoni. As a group the rodents were most susceptible to infection and the carnivores the least. Arvicanthis niloticus was especially susceptible.

Martins ^{228/} reviewed data up to 1958 on the non-human vertebrate hosts of the human schistosomes and concluded that the

problem of such reservoirs was much more important in the Americas than in Africa. However, Miller ^{229/} found natural infections of S. mansoni in the baboon, Papio doguera, as did Nelson ^{230/}. This animal appears to be a good natural host and may contribute to the transmission pattern in certain localities.

Table 1 presents information on recorded findings of natural infections of lower animal hosts with S. mansoni. It will be seen that the number of reservoir hosts in Brazil is imposing. In addition, experimental infections with S. mansoni have been established in other animals in Brazil. In many of the infections the percentage of animals infected in nature was fairly high.

It is evident that the situation in Brazil needs further study. Search should be made for additional reservoir hosts, including domestic animals. It would be pertinent also to determine the role of lower vertebrate animals in transmission of the disease elsewhere in the Americas.

In arriving at such a determination, evaluation should be made of the ability of any particular animal to contribute materially to the transmission pattern. There are marked differences in the response of lower animals to S. mansoni infection. For instance, von Lichtenberg et al. ^{231/} studied the tissue reaction to infection in 14 species of wild mammals exposed to S. mansoni by Bruce et al. ^{232/}. In some, eggs failed to reach the intestinal lumen, in others development was arrested before adulthood was attained, and in certain ones the cercariae were trapped in the corium and subcutaneous tissues. Kuntz ^{233/} studied the egg producing or egg

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passing potentials of a series of lower vertebrates and 2 primates infected with S. haematobium. Viable eggs were not passed by albino or wild rats (R. rattus), or by hedgehogs (Hemiechinus). In hosts passing eggs the counts were not great but data did suggest host-parasite relationships which might permit continuance of the parasite cycle. Egg passage was erratic, beginning with a few eggs, then building up to a peak, followed by a diminishing number. There was no close correlation between the sites of egg deposition along the intestinal tract and the numbers of eggs produced. The data revealed the possibility of lower vertebrates serving as reservoirs under favorable circumstances.

It would be helpful if a relative transmission index could be established for lower vertebrate hosts, as was done for S. japonicum by Pesigan et al. ^{74/}. After such an evaluation, field experiments might be carried out to throw additional light on the problem before intensive control campaigns are attempted.

In connection with the reservoir host problem, it is worthy of note that Luttermoser ^{234/} showed that rodents can become infected with S. mansoni after ingesting infected snails. Fifty-five per cent of 45 rodents of six species became infected after eating specimens of A. glabratus and Physopsis globosus.

TABLE I

Record of natural infection of lower vertebrate animals
with Schistosoma mansoni.

Order	Species	Country	Author	Date
Primates	<u>Cercopithecus aethiops sabaesus</u>	St. Kitts	Cameron	1928
	<u>Papio doguera</u>	East Africa	Miller	1960
			Nelson	1960
Rodentia	<u>Gerbillus pyramidum pyramidum</u>	Egypt	Kuntz	1955
	<u>Mastomys coucha</u> ^x	Belgian Congo	Schwetz	1954
	<u>Pelomys fallax</u> ^x	" "	"	1954
	<u>Oenomys hypoxanthus</u> ^x	" "	"	1954
	<u>Dasmys bentleyae</u> ^x	" "	"	1954
	<u>Lophuromys aquila</u> ^x	" "	"	1954
	<u>Rattus rattus</u>	" "	"	1955
	<u>Mastomys sp.</u>	South Africa	Pitchford	1959
	<u>Otomys sp.</u>	" "	"	1959
	<u>Dasymys helukus</u>	Kenya	Nelson	1960
	<u>Nectomys squamipes</u>	Brazil	Amorim, Rosa & Lucena	1954
	<u>Holochilus sciureus</u>	"	" " "	1954
	<u>Oxymycterus angularis</u>	"	" " "	1954
	<u>Zygodontomys pixuna</u>	"	" " "	1954

x Infected with Schistosoma mansoni var. rodentorum.

TABLE I (Continued)

Order	Species	Country	Author	Date
	<u>Oryzomys subflavus</u>	Brazil	Amorim, Rosa & Lucena	1954
	<u>Rattus rattus frigidus</u>	"	Barbosa, Dobbin & Coelho	1953
	<u>Oryzomys mato Grossoe</u>	"	Martins, Martins & Brito	1955
Rodentia	<u>Nectomys squamipes aquaticus</u>	"	" " " "	1955
	<u>Rattus norvegicus norvegicus</u>	"	" " " "	1955
	<u>Cavia aperea aperea</u>	"	" " " "	1955
	<u>Zygodontomys lasiurus</u>	"	" " " "	1955
	<u>Leppus (sic) cuniculus</u>	Venezuela	von Schilling & Henriquez	1957
Insectivora	<u>Crocidura luna</u>	Belgian Congo	Stijns	1952
Marsupialia	<u>Didelphis aurita</u>	Brazil	Travassos	1953
	<u>Didelphis paraguayensis</u> <u>paraguayensis</u>	Brazil	Martins, Martins & Brito	1955

4. Research Relating to the Human Host.

The human host is one of the most perplexing of the many faceted problems associated with schistosomiasis. Unknowingly or unwittingly he exposes himself to infection. The habits and customs which contribute to this exposure are usually firmly fixed, if not immutable; at least they are not readily amenable to swift and permanent correction. Once infected, the parasite finds in the body of the host a citadel which for the most part is impregnable and unassailable. Man's natural defenses can aid him but in many cases these defenses are inadequate to combat the parasite and rescue him from its acute and chronic effects. Chemotherapy may help in combating the disease but such is of little value once material damage has been inflicted. For these reasons, many problems of human host-parasite relationships need to be solved. Some of these problems are discussed below:

(a) Development of more effective and safer drugs without appreciable side effects for treatment of schistosomiasis. The chemotherapy of schistosomiasis has been singularly marked by lack of any substantial progress since Christopherson ^{235/} carried out the first sustained trials with tartar emetic in 1918. Other trivalent antimonials (Fuadin, Anthiomaline etc.) have been employed also but all such antimonials have certain undesirable side effects. These compounds have been used by different clinicians in varied dose regimens. Reports of efficacy vary markedly, although S. haematobium seems to be more susceptible than the other species.

Miracil D. (lucanthone) (1-diethylaminoethylamino-4-methylthioxanthone hydrochloride), which is given orally, has provided good results in the hands of some workers but has failed to offer the desired efficacy. The disagreeable side effects discourage patients from taking a full course of treatment.

More recently Friedheim has introduced TWSB (antimony-a, β -dimercapto-succinate). Friedheim and de Jongh ^{236/} found that in 20 cases of S. haematobium infection a single well tolerated intramuscular dose of TWSb stopped the excretion of viable eggs within 3-25 days. Salem et al. ^{237/} concluded that TWSb is a highly efficient drug for both forms of schistosomiasis in Egypt. The cure rate for S. haematobium was 87 per cent, for S. mansoni 82 per cent and for mixed infections 70 per cent. Davies ^{238/} stated that a dosage of 2 gms. gives a satisfactory rate of cure against S. haematobium but that the drug is disappointing in S. mansoni infections. Davies thought that the considerable side effects render the drug unsuitable for ambulatory patients.

A new series of compounds which appears promising comprises the tris (p-aminophenyl) carbonium salts (TAC salts) reported on by Thompson et al. ^{239/}. TAC pamoate, TAC hydroxide and TAC chloride are capable of killing a high proportion of mature and immature worms in mice and monkeys at well tolerated dose levels, are more effective in moderate doses for prolonged periods than in high doses for shorter periods, act slowly and probably by interfering with nutrition, and are not antagonized by p-aminobenzoic acid. Indications of activity of TAC chloride and TAC pamoate when administered

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orally have been reported for both S. mansoni and S. haematobium in man by Burnett and Wagner ^{240/}. TAC pamoate orally is said to have some effect on S. japonicum ^{239/}.

Other drugs have been employed and still others are under development. The considerable variation in therapeutic effects reported by numerous clinicians raises the question concerning the reasons for such variability. One clue concerns the influence of dietary factors. In this connection, Luttermoser and Dewitt ^{241/} in tests with mice infected with S. mansoni noted that Fuadin was 4 to 16 times more effective in animals on semi-synthetic diets than in those on crude commercial rations. The relationship of diet to therapeutic efficacy needs further exploration.

The development of new, more effective and safer chemotherapeutic agents in schistosomiasis is an expensive process and there are few leads available. Research of this type is usually regarded as unrewarding in medical schools and research institutions. It has largely been left up to commercial concerns. Certainly more intensive search is warranted not only for the relief of infected individuals but because of the potential value of an effective drug for control purposes.

(b) Studies on the possibilities of chemoprophylaxis. The availability of an efficient prophylactic agent in schistosomiasis would be of benefit in a number of ways. Such a compound could well obviate the dire effects of massive exposure, be of great value in control campaigns and fulfill humanitarian needs in protecting populations against repeated exposure to infection. Such visuali-

zation of prospective benefits is of course predicated on the discovery of a drug which would provide effective protection over a considerable period of time. At present no such drug is in prospect. However, the recent development of a long-term malaria prophylactic compound lends encouragement and would seem to indicate that the goal is not an impossible one. A good prophylactic agent against schistosomiasis would need to be stored in the body for a considerable period of time, be released readily, be effective in destroying the penetrating cercariae or the early stages of the parasite, and exert no harmful side effects. The life cycle pattern of the human schistosomes is of course different from that of the human malaria parasites but there are similarities which give some hope that the progress achieved in long-term malaria prophylaxis is not impossible in schistosomiasis.

A few observations on chemoprophylaxis are on record.

De Meillon et al.^{242/} employed Hoechst S. 616 against S. mansoni in mice. The drug prevented infection when given up to 4 days following exposure. It did not have any effect when used from the 10th to 35th day after exposure. However, from the 35th day on a single oral dose of 40-50 mg./kg. of body weight gave about 100 per cent cure. Luttermoser et al.^{243/} tried 1-manleiny-4-3'-chloro-4'-methyl-phenyl)-piperazine (Hoechst S 688) on mice and monkeys. When given to mice up to 3 days after exposure to S. mansoni, the compound prevented many of the larval schistosomes from developing. There was some evidence of prophylaxis against S. japonicum. No cures were obtained in infections with this parasite although there was a strong therapeutic effect against S. mansoni.

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Bruce et al. ^{244/} reported that TWSb administered intramuscularly in doses well below toxic levels exerted a strong prophylactic and therapeutic action in monkeys infected with S. mansoni. Later, Bruce and Sadun ^{245/} showed that TWSb administered intramuscularly to Macaca mulatta monkeys experimentally infected with S. mansoni resulted in suppressing the passage of eggs in the feces. Temporary suppression was obtained with a single dose of the drug or by three doses given 2 weeks apart. Three doses 3 weeks apart or 5 doses at 2-week intervals practically eliminated eggs from the stools and greatly reduced the number of worms recovered at autopsy. No symptoms of drug toxicity were noted.

The amount of research effort which has been expended in this field is thus relatively meager in spite of the potential rewards. It is hoped that more attention will be paid to the problem in the future.

(c) Studies on the mode of action of schistosomocidal drugs.

This is a field in which a considerable number of observations have been made but yet a subject which needs further exploration.

Because trivalent antimony compounds have constituted the "sheet anchor" treatment of schistosomiasis, more information is available concerning their mode of action than is the case with other compounds.

Khalil ^{246/} observed that antimony is excreted mainly by the kidneys and only about 3 per cent is eliminated through the gastrointestinal tract. Changes in the ova occur shortly after the beginning of tartar emetic treatment. Khalil did not think that

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antimony exerts a direct action on the ova but that changes in the osmotic pressure were responsible. Fuadin apparently has a similar effect on the ova.

Bartter et al.^{247/} studied the excretion of radioactive tartar emetic in the human subject. Following a single intravenous dose, rapid elimination occurred during the first two days followed by a slower rate over the next 5 days. Approximately 80 per cent was eliminated by the kidneys and 20 per cent through the gastrointestinal tract. Since the blood level of antimony is of therapeutic importance in schistosomiasis, Bartter et al. suggested careful attention to the size and frequency of doses.

Bang and Hairston^{248/} reviewed the action of antimony on schistosomes. They found that the compound first produced degeneration of the yolk gland of the female, then degeneration of the ovary and shrinkage of the entire worm. Some degeneration of the testes in the male was noted. There was apparently no effect on the egg. When dogs with S. japonicum were treated with antimony, a shift of adult worms occurred from the mesenteric veins to the portal vein and its branches. Hewitt and Gill^{249/} observed a pronounced shift of mature S. mansoni to the lungs of mice treated with various regimens of tartar emetic and Miracil D. The magnitude of the lung shifts equalled or exceeded the collateral hepatic shifts induced by the therapy. Live adults were found in the lungs relatively early after the beginning of treatment. Geake^{250/} showed that lung shift increases with age of infection. However, significantly more worms migrated to the lungs in mice treated with tartar emetic and

Miracil D than in untreated animals regardless of the drug employed. The strain of mice did not affect the degree of lung shift. The shift of adult schistosomes as a result of therapy may represent an attempt to escape high concentrations of the drug in the mesenteric veins or may be associated with the action of the drugs on the neuromuscular system. A further elucidation of the phenomenon might provide a clue to the mechanism of drug action.

It is quite apparent that many therapeutic compounds owe their effectiveness to a direct or indirect action on enzyme systems. In schistosomiasis, Mansour and Bueding ^{251/} found that organic antimonials had no effect on sulfhydryl enzymes which are usually inactivated by arsenicals. However, antimonials markedly reduced the rate of glycolysis of fructose-6-phosphate indicating that phosphofructokinase activity is inhibited. Bueding and Mansour ^{252/} believed that this action could account for the schistosomocidal effect of trivalent organic antimonials, although interference with other mechanisms should not be excluded. On the other hand, Bueding et al. ^{253/} could detect no inhibition of the oxidative metabolism of adult S. mansoni following the administration of a cyanine dye which was effective against the filariid parasite, Litomosoides carinii. Bueding and Peters ^{254/} reported that a number of naphthoquinones inhibited glycolysis of S. mansoni in low concentrations. The mechanism was different than that encountered in malaria parasites and in certain other situations. Apparently it was not connected with inactivation of sulfhydryl groups. Bueding ^{255/} found that a series of alkyl-dibenzylamines demonstrated marked

activity against S. mansoni in vitro. There was a reduction in the motility of the worms which was preceded by an inhibition of glucose utilization and by increased glycogenolysis. Since higher concentrations of the compounds did not affect enzymes concerned with the carbohydrate metabolism of the worms, it was concluded that the antischistosomal activity of the compounds was brought about by an inhibition of the transport of glucose into the parasite. These compounds were found to potentiate the therapeutic activity of antimonials; apparently the parasite is more vulnerable to the simultaneous inhibition of glucose uptake and phosphofructokinase activity. With the TAC compounds, chemotherapeutic effect is preceded by an inhibition of the specific acetylcholinesterase activities in the central ganglia, nerve trunks and neuromuscular endings in S. mansoni. This biochemical reaction apparently is responsible for paralysis of the oral sucker, the pharynx and the acetabulum. The resulting depression of coordinated muscular activity of these organs in turn could account for loss of attachment of the worm and/or the slow development of a nutritional deficiency as a result of the decreased ingestion of red cells by the parasite ^{256/}.

Hawking and Ross ^{257/} stated that Miracil D is rapidly absorbed from the intestinal tract. After single human doses of 0.2 gm., the concentration in the blood rises to about 1.0 mgm. per liter at 2-1/4 hours. Over 90 per cent of the drug is degraded in the body and only about 7 per cent is excreted in the urine. There is little tendency for the drug to accumulate in the body. Concentration in the plasma is about twice that in the erythrocytes.

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Watson et al. ^{258/} showed that a correlation exists between blood levels of the drug and the urea clearance rate. In experimental animals, the drug caused the adult worms to retreat from the mesenteric veins to the portal vein and its branches. A direct lethal action is exerted on adult schistosomes. Eggs in the wall of the intestine became blackened and shriveled. Newsome and Robinson^{259/} conducted observations on the metabolites of Miracil D. The drug is believed to act through metabolites but these workers could not find activity in fecal extracts, urine extracts or in acid insoluble serum extracts.

Obviously this is a field in which much more research is indicated. Additional knowledge concerning the mode of action of presently available compounds may provide information of value in the search for more effective remedies.

(d) Studies on the immune mechanisms in the human host and development of methods for determining and measuring the acquisition and extent of resistance to Superinfection. It has been mentioned previously that there are apparently differences in the susceptibility of different individuals to schistosome infection as well as differences in the degree of clinical involvement. Experimental observations on various lower animals add confirmation concerning the existence of this resistance. A considerable amount of research has been conducted in this regard. Only a few of these observations need be mentioned here. Vogel and Minning^{260/} conducted experiments with S. japonicum in Rhesus monkeys over a period of

15 years and demonstrated that a true resistance was induced by previous infections. Partial resistance against challenging infections became evident after 10 months or longer and complete resistance after 14 months or longer. Sadun and Lin ^{261/} found that monkeys, rabbits, and mice developed an acquired resistance to S. japonicum following previous infection with the same trematode. Naimark et al. ^{262/} reported that no increase or renewal of egg production occurred when Macaca mulatta monkeys were challenged 2 years after a single exposure to 1,000 cercariae. When monkeys were subjected to a series of 26 monthly exposures of 25-50 cercariae each, egg production declined sharply after 300 days. Some of the animals acquired only light infections and failed to resist additional exposures 250-500 days later. Considerable individual variation was exhibited both to natural and acquired resistance. Li Hsu["] and Hsu["] ^{263/} infected M. mulatta with a non-human Formosan strain of S. japonicum. Subsequent challenge with a human strain of the parasite indicated that the monkeys had developed a considerable resistance which was individually variable in terms of egg output after challenge. Sadun et al. ^{264/} reported that resistance to superinfection with the Formosan and Japanese strains of S. japonicum was acquired by mice previously infected with the homologous and heterologous strains. The Formosan strain induced a greater degree of resistance.

Few attempts have been made to measure in immunological terms the nature and degree of resistance induced by a schistosome infection. Vogel and Minning^{260/} were unable to correlate rise in resistance with the titer in complement fixation tests.

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In fact, to date there is no evidence that serologically detectable antibodies are related to the resistance of the host. Much more needs to be discovered concerning the mechanisms of immunity both as regards the cellular and humoral roles in this phenomenon. Improvement in immunological techniques in recent years may lead to a clearer interpretation of the stimuli which induce resistance. The problem still remains of estimating by some ready means the magnitude of resistance invoked by initial or repeated exposure to schistosome infection. If methods are developed for artificial immunization, the availability of measures for estimating the degree of resistance will no doubt be of considerable value in determining the need for such protection.

(e) Additional studies on the fluorescent antibody and schistosome plasma charcoal techniques for the diagnosis of schistosomiasis and an evaluation of their usefulness in epidemiological surveys.

A review of various immunological tests for detecting schistosome infection has been made in Section II-4 (page 15). Of these, the fluorescent antibody reaction ^{46,47/} shows great promise and appears to be highly specific. It is useful for field surveys since it can be carried out with finger blood dried on filter paper ^{48/}. However, the actual test is carried out in the laboratory. A more recently developed technique is the schistosome plasma charcoal (SPC) method ^{265/}, which also gives promise of great specificity and can be easily and rapidly carried out in the field. In this test, a cercarial antigen devoid of non-specific antigenic lipids is employed. An antigen emulsion is prepared by adsorbing the cercarial

antigen on to cholesterol lecithin crystals, centrifuging and re-suspending the sediment with a solution containing charcoal. Three drops of finger blood are taken and the cells permitted to separate from the plasma on plastic coated cards. The cards are rotated for a few minutes. In positive cases, diffuse flocculation of the adsorbed charcoal follows. A compact field kit is available. The test can be carried out rapidly at a relatively low cost per individual.

Widespread application of these tests is desirable to gain further information concerning their efficacy and specificity. They may prove to be highly desirable for epidemiological surveys as a replacement for the ponderous and time consuming method of stool examination for S. mansoni.

(f) Studies on protective immunization. Artificial immunization against helminth parasites has been attempted with a number of species. Stoll ^{266/} has reviewed this subject and has summarized much of the early work. Probably the most successful vaccination has been in connection with the lungworm, Dictyocaulus viviparus. Jarrett et al. ^{267/} observed that infection of calves with this parasite confers a high degree of resistance to reinfection. This can result from a single sub-lethal dose or a series of small repeated doses of larvae. Immunized animals exhibit on challenge a rapid antibody response to the complement fixation test and a striking reduction of worms reaching the lungs and the number of larvae appearing in the feces. In further studies, Jarrett et al. ^{268/} employed vaccination with third stage larvae of the parasite

inactivated partially by exposure to 40,000 roentgens of X-ray. All experimental calves received 1,000 larvae as the initial dose administered orally and a second dose of 4,000, 2,000 and 1,000 larvae, respectively. All the vaccinated calves were completely resistant to reinfection when challenged with 10,000 normal larvae. On the other hand, whole worm D. viviparus antigen in Freund's adjuvant failed to produce consistent protection and was found to be of little practical value ^{269/}. D. viviparus larval antigen is now available commercially and is employed on a large scale in the United Kingdom. Jarrett et al. ^{270/} attempted immunization against Haemonchus contortus in sheep with radiated infective larvae. Larvae subjected to 40,000 and 60,000 roentgens produced a good immunity against reinfection.

In addition to the foregoing, experiments with certain other helminth parasites have indicated the immunizing effect of irradiated larvae. Vellella et al. ^{271/} reported success in immunizing albino mice against S. mansoni with cercariae irradiated with Cobalt⁶⁰. The amount of irradiation varied between 1,000 r.e.p. and 7,500 r.e.p. Mice receiving 5,000 and 7,500 r.e.p. irradiated cercariae were entirely refractory when challenged. Smithers ^{272/} obtained variable results with irradiated cercariae in monkeys. He concluded that large numbers of such larvae are required to produce even incomplete protection in Rhesus monkeys. Hsu et al. ^{273/} conducted similar experiments on mice and Rhesus monkeys with a human strain of S. japonicum. In monkeys, cercariae irradiated at 1,700 and 2,000 roentgens, respectively, were employed as

immunizing dosages. The mean number of eggs of the first 30 days of the patent period in the immunized monkeys varied from 0 to 36 and in the non-immunized monkeys the numbers ranged from 1,220 to 46,035. It would appear that the degree of immunity conferred is somewhat proportional to the numbers of irradiated cercariae employed and hence related to the degree of tissue response.

Studies with attenuated cercariae may be helpful in gaining a great insight into the mechanisms of immunity in schistosomiasis. Additional research is warranted also in refining methods of immunization by this means, although practical application at this writing may seem to be a remote possibility.

(g) Studies on the effect of the parasite on the physiology of the human host. It is somewhat surprising that little attention has been paid to the physiological alterations induced in the human host by schistosome infection. These alterations must in many cases be of considerable significance and in turn may be associated to a large extent with the progress of the disease. A few observations have been made on experimental animals and a limited number on man.

Daugherty et al.^{274/} studied liver function in mice infected with S. mansoni. There was evidence of increased size of the organ, increased water content, decreased oxidative deamination of amino acids, and a failure in ammonia metabolism. Daugherty^{275/} showed that livers of infected mice had a reduced ability to oxidize succinic acid despite the fact that endogenous respiration was little affected. Tyrosinase activity was unaffected but the glycolytic mechanism was somewhat reduced in activity. Garson et al.^{276/}

observed alterations in serum glutamic-oxaloacetic transaminase (SGO-T) in bisexual infections in mice after 2 to 10 weeks following infection. However, such alterations were not observed in mice with male worm infections only.

Ghalioungui et al.^{277/} studied steroid metabolism in bilharzial cirrhosis of the liver and infectious hepatitis. The levels of 17-ketosteroids were distinctly lower than normal. Cases of ascites showed the most pronounced diminution. Administration of 50 mgm. of testosterone propionate intramuscularly in 17 cases was followed by an average daily rise of 2 mgm. which is much lower than the normal rise. Administration of 40 mgm. of ACTH in 4 cases was followed by the normal fall in circulating eosinophils but the 17-ketosteroids did not rise appreciably. The following abnormalities were noted in 25 cases of bilharzial cirrhosis. High blood and urinary estrogens, low urinary gonadotropins, low 17-ketosteroids, and high gluco-and mineralo-corticoids.

Handford^{278/} studied patients infected with S. mansoni and/or S. haematobium in Egypt. Blood $\text{NH}_3\text{-N}$, urea, glutamic and keto acids were measured in 29 patients with hepatic fibrosis associated with advanced disease and malnutrition. Routine liver function tests (BSP clearance, thymol turbidity and bilirubin index) were elevated in all cases. Despite evidence of liver failure and pathological involvement, none of the biochemical parameters measured were significantly elevated relative to the controls. Fripp^{279/} noted that the presence of S. haematobium eggs in the urine of otherwise apparently healthy East African males

was usually accompanied by an increase in the activity of urinary B-glucuronidase. Variation in the level of enzyme activity was paralleled by variation in egg output in the urine, with maximum values occurring during the early afternoon. It was tentatively suggested that the increased enzyme activity was related to the degree of infection.

A number of workers have studied alterations in the serum protein components in schistosomiasis. Azevedo et al.^{280/} observed a negative correlation between the sedimentation rate and the albumin fraction of the serum in patients with S. haematobium. There was a positive correlation between the sedimentation rate and gamma globulins. Sadun and Walton^{281/} found that persons with proven schistosome infection had significant increases in total protein and in the relative proportions of alpha-2, beta and gamma globulin fractions, with a corresponding decrease in the relative proportions of alpha-2, beta and gamma globulin fractions, with a corresponding decrease in the relative proportions of albumin.

The great penetration of schistosome eggs into the wall of the bowel and other organs must be associated with physiological changes. It will be evident that little research has been done on the physiological aspects of infection and undoubtedly this would be a profitable field for additional investigation.

(h) Research on the pathogenesis of infection by all stages of the parasite. Many observations have been made on this subject but much more needs to be learned. Marked variations occur in the cellular response to cercarial penetration. In individuals sensi-

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tized by previous exposure, the inflammatory reaction is usually more intense than in non-sensitized persons. However, there are exceptions and occasionally the non-sensitized individual will be markedly affected. The nature of the response has not been entirely elucidated. The inflammatory reaction may be directly associated with the trapping within the layers of the skin of the penetrating cercariae. It is not certain whether the immobilization and death of the cercariae is initiated by a cellular response or whether humoral factors may be involved also.

It is quite evident that unisexual infections with male or female worms seldom produce any pathology. It is not known to what extent metabolic products of the adult worms are involved in the pathological picture, as metabolic end products in single sex infections may be different than those in bisexual infections.

The role of the egg as a pathogenic agent is well recognized but the exact nature of the stimulus is little understood. There is increasing evidence that the cellular reaction is not merely a foreign body response. Possibly the response is triggered by secretions of the egg or that the presence of the egg stimulates an antigen-antibody reaction in the surrounding tissue. Pulmonary lesions due to egg deposition await similar elucidation as to the nature of the cellular response. As previously noted (Section III, page 26), in Pernambuco, Brazil there is a relatively high incidence of pulmonary involvement in patients with S. mansoni. In necropsy studies in Puerto Rico, Koppisch ^{282/} found schistosome ova in the lungs of 4 of 94 minimal cases of the disease, 5 of 21

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moderately advanced cases and 7 of 11 severe cases. Suárez and Hernández Morales ^{283/} noted the wide discrepancy between X-ray findings and clinical evidence of lung involvement in Puerto Rican patients. It would appear that such occurs more frequently in the Americas than is usually recognized and that additional clinical observations are in order.

Other than polyp and papilloma formation, mechanisms of damage to the intestinal tract have been little studied in S. mansoni infections. There are few reports of small intestinal involvement, although this does occur in severe S. japonicum infections. Koppisch ^{282/} observed eggs in the wall of the small intestine in 16 of 63 cases coming to necropsy with the largest percentage in the severe cases. Eggs were also found in the pancreas in 9 of 114 necropsies. Few clinical studies mention any symptomatology associated with invasion of the small intestine or pancreas. It would seem, however, in severe cases especially that the pathology produced in these organs might be of some significance.

(i) Carefully controlled group studies in a highly endemic area in which control measures are not operative to determine the effect of fortified diets on the symptomatology of the disease and the egg output. There have been few attempts to evaluate the effect of the nutritional level on the severity of schistosomiasis, although there seems to be a consensus of opinion that the well nourished individual is better able to withstand the onslaught of the disease. Rodrigues da Silva ^{284/} thought that good nutrition

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must be an important factor in helping the individual to resist the "stress" of the aggression. Diaz-Rivera et al.^{285/} voiced the opinion that in Puerto Rico most of the cases of hepatic cirrhosis in patients with Manson's schistosomiasis resulted from a combination of factors involving severe nutritional diet, and if intense, the effects of the parasitic infection. Walker^{286/} thought that the nutritional state had little measurable influence on S. haematobium infections in Bantu children. However, he was mainly concerned with associating the nutritional level with the production of anemia in the children. Dewitt^{287/} reported on a 15-month study in Puerto Rico in which undernourished individuals with schistosomiasis were given an enriched diet over an extended period with great benefit. Liver function tests which initially were abnormal in 60 percent of the cases rapidly returned to normal or showed marked improvement. No such improvement was noted in individuals in a control group. A modified intensive treatment with Fuadin in patients in both groups was effective but no differences were noted in treatment response.

Experiments with deficient diets in laboratory animals have given conflicting results. Krakower et al.^{288/} reported that rats on a vitamin A deficient ration were less resistant to S. mansoni than rats on a normal diet. The same workers^{289/} noted that a vitamin C deficient diet had no effect on development of the worms; however, shells of eggs produced by the female worms were abnormal and there was some question concerning the viability of the miracidia. DeWitt^{290,291/} experimented with diets producing nutritional liver disease. Mice infected with S. mansoni and maintained on a Torula

yeast ration deficient in cystine, selenium and vitamin E harbored 69 per cent more worms than animals on a complete diet. However, somatic development of the worms was markedly impaired and most of them did not reach sexual maturity. DeWitt ^{292/} reported that S. mansoni infected mice showed a definite decrease in ability to utilize fat and protein. In another study, the same author ^{287/} maintained mice on a low protein diet deficient in lipotropic substances with the result that adult worms were stunted and egg production by the female worms was reduced by more than 90 per cent. A somewhat similar study conducted in South Africa by De Meillon and Paterson ^{293/} showed that a diet generally lacking in protein had adverse effects on an Egyptian strain of S. mansoni in mice. The worms were stunted and the few eggs produced appeared to be abnormal.

Coutinho-Abath et al. ^{294/} studied the influence of dietary protein levels on schistosomiasis mansoni in Swiss albino mice. Three groups of animals were divided in accordance with the type of diet, which consisted respectively of low protein, normal diet and high protein diet. The protein level influenced the activity of the liver R.E.S. The inflammatory response to the presence of schistosome eggs in the liver was particularly intense in the high protein fed animals. While liver regeneration was noted in animals on all three types of diet, regeneration was more pronounced in those given the high protein diet. Coutinho-Abath ^{295/} had previously experimented with Swiss mice maintained on the above-mentioned types of diet to determine the effect on the penetration of schistosome

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cercariae. Each group of animals was divided into sub-groups consisting of controls, those given a single infection and those exposed to multiple infections. A local reaction occurred in the skin of the mice regardless of the type of diet. However, in animals exposed to a single infection, the inflammatory reaction to the invading cercariae was slight and transitory but was more pronounced in mice on a high protein diet. In animals receiving a multiple infection, the reaction appeared earlier and was more intense, especially in the animals on a high protein diet.

The subject is worthy of experimental investigation and in the Americas probably one of the areas best suited to a study of this sort would be in Northeastern Brazil, where it is known that the nutritional level of the population is markedly low. Furthermore, there are localities in this region in which schistosomiasis presents severe clinical manifestations. The age at which these severe symptoms become evident is variable. In one survey in Pernambuco ^{296/} such symptoms began to make their appearance in the age group 5-9 but the percentage did not become significant until the ages of 10-14. In another study ^{297/}, in the same State, splenomegaly did not develop before the age of 10, although initial infection was acquired as early as 3 years of age. A captive population would no doubt be essential for such a study and school children would well serve the purposes of the investigation. Because of the time factor involved in the development of severe schistosomiasis, the study would of necessity be a long term one, even though nutritional supplements would be started with individuals entering primary school for the first time.

The suggested investigation would need to be staffed by personnel in a variety of disciplines and would require the collaboration of epidemiologists, nutritionists, clinicians, parasitologists, public health nurses, and others. A thorough statistical evaluation of all phases of the project would need to govern the areas to be selected, the number of participating individuals, the number infected, the number with clinical symptoms, and other factors. An initial epidemiological survey of proposed areas for investigation would be required in order to determine the patterns of transmission of the disease and should be repeated at intervals to determine any changes in the habits of the children or other alterations which might influence the exposure pattern. Initial and frequent examinations would need to be conducted to evaluate the degree of schistosome infection and to determine whether participants were infected with other parasites. Initial and frequent nutritional evaluations would be required as would be clinical examinations to determine the progress of the disease. Close surveillance would need to be maintained for other illnesses.

While such a project would require a considerable staff and be relatively costly, the information derived from it would no doubt be of great value in any control campaigns against the disease.

(j) Group studies to establish clinical gradient standards for schistosomiasis in the americas to serve as a base line for determining the economic impact of the disease on the individual and the community. The difficulties in calculating the economic effects of schistosomiasis have already been pointed out in Section IV

(page 34). In only one area has a concerted effort been made to evaluate the economic impact on the community. This study was carried out as part of the WHO cooperative project on the Island of Leyte, Republic of the Philippines ^{74,75/}, where Schistosoma japonicum is endemic. Estimates of the economic burden of the disease have been made for a few other areas but the data have not been based on carefully designed and conducted observations. It has been emphasized previously that clinical involvement is extremely variable. Even in highly endemic areas some individuals may be only lightly infected and consequently suffer little or no disability from such infection. The establishment of some standard of clinical gradients for schistosomiasis mansoni would enable the collection of more accurate and worthwhile information on the economic aspects of the disease. The difficulties presently encountered in control have been reviewed elsewhere in this document. Financial support for the application of control measures could well be enhanced if health authorities were in a position to emphasize the drain on the resources of the individual and the community.

Obviously, the establishment of standards to measure the degree of clinical involvement presents great difficulties. Certainly such measurements cannot be accurately derived from a captive population such as hospitalized individuals or school children. Persons seeking medical attention are usually in terminal stages of the disease and infection in children has not progressed to the point that it would be at all representative. A study of this

sort would necessarily have to be conducted in a community which would be typical or as near typical as possible of the average endemic area in the country or countries involved. The study should be controlled by similar procedures in a representative community in a non-endemic area since it is obvious that many conditions other than schistosomiasis contribute to ill health or loss of well being and these other conditions would need similar evaluation to determine their influence on loss of working capacity and cost of illness.

There are of course many approaches to an evaluation of clinical involvement. The first and obvious one is to determine the presence or absence of infection in all individuals in the community. For this purpose, employment of one of the newer immunological tests might be indicated as an initial screening method, to be followed by stool examinations and egg counts by the Stoll technique or one of its modifications. While such counts are not specific in indicating the degree of infection, on a mass basis they do serve to provide a general idea of the relative degree of involvement. Here, however, it must be kept in mind that in the late stages of schistosomiasis mansoni, egg production is limited or may be entirely absent.

In such a study, close attention should be paid to the epidemiology of the disease in the community and the patterns of transmission. If changes occur in these patterns, they necessarily might have a considerable bearing on the other aspects of the investigation.

Clinical manifestations should be carefully surveyed and evaluated and physical examination should be supplemented by all laboratory methods which could conceivably provide supporting information. Naturally the study would require the clinical skills of physicians thoroughly familiar with the disease and its many manifestations supported by the capabilities of various clinical specialists.

Many variable factors would no doubt be encountered in such a proposed investigation. Some or all of these factors might have a substantial influence in introducing errors into any conclusions regardless of the capabilities and the skills of the supporting staff. Final evaluation then should take cognizance of circumstances or things which might introduce sources of error into the calculations.

In evaluating illness from schistosomiasis, acute episodes as well as chronic disability should be noted. The frequency of disabling attacks, the severity of such attacks, and the duration of disablement are criteria which would require measurement. Deaths attributable to the disease, if occurring during the course of the study, would need to be evaluated in economic terms. The WHO Expert Committee on Health Statistics has made recommendations concerning definitions which should be followed in any effort to appraise economic effects of illness. The various kinds of loss caused by ill health are reviewed in Section IV of this document.

The present proposal is projected with a clear concept of the difficulties which will be encountered. However, need for the

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information to be derived from such an investigation warrants its encouragement on the part of health authorities, since it would undoubtedly strengthen their hand and better enable them to elicit the financial support essential for a beginning campaign against the disease.

(k) Carefully planned and precisely conducted controlled experiments in an attempt to measure the impact of schistosome infection on the mental development and the progressive learning capacity of children of pre-school and primary school age. There has been a suspicion that an infection with various species of schistosomes is responsible for a slowing of the mental development and the learning capacity of infected children. The observations in this regard have often been at variance and there is no determinate information concerning these factors. Experiments on certain lower animals add some strength to the idea but here again some of the experiments are difficult to interpret.

Keiser ^{298/} called attention to the striking effect of urinary schistosomiasis on the educational attainment of children in Transvaal schools. He reported that children infected with the parasite before they enter school may be dull and apt to be classed as mentally retarded and unfit to take advantage of educational facilities. If infection is contracted after school age is reached, the level of scholastic attainment deteriorates and the children are unable to move up to higher classes with others of their age group. Improvement in learning capacity took place after treatment and

continued unless reinfection ensued. It was not believed that scholastic retardation caused by schistosomiasis bore any relation to deficiency in intelligence.

Loveridge et al. ^{299/} conducted observations on school children in Southern Rhodesia, where instructors associated onset of memory lapses and inability to concentrate with schistosome infection. Actually, it was found that schistosomiasis appeared to have an adverse effect on the scholastic attainment of children of European parentage. However, the reverse was true of infected native African children who seemed to have a better scholastic record than did their non-infected companions. Loveridge et al. offered no explanation of their observations in this regard.

In Tanganyika, Jordan and Randall ^{300/} found that infected children had higher average marks than those which were uninfected. However, these authors stressed that this circumstance did not mean that the infected children could not have done better if they had not been suffering from the disease. The improvement in class position which followed treatment suggested that infection was in fact reducing the scholastic ability. The children in question carried S. mansoni and/or S. haematobium.

Huang et al. ^{301/} studied a population in China, in which 4 per cent of 623 individuals were dwarfs. Twenty-one of these of ages 16 to 20 years had the physical development of 12 to 13 years of age. These individuals were physically weak and lacked stamina, although quite well proportioned. Mentally they were said to be normal, although apparently no effort was made to measure their learning capacity.

In studies in lower animals, Kershaw et al.^{302/} reported that a low grade schistosome infection retards the learning process in white rats, as assessed by the numbers of errors made in solving a "T" maze. The effect was proportional to the intensity of infection but the infection did not interfere with the recollection of what had already been learned. The effect was an indirect one and not due to invasion of the brain by the parasite.

Stretch et al.^{303/} investigated water-maze discrimination and activity of mice. Acute schistosomiasis reduced the animals' capacity to learn a simple discrimination, an effect which may have been due in part to a reduction in activity.

Stretch et al.^{304/} reported on the effect of acute schistosomiasis upon the learning in rats under different levels of motivation. Hooded rats were exposed to 500 cercariae each of S. mansoni 18 weeks before discrimination training was begun. The resulting low-grade infection of several month's duration did not retard discrimination learning in the rat. Stretch et al.^{305/} exposed hooded rats to 500 cercariae of S. mansoni and measured their rate of learning under different strengths of "drive" by an underwater swimming test. Learning was retarded at low levels of drive but not at high levels. Acute infection with low-grade schistosomiasis therefore reduced motivation to solve a problem, rather than reducing learning ability per se, i.e., it was thought to result in a state of "lethargy"

In further experiments on this problem, Stretch et al.^{306/} tested the effect of light repeated exposures to schistosome infection over a six weeks period. Under such conditions, the behavior

of albino mice was investigated in water-maze discrimination and swimming activity experiments. Repeated exposures to light infection gave no discernible effect in the discrimination test, but differences were observed in the swimming test. Thus the capacity of mice to learn a simple discrimination problem was not reduced, whereas, as noted previously ^{303/} a heavier infection was responsible for a reduction. In connection with the animal experiments, Brewster et al. ^{307/} conducted tests which demonstrated that the very slight and questionable reduction of appetite which may occur during a schistosome infection can hardly be responsible for the alterations in the psychological performance of rats with acute schistosomiasis.

At present the effect of a schistosome infection on the scholastic attainment and learning capacity of children is certainly in doubt. However, some of the observations are interesting and the results of the animal experiments would seem to lend some degree of confirmation to the fact that such may take place. There is no doubt that the field should be explored further, preferably by a qualified team of experts in the various disciplines involved.

(1) Pilot control experiments to determine in communities with similar epidemiological patterns the relative efficiency of the separate application of various control measures such as sanitation, health education, molluscicides and chemotherapy. In most endemic areas of schistosomiasis in which attempts have been made to control the disease nearly all available methods have been utilized. There are a few exceptions to such broad attack. For instance, in the

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Gezira area of the Sudan, chemical barriers and wire screens have been employed almost exclusively for control of snail vectors in the irrigation system 173,174/. In the WHO cooperative project on the Island of Leyte, Republic of the Philippines, major dependence has been placed on engineering procedures and remedial agricultural practices 74,212/. In one locality in Brazil, health education alone is reported to have been effective in curbing the disease 89/.

Previous philosophy has dictated the all out approach. Past experience in most areas has shown the rationale of such policy at a time when the efficacy of various methods left much to be desired. However, newer knowledge is available from recent research. More effective molluscicides have been developed; increasing provision has been made for sanitary facilities in some endemic areas and the public health education approach has been enhanced through new techniques. The only area in which distinct progress has not been made is in chemotherapy. However, there is present hope that some of the newer drugs will offer greater efficacy.

If not already here, the time will soon come when it will be highly desirable to know the relative efficacy of individual control procedures. It may not be essential in the future to adopt the scatter approach to control. In fact, it may prove to be more advantageous to concentrate all efforts on a single method, if such method gives promise of an adequate degree of effectiveness. In such event, a concentrated spearheaded attack may turn out to be more economical. However, before health authorities can chance such a change of policy, a further appraisal is needed to delineate the

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advantages, disadvantages and relative efficiency of different methods. It would be desirable to conduct additional research to this end, preferably in several endemic areas presenting similar transmission patterns.

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