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CONTROL OF SCHISTOSOMIASIS MANSONI: AN OUTLOOK FROM CURRENT EXPECTATION

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Soon after the end of World War II, Brazil was visited by Dr. Fred Lowe Soper, who had worked among us for about 20 years, contributing decisively, as the Representative of the Rockefeller Foundation, to organize and carry out the anti-*Aedes aegypti* program which resulted in its eradication from the national territory in 1955, and to fight against *Anopheles gambiae,* which had invaded the northeast of the country and was eradicated in two years of campaign. He left behind a legion of friends, who paid him homage with an informal banquet. His enthusiasm over the marvellous results obtained with the application of DDT in the prevention of habitual epidemics among troops in previous wars gave strength to the ideas of "species eradication" which he, together with D. Bruce Wilson, had explained in 1942, in the inaugural issue of the Journal of the National Malaria Society. In fact, louse-born typhus, which spread freely during World War II in such countries as Italy, Poland, Russia, Iran, Egypt and Japan, in northern Africa and in concentration camps in Germany and Austria, had its dissemination stopped with the arrival of DDT. His enthusiasm was so great that, usually succint, sometimes almost laconic in verbal expression, he extended his thank-you speech for almost an hour. At a certain point, he said more or less: "I suggest that the malariologists here present consider another profession while there is still time, because in a few years you may be jobless". I was then working at a branch of malariology, and was seated between two malariologists, one of whom asked me, "What will your new profession be?". "Geneticist", I answered. Of course it was not my intention to become a professional geneticist. I was simply expressing, as a joke, a feeling originated from the recognition of some facts recorded in the scientific literature.

Several species of scale insects attacked citrus trees in California. The most efficient method of controlling them was fumigation with hydrocyanic gas applied at regular intervals in a concentration which killed nearly 100% of them. In 1913, it was observed that one of those species – *Saissetia oleae* – was resisting treatment in orchards near Charter Oak, Los Angeles county. By 1925 this resistant strain spread over a citrus belt for a distance of about 60 km, so that attempts to control it by fumigation were abandoned (Quayle, 1938). The same happened to two other species at Corona and Riverside, with spreading to large areas. Studies by Quayle (1938), Dickson (1941) and others showed that resistance was due to a gene with incomplete dominance.

The codling moth – *Carpocapsa pomonella* – which attacks apple and pear trees was being fought in the United States with sprays containing arsenic and other toxicants. With time, it was observed that progressively more and more frequent treatments were required to maintain control. Besides the selection of resistant strains, this species evolved a race that began to attack walnut trees as well: first in northern California in 1909, and then in southern California in 1918. Studying the subject, Smith (1941) said that economic entomologists were confronted with a situation when methods of control once considered satisfactory might no longer suffice because the pests to be controlled underwent changes themselves.

These observations, perhaps because they were made in plant parasites, did not seem to attract the attention of epidemiologists. The surge of optimism brought about by the success of DDT and the prospect of other equally strong or stronger insecticides to be developed greatly discouraged the interest in malariology, so that, when in 1976 the National Research Council of Brazil initiated a program to stimulate malaria research, the number of candidates was surprisingly small. Unfortunately, this euphoric mood did not last. After a period of experimental applications in the Italian province of Latina, DDT was applied on a national scale as of March 1946, but already in May 1947 the first resistant specimens of

Musca domestica were detected by Saccà (1947), and of *Culex pipiens* by Mosna (1947). Other insecticides were used in succession, until it happened that, in late 1951, domestic flies of all the malarial areas of Italy were resistant not only to DDT but also to methoxychlor, chlordan, dieldrin, BHC and several other products (Hess, 1952). It is common knowledge that resistance of many other insect species throughout the world has been recorded.

Chemical control of vectors

I considered this long introduction necessary before going on to the fight against *Schistosoma mansoni* vectors by chemical agents. Resistance to molluscicides has been less investigated than that to insecticides, and here I would like just to refer to the demonstration, by Sullivan et al. (1984), of the tolerance to niclosamide and copper sulfate of a laboratory strain of *Biomphalaria glabrata*. My concern about this matter originates from observations made over 30 years ago (Paraense et al., 1954, 1955), when we attempted to explain the reappearance of snails in well-isolated biotopes intensively treated with sodium pentachlorophenate. Contrary to the predominant view that the new specimens had come from outside the biotopes or from areas not reached by the molluscicide, we observed that many snails normally buried themselves into the mud of the breeding places, concluding that those in such situation were not affected during mollusciciding. The relatively frequent finding of snails buried at different depths, up to the maximum investigated of 40 cm, seemed to indicate that this was a customary, perhaps cyclic, process inherent in their protection or nutrition behavior, or perhaps both, which could be fit into the concept of vertical migration. Most significant, however, was the finding of living snails buried in the soil, also up to 40 cm and about 2 m distant from the normal edges of the biotopes. The snails reached that situation at the peak of the rainy season, following the overflowing water. With the reversion of the water to its normal bed, after the rainy season, they remained isolated in transient pools left by the receding waters. As the pools progressively dried, the more resistant snails would dig down accompanying the progressively deeper level of moisture, where live specimens were found, naturally in gradually decreasing numbers, during the entire dry season. We concluded that re-invasion of the water bodies rendered negative by the molluscicide could only be attributed to the specimens that were buried in the mud of the biotope bottom during mollusciciding, and to those that had been able to resist the climatic severities within the ground, both below the bottom and in the surrounding soil exposed to flood during the rainy season. These observations were confirmed by Schwetz (1956) in the former Belgian Congo and in Uganda.

While presenting these results at a Congress, an outstanding parasitologist asked me how could a pulmonate mollusc, which by definition needs air to breath, live for so long while buried in the soil. I answered that, from an ecological point of view, our observations were not at all original. Cawston (1927) had found *Biomphalaria pfeifferi* buried at a depth of 13 cm in South Africa. Without entering in particulars, I recall that Pelseneer (1935: 354-355) mentions observations by various authors on 23 terrestrial pulmonate molluscs that can remain for months hibernating or estivating at varying depths up to 2.70 m *(Testacella scutulum)*. Aquatic animals highly sensitive to lack of water or its dissolved oxygen, like copepods, ostracods, platyhelminths, nematodes, annelids, insect larvae, and especially molluscs and fish, also can survive buried in moist or dry mud. Many species of the mentioned groups, existing in Central Africa and Australia, have been studied from samples of dry mud. Numerous instances and references on this subject, including fish that resist buried in dry mud in Sri Lanka, Celebes, Europe and North America, can be found in the book "Ecological Animal Geography" by Allee & Schmidt (1951: 420-422).

All the buried specimens of *B. glabrata* found alive, when placed separately in aquaria, would eliminate feces composed exclusively by the mud which had surrounded them, and a few days later would deposit self-fertilized eggs. I consider these two facts highly important. If you examine the gut contents of a planorbid removed from its natural biotope, you will notice that they consist almost entirely of mud from the substrate. On the other hand, a single specimen of *B. glabrata*, under favorable conditions of food and temperature, can produce, in 90 days, three generations of viable offspring totalling nearly 10 million individuals (Paraense, 1955). These data led me to conclude that chemical control of *Biomphalaria* will be effective only when the molluscicide is capable of being retained by the mud of the substrate, which is obligatory food for the mollusc in natural conditions, and of maintaining a residual action until it is ingested by the animal when it emerges from its burying cycle. Research on effective molluscicides has led to the production of active substances in progressively smaller concentrations, but in this way, even though they may act in homeopathic doses, they will not solve the problem. Even the slow-release formulations have not yielded the desired results.

Biological control of vectors

While a child, I was strongly impressed by a copy of the nine engravings by John Dunstall of scenes during the great plague of London in 1664-1665. With time I learned that major epidemics, not only plague as other infections, had devastated populations in many parts of the world, and certainly even before the first historical record, among the Philistines, 11 centuries before Christ, as described in I Samuel, 1:5. During the great cycle of the 14th century, death by plague exterminated up to three-fourths of several European populations. Particularly in the case of England, hit in 1348 by the pandemic plague then called "Black Death", which had invaded Europe the year before, deaths in 1349 reduced the population by at least a third in only a few months. The incidence and virulence of the epidemics gradually decreased over the following centuries, and the last sporadic cases were recorded in 1679 (Meyer, 1972). According to Meyer, plague in England stopped spontaneously, since effective quarantine was really not established until 1720.

Since 1939, experiments by Webster & Hodes, from the Rockefeller Institute, had demonstrated that oral instillation of 5 million *Pasteurella enteritidis*, the agent of typhoid infection of mice, in animals of a strain considered genetically pure, regularly killed 95 to 100% of the animals. In other not specifically selected strains the mortality was 50 to 60%, and only about 10% in a strain selected for resistance.

Countless similar examples could be evoked to demonstrate that, even in populations naturally or experimentally selected for susceptibility to infection, there are always resistant individuals. I do not know of any highly lethal epidemics, like those of measles among Indian tribes, which had annihilated all of the individuals. If this were not the case, mankind who, prior to the development of modern curative and preventive agents, was hit by successive epidemic and pandemic waves of various etiologies would not have outlived so much as to give us the opportunity of meeting tonight. The snail vectors of schistosomes cannot escape genetic laws, and individuals resistant to infective agents used until now also have to their advantage a high prolificacy. Among the investigations on this subject, including microbial agents, parasites, predators and competitors, some ones pointed to satisfactory results under laboratory conditions, but only seldom (and in my opinion undecisively) under natural conditions. I will refer to the more successful along this line.

Parasites

Investigating multiple infections by larval trematodes in a lymnaeid from Michigan, Cort et al. (1937) suggested the existence of immunity or antagonism between some of those parasites. The hypothesis of antagonism was confirmed by Lie et al. (1965) among several trematode species parasites of *Lymnaea rubiginosa*, and by Lie (1966) between *Echinostoma* sp. and *B. glabrata*. In these investigations redia-producing species were dominant and sporocyst-producing ones were eliminated. The primary cause of sporocyst destruction was not then explained, there having been noticed that they died and were consumed by rediae. Further laboratory and field investigation showed that *Echinostoma malayanum* rediae acted directly as predators of *Schistosoma spindale* sporocysts and cercariae in *Indoplanorbis exustus* (Heyneman & Umathevy, 1967, 1968). Afterwards Lie and his group found that rediae of several echinostomatids acted as predators not only on sporocysts of *S. spindale, S. mansoni* and *Trichobilharzia brevis*, but also on rediae of various echinostomatids that were dominant in other combinations. Predation could be observed and photographed through the shell of albino *B. glabrata*. Both sporocysts and rediae also performed passive, indirect antagonism, giving rise to retardation in development, regression, degeneration or suppression of the affected species. Reviews including subsequent studies along this line were published by Lie et al. (1968) and Lim & Heyneman (1972).

The most effective antagonist of *S. mansoni* was the strigeoid trematode *Ribeiroia marini*, first described by Marín (1928) as Cercaria III, shed by *B. glabrata* in Puerto Rico. It was redescribed, as well as its progenitor redia, by Faust & Hoffman (1934), under the name of *Cercaria marini*. Its life cycle was described in detail by Basch & Sturrock (1969). Under natural conditions the cercaria encysts as metacercaria on fish and develops into adult in herons. Harry (1965) had observed that the rediae destroyed the ovotestis of parasitized biomphalarias. Parasitic castration is frequent among molluscs infected with sporocysts and chiefly rediae of trematodes, having been long described by many workers (for example Lespès, 1857; Pelseneer, 1895). The latter (Pelseneer, 1906) named *Cercaria emasculans* a larval trematode that destroys the gonad of the prosobranch *Littorina rudis*. Nagano (1927), having observed that a species of *Bithynia*, vector of *Clonorchis sinensis*, was susceptible to infection by eight other trematode species, suggested its superinfection to sterilize it by castration for clonorchiasis control. During monthly observations in Belo Horizonte city, from February 1949 to January 1950, I found infection rates of *B. glabrata* with larval trematodes (at least 8 species, besides *S. mansoni*) between 23 and 81%, exceeding 45% for 9 months. Commenting on these results (Paraense, 1953), I emphasized the injuries to the digestive gland and ovotestis as causes of high mortality and castration, and the possibility of biological control for prophylaxis with recourse both to dissemination of nonhuman trematodes and to natural enemies. Bayer (1954) found larval forms of at least 7 trematode species in *Biomphalaria pfeifferi* and 4 in *Bulinus africanus* at Durban, South Africa, destroying mainly the digestive gland with great mortality. Following Le Roux's (1953) example, he proposed, as a measure of biological control, the use of trematode-infected ducks as predators of snails and disseminators of infection among them.

Basch et al. (1970) observed that in *B. glabrata* infected with *S. mansoni* a superinfection with *R. marini* causes degeneration of sporocysts and great reduction in cercarial shedding. Huizinga (1973) adapted a strain of *R. marini* to the stomach of laboratory rats. He noticed that its rediae damaged the digestive gland and ovotestis of *B. glabrata*, castrating it and causing its premature death, and that a primary infection by *Ribeiroia* inhibited a subsequent infection by *S. mansoni*. These experiments, carried out in outdoor tanks, demonstrated that *Ribeiroia* is not a sufficiently effective direct antagonist of *S. mansoni*, but has the great advantage of causing castration and high mortality in *B. glabrata*.

In the aforementioned and many other experiments there were always a number of molluscs which did not contract either simple or multiple infections.

While studying the development of *R. marini* in *B. glabrata* at Basse Terre island (Guadeloupe) Golvan et al. (1974) observed natural infection rates beyond 90% during the dry season, that the favorite location of the rediae in the snail ovotestis rendered all of the parasitized specimens sterile by castration, and that the cercariae encysted into metacercariae on the fishes *Tilapia mossambica* and *Poecilia reticulata*. In addition, Nassi (1978) did not find the parasite in aquatic birds, including Ardeidae, noting that the definitive host in Guadeloupe are the common rats, *Rattus rattus* and *R. norvegicus*, as previously shown by Combes et al. (1975). Reproducing in the laboratory the whole life cycle of the parasite, and based on those experimental data and on field observations, the foundations for the biological control of *B. glabrata* in Guadeloupe became established (Nassi, 1978).

A pond at Grande Terre was chosen as experimental field (Nassi et al., 1979a). From September 1976 to July 1977 great amounts of *Ribeiroia* eggs from the feces of laboratory rats were introduced daily into the pond. Egg introduction began one month before the demographic explosion of *B. glabrata* which takes place as the pond begins to fill with rainwater. Five weeks later, about 6% of the molluscs were shedding cercariae. The infection rate increased gradually until it reached 40% in the 10th week. Between weeks 8 and 10 the population underwent a marked decline, indicating a violent pathogenic action of the parasite against the young stages of the snail. As of week 8 infected snails of all sizes were found. Soon the infection rate stabilized, exceeding 50% only twice. Stability was suddenly shattered between weeks 38 and 41, when the water level dropped very much during the dry season, and the infection rate increased up to 90%, owing probably to a greater concentration of miracidia in a smaller water volume.

This experiment was extended for another 5 months, until December 1977 (Nassi et al., 1979b). Describing the results, the authors mention a collection made in week 41 (early June 1977): of 30 collected specimens, 25 were shedding cercariae, 4 also shed within 5 days, and only one specimen was negative. Thus, the infection rate in this sample, collected just before the peak of the dry season, was of approximately 97%. An exhaustive search was made toward the end of June, but not a single specimen was found. Egg introduction was then delayed until the start of the next rainy season, when the water level began to rise and the *Biomphalaria* number in the biotope was estimated at about 50, two-thirds of them being parasitized. So, the reproductively active population in the pond was of only about 15 individuals. The previous generation disappeared during the first half of September, and consequently the infection rate fell to a minimum. The new generation was estimated at about 800 individuals. Its infection rate reached the same 40% of the previous year, but a month-and-a-half earlier, and exceeded 85% in November and December instead of stabilizing as in 1976. Afterwards, the rate decreased with the populational decline, being about 50% in late December. According to samples taken in the first quarter of the following year (1978), the population was made up of only a few dozen individuals. Parasitized molluscs were still present in January 1978. Finally, rare specimens were collected in March, none of which were infected.

A similar field experiment was conducted by Golvan (1978) in another pond at Grande Terre. About that experiment he expressed himself as follows: "It resulted in complete disappearance of *B. glabrata* from that pond. We have achieved there, for the first time, the eradication of a schistosomiasis vector population by a specific and easily controlled pathogenic agent. Without undue optimism we believe that those methods of biological struggle, if we are able to adapt them to local ecologic conditions, will make possible, in the future, the eradication of vector-borne diseases".

Perhaps it went unnoticed to me, but in the literature after 1978 I did not find any reference to further observations in the two mentioned biotopes. It would be worth while to follow up those environments for a few years to verify the fate of the remnant population in the former and the reality of eradication in the latter.

In the first case (Nassi et al.) the population had been so much reduced that not a single specimen was found on an exhaustive search. However, the snails reappeared in the next rainy season, giving rise to a population estimated at 800 individuals. After the inducement of a new epidemic wave, only rare, uninfected specimens were found in the last searches (March 1978). It may be presumed that those non-parasitized remnants were genetically refractory to *Ribeiroia*. Those few individuals became the reproductively active population that would assure restocking the biotope between two periods of relative abundance. Following the rules of genetic drift, those remnants would maintain, or even increase, the level of refractoriness in the population. Such cyclic fluctuations are common among natural populations whose growth form is regulated by seasonal periodicity. The study by Nassi et al. (1979a, b) is highly important as it demonstrates the influence of a parasite on the growth form of the host population in a closed biotope. However, for practical use in control of *S. mansoni* vector high contamination of the pond by parasite eggs must be indefinitely maintained. In open systems with interchange perhaps this might be feasible in the comparatively small area of Guadeloupe, about 1,800 km^2, but not in the 1,000,000 km^2 endemic area of Brazil.

In the second case (Golvan), if eradication of *B. glabrata* is confirmed, it can be considered an exceptional outcome, due perhaps to a very limited genetic variability in that population.

Competitors

Competition between schistosome vectors and other molluscs aiming to eliminate the former is a current line of investigation. As widely known, the intended result is based on the principle of competitive exclusion (Gause's hypothesis), which states that two species with similar ecological requirements cannot successfully live together for any length of time, because of their competition for all the basic requirements for life. The concept of competitive exclusion, therefore, is inseparable from the concept of ecological niche. In the city of Salvador, capital of the state of Bahia, there is a lake called "Dique do Tororó", the remnant of a once long defensive ditch dug by the early Portuguese settlers for protecting the small village from attacks by land. It was mentioned as the "Dique" by Spix & Martius (1828:636), who described it as a ditch extending along the east end of the "Arrabalde dos Barris", whence the name "Lac Baril" which appears in some descriptions of molluscs of Bahia published by Moricand. One of these studies (Moricand, 1853) refers to the existence of several molluscan species in the lake, among which *Biomphalaria glabrata* (under the names *Planorbis olivaceus* and *P. dentifer*), *Pomacea lineata* and *P. decussata*. Until about 15 years ago the Dique abounded with aquatic vegetation, predominantly *Eichhornia* and *Pistia*, supporting an enormous population of *B. glabrata*. Deepening and straightening of the margins, clearance of practically all aquatic vegetation and introduction of *Tilapia* resulted in drastic reduction of the snail population. In 1981 I received for identification a batch of the prosobranch mollusc named *Melanopsis brasiliensis* by Moricand (1839), and collected by Dr. Italo Sherlock, who was astonished by its extreme abundance. In October 1985, searching the Dique for snails, I found a well-established population of *B. glabrata* coexisting with pomaceas, tilapias and thiarids, which according to numerous reports are its natural enemies. Except for the tilapias, this coexistence has been going on at least since Moricand's time, more than 130 years ago. If you visit Pureza, a town in Rio Grande do Norte, and walk along a balustrade on the left bank of the Maxaranguape river where, after the so-called "Fonte", it broadens into a wide water blade, you will see large amounts of pomacea coexisting with *Biomphalaria straminea*. The same can be seen in the marshes of the Entre Ríos province in Argentina, where abundant pomaceas are mingled with *Biomphalaria tenagophila*, and in many other areas of South America.

To enhance the probability of biological control through competition, ideally it would be advisable to introduce into a *B. glabrata* biotope as many individuals of the candidate control species as those of the resident population. In practice, this means that the greater the introduced amount of the candidate control species, the more quickly may be its effectiveness assessed. My own experience with competitive exclusion is limited to two episodes, and has no practical consequence in vector control. The area of Rio de Janeiro is included in the range of *B. tenagophila*. In 1949, Professor Émile Brumpt asked me to send him specimens of *B. glabrata* as a contribution to the renewal of his laboratory colonies lost during the Nazi occupation of Paris. At that time I was ignorant of planorbid taxonomy, and some specialists asserted that all planorbids similar to those I used to see in the bodies of water on the campus of the Oswaldo Cruz Institute belonged to the species now called *B. glabrata*. Thus I sent Prof. Brumpt a batch of specimens from a creek which flowed entirely in the campus, rising in a swampy area and discharging into the Guanabara bay. Later, when I began to study the planorbids, I noticed that *B. glabrata* was confined to the area of that creek, while all the other bodies of water were inhabited by *B. tenagophila*. Inquiring into the subject, I learnt from a former Adolpho Lutz's assistant that in 1915, during his pioneer investigations on the Brazilian planorbids, that eminent biologist sent for *Planorbis olivaceus* (now *B. glabrata*) from the northeastern city of Aracaju, because he did not succeed in infecting with *S. mansoni* the planorbids of Rio de Janeiro. The newly arrived specimens were placed in a concrete tank near the creek. On a pouring wet night the tank overflowed, discharging snails into the creek. In 1963, I suggested that a young researcher under my guidance should investigate the planorbid population in the creek system and see whether it still contained *B. tenagophila*. Of 819 collected specimens, 2 were of *B. tenagophila* (Magalhães, 1966). This involuntary natural experiment showed that, after 50 years of successful competition, the dominant species did not manage to eradicate the resident one. Now the environment where that process took place has been radically changed by human action, so it is impossible to predict whether the process would have led to the effective eradication of *B. tenagophila*, or to a future equilibrium or semiequilibrium between the two species, or perhaps to the reversal of the process as a consequence of contingent natural changes in the environment.

The second episode took place in Belo

Horizonte, an absolute domain of *B. glabrata*, where *B. tenagophila* had not been found till then. In a perfectly isolated small pond on a hill in a suburb of the city, and with a population of *B. glabrata*, I found some albino specimens of *B. tenagophila* in mid-1961. Until then I only knew of albino *B. tenagophila* in Itajubá, southern Minas Gerais, and in São Paulo city. Investigating the subject, I learnt that a kind of waterlily from the Horto Florestal (plant nursery) had been introduced into that pond. I visited the Horto and found there an exclusively albino population of *B. tenagophila* in the waterlily's nursery; I was then assured that the plant in question had been brought from São Paulo. In August 1962 I collected 382 specimens from that pond: 339 were of *B. tenagophila* and 43 of *B. glabrata*, all of which were returned to the water. Monthly samples taken thereafter pointed to a steady increase of *B. tenagophila* in relation to *B. glabrata*. The ratio between them gradually changed to 119: 13 in February 1963, and 97:0 in March. Fortnightly sampling over the next three months gave the ratios 86:1, 147:1, 116:0, 98:0 and 123:0. In 1984 I went back to the spot to verify the situation, but urbanization had done away with the pond. Laboratory investigations showed that *B. tenagophila* had higher infection rates by trematodes and lower prolificacy than *B. glabrata*. In spite of those major disadvantages, the newcomer apparently drove out the resident species.

In both cases the foreign species became dominant in spite of being initially less numerous. Unfortunately these examples of competitive exclusion do not yield practical benefits because both species are vectors of *S. mansoni*.

Among the attempts to control the vectors through competition those that make use of the ampullariid *Marisa cornuarietis* and the planorbid *Helisoma duryi* are worth mentioning.

M. cornuarietis has been used since Oliver-González et al. (1956) and Chernin et al. (1956) observed that it controlled *B. glabrata* populations in natural environments and under laboratory conditions, respectively. It acts as competitor and predator, not only in relation to the food requirements of *B. glabrata* but also devouring newly hatched or even somewhat grown specimens, as well as the egg masses stuck to the vegetation, and interfering, in some not yet explained way, with the vital processes of the vector. It is not a question, in this case, of a selective ingestion of egg masses, because the target is the vegetation itself. Owing to its great voracity, *Marisa* literally devastates the aquatic vegetation. In Puerto Rico I saw a few ponds from which it had eliminated *B. glabrata*, and they seemed big excavations containing only water. In running waters and swampy areas, both in Puerto Rico and the Dominican Republic, its efficacy was doubtful. It cannot be introduced into rice and watercress fields, and into other wet-cultivated crops.

Helisoma duryi, a planorbid of an historically Nearctic genus which has spread through Middle America, has been found breeding naturally in South America west of the Andes, down to Lima, Peru. It has also reached several Antillean islands. For some time now it has been found, outside that range, in eastern South America (Venezuela*, Brazil*, Uruguay*), Germany (Düsseldorf*), southwest Asia (Iraq, Israel*, Saudi Arabia), several African countries, and Tahiti*. In May 1982 I received from Dr Gary E. Rodrick, of the University of South Florida, several specimens collected from the Maipo river, at Talagante, Chile, where the species must have been recently introduced, since I did not find it during intensive collecting in that area and over the region of Chile between Coquimbo and Tarapacá provinces (Paraense, 1966). Expatriate populations are often found in artificial environments such as aquaria and ornamental ponds.

Many laboratory experiments have shown that *H. duryi* competes with *S. mansoni* and *S. haematobium* vectors, not only in relation to food requirements but also by devouring their egg masses and interfering, in some not yet defined way, with the vital processes of those vectors (review by Frandsen & Madsen, 1979). It has the advantage of being refractory to schistosome infection and seems not to produce undesirable effects on the environment. Reading of the mentioned review leaves the impression that the few experiments till then carried out in the field had been inconclusive. The results of further pilot studies were discouraging, pointing to the preference of *H. duryi* for a different ecological niche from that of the target species (OMS, 1985).

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* Personal observations.

In August 1972 I found an abundant population of *H. duryi* in the state of Goiás, Central Brazil, certainly introduced with water plants. That population inhabited a pond (Lagoa da Pedra) connected to the river Canabrava, coexisting with the planorbids *Biomphalaria straminea, B. schrammi, Drepanotrema anatinum, D. lucidum* and *Plesiophysa ornata,* besides ancylids, physids and ampullariids (Paraense, 1976). There was also a very large population in a small isolated pond formed by the river's overflow during the recently ended rainy season. In the subsequent dry season the isolated pond disappeared and, surprisingly, not a single molluscan shell could be found on its former bed, while in the permanent pond *Helisoma* continued to coexist with the other species. For lack of time and opportunity I have postponed another visit to the spot.

Chemotherapy in control

Schistosomiasis control by drugs has been attempted in many communities. I will not dwell on this aspect, since in all of the instances a larger or smaller portion of the population continued to pass schistosome eggs, be it due to drug inefficacy in individual cases, or parasite resistance, or contraindication of the drug in cases of pregnancy, hepatic, renal, nervous and cardiac dysfunction, and other reasons. In spite of those limitations, well-planned programs based on recently developed safe and effective drugs have attained the primary goal of chemotherapy in schistosomiasis control – reduction of morbidity to levels below public health importance (e. g. Sleigh et al., 1986).

Health education

It has become a commonplace that, at our present state of knowledge, schistosomiasis control is not feasible through isolated measures. Like any vector-borne disease, schistosomiasis is a complex ecologic phenomenon, in which the parasite has as its immediate environment, successively, the definitive host, water, the intermediate host, and again water. It is logical, therefore, to conclude that its control depends on integrated measures aiming at all phases of the parasite life cycle. As an isolated measure, the only really effectual one would be health education. But for it to become operative two obstacles must be removed – a material one, and another behavioral or, as I prefer it, instinctual. The material obstacle is determined by the low socioeconomic standard of the involved communities, which live in environments lacking basic sanitary conditions. I will never forget an extreme example, in the interior of Minas Gerais, when I came accross a woman taking water for domestic use from the only creek available to the village, teeming with infected snails. In response to my explanations and recommendations, she said that she knew the water was infective, that for lack of money she could not buy extra fuel to heat the water and thus kill the cercariae, or extra containers to store water for a few days and so inactivate the cercariae. The instinctual obstacle has to do with the well-known difficulty in inducing behavioral change associated with the tyranny of natural selective forces. It is unquestionable that in rural areas schistosomiasis is acquired mainly during childhood. And it is not mere coincidence that the hours of most intense solar radiation, in which the freest people in the rural environment – just children – are urged towards a refreshing swim, are also the hours in which the largest numbers of cercariae are released. Many times have I seen children in communities selected for integrated control programs and intensively indoctrinated by health educators, to delight in infective baths, even though aware that they were receiving doses of cercariae.

In addition to the mentioned obstacles, in Brazil's case there is still the insufficiency of public resources to control the immense endemic area. After all, there are many other problems and diseases competing for the available resources.

Vaccination

In a series of studies on the genetics of *Drosophila pseudoobscura* published from 1935 on, Dobzhansky noticed that the populations of this fruit fly could be characterized by the presence or absence or by relative frequencies of certain types of Y chromosome, of gene arrangements in the third and X chromosomes, and of several modifying genes. Analysis of these characteristics showed that the genetic composition of populations of some localities changed from month to month, coincidently with the annual climatic cycle, and were therefore reversible. Essential in this discovery is that the observed changes revealed a great plasticity of the species genotype, and might be regarded as models of adaptative evolutionary changes on the racial and higher levels (Dobzhansky, 1943). In short, a population of drosophila shows, in a given month, a relative frequency of gene arrangements that reappears in the same month for consecutive years. Those changes are produced by natural selection, and represent adaptative reconstructions of the population genotype that facilitate survival in different seasonal environments (Dobzhansky, 1947).

In 1940a, b, Timoféeff-Ressovsky also described cyclic changes in the genetic composition of natural populations of the ladybird beetle *Adalia bipunctata* and of *Drosophila melanogaster.* Similar changes were recorded by other workers in longer lived organisms.

It may seem strange to the immunologists here present, but to me these cyclic changes have the same meaning as the antigenic variation and, in general, the parasite evasion of the immune response. The similarity extends even to the reversibility of the cyclic changes in drosophila and of the antigenic variation in trypanosomes, and also to the differences, according to the geographic origin, in the repertoires of cyclic changes in drosophila and of variable antigenic types in trypanosomes. This is another example of the fact that nature often uses several means to attain the same end. These variations are all the result of a continuous process of adaptation to environmental oscillations. In the case of insects, the selective factor is represented by seasonal oscillations. In the case of parasites, the immediate environment is the host's organism which, being a biological system, is also undergoing unceasing variation, although oftenest buffered by homeostatic mechanisms. Thus the host-parasite relationships result from a process of coevolution, that is, of coadaptation to continual variation in both partners.

While making these comments, I think of the tremendous difficulties involved in the search for a vaccine against the schistosome, which has shown a multiform capacity to fit in with the attack strategies of its hosts. The worker who tries to attain this goal has to deal with a highly complex parasite which possesses, although apparently less evolved, but not less efficient, basically all the organic systems of its definitive host. This means that the vaccinal antigen has to be carefully selected lest it should unleash some kind of experimental autoimmunity. A promising approach seems to be the recent one by Lanar et al. (1986), who obtained significant protection in mice vaccinated with paramyosin, whose occurrence in Schistosomatidae was first verified by them. This protein, originally recognized and studied in the adductor muscle of the bivalve shell, confers the property of prolonged tonic contraction upon that muscle, thus enabling it to keep the shell tight shut. So far paramyosin has been found exclusively in some muscles of invertebrates belonging to about seven phyla. It makes up the core of the thick filament, and can be compared to a slender rod completely wrapped up by myosin. Now a question: if paramyosin is completely surrounded by myosin, how can it be reached by the antibody? To my knowledge, the combined techniques of electron microscopy and X-ray diffraction show that the fundamental filament structures are very similar in the muscles of both vertebrates and invertebrates. It is probable, therefore, that myosin in the two groups is so similar that it must be attacked by specific antibodies, in the parasite as well as in the host, to expose paramyosin in the schistosome. According to Lanar et al. (1986), the mechanisms of schistosome destruction induced by the vaccine seem to be cell-mediated rather than humoral, so that paramyosin need not be surface-exposed to trigger the presensitized T lymphocytes that in turn activate macrophages for parasite killing. They presume the cell-mediated response could be stimulated by paramyosin molecules or fragments released from parasites as a consequence of either normal protein metabolism or spontaneous parasite attrition.

Japan's achievement

We will be meeting here for the next few days to debate possible solutions to the schistosomiasis problem. Remembering what was said in this speech, it seems that unfortunately all aspects of the problem are still awaiting a definite solution. Perhaps somebody might be thinking of Japan, which managed to control schistosomiasis.

To cut a long story short, I will summarize the case. Before World War II there were in Japan only five relatively small and well-circumscribed foci of schistosomiasis (Faust, 1929; Hunter et al., 1982). By the end of the war the need for increased food production gave rise to numerous small vegetable gardens, even in densely populated areas, where every bit of soil was under cultivation. As chemical fertilizers were not available, gardens and farms were often fertilized with human manure. Consequently there was a dramatic increase in parasitism, with over 90% infection with intestinal helminths or protozoa, or both, in samples of the populations of 29 prefectures. By way of example I will mention Nagatoishi, which had the highest prevalence of schistosomiasis (72.9%) and the highest parasite density index. The following is a synopsis of the pertinent data from Hunter et al. (1982). Nagatoishi was devoted to paddies except for a few roads, paths, houses and school. It was surrounded by a dike built to prevent flooding from the neighboring river which overflowed its banks four or more times a year. Nearly all of the rice paddies were situated within the dike. The population of 1,050 persons occupied an area of 60 ha. Chemical treatment of the area with sodium pentachlorophenate began in 1950, being applied twice a year, in spring and fall (when irrigation of the paddies was not in progress) until 1972, when it was replaced by another molluscicide (3,5-dibromo-4-hydroxy-4-nitroazobenzene, Yurimim). The number of new cases of schistosomiasis requiring treatment dropped from 30-35 per year to five in 1950 and zero in 1951. In 1953 a major flood breached the dike; most of the houses were flooded with muddy water for three weeks. In 1954 children had a dramatic increase in infection believed to be a direct result of the flood. A significant (99.5%) reduction in the numbers of surviving snails was achieved. All the irrigation ditches were concreted from 1954 to 1958 (from 1956 to 1980 concreting of the paddy irrigation ditches in all of the endemic areas was carried through). All the swampy areas were reclaimed. A fertile area filled with paddies and vegetable gardens, but with abundant infected snails, was converted into a golf course. Plants whose roots sheltered snails were dug up and burned. The population was aware of the problem and freely participated in the program. In 1970 it was reduced by emigration to 800 with only 20 ha still being worked. Between 1972 and 1975, 17 buildings and 600 apartments were built and soon occupied. By 1978 all children were negative for *S. japonicum* infection. In spite of successful control, *Oncomelania hupensis nosophora* still persisted. "All the available evidence indicates that control of schistosomiasis japonica has actually been achieved and suggests that within the next decade the disease will be *eliminated* from Japan" (Hunter & Yokogawa, 1984). In 1980, except for several very small endemic foci, schistosomiasis was not being transmitted to humans in Japan, having been reduced to a zoonosis among rodents, with a few residual human cases, humans being still at risk (although exceedingly low) of acquiring the disease (Hunter et al., 1982; Hunter & Yokogawa, 1984).

The success of the enterprise was due to a combination of several factors. First, to be Japanese; and next: smallness of the whole endemic area, good planning, hard work, community awareness of the value of health, support from local and national governments, urbanization and socioeconomic development.

Japan's example is remarkable, but can hardly be followed by countries with vast and diversified endemic areas. Along with that kind of effort, other resources are needed which can only be created by those who, in laboratories and in the field, commit their intelligence and skill to the search for solution of problems of such great complexity.

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