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VECTOR CONTROL OF SNAIL-TRANSMITTED DISEASES

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This brief review of research on the vectors of snail-transmitted diseases focuses on two Asian nations where these parasitic diseases are a major problem.

In late 1982 I visited Thailand and the Philippines with support from the Agency for International Development to explore the possibilities for developing collaborative research programs with local scientists. The report is in five parts:

1. Notes on snail-transmitted diseases and their importance in Southeast Asia.

2. Notes on existing vector control techniques which leave a lot to be desired and suggest the need for additional research.

3. Thailand - comments on a strong national research program supported by W.H.O. and the Rockefeller Foundation.

4. The Philippines - vector control is an integral part of foreign-assisted development projects but research support is inadequate.

5. Discussion - prospects for collaborative research on vector control and suggestions for possible A.I.D. involvement.

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Table 1

Medically and economically important
snail-transmitted diseases in Southeast Asia

Disease	Estimated Prevalence		Remarks
	Thailand	World	
Schistosomiasis (blood flukes)	10,000	250,000,000	dysentery, intestinal and hepatic cirrhosis
Paragonimiasis (lung flukes)	6,000,000	8,000,000	lung and brain damage
Clonorchiasis (liver fluke)	none	20,000,000	linked to liver cancer
Opisthorchiasis (liver fluke)	6,000,000	10,000,000	linked to liver and bile duct cancer
Fascioliasis (sheep liver fluke)	few	1,000,000	economically significant livestock pest
Fasciolopsiasis (giant intestinal fluke)	10,000,000	20,000,000	heavy infestations damage intestines
Echinostomatidiasis (intestinal flukes)	5,000,000	40,000,000	economically significant chicken duck pest
Angiostrongyliasis (rat lungworm)	few	few thousand	can cause brain damage
Heterophyidiasis (intestinal flukes)	thousands	few million	intestinal and visceral damage
Gastrodisciasis (intestinal flukes)	rare	few thousand	diarrhea

Introduction

Snail-transmitted diseases are among the great neglected diseases of mankind. Affecting more than 10% of the human population they include a dozen diseases of varying morbidity (Table 1). Although the majority of infections are debilitating rather than life threatening they contribute significantly to the disease burden in many parts of the developing world.

The snail-transmitted diseases are caused by parasitic worms which as adults may invade various parts of the human body. These worms range up to two inches in length but most are a quarter that size. Depending on their species they inhabit the blood vessels, the intestine, the lung, the bile duct and liver; occasionally they get lost and end up in the membrane surrounding the brain. Disease is caused by the movements and metabolism of the worms themselves and by the bodies immune response to the thousands of eggs they produce.

The parasite's eggs, which are excreted in vast numbers, hatch in water and proceed through a series of larval stages. One or more of these larval stages involves a period of life in the tissues of a specific immunologically suitable freshwater snail (Table 2). The larval parasite typically reproduces asexually within the snail and large numbers of daughter larvae emerge. The larval phase which emerges from the snail will, depending on the species, seek out a second intermediate host or proceed directly to the final host - man. Many species which have second (and a few which require even third) intermediate hosts utilize other snails, freshwater fish, crabs and shrimp. Other species spend their second major larval stage on the leaves of aquatic plants. After these complex larval stages are complete the parasite invades man and other mammals or birds to mature and reproduce sexually. Infection comes from skin contact with polluted water or the ingestion of larvae in uncooked infected snails, fish, crustaceans, or plants.

Table 2

Medically important snail-transmitted parasites in Thailand and the Philippines

Parasite	Life cycle		
	First larval stage host snail	Second larval stage	Final Host
Schistosoma			
S. japonicum	Oncomelania	in water	man, mammals
S. mekongi	Tricula	"	man, dogs
S. spindale	Indoplanorbis	"	cattle, buffalo
S. incognitum	Lymnaea (Radix)	"	rats, dogs
Paragonimus	Brotia in Phil.		
P. westermani	unknown in Thai.	crabs, shrimp	man, cat, dog
P. heterotremus	"		man, mammals
P. siamensis	"		cats
Opisthorchis			
O. viverrini	Bithynia	fish	man
O. felineus	Bithynia	fish	man, cats
Fasciolopsis	several in Phil.		
F. buski	unknown in Thai.	on water plants	man, pig
Echinostoma			
E. spp.	several species (Thiara, Pila)	fish	man, mammals, birds
Angiostrongylus			
A. cantonensis	several (Achatina, Pila)	crabs, shrimp	man, rats
Heterophyes			
H. spp.	several (Thiara, Semisulcospira)	fish	man, mammals
Gastrodiscus			
G. hominis	not known	on water plants	man, mammals

In many parts of the world where snail-transmitted diseases are a problem, infection (especially of children), is almost unavoidable in the normal conduct of life.

Schistosomiasis is the best-known group of snail-transmitted diseases. Between 200 and 300 million people suffer its debilitation. Symptoms include fever and malaise followed by chronic dysentery or cystitis, and hepatic fibrosis and enlargement of the spleen. The course of the disease depends on the number of parasites and on the age and general health of the individual. The disease is widespread in the tropics and subtropics and has recently increased in prevalence as a result of population growth and irrigation projects. The latter, undertaken with the intent of improving agricultural productivity or providing hydroelectric power have actually exacerbated the health problem by increasing the habitat of the parasite and its intermediate hosts.

Control programs for schistosomiasis are multifaceted as there is no easy way of preventing the infection of humans or the transmission of the parasite. Although improved sanitation and public health education coupled with general improvements in the standard of living have solved the problem in Japan and Puerto Rico such changes cannot be realized easily in most of the world. For other countries hope lies in a combination of vaccine development, chemotherapy, snail control, habitat alteration and sanitary engineering. Vaccines are being developed but, for biological reasons peculiar to worms of this type, it is unlikely that they will be perfected in this century. A new drug, praziquantel, is now available to treat the infected who can afford it and, unlike its antecedants, it does not appear to be carcinogenic or plagued with devastating side effects. Useful as it will be in the next decade we must anticipate, however, that resistant strains of worms will evolve and that long-term disease control cannot be based on chemotherapy alone. That leaves snail control and habitat alteration as prime techniques for the long-term control of

disease transmission.

Less attention has been given to the other snail-transmitted diseases of man and his domestic animals (Table 1). It must be emphasized that there are over 40,000 known species of parasitic worms and that each of the diseases on the list may be caused by several different parasites. For most of these parasites and diseases even diagnosis is a problem. For this reason, and the fact that very few surveys for these parasites have been undertaken, the numbers of infected people given in Table 1 are informed guesses rather than verifiable counts. Nevertheless, there can be little doubt that these diseases impact hundreds of millions of people. The economic costs of these infections are unknown; they probably amount to 10-100 times the amount now spent on research and control. The Edna McConnell Clark Foundation of New York has estimated that only 4.5 cents is spent on research worldwide for each case of schistosomiasis. For comparative purposes - over $209 research dollars are spent for each case of cancer in the U.S.

The snail-transmitted diseases of Asia have received less attention than those of Europe, Africa and the Americas. This is unfortunate as they are locally significant and likely to continue to retard societal development for the foreseeable future. In each country the nature of the disease problem differs and the governmental response has taken a different direction. In China, schistosomiasis control is being sought through sanitary engineering and snail control by habitat alteration. In the Philippines, snail control measures are required by law on all new agro-development projects. In Thailand, where four snail-transmitted diseases afflict a large proportion of the population (Table 1), the government has encouraged research on vectors and their control.

Improved methods of vector control are urgently needed as existing techniques are too expensive and ineffective in the long-term. They will be required in the

future, even if vaccines and effective drugs become available, as the parasites will evolve resistant strains and continue to cycle through mammals other than man. It is a sad commentary on the state of medical malacology, a field that lags far behind entomology in the application of the principles of population ecology and genetics to control problems, that research on snail control remains so inadequate.

Methods of Snail Control

1. Chemical methods of reducing vector snail numbers

Molluscicides are non-specific broad spectrum poisons of unknown long-term ecological impact on the communities in which they are applied. Frescon and Bayluscide have been used with satisfactory short-term results in parts of Africa but have found little use in Asia where snail habitats are more dispersed. Local snail erradication has proven almost impossible to achieve and reinvasion and repopulation occur very rapidly when treatment ceases. These substances consequently have limited long-term utility in disease control. They have also become too expensive for use in most developing countries.

Molluscicides of plant origin are being sought in some areas to replace imported and expensive synthetic chemicals. In the Philippines the seeds of the tubang-bakod (*Jatropha curas*) and tuba (*Croton tiglium*) as well as the bark of the gogo plant were found to have molluscicidal properties but research on these substances does not appear to have been sustained.

Molluscicides will play a diminished role in future long-term control schemes.

2. Biological control of vector snails

There have been several attempts to control disease transmission by adding competitors, predators, parasites or pathogens to snail colonies. Such biological control techniques have been very successfully applied to some insect pests. Although the snail control techniques proposed so far have worked locally or have some theoretical promise none have received enough scientific attention to be considered of proven merit.

The South American snail Marisa cornuarietis was introduced to Puerto Rico 30 years ago and in some ponds and lakes it was found to replace Biomphalaria glabrata the vector of Schistosoma mansoni. Marisa eats Biomphalaria eggs and young and under laboratory conditions it is a competitively superior herbivore. In 1979 Jobin reported being able to reduce a population of Biomphalaria and their schistosomes by introducing 20,000 Marisa locally. This result is important because control was achieved quickly and inexpensively. Even before Jobin's result Marisa and another species, Helisoma duryi, had been introduced in Egypt to control Biomphalaria and Bulinus. As yet, however, no convincing evidence has been presented to show that either species has real promise in Africa.

At the same time on Jobin's experiment in Puerto Rico a group of French scientists attempted to control Biomphalaria glabrata in a single pond on Guadeloupe by using a sterilizing echinostome Ribeiroia. (The echinostomes are intestinal flukes with molluscan larval stages.) Despite technical problems and poor experimental design the results were encouraging.

Earlier in the 1970's some quite careful work was done to see if the larvae of another echinostome would outcompete the larval schistosomes within

infected snails. Although these antagonism experiments were aimed at parasite control directly rather than at vector control it is appropriate to mention them here. Lie and Heyneman (University of California San Francisco) conducted a number of small-scale field trials in Malaysia and Thailand in the early 1970's. Some of these experiments were successful in reducing the transmission of S. spindale (a water buffalo schistosome) through the snail Indoplanorbis exustrus, others were not. As promising as this approach to schistosome control may be it is presently impractical.

Other workers have attempted to find fish, aquatic insects, parasitic flies, pathogenic bacteria, fungi and protists that might be useful in reducing vector snail numbers. Very little effort has been put into research of this type and it is not surprising that most of it has been scientifically unsatisfactory and unproductive. There are other reasons why it has not proved as easy to develop biological control techniques for snails as it was for some plant insect pests. First vector snail populations are rarely regulated in nature by their enemies. Second, our knowledge of snail biology is still most unsatisfactory. There are at least ten times as many professional entomologists as there are malacologists. Biological control techniques for snails will simply take longer to develop then they did for insects.

I feel obliged to insert a cautionary note before discussing other types of snail control. The introduction of animals for control purposes has occasionally backfired with serious ecological and economic consequences. Introduced species can themselves be vectors of other diseases. Other species become pests in their own right when removed from their natural environment. What if Marisa began to eat rice after it was introduced to Africa? What if an echinostome began to infect man instead of just local rodents? Although bio-

logical control of vector snails and their parasites remains a real possibility a great deal of careful research must precede field trials of any new technique.

3. Vector snail control by habitat alteration.

One of the most direct ways of reducing the size of snail populations is to reduce the carrying capacity of their environment by habitat alteration. Just as malaria was controlled by draining mosquito-infested swamps, it has been possible to eliminate schistosomiasis by destroying snail habitats. Snail populations have been reduced by canalizing streams, destroying aquatic and littoral vegetation, draining swamps, deepening ponds and stocking them with fish, or filling them in. As the following notes on the Philippines indicate such techniques can be locally significant.

Habitat alteration can have numerous benefits apart from disease control. It typically leads to increased food production. Improved drainage or irrigation result in higher crop yields. Conversion of swamps to fish ponds results in increased protein availability. On the other hand, habitat alteration if improperly planned can have serious negative effects. Often habitat simplification results in the local extinction of beneficial species and outbreaks of species that had not previously been pests. Habitat alterations most serious drawback remains however the high cost of construction and maintenance.

4. Schistosome control by genetic manipulation of vector snail populations.

Some insect pests have been controlled by swamping local populations with large numbers of sterilized or cytoplasmically incompatible males of the same species. Despite the few spectacular successes with insects it was argued 20 years ago that the technique would not work with freshwater snails. These

theoretical criticisms are now known to be unsound but research on this possible control technique has yet to be undertaken.

I have suggested a second approach to the problem of disrupting schistosome life cycles by releasing genetically resistant individuals of the normal intermediate host snail species at sites of disease transmission. Such genetically resistant snails can be isolated by artificial selection procedures, mass-reared, and their descendents returned to the population from which they were derived. The method is based on evidence that intermediate host specificity is pronounced, that snail susceptibility and larval schistosome infectivity are both under oligogenic regulation, that natural selection will favor genes for resistance, and that miracidia cannot discriminate between susceptible and resistant snails. If sufficient numbers of resistant snails are released then the resultant genetic perturbation may be too great for the longer lived schistosome population to adjust behaviorally or evolutionarily. Under certain ecological circumstances it may be possible to significantly reduce the transmission cycle within a few years. This relatively simple scenario for genetic control is not new; it first appears (in simpler form) in the literature 25 years ago. Its potential has been generally ignored, however, because of objections raised by some early discussants. These objections were premature and it is now recognized that the failure to recognize intraspecific variability in response to infection has hindered experimental investigation of host-parasite relations and may have delayed the development of adequate control measures.

Research on the Vectors of Snail-transmitted Diseases in Thailand

As noted above snail-transmitted diseases pose a particularly significant public health problem in Thailand. In addition to schistosomiasis, which is increasing

in range and prevalence, paragonimiasis, opisthorchiasis and fasciolopsiasis are locally important (Table 1). Perhaps a third of the rural population carry snail-transmitted parasites at some point in their lives.

There is a national center for research on snail vectors and parasites at Mahidol University. Mahidol University is the relatively new national medical school established along American lines with help from the Rockefeller Foundation. Most of the faculty are Thais who have received graduate education in the United States and Europe and much of the instruction is in English. Scientific research is encouraged.

The Centre for Applied Malacology in Southeast Asia was established in late 1978 at Mahidol University with an Institution Strengthening Grant from the World Health Organization Special Programme for Research and Training in Tropical Diseases. The long-term objectives of the Centre are to:

1. undertake research and training programmes of particular relevance to the region;

2 function as a reference laboratory for snail-host identification and advisory services, as well as maintenance of living and preserved mollusc/parasite stock materials;

3 collaborate closely with and assist in the coordination of other laboratory and field programmes on applied malacology.

The Centre's subsidiary objectives include

a. the development and standardization of methods, terminology, diagnostic procedures and field control strategy;

b. the distribution, upon request, of standard snail and parasite strains and preserved specimens;

c. the development of training programmes at both professional and subprofessional levels;

d. the preparation, publication and dissemination of information;

The Applied Malacology Center (AMC) has established an administrative structure and procedures for the operation of the multi-laboratory research unit. In 1982 the AMC had a participating staff of two dozen faculty members representing the Schools of Science (Departments of Biology and Microbiology), Tropical Medicine and Public Health (Appendix A). The AMC is coordinated by Dr. Suchart Upatham, a Professor of Biology and Associate Dean of the Faculty of Science.

AMC activities are scattered around the various participating laboratories. The group in the Department of Biology have ample space (about 12,000 sq. ft.) and reasonably equipped laboratories. There are specialized facilities for culturing snails and parasites, testing molluscicides, immunoelectrophoresis, cytogenetics, parasitology and microscopy including SEM. There is a small but functional malacological library and a reference collection of molluscs. The museum now has samples of 84 taxa of biomedical importance collected from throughout Thailand. The AMC overseas the training of graduate students, there are currently four M.Sc. students and three visiting fellows from Saudi Arabia, Somalia and China. In addition four members of the staff are currently on leave completing doctoral studies at the University of Michigan.

The collection of live snails and parasites maintained at the AMC is unequalled in Asia. 17 species or subspecies of biomedically important snails and 8 species or subspecies of Schistosoma and Opisthorchis are being cultivated (Table 3). Other species are available locally.

This unique collection is the focus of most of the experimental research conducted at the AMC. On-going projects include:

Table 3

Snails and Parasites Cultivated at the

Applied Malacology Center, Thailand

Snail	Parasite
Oncomelania hupensis quadrasi	Schistosoma japonicum (Philippines strain)
O. h. lindoensis	S. japonicum (Indonesian strain)
O. h. hupensis	S. japonicum (Chinese strain)
O. h. nosophora	S. japonicum (Japanese strain)*
Tricula aperta (alpha race)	S. mekongi
T. aperta (beta, gamma races)	"
T. bollingi	S. sinensium*
Robertsiella kaporensis	S. japonicum (Malaysian strain)
Indoplanorbis exustus	S. spindale*
Lymaea rubiginosa	S. incognitum*
Biomphalaria glabrata	S. mansoni
Bulinus truncatus	S. haematobium
Bulinus abyssinicus	"
Bithynia s. siamensis	Opisthorchis viverrini
B. s. goniomphalos	"
B. funiculata	"

* not in laboratory culture in November 1982.

1. studies on the effects of method of exposure, cercarial concentration, and length of exposure on the infection of mice by Schistosoma mekongi.

2. studies on the effects of water pH, temperature and salinity on the infection of mice by S. mekongi.

3. studies on the effects of cercarial concentration and length of exposure on the infection of mice by S. japonicum (Philippines strain).

4. studies of the effects of miracidial loads of S. japonicum (Malaysian strain) on the snail Robertsiella kaporensis.

5. studies of infectivity of cercariae of S. japonicum (Malaysian strain).

6. studies of cercarial shedding patterns of S. japonicum (Malaysian strain) by Robertsiella kaporensis.

7. scanning electron microscope (SEM) study of the tegumental surface of adult S. mekongi. SEM study of adult S. incognitum, a parasite of rats and dogs.

8. studies of enzymatic variation in three races of the snail Tricula aperta by isoelectric focusing.

9. studies of enzymatic variation in three types of Bithynia (the intermediate-host snail of Opisthorchis) by isoelectric focusing.

10. comparative studies of soluble proteins from adults of S.mekongi S.japonicum (Philippine and Malaysian strains) by SDS gel electrophoresis.

11. studies on the biology of S. sinensium, a Chinese animal schistosome recently discovered in Thailand.

12. field studies of the population dynamics of the beta race of the snail Tricula aperta in the Mun River.

13. studies of the migration and development of S. mekongi in Tricula aperta.

14. studies of reproductive anatomy of S. mekongi.

15. studies of the effects of some physico-chemical factors on the infectivity of S. haematobium larval stages.

16. studies of the effects of various physico-chemical factors on the infectivity of S. mekongi miracidia.

~~17. biosystematic studies of Pila snails.~~

This diverse research program is supported in large part by grants from outside Thailand. The AMC has received a 5-year developmental grant from the UNDP / World Bank / WHO Special Programme for Research and Training in Tropical Diseases. In

1981-2, the third year of the project, the AMC was awarded $63,000. In addition, the Center has received smaller grants from the Rockefeller Foundation for the study of opisthorchiasis. These awards are very cost-effective because salaries are much lower in Thailand than the U.S. For example, $12,000 pays the annual salaries of the 2 technicians with B.Sc. degress and 4 laboratory assistants responsible for snail cultivation, maintenance of schistosome cycles and field work on Tricula aperta.

The AMC has established linkages with scientists working at the Institute for Medical Research in Kuala Lumpur, the University of Indonesia in Jakarta, the Institute of Public Health in Manila, the First Shanghai Medical College, the University of Somalia and the University of Michigan. Although most of the research in Thailand is now performed by well-trained Thais there is a long history of foreign involvement in the national scientific enterprise and American researchers have been concerned with snail-transmitted diseases there since the 1950's.

Vector Control and Research on Snail-transmitted Diseases in the Philippines

Serious interest in snail-transmitted diseases in the Philippines began after whole teams of U.S. Army bridge builders contracted schistosomiasis in late 1944. Following the war snail and parasite surveys were initiated to determine endemic areas. Commencing in 1954 a major W.H.O. sponsored project was undertaken on Leyte. The purpose of the Leyte Pilot Project in which several American scientists participated was to conduct research on epidemiology and experiments on control. This project, which remains perhaps the best documented epidemiological study, led ultimately to a four-pronged approach to disease control in the Philippines. This involves the treatment of infected individuals, snail control by agro-engineering methods, environmental sanitation, and health education. Snail control was achieved

by drainage of habitats, conversion of swampy depressions into fish ponds, and changes in the rice planting pattern. In 1956 after preliminary experiments were completed, an attempt was made to interrupt transmission of schistosomiasis in the whole municipality of Palo, Leyte. Snail populations were reduced over 85% and prevalence in children showed a significant reduction by 1959. The cost of the habitat alteration was high but amounted to less than the annual cost of the disease. Unfortunately, the effort was not sustained and schistosomiasis remains a problem in Palo; in December 1980, 1 in 3 people in the town still had schistosomiasis (over 9000 cases). The government has built a schistosomiasis clinic and hospital there and the Japanese provided some research buildings and equipment.

Following the initial success of the Leyte Pilot Project four Schistosomiasis Advisory Teams were created in 1961 to provide technical assistance to the four Regional Health Offices. UNICEF provided vehicles and equipment but little was accomplished in the absence of other funding. With the realization of the magnitude of resource requirements and the need for interagency cooperation in the control of schistosomiasis the National Schistosomiasis Control Commission was created in 1966. This was subsequently strengthened by reconstitution as the Schistosomiasis Control Council which has a board and committees representing twelve government agencies. Initially, this organization tapped foreign commodity assistance from the USAID/Food for Peace Program and later from the UN/FAO World Food Program in the implementation of its various control projects, particularly snail control. Again, the level of funding was quite inadequate to the task of disease control.

Since 1976 the government has made schistosomiasis control an integral part of agro-development programs in endemic areas and provided funds for this purpose. There are now nine locally funded projects in different provinces and seven foreign-assisted programs (two integrated rural development programs and five irri-

gation development projects). These development projects involve 22 provinces where schistosomiasis is a problem. They are supported primarily by loans from either the International Bank for Reconstruction and Development or the Asian Development Bank and each project has been designated for a 5-year implementation period, the earliest of which started in 1976. This infusion of foreign assistance has seen the annual budget of the Schistosomiasis Control and Research Service (S.C.R.C.) grow from about 2 million pesos in 1974 to 22 million pesos (about $3 million) in 1981.

Today the following control measures are employed:

1. Case detection by microscopical examination of fecal smears and treatment of confirmed cases with praziquantel.
2. Health education by means of seminars, community assemblies and the use of mass media including radio.
3. Environmental sanitation by provision of water-sealed toilets, safe water supplies, footbridges, and control of stray animal hosts.
4. Snail control by drainage, ponding, clearing, filling, mollusciciding and improved rice farming.

These measures have been employed with varying degrees of success. Poor community response to parasite surveys and to lectures, funding problems, delays in the procurement of equipment and personnel recruitment problems have hindered the execution of the control plans. Mass treatment of infected individuals is held up until the drug praziquantel is more fully tested. Nevertheless, there has been some progress as these three examples of S.C.R.S. projects show. In Sorsogon, where 89% of the people were examined in two small villages and all infected individuals were treated with praziquantel, prevalence dropped from 43% to 17% and annual incidence fell from 15% to 5%. In a Leyte project, where multiple control measures are being implemented, prevalence among children has already decreased from 20% to 12% and annual incidence has declined from 19% to 7%. This reduction in disease transmission was associated with the treatment of 9,367 people, the construction or improve-

ment of 122 km of drainage canals, the installation of 494 water pumps and the provision of 1,966 water-sealed toilets. Finally, in an on-going project on Mindoro, where 6,180 people received chemotherapy and the local snail population was halved, the prevalence has dropped from 5.2% to 2.5%.

The S.C.R.S. attempts to control schistosomiasis in the Philippines are undoubtedly meeting with local success. Clearly, interagency teams of biologists, engineers and medical technicians can reduce prevalence to acceptable levels within 5 years. What is not clear is whether these local projects can ever be extended to other endemic areas. More importantly, it is predictable that most gains will be lost if control efforts cease at the end of each development project.

It is therefore pertinent to inquire what type of research is being conducted by the S.C.R.S., research that might support their present efforts or lead to improved low-cost techniques for future use. In recent years the S.C.R.S. has been conducting research in three areas: chemotherapy, diagnosis and molluscicides. The work on chemotherapy has focused on the testing of the new drug praziquantel on humans. Some of the trials are directed by Dr. Ernesto Domingo of the University of the Philippines Medical Center with support from the Edna McConnell Clark Foundation of New York. The trials show the drug to be preferable to any other available; efficacy is good following 2-3 doses in a single day and toxicity is mild and transient. The drug kills adult worms and relieves symptoms of disease. It does not, however, prevent reinfection. A second area of S.C.R.S. interest involves diagnosis. Traditionally, stool samples have been examined by technicians for eggs. Work by Dr. Edito Garcia at the University of the Philippines Institute of Public Health has led to the development of a simpler, more quantitative, Kato-Katz thick smear technique. Serodiagnostic techniques are also being sought. In a project funded by the N.I.H. and the Clark Foundation, researchers from the University of

Chicago joined with S.C.R.S. staff in an attempt to develop an ELISA test for S. japonicum soluble egg antigens. Finally, as noted above, the S.C.R.S. has in the past sought molluscicides of plant origin. None of its discoveries in this area have been developed to the point where they can be used in the field.

There is in fact very little research going on at the S.C.R.S. headquarters or Palo Research Center. With the exception of the praziquantel trials most of the above mentioned projects were conducted at other institutions. The laboratories at Palo were built by the Japanese International Cooperation Agency and used by Japanese researchers during the 1970's. They are poorly equipped and supplies (including praziquantel) are often stolen before arrival. With the exception of the physicians there do not appear to be any Ph.D.-level research scientists on the staff of the S.C.R.S.

Snail control is the responsibility of S.C.R.S. malacologists. I met two at the Palo Center and there are at least 20 more assigned to various development and public health projects around the country. These technicians generally have a college degree in zoology or medical technology. Their prime responsibility lies in locating and monitoring snail colonies involved in disease transmission and assisting in attempts to reduce snail numbers by habitat alteration. To increase their effectiveness the S.C.R.S., with support from the W.H.O (Western Pacific Region), sponsored national training courses in medical malacology in 1980 and 1981. These 2-3 week workshops on molluscan biology were taught by Dr. J. B. Burch (University of Michigan) and faculty from the Institute of Public Health and the Department of Zoology, University of the Philippines.

Research on snail-transmitted diseases is being carried out at laboratories in the University of the Philippines and three other locations in Manila (Appendix A).

1. Department of Parasitology, Institute of Public Health, University of the Philippines. The department is primarily concerned with training undergraduates in public health but several staff members have expertise with snail-transmitted diseases and 2-3 are maintaining research programs with graduate students. Foremost among these is Prof. Edito Garcia whose work on immunological aspects of schistosomiasis is funded by the W.H.O. His research is relevant to vaccine development and disease diagnosis. Garcia is also collaborating with Dr. Graham Mitchell of the Walter and Eliza Hall Institute of Australia on an immunodiagnosis problem. He maintains S. japonicum (4 strains from different Philippine islands) and its intermediate-host snail in the laboratory. His research opportunities are limited by constraints of time, space, and the fact that the Department's total annual budget for supplies is $1,000. He has had to decline some requests for collaboration with U.S.-based research groups.

2. Department of Zoology, University of the Philippines. After a series of meetings in August 1981, a group of faculty members organized a research team aimed at working on selected aspects of freshwater gastropods of medical and economic importance. The groups objectives are to: obtain basic information on selected snails, establish a snail reference collection for the Philippines, use the information obtained for a more logical malacological program in the control of snail-transmitted parasites, and provide advanced training in the field of malacology. The program is headed by Dr. Ruben Umaly and the group has Dr. Bonifacio Dazo (W.H.O., Manila) and Dr. J. B. Burch (University of Michigan) as technical advisors.

This program is in its infancy and lacks adequate research facilities and funding. Nevertheless, it has promise: Umaly and his graduate students are

working on a variety of projects including: ecology of Oncomelania hupensis; growth, development and reproduction of Pila; studies of hemolymph (and the effects of irradiation) on Oncomelania; systematic studies of the lymnaeid Radix; and a biogeographic survey of freshwater snails.

Also in the Zoology Department is Mr. Rolando Garcia, a malacologist who is completing a doctoral thesis on Paragonimus. He is also studying marine molluscs of economic importance with support from a German foundation.

3. U.S Naval Medical Research Unit No. 2 (NAMRU-2). This U.S. research laboratory has recently been moved from Taiwan to Manila. The Unit is temporarily housed in cramped quarters in the old San Lazero Hospital Compound near the Ministry of Health's Bureau of Research Laboratories. Under the scientific direction of Dr. John Cross, the Unit continues to do high quality field and laboratory research on snail-transmitted diseases. Recent efforts have focused on schistosomiasis and angiostrongyliasis.

4. Other laboratories. There is some interest in parasitology at the University of the Philippines School of Veterinary Medicine in Los Banos and at the new Institute for Tropical Medicine in Alabang. A German scientist from Munich is spending a couple of years at the latter laboratory studying schistosome antigens. Finally, the National Science Research Center has a new laboratory near the University's Department of Zoology. Five members of its staff have interests in malacology and there has been some discussion of the possibility of basing a national malacological research institute there. I was unfortunately unable to visit the NSRC or establish the nature of its present programs.

Prospects for Collaborative Research on Vector Control

I travelled to Asia in late 1982 to explore the possibilities for establishing collaborative research programs on the vectors of snail-transmitted diseases. Stemming from my interests in the genetic characterization of species and host-parasite coevolution I had some general research problems in mind:

1. the resolution of numerous taxonomic problems involving snails and parasites by means of multilocus characterization of infra- and interspecific genetic variability.
2. the establishment of whether laboratory strains of parasites and snails are appropriate genetic models of the populations they represent.
3. the study of variation in snail-schistosome compatibility with a view to developing a new genetic control technique.

The first two problems would be studied by electrophoresis and the biochemical staining of specific gene products. Snails and parasites would be collected and maintained in an Asian laboratory and flown to my laboratory for genetic analysis. Electrophoresis apparati are available in many Asian laboratories but they are not being used on the scale necessary to resolve the above problems. The chief impediment to doing this work in Asia is the cost and difficulty of obtaining the large number of biochemical reagents required. Accordingly, my initial intent was to try to find a collaborator with snails or parasites in their laboratory and a desire to resolve some of the taxonomic problems. The cost of conducting this research in such a collaborative manner would be about one third of the cost of doing all the work in the United States.

The third research problem would involve a series of selection experiments for variation in snail infectivity and schistosome susceptibility. These experiments would take 2-3 years and would require trained technicians and laboratory space in Asia. They would thus involve a much closer collaboration than the first two problems and a much greater commitment on the part of the Asian collaborator.

There were two other constraints on my developing a collaborative research program. First, I was anxious to complement on-going research projects and avoid projects which local scientists would prefer to tackle on their own. Second, it was necessary to ensure that the foreign institution welcomed the proposed collaborative program.

I was partially successful in achieving my objectives. I have developed a collaborative research proposal with Dr. Edito Garcia (Institute of Public Health, University of the Philippines). Garcia and I plan a 2-year study of the genetic variation of Schistosoma japonicum and its vector snail Oncomelania hupensis in the Philippines. This work would complement his own and his institution encourages such collaborations with foreign scientists. The animals will be cultured in his laboratory in Manila and frozen specimens will be moved to San Diego for genetic analysis. This grant proposal will be submitted to N.I.H. in March 1983 and will have a budget of about $45,000 per year. This study could not be done in Garcia's present laboratory because of the lack of space and equipment. (We estimate it would cost $12,000 for renovations and $50,000 for equipment to establish a laboratory for electrophoretic work in his department. This would be difficult to justify at present.)

Research on vector snails is severely limited in the Philippines by a lack of laboratory facilities and trained personnel. Other scientists with whom I discussed my ideas (at the University of the Philippines, Department of Zoology and at NAMRU-2 welcomed my interest in snail-transmitted diseases but lacked the space or facilities to contemplate a collaborative research program at this time. They would clearly benefit from having a national laboratory similar to the Applied Malacology Centre in Thailand. Such a facility has been proposed by several scientists to the World Health Organization in the last few years but that organization is unlikely to support a second Asian center at present. I think a very strong case can be made

for developing an Applied Malacology Center at the University of the Philippines or the National Science Research Center. Such a laboratory could provide an environment for creative research on vector control and have objectives similar to those of the Thai Malacology Centre. It could also function as a host-laboratory for foreign scientists who otherwise are unable to conduct their research (Appendix C).

As noted above, the situation in Thailand is quite different from that in the Philippines. Research facilities are excellent and the major needs are for funds for the training of professional personnel and research supplies. The research programs of the Applied Malacology Centre are almost totally dependent on foreign support and the major program grants from the World Health Organization are diminishing on the understanding that Mahidol University would begin to absorb the recurrent costs. Unfortunately, a hiring freeze and limited budget allocations from the Thai government will prevent the planned local take over of funding and the Centre's research programs are in jeopardy. This situation effects the type of collaborative programs foreigners can hope to set up with the Applied Malacology Centre.

I am now exploring the possibilities of collaborative research with Dr. Suchart Upatham the coordinator of the Applied Malacology Centre. Genetic problems of the type I am interested in are presented by 3 of Thailand's 4 major snail-transmitted diseases (Table 1 and Appendix B). Suchart and his colleagues have begun work on these problems but their electrophoretic surveys have been limited. We discussed possible collaboration involving field and laboratory work in Thailand and more comprehensive population-level studies of genetic variation in San Diego. The proposed genetic studies cannot be done properly unless they are linked to on-going field studies. It was agreed that ideally we should seek funds to facilitate research in Thailand and permit local scientists to bring their material to my laboratory for the month or two it would take to run the gels and analyze the data.

Such a collaboration, which would support research in Thailand year-round and involve my laboratory for 4-6 months, would cost about $60,000-70,000 per year. A minimal collaboration supporting only the genetic analyses in San Diego and the costs of specimen preparation in Thailand would cost $20,000-30,000 per year depending on the project. As funding is the limiting factor we will be discussing these ideas with the few granting agencies interested in supporting research on vector control of snail-transmitted diseases.

Finally, I should perhaps reiterate why the genetic studies I propose are significant in the overall effort of controlling snail-transmitted diseases. First, it is well-established that genetic characterization will facilitate the correct identification of parasites and vectors and reduce the chances of wasting resources on controlling the wrong species. Second, the proposed work will enable us to recognize imported parasites - an increasing problem in southeast Asia with its large number of refugees. Third, it will permit more rigorous comparison of results obtained in different laboratories. Presently, parasite and vector strains are poorly defined and such comparisons may be misleading. Fourth, genetic characterization of laboratory strains and field-collected samples will provide a quantitative indication of whether the former are appropriate models of the real animals they represent. Fifth, these studies will be useful to scientists working on other types of disease control (vaccine development and drug efficacy) where intraspecific variation may be far more important than is presently allowed. It will also allow us to monitor the organism's genetic response to the application of molluscicides and chemotherapeutic drugs. Ultimately, these studies of the evolution of hosts and parasites should lead to the development of new control techniques based on the genetic manipulation of one or both populations.

Appendix A.

Some scientists working on vectors of snail-transmitted diseases in Southeast Asia

Thailand - Applied Malacology Centre, Mahidol University, Bangkok

Dr. Suchart Upatham	Department of Biology
Dr. Vithoon Viyanant	"
Dr. Warren Brockelman	"
Dr. Maleeya Krautrachue	"
Dr. Chamlong Harinasuta	Faculty of Tropical Medicine
Dr. Santasiri Sornmani	"
Dr. Viroj Kitikoon	"
Dr. Pusadee Butrchum	"
Dr. Prasong Temcharoen	Faculty of Public Health
Dr. Jurapon Viboonyavatana	"
Dr. Prasert Sobhon	Department of Anatomy

Philippines

Dr. Alfredo Santos	Schistosomiasis Control and Research Service
Dr. Bayani L. Blas	" "
Mr. Erakho Banez	" "
Dr. Bonifacio C. Dazo	World Health Organization, Manila
Dr. Edito Garcia	Institute of Public Health, University of the Philippines
Dr. Noenette Jueco	Institute of Public Health, U.P.
Dr. Ruben C. Umaly	Department of Zoology, U.P.
Mr. Rolando G. Garcia	Department of Zoology, U.P.
Dr. John Cross	NAMRU -2, Manila
Mr. Jamie J. Cabrera	National Museum, Manila

Appendix B.

Possible Topics for Collaborative Research between U.C.S.D. and the Applied Malacology Centre, Mahidol University, Thailand.

Schistosomiasis

Although there are perhaps 50 million cases of this blood fluke in Asia and 250 million worldwide this disease is not common in Thailand. The parasite Schistosome japonicum which ranges from Japan and China south to Indonesia is quite rare and the few cases are probably imported by travellers. S. spindale and S. incognitum which normally parasitize buffalo and field rats get into people occasionally. S. mekongi, the newly discovered parasite of man and dogs in Laos and Cambodia, infects about 10,000 people in northeast Thailand. More cases are being imported by refugees and the disease could increase in prevalence as its vector snail (Tricula aperta, beta race) is widely distributed. Neither the Asian schistosomes nor their vector snails have been adequately characterized genetically. My own study of S. mekongi, for example, was based on a very small sample of parasites from Laos. A number of projects are being discussed to resolve some of the obvious problems.

The genetic relationships of the various geographic strains of S. japonicum needs to be established as there are some important regional differences including the ability to infect man. Laboratory strains from China, Mindoro, Malaysia and Indonesia are available at the Applied Malacology Centre and could be compared with animals from China, Leyte, Japan and Taiwan maintained by the N.I.H. in this country. We can now determine genetic relationships by surveying allozymic variation at more than 20 loci. Similarly, the relationship of S. japonicum to other species cultured at the Applied Malacology Centre (Table 3) could be established. This would resolve some taxonomic problems. More importantly, the results may explain why it is that only some of these species can infect man and this information may in turn lead to the development of new control techniques.

One of the interesting problems posed by the vector snails in Thailand involves Tricula aperta which occurs in 3 races: alpha, beta and gamma. These races differ in their geographic distribution, morphology and enzyme profiles (as determined by isoelectric focusing). Gel electrophoresis and biochemical staining for 20-30 structural gene products can now be used to establish the real genetic relations of these taxa. Similarly, it would be interesting to know more about the genetics of T. bollingi which has recently been found to transmit S. sinensium in northern Thailand. As with the schistosomes, the genetic data on their vector snails will be applicable to the disease control problem.

Opisthorchiasis

Two species of Opisthorchis liver flukes debilitate about 6 million Thais. The parasites are acquired by eating minced raw fish (koi pla). They cause one of the most important liver diseases in northeast Thailand and are associated with the development of adenocarcinoma of the bile duct. Two U.S. scientists, Sadum and Wykoff, elucidated the life cycle of these parasites in Thailand in the 1950's and 1960's.

A very similar parasite called Clonorchis infects 20 million Asians from Vietnam north to Japan but is apparently not found in Thailand. Some workers have questioned the validity of the genus Clonorchis and, despite its widespread use, argue

that it should be synonymized with the older name Opisthorchis. This issue can probably be resolved by electrophoretic analyses of the parasite's proteins. This would establish how much genetic divergence has occurred among the structural genes since the two groups of parasites shared a common ancestor. A start could be made by examining the parasites in cultivation in hamsters at the Applied Malacology Centre. Such a study would also establish whether these worms are self-fertilizing as is widely claimed or merely facultative hermaphrodites.

In Thailand, Opisthorchis viverinni is transmitted by Bithynia s. siamensis, B. s. goniomphalos and B. funiculata. These three snails are now cultured at the Applied Malacology Centre and 7 of their enzymes have been studied by isoelectric focusing. As expected the two subspecies appear to be more closely related to one another than to B. funiculata. These distances could now be quantified and expressed in terms of genetic substitutions per locus by an electrophoretic survey of 20-30 enzymes.

Two years ago the Rockefeller Foundation funded a multidisciplinary research project on opisthorchiasis at the Applied Malacology Centre. Field work at Kong Kaeo water reservoir points to a number of problems that deserve further study. Parasite control might be based on the bionomics of the snails and the four species of cyprinoid fish that serve as vectors if more information was available. A strong case can be made for more ecological work on the fish themselves as they are the source of human infections.

Paragonimiasis

The common lungworm, Paragonimus westermani, which infects about 6 million Thais is contracted by eating inadequately cooked freshwater crabs and crayfish. Operculate snails of the genera Thiara, Brotia and Semisulcospira serve as the first intermediate host elsewhere in Asia but recent attempts to find vector snails in Thailand have failed. Clearly ecological and parasitological field work is necessary to establish the details of the life cycle. There is little hope of controlling the disease until its natural history is understood.

There are at least 4 and possibly 6 species of lung worms involved in human infections in Thailand. The various species are defined in terms of morphological features of the adults, eggs, and larval stages. Nothing is known about the genetic relationships of the various species and no attempts have yet been made to identify the species by biochemical means. Clearly, if material were available electrophoresis should be employed to resolve the taxonomic problems of this group.

Fasciolopsiasis

Fasciolopsis buski is an intestinal worm that grows to 3 inches in length. It is not widespread in Thailand but locally 30% of the population may be seriously infected. The parasite is acquired by eating a popular vegetable, the water caltrop on which the larval worm encysts. As in the case of the lung worms the intermediate host snail is unknown in Thailand (although elsewhere the snails of the genus Segmentina are involved). Little can be done about vector control until ecological field work identifies the snails involved.

Appendix C.

U.S. scientists who have worked in Asia on snail-transmitted diseases recently.

Dr. Jack B. Burch
Museum of Zoology
University of Michigan
Ann Arbor, MI 48109

Dr. John Bruce
Center for Tropical Diseases
University of Lowell
Lowell, MA 011854

Drs. John H. Cross and W.P. Carney
U.S. Naval Medical Research Unit-2

Dr. George M. Davis
Academy of Natural Sciences
19th and the Parkway
Philadelphia, PA 19103

Drs. Donald Heyneman and K.J. Lie
The Hooper Foundation
University of California Medical School
San Francisco, CA 94143

Dr. Robert M. Lewert
Department of Microbiology
University of Chicago
Chicago, Il 60637

Dr. Curt R. Schneider
formerly, Coordinator
Mekong Schistosomiasis
Control Project
Bangkok

Dr. Kenneth S. Warren
The Rockefeller Foundation
1133 Avenue of the Americas
New York, N.Y. 10036

Dr. David S. Woodruff
Department of Biology
University of California
La Jolla, CA 92093

There are many other U.S. scientists actively involved in research on Asian snail-transmitted diseases but who, for one reason or another, are not working in Asia. They include Asch (S.U.N.Y., Buffalo), Bueding (Johns Hopkins), Byram and von Lichtenberg (Harvard), Cain (Iowa), Cheever (N.I.H.), Chu (Loma Linda), Fletcher (Yale) and Voge (U.C.L.A.). An equal number worked in Asia in the 1960's or early 1970's.