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SCOPE OF WORK

FOR

PROJECT ANALYSIS AND DESIGN TEAM

SCHISTOSOMIASIS COMPONENT

SCIENCE AND TECHNOLOGY FOR DEVELOPMENT PROJECT USAID/Egypt

November 11, 1986

by

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AR-034

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I. BACKGROUND

Throughout the twentieth century, schistosomiasis has been regarded as a major public health problem in Egypt. The transmission of the infection to humans is inexorably linked to the patterns of irrigated agriculture upon which Egyptian crop production depends. These agricultural practices provide breeding grounds for the parasite's snail intermediate hosts and bring the populations into close contact with the waters in which the snails reside. An estimated 20 million Egyptians are at risk to the infection, and symptoms of the infection are evident in significant numbers of children between the ages of 5 and 15.

Despite millions of dollars expended on chemotherapy, snail control, and environmental management during the last three decades, impacts of the disease on public health appear to be worsening. Village prevalence rates in areas of the Nile Delta have been measured at between 40 percent and 72. Furthermore, epidemiological studies performed in the Delta region over the last 10 years have shown that there are changes in the relative rates of infection with the urinary form of the disease caused by *Schistosoma haematobium* and the intestinal form caused by *Schistosoma mansoni*. Why this has occurred and its impacts upon human health are widely debated, but there is little disagreement about the increasing seriousness of schistosomiasis as a public health problem is growing.

The Egyptian science and technology community, assisted by A.I.D., NAMRU-3, CDC and NIH, has been actively engaged in research directed toward developing new tools and approaches for reducing the impact of schistosomiasis. The present state-of-the-art, however, appears unequal to the task. The efforts of the U.S.-sponsored PL-480 and the University Linkages Programs have produced a unique cadre of well-trained Egyptian scientists who are capable and actively engaged in research aimed at the control of schistosomiasis. However, their efforts are in need of focus and direction if significant operational progress is to be made in reducing transmission to the point at which it will no longer be a significant public health problem.

Focusing Egyptian research efforts toward reduction of the public health impacts of schistosomiasis is the central theme of this component of the A.I.D., Science and Technology (S&T) for Development Project.

II. PROJECT DESCRIPTION

The schistosomiasis research component of the Science and Technology for Development Project is intended to be a multifaceted effort to bring to bear the combined weight of Egyptian and U.S. technical expertise on the problem of reducing the public health impact of schistosomiasis in Egypt. Toward that end, the project plan envisions a focused and intensive seven-year program to address six approaches selected as having the highest potential for bringing about a successful result.

The Project Analysis and Design Team will be responsible for developing a well-coordinated structure and framework for the implementation of this important S&T effort. It also is essential that the design will ensure maximum technical participation by both Egyptian and U.S. professionals and their sponsoring institutions and that as much of the effort as is technically feasible will be carried out in Egypt.

A. Goal, Purpose and Objectives

The goal of the project is to assist the Government of Egypt to ensure a population free of morbidity from schistosomiasis.

The purpose of the project is to develop the tools, methods and information necessary to reduce the impact of schistosomiasis to a point where it is no longer a significant public health problem.

The project objectives include the following:

- the development of an effective vaccine for schistosomiasis;
- maximization of effective chemotherapeutic regimens for the treatment of individuals already infected;
- the development of sensitive and specific diagnostic tests for the detection and monitoring of schistosomiasis infections and therapy;
- the development of a comprehensive data base of information regarding the prevalence, incidence distribution and pathological impact of schistosomiasis in Egypt;

- the elucidation of important socio-economic factors which perpetuate the schistosome's cycle of infection; and

- the development of operational strategies for applying existing and expected control methodologies to field situations (i.e., health education, vaccine and drug distribution and coverage, snail control, cost/benefit analysis and epidemiological assessment of impacts).

A final objective is to establish a biomedical research system in Egypt capable of addressing other Egyptian disease problems such as leishmaniasis, malaria, diarrhea and childhood diseases.

B. Project Components

The goal, purpose and objectives of the project will be pursued through a constellation of interrelated research and development efforts which may be related to one or more of six project components. Other productive lines of investigation might be proposed which fall outside of the categories presented here. The project can succeed, however, only if the participants work toward a limited number of realistic, attainable, and well-defined objectives. The following components appear to be the most likely areas of endeavor to achieve the stated goal.

1. Vaccine Development

Historical information indicates that resistance to natural infections of schistosomiasis increases with age, suggesting that some immunological factor(s) mitigates or reduces further infection. More recent scientific discoveries have evolved from investigations of the interaction between genetic material of larval schistosomes and cells of the host. They have raised expectations that a protective antigen or antigens may be developed that will destroy larval schistosomes during the early stages of infection. Through this component of the S&T project, basic and applied research will be conducted to produce a vaccine which may be used to immunize people against future infection.

2. Improvement of Diagnostic Techniques

Present techniques for the epidemiological assessment of schistosomiasis in populations rely largely upon microscopic examination of urine and stool specimens in a search for eggs of the parasites.

Current thinking casts considerable doubt upon the correlation between the numbers of eggs detected and the total worm burden in the infected patient. Similarly, there appears to be less association than previously suspected between the quantitative egg count in stool or urine and the amount of pathology in the host. Modern immunological and biochemical techniques hold promise for rapid assessment of infection and pathology through examination of minute samples of blood serum. This component of the S&T project will promote research into the application of these state-of-the-art techniques to detect infection and assess chemotherapeutic and vaccine efficacy.

3. Epidemiology

Present information regarding prevalence, incidence and distribution of schistosomiasis in both humans and snails is limited to a few geographical localities in Egypt. This project component will be directed at expanding basic information about infection in other geographical areas, among various age cohorts of the population, and will provide insights into such parameters as intensity of transmission, seasonality of transmission, incidence of infection, and human pathology. It is only through collection of baseline information of this type that the efficacy of vaccines, drugs, and environmental control measures can be evaluated.

4. Chemotherapeutic Regimens

Pharmaceutical science has produced a number of drugs capable of curing or remarkably reducing worm burdens in infected individuals. In mass treatment, however, many of these preparations have limited application due to excessive cost. There also is concern that indiscriminate use of these compounds may hasten the development of drug resistance, thereby limiting their future effectiveness. This project component will support efforts to determine the most effective methods of application of antischistosomal compounds to reduce morbidity and mortality and to preserve their utility for the longest period of time.

5. Socio-Economic Factors Affecting Transmission

The cycle of schistosomiasis transmission is linked to a number socio-economic factors which tend to negate control efforts and ensure reinfection. These factors include: water contact during the practice of irrigated agriculture; distribution of eggs during religious ablution; bathing in snail-infested waters; and recreational swimming. This component will be directed toward the study of schistosomiasis-promoting socio-

economic practices and the development of approaches to prevent reinfection through techniques such as health education, improved sanitation, early self-diagnosis and behavior modification.

6. Operations Research

The mere existence of effective tools such as drugs, molluscicides, health education messages or even vaccines, does not guarantee that schistosomiasis transmission can be controlled, or morbidity reduced. It is only through efficient delivery and monitoring of their impact that the desired effect can be achieved. The Operations Research component of the S&T project will promote investigation of improved systems to deliver and monitor interventions of all types, in order to target efforts, ensure continued efficacy, and to conserve resources.

C. Expected Outcomes

By the end of the project, it is expected that the schistosomiasis component of the Science and Technology for Development project will have achieved the following outcomes:

- A fully developed candidate vaccine suitable for testing and clinical evaluation.

- The existence of a full range of immunodiagnostic and biochemical tests capable of rapid assessment of schistosomiasis infection and pathological impact, and evaluation of drug and vaccine efficacy.

- A comprehensive, country-wide data base containing information about prevalence, incidence, geographical distribution and age-specific infection rates of schistosomiasis in humans.

- A comprehensive, country-wide data base containing information about the distribution, prevalence, infection rates and bionomics of schistosome vector snail species.

- Protocols for maximizing the efficacy of available chemotherapeutic agents, and that take into account optimum dosage schedules, drugs in combination, and target populations (both those at greatest risk and those most likely to perpetuate the infection cycle).

- A comprehensive plan for overcoming socio-economic factors related to the perpetuation of transmission.

- A set of operational action plans for applying the tools developed by the project (i.e., vaccines, drugs, mulluscicides, environmental modifications, health education) to national schistosomiasis control.

- An action plan for monitoring the impact of all interventions to be employed.

- A research and development system with potential for application to other significant public health problems in Egypt.

III. SCOPE OF WORK FOR ANALYSIS AND DESIGN TEAM

A. Relationships and Responsibilities

The schistosomiasis component of the Science and Technology for Development Project will be designed in Egypt in March and April of 1987. The team leader, who will also be an epidemiologist, will coordinate the design and activities of the design members. The team leader will coordinate his/her efforts with Mr. Lawrence Ervin, Director USAID Office of Science and Technology. Coordination from the GOE will come through designated representatives of the Ministry of Health (MOH) and/or the Egyptian Academy of Scientific Research and Technology (ASRT), and through them, to the Egyptian universities and institutes responsible for research and development activities in schistosomiasis.

The Analysis and Design Team is expected to work closely with each organization in carrying out its tasks but will be responsible to the USAID S&T Director for the general coordination and completion of all tasks.

The Scope of Work Team provided by the S&T/Health Vector Biology & Control Project has developed a collection of literature that will be useful to the Analysis and Design Team. This resource, along with other essential technical reports, will be provided to the team members by USAID/Cairo, on their arrival.

B. General Tasks to be Performed by the Team

Under the direction of the Epidemiologist/Team Leader, the Project Analysis and Design Team will perform the following tasks:

1. Review the project paper which describes the Science and Technology for Development Project and assess the schistosomiasis component for its relevance to the Egyptian situation and to the goals and objectives of the entire effort.

2. Visit all institutions with stated capabilities in the areas of schistosomiasis research and development and assess possible contributions the institutions might make to the collaborative effort. This assessment should include performance on past collaborations and an inventory of resources which might be dedicated to the research program.

3. Review past research activities and publications of potential investigators and prepare an analysis of possible contributions which they might make to the individual components of the planned program. Egyptian investigators should be made aware of this task well in advance so they have time to prepare.

4. Develop a management plan for the overall implementation of the project. The plan must accommodate participation of both U.S. and Egyptian institutions and investigators. It should detail the mechanisms by which the proposed steering committee, secreteriat, participating institutions and investigators will interact.

5. Review all issues raised by SOW Team in section III.D. and devise appropriate solutions for them.

6. Assess needs for technical participant training, identify appropriate institutions where training might take place, and devise an appropriate participant training plan.

7. Identify potential linkages between Egyptian and U.S. universities and institutions which might serve to advance the research program. Some initial ideas might be developed from the annexes of this document.

8. Devise a logistical plan which will ensure the procurement, shipping, receiving and movement through customs of isotopes, reagents, and supplies needed for the research effort.

9. Develop the structure of the peer review mechanism which will assess the relevance of individual research activities to the project objectives, and ensure that the planned activities represent sound, implementable research ideas.

10. Assess manpower requirements for technical support, analyse the supply of such manpower, and devise an in-country training program to meet any deficiencies identified.

11. A certain that intended research activities conform with GOE requirements, particularly in the areas of drug trials and vaccine development. An ad hoc committee should be convened to ensure review of proposed research in this regard.

12. Devise a technical support plan which will ensure the flow of goods and services that must be obtained in Egypt, such as biological materials (snails, worms and larvae) standard reagents, and lab/field supplies.

13. Devise a tripartite (GOE/U.S. Institutional/USAID) biannual review mechanism for assessment of progress on all research efforts. This review should include assessment of technical progress, fiscal responsibility, management performance, and site visits.

14. Develop requirements for a reporting system that will document progress, problems and planning for each investigative, support and management component of the project on a semiannual or quarterly basis.

15. Develop a plan for involving Egyptian counterparts in the planning process.

C. <u>Tasks Related to Specific Components</u>

In addition to the general tasks outlined in section III.B., the Project Analysis and Design Team will be required to draw up a planning section which addresses each of the subcomponents of the schistosomiasis S&T project. The responsibilities for the analysis and design of each subcomponent have been assigned in section V. The outline for each subcomponent will be as follows:

I. Background
II. Statement of the Problem
III. Current Status of the Problem
IV. Component Description

A. Goal
B. Purpose
C. Objectives
D. Activities
E. Management of Component
F. Participants

V. Issues

VI. Summary Statement

The Scope of Work Team has visited with potential investigators and collaborative institutions in Egypt and prepared a synopsis of resources which is included in Annex 2. In addition, the SOW Team has reviewed the background and a number of issues related to each component which may be useful in developing the analysis and plan. These appear in Annex 1.

The following are specialized tasks which will be required in the performance of the analysis and design of each of the subcomponents.

1. Vaccine Development

The analysis and design of this component will be headed by the immunologist with specific contributions by the molecular biologist, diagnostics specialist and epidemiologist who will constitute the working group. The team is to assess the capabilities for vaccine research and development in Egyptian laboratories, and to critique their past achievements, current activities, and future contributions in this endeavor.

The team will pay close attention to the specific capabilities for vaccine research and development which include: adequate laboratory space; laboratory equipment, such as centrifuges; laminar flow hoods; CO_2 incubators; spectrophotometers; liquid scintillation counters, Gama counters, audioradiography equipment; and various types of polyacrylamide gel electrophoresis equipment. An in-depth knowledge of the technical expertise of the professional, and most importantly, support research staff is a desired outcome. The team should determine the level of commitment that will be available from the scientific staff and administration of each institution. A

thorough assessment of the capability of the potential Egyptian collaborators in providing a superior support facility with respect to providing schistosome material and experimental animals (mice) on a constant basis must be made, and a detailed organizational plan developed to correct any deficiencies.

Of particular importance will be the evaluation of potential collaborators to develop a superior, highly productive research focus on schistosome molecular biology, including recombinant DNA methodology oriented to vaccine antigen(s) identification, assessment, and production.

2. Improvement of Diagnostic Techniques

The analysis and design of this component will be headed by the specialist in diagnostics, with specific area contributions to be made by the immunologist, molecular biologist and epidemiologist who will constitute a working group. The team will assess the capabilities for innovative immunological and biochemical approaches to schistosomiasis diagnosis by Egyptian laboratories and investigators. It will critique their past achievements, current research activities, and plans for future contributions to this component.

The team will pay close attention to the current abilities and facilities of Egyptian laboratories to isolate, fractionate and characterize schistosome antigens, to assay biochemical parameters, and to conduct molecular biologic research, including recombinant DNA methodology. The team must assess Egyptian laboratories' specific capabilities to initiate the research by virtue of current equipment and facilities (centrifuges, equipment for protein separation and fractionation, CO_2 incubators, liquid scintillation counter, Gamma counters, spectrophotometers, autoradiography equipment, polyacrylamide gel electrophoresis equipment, ELISA readers, and high performance liquid chromatograph). The team must clearly differentiate the well-known capacities of Egyptian scientists in applied immunodiagnostics in schistosomiasis from the capability to develop new and innovative diagnostic methodologies for schistosomiasis. It is critical that the team ascertain the extent of technical expertise of the professional, and most importantly, support research staff in Egyptian institutions. A thorough assessment must be made of the abilities of the potential Egyptian collaborators to provide a superior support facility with respect to provision of schistosome materials for antigen analysis and for biochemical analysis.

3. Epidemiology

The analysis and design of this component will be headed by the epidemiologist, with major contributions from the data management specialist. In some phases of the design, the team leader will enlist the aid of the specialists in diagnostics, chemotherapy, anthropology/sociology and malacology. The team will identify institutions and epidemiologically oriented research units that have demonstrated competence and research productivity in the sound application of epidemiologic principles and quantitative methodology to population-based studies in schistosomiasis. The team is expected to identify those units capable of conducting longitudinal cohort studies in all endemic areas of Egypt, utilizing sound state-of-the-art data management tools and methods. The team must identify institutions and units that have demonstrated competence, a history of research productivity, and potential in population-based studies on morbidity patterns.

In the assessment of schistosomiasis epidemiology in Egypt, the team will identify deficiencies in current epidemiologic knowledge of schistosomiasis with particular focus on the impact of control programs on prevalence, incidence, and morbidity patterns. Concurrent with other components, the epidemiology team will ascertain the operational inefficiencies in past and current schistosomiasis control programs in Egypt. The team will incorporate improved methodologies into the project design with respect to epidemiology and control strategies.

4. Chemotherapeutic Regimens

The chemotherapy specialist will undertake the following tasks:

a. Analyze the conceptual subcomponent design as described in the S&T for Development Project Implementation Order for Technical Assistance (PIO/T), and assess the approach as it relates to the schistosomiasis situation in Egypt.

b. Address issues identified in the PIO/T document and develop appropriate solutions or responses.

c. Review status of the chemotherapy (including laboratory research and field treatment program) component of the schistosomiasis control program in Egypt. Make appropriate research and development recommendations including such aspects as new approaches to drug-

delivery systems, improved regimens to achieve better efficacy and/or higher cure rates, the potential of drug resistance occurring in Egypt, methods to reduce costs of treatment schemes, and treatment strategies to control morbidity.

d. Identify deficiencies in resources at Egyptian institutions and make recommendations as to what is needed to carry out the R&D component of the S&T program (personnel, training, logistics).

e. Identify any new antischistosomal agents which could be subjected to laboratory and clinical trials within the framework of the S&T program.

f. Develop plans for integration of the chemotherapy component into the overall scheme of the S&T program.

g. Plan in-depth plans for pharmacokinetics and biochemistry research within the framework of the S&T program.

5. <u>Socio-Economic Factors Affecting Transmission</u>

a. Analyze the conceptual subcomponent design of this unit as described in the S&T for Development PIOT and assess the approach as it relates to the schistosomiasis situation in Egypt.

b. Review all components of the S&T program for their impact on the socio-economic structure in areas where new methodologies and research development will be used.

c. Review the current Egyptian schistosomiasis control program, identify existing social and economic constraints, and devise research programs to attempt to overcome the constraints within the framework of the S&T program.

d. Address issues identified in PIO/T which apply to socio-economic aspects and develop appropriate solutions and response.

e. Develop research plan to study and define water-contact patterns, within the social and cultural structure of communities, as they relate to schistosomiasis transmission.

f. Prepare detailed documentation of all social, cultural and economic constraints in all areas in Egypt where schistosomiasis is endemic or where transmission occurs.

g. Determine the potential impact of methodologies such as new drug delivery systems, vaccines, drugs, control methods such as biological agents, and engineering alternatives.

h. Anticipate the social, cultural and economic consequences if certain behavioral patterns are changed in communities to achieve the proposed control objectives of the S&T program.

6. Operations Research

The malacology specialist will conduct the following tasks:

a. Analyze the conceptual subcomponent design as described in the S&T for Development PIOT and assess the approach as it relates to the schistosomiasis situation in Egypt.

b. Address issues identified in PIOT document and develop appropriate solutions or responses.

c. Review status of the snail-control program component of the schistosomiasis control program in Egypt and make appropriate research and development recommendations including alternative and/or new approaches to improve overall efficacy and to meet the objectives of the S&T program.

d. Where appropriate resources (such as equipment, technical and professional personnel) do not exist, recommend what is needed to carry out the R&D component of the S&T program (i.e., training, logistics).

e. Design plans for full integration of the malacological component into the overall S&T schistosomiasis program, especially in the areas of resources development, operational research, and socio-economics.

f. Address the need to incorporate data-management capabilities into the malacological aspects of the operations research component of the S&T program.

g. Review the present status of research and field efficiencies of biological control of snail intermediate hosts in general and, in particular, by intermolluscan competition. In addition, develop a scheme for field testing snail competitors as biocontrol agents. Include costs, training needs, research requirements, and safety regulations.

h. Identify any new molluscicides including chemicals, plant products or engineering alternatives which could be targeted for laboratory and field trials within the framework of the S&T program.

i. Review all components of the S&T program for compliance with Egyptian environmental impact regulations.

j. Review the status of all components of the Egyptian schistosomiasis program as they relate to provision of safe water by year 2000, and make appropriate recommendations for research and development within the S&T program.

k. Identify new environmental alternatives for snail control, such as engineering alterations, water-velocity controls, fencing, and front bridges which can contribute to control and/or transmission reduction.

D. Issues to be Addressed by the Team

The Scope of Work Team has identified a number of issues with potential for compromising the final outcome and implementation of the project. This is not to suggest that they are the only issues of importance, but their resolution is regarded as crucial to project success.

Linkages between Financial Disbursement and Productivity

Targeted research and development efforts are not the norm of scientific endeavor in Egypt; nor are they common in the United States. There is considerable risk that investigators will pursue research in line with their individual professional interests, and thus diffuse the R&D effort. The project management plan would do well to consider mechanisms for monitoring the progress of investigators realistically, objectively, and frequently, and to link continued funding to productivity. The solution may well be assistance by an impartial and independent disbursement and monitoring unit or agency.

Technical Support for Research Efforts

Past efforts of programs such as the PL-480 and University Linkages Projects have assisted Egypt in the development of a cadre of trained professionals with considerable ability to conduct research in schistosomiasis. What is missing is the cadre of highly trained technicians required to support their efforts. In Egypt, needs for technical assistance are filled primarily by unpaid graduate students. Their commitments to the investigators are frequently interrupted by educational activities, and terminate when their educational programs are finished. Professional technicians such as those who form the backbone of scientific research in the United States are virtually nonexistent in Egypt. Considering the labor-intensive, highly skilled nature of the investigations to be pursued in attainment of project objectives, some mechanisms, such as in-country training and salary support for developing a technical staff, should be devised.

Supply of Biological Materials for Research

The continuous supply of standardized biological materials (i.e., snails, worms and larvae) for use by investigators, particularly in the areas of immunological and vaccine studies, must be ensured. At present there is no indigenous unit with the capacity or mandate for filling that need. The standard practice is that each investigative unit produces its own biological materials. For purposes of the project, this practice would be duplicative, expensive and would lack standardization. Some consideration should be given to the development of a centralized technical support unit capable of meeting these needs. It is possible that other functions, such as technician training, could be centered in such a unit.

Commitment of Egyptian Scientists

Low salary levels of Egyptian scientists often require them to take on additional work and have been cited as a constraint to achieving their full commitment to research efforts. In previous efforts, project funds were directed toward salary supplementation to offset the need for outside employment. The Project Analysis and Design Team should examine this factor carefully and devise a plan acceptable to USAID/Cairo which will address this potential constraint.

Interagency Cooperation

There is little historical evidence of interagency cooperation between S&T factions of the Egyptian research community. Since cooperation of this nature is central to the success of the project, the team must address the mechanisms by which it will be accomplished.

Peer Review

All activities undertaken by project investigators should be submitted to peer review in order to ensure their scientific quality and contribution to the central objectives of the project. The criteria to be used in the peer review process should be developed by a joint panel of Egyptian and U.S. scientists and USAID personnel. (A comprehensive model for such a review process may be found in "Assessment of Science and Technology and AID Assistance in Egypt, Volume II" CDC Attachment 4).

Logistics and Supply

Progress of the project toward attaining its research goals will depend heavily upon the timely provision of a wide variety of commodities of a specialized nature. Many of these commodities are not available in Egypt and must be procured and imported. The services of a procurement and shipping agency or unit in the United States would be valuable in facilitating the process. An agency to receive and clear goods in Egypt as well as a government agreement to expedite the clearing process is essential.

Pre-Implementation Meeting

The development of a targeted research activity which will involve investigators from both Egypt and the United States is a complex undertaking. Many misunderstandings and misconceptions about goals, facilities, collaborative arrangements and available services may be avoided by bringing key participants together prior to the implementation phase of the project. Since many of the uncertainties are centered around capabilities and constraints in Egypt, it would be appropriate to hold such a meeting there.

E. Performance of Specific Project Analyses

In addition to the design tasks detailed above, the team will be required to carry out the specific project analyses

which are described in A.I.D. Handbook 3, Chapter 3. The team will include members who are experienced in the performance of these analyses. These analyses form the basis for assessing project feasibility and for identifying shortcomings of the project design during the planning process.

1. Economic Analysis

The responsibility for performance of the economic analysis will rest with the financial analyst/economist. This team member will analyse the costs of the project in relation to the expected benefit. Since the benefits expected must be measured in both social and financial terms, the procedures to be used will require a combination of cost-benefit analysis and least-cost analysis.

2. Financial Analysis

The financial analyst/economist also will be responsible for this analytical step. The least cost analysis procedures will by the most likely to apply to this research and development project.

3. Social Soundness Analysis

The anthropologist/sociologist will be responsible for the Social Soundness Analysis. In addition to the identification of beneficiaries and estimation of impact and social acceptability, particularly in field trials, the team member is expected to develop issues which may impact upon the field aspects of the effort, i.e., epidemiological surveys, drawing of blood for immunological surveys, and field trials of vaccines and pharmaceuticals.

4. Administrative Analysis

The team leader will have primary responsibility for the administrative analysis but will draw heavily on the project design specialist for procedural assistance. The anaylsis depends heavily upon the analyst's ability to assess the capability and commitment of participants to carry out their obligations within the plan. Much of the assessment, therefore, will require informed judgments based on experience with Egyptian and U.S. institutions.

5. Technical Analysis

The performance of a prospective technical feasibility analysis on a multifaceted research and development project is likely to be a significant challenge. The most important outcome should be the development of a range of technological options and channels of technical assistance which may be called upon during implementation. These might include specialized consultants through PASA/RSSA agreements or Personal Services Contracts. Assistance in R&D might be more appropriately obtained through subcontracts with private sector companies. These mechanisms may come into play if needs for genetic engineering services or reagent development are identified as constraints. The team leader will take responsibility for the technical analysis but will require assistance from all technical design team members.

6. Environmental Analysis

The environmental specialist/engineer will be responsible for this analysis. Since the project is a research effort, it should be exempted from most environmental restrictions. Therefore, analysis beyond the stage of an IEE is not anticipated.

F. Project Design Review

The complex nature of the project and its six components and the need to employ technologies which are themselves complex will require continuous modification of the project design. The project design should be examined from an objective standpoint once the elements of the project have been identified. For this reason, a Project Design Review will be held for two to three days at the begining of the sixth week to examine progress and to assess the feasibility of all mechanisms, approaches and technologies which are central to the project's implementation. It is recommended that five informed individuals (two U.S., two Egyptian and one A.I.D. S&T/Health) uninvolved in the design process be included in the review. The begining of the sixth week has been chosen because all designers and counterparts will be present and sufficient progress on the design will have been made to warrant review. Additionally, there will be enough time remaining to make adjustments in the design, if needed.

G. Development of the Logical Framework

Major responsibility for the development of a logical framework will be assigned to the project design specialist. Because the logical framework is a major planning tool, it will

be drafted during the first week of the design process and completed before the Project Design Review. The format and content of the logical framework must follow the guidelines contained in A.I.D. Handbook 3.

H. Drafting of the Request for Proposal (RFP)

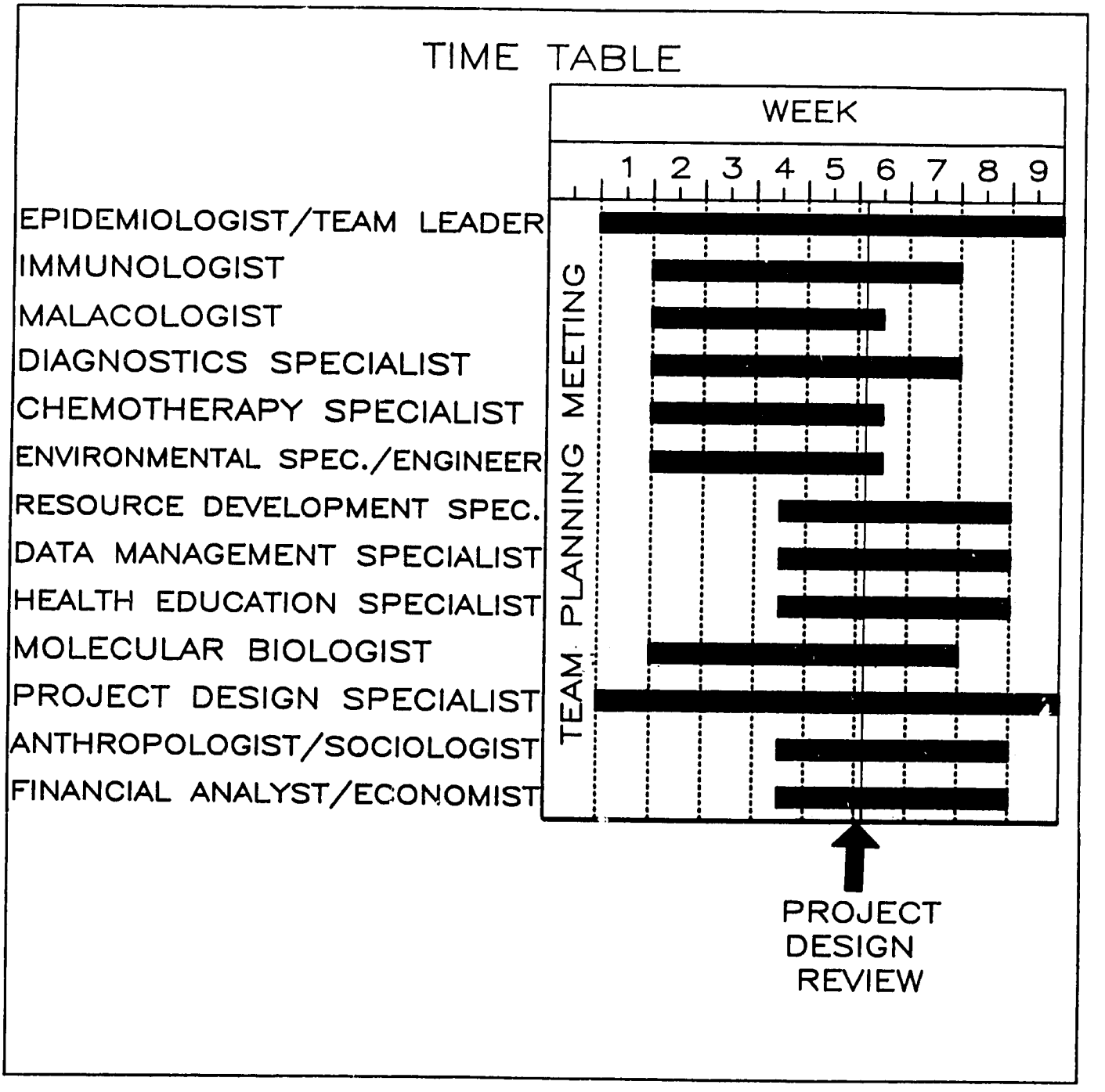
This task will be undertaken by the project design specialist and will necessitate the incorporation of all design elements (administrative, logistical, managerial, and technical) into a document which may be used for solicitation of bids for implementation of any and all aspects of the project.

I. Team Planning Meeting

In consideration of the size of the team and the complex nature of this design effort, a Team Planning Meeting (TPM) will be held in Washington prior to the departure of team members for Egypt. This three-day exercise will bring the 13 team members together in order to establish working relationships, responsibilities, benchmarks, formats, and consultant/client relationships, and to allow the team access to outside specialists who will not participate in the effort. The TPM also will allow for a detailed briefing on project goals, objectives and background as well as an opportunity to identify resources which exist in Egypt or those which must be taken there.

IV. TIME TABLE

The Project Analysis and Design Team will perform its services over a period of two months commencing in or about March 1987. The following timetable details the participation of each specialist over the nine-week assignment in Egypt.


TIME TABLE
WEEK
1 2 3 4 5 6 7 8 9
EPIDEMIOLOGIST/TEAM LEADER
IMMUNOLOGIST
MALACOLOGIST
DIAGNOSTICS SPECIALIST
CHEMOTHERAPY SPECIALIST
ENVIRONMENTAL SPEC./ENGINEER
RESOURCE DEVELOPMENT SPEC.
DATA MANAGEMENT SPECIALIST
HEALTH EDUCATION SPECIALIST
MOLECULAR BIOLOGIST
PROJECT DESIGN SPECIALIST
ANTHROPOLOGIST/SOCIOLOGIST
FINANCIAL ANALYST/ECONOMIST
TEAM PLANNING MEETING
PROJECT DESIGN REVIEW

V. PERSONNEL

The Project Analysis and Design Team will consist of the below personnel listed. (Under separate cover, at least two nominees will be named for each position). Complete resumes and biodata will be submitted to USAID/Egypt for each nominee selected. Participation of any candidate is subject to the candidate's own interest and availability once the time for the assignment is fixed.

Team members will include the following:

Epidemiologist with experience in Egypt in schistosomiasis epidemiology to serve as team leader.

The epidemiologist must be familiar with project design, mechanisms of peer review, project monitoring and management, and a wide variety of field applications related to schistosomiasis research and control. He/she will work closely with the project design specialist and will be responsible for the formulation of the final design. The epidemiologist/team leader will coordinate the efforts of other team members and must be conversant with all of the technologies represented by the project components. A physician is preferred for this position. (two person months)

Immunologist with extensive and in-depth experience in schistosomiasis vaccine research and development.

The immunologist will be the group leader; the molecular biologist and the diagnostics specialist will be integral contributors to the vaccine component's activities. The immunologist must be a bench scientist actively involved in experimental vaccine research that incorporates state-of-the-art technologies. The immunologist must be able to work effectively in a team coordinating the efforts of the other members and must have working experience in schistosomiasis immunology in Egypt. (one and one-half person months)

Malacologist with experience in Egypt and in design, development, administration and evaluation of snail control programs.

The malaciologist will design all malacological aspects of the program as well as recommend program design changes when necessary. Particular attention should be given to training and research in immunotaxonomy, biological control and

development of new delivery systems for molluscicides, laboratory and field trial methodologies, and sampling techniques, including population dynamics for target and non-target organisms in the various habitats. He or she also should be able to plan organization of survey and surveillance teams, if warranted, and design programs for identification and mapping of transmission sites, water-contact studies, data analysis, and ecological aspects of snail-parasite interactions.

The malacologist should also assist in identification of Egyptian institutions and scientists with malacology capabilities and make recommendations for training of both technical and professional personnel.

The malacologist will have responsibility for preparing the operations research subcomponent of the project plan. (one person month)

Diagnostics specialist with extensive schistosomiasis research experience and current focus on development of new diagnostic approaches for schistosomiasis, particularly in the application of immunoassays and molecular biologic assays.

The diagnostics specialist must have a thorough training in immunochemistry and biochemistry and be committed to improvement of diagnostic tests for schistosomiasis. This person must be familiar with all methods of direct diagnosis of schistosomiasis with Egypt-experience in the application of diagnostic tests. The individual must be able to work effectively in cooperation with other members of the Analysis and Design Team. (one and one half person months)

Chemotherapy specialist with experience in the pharmakinetics and biochemistry of antischistosomal drugs.

The chemotherapy specialist will design an appropriate research and development plan for chemotherapy and will assess the capabilities of Egyptian scientists in this area. Plans also should be developed for laboratory studies and clinical trials of new compounds if and when they become available. Research plans should be directed towards drug delivery-systems, drug-combinations, mode of action of current antischistosomal agents, drug resistance, toxicity, field evaluation of treatment programs, cost-benefit analysis of chemotherapeutic options, and effectiveness of improved drug regimens.

This specialist should identify training needs and interact closely with the molecular biologist, immunologist, and epidemiologist as they plan their research and development approaches for the program. (one person month)

Environmental specialist/engineer with experience in Egypt in design, development, administration and evaluation of water-component aspects of schistosomiasis control programs.

This specialist will work closely with other specialists such as the malacologist, epidemiologist, and resource development specialist to ensure that all environmental issues are addressed within the framework of the program. He or she should closely examine the design of all research projects concerned with interventions for provision of safe-water supplies, as well as water analysis and sanitation aspects of the program.

The environmental specialist/engineer also will assist in identifying Egyptian institutions and scientists with expertise in this area, and in identifying training needs for this program. The environmental specialist/engineer also will be responsible for preparing the Initial Environmental Examination (IEE). (one person month)

Resource development specialist to develop mechanisms for the support of the R&D effort in Egypt.

This team member must be familiar with techniques for the mass cultivation of snails, rearing of animals for use in experimental models, production of larval forms of the parasite (i.e., cercariae, miricidia, and eggs), production of adult worms in quantity, and training of individuals to accomplish these tasks. Since both *Schistosoma mansoni* and *S. haematobium* occur in Egypt, the specialist must be familiar with both life cycles and their intermediate hosts. He or she must be knowledgeable about harvesting specimens and the techniques of primary preparation of specimens for experimental use (i.e., lyophylization, freezing, quantitation). This specialist will work closely with the molecular biologist, immunologist, malacologist, diagnostics specialist, and team leader to assess the needs of the program for both biological materials and training and to devise a plan for providing them. (one person month)

Data management specialist to devise a computer-based system for monitoring and coordinating the information which will result from the implementation of the project's components.

This specialist must be familiar with a wide variety of computer hardware and software and able to apply it to the management of scientific information. The data management specialist will serve as a resource person to all team members and will be responsible for devising a multiple-use, interactive system for tracking epidemiological, malacological, field trial, and sociological data. The specialist should have experience in developing such a system. (one person month)

Health education specialist to address the needs of the Socio-Economic Factors Affecting Transmission Component of the project.

The specialist should be familiar with a wide variety of health education techniques and methodologies including Knowledge, Attitude and Practice (KAP) studies, communications, social acceptance monitoring, occupational health, and behavior modification. The health education specialist will work closely with the anthropologist/ sociologist in the design of a comprehensive program in socio-economic factor research and in identifying potential collaborations between Egyptian and U.S. scientists. (one person month)

Molecular biologist with thorough knowledge of the application of molecular biologic techniques, including recombinant DNA methodology, in schistosomiasis research.

The individual should have a sound foundation in schistosome biochemistry and be committed to applying knowledge towards vaccine development. The person should be able to work effectively as a team member and to contribute to the design of new diagnostic methods as well as vaccine development. Experience in schistosomiasis research in Egypt is desirable. (one and one half person months)

Project design specialist to coordinate the writing of the Project Analysis and Design Team's report.

The format to be used in the report is identical to that used in the development of a Project Paper (PP). This specialist, therefore, must be experienced in the A.I.D. project design process and must have written PPs.

Experience in Egypt would be helpful. The project design specialist will work closely with the Team Leader to clearly delineate the project design and to coordinate the specific project analyses. The specialist will be responsible for the development of the logical framework and the writing of the RFP. (two person months)

Anthropologist/sociologist, preferably with experience in Egypt, to work closely with the health education specialist in designing a detailed plan for implementing the Socio-Economic Factors Affecting Transmission component of the project.

This specialist also will identify possible social constraints related to the implementation of other components (i.e., phlebotomy, attitudes toward the collection of social data, water use practices). The anthropologist/sociologist will write the Social Soundness Analysis for the report. (one person month)

Financial analyst/economist to address program issues related to cost and returns.

This specialist also will serve as a resource to other team members in the devlopment of budget and cost figures related to the project's financial plan. The financial analyst/economist must have experience in A.I.D. project paper development. In addition to developing the financial plan, the specialist will be responsible for performing the economic and financial analyses. (one person month)

VI. BUDGET

Budget information is on file at the VBC Project office.

ANNEX 1

BACKGROUND AND CURRENT STATUS OF SUB-COMPONENTS

A. COMPONENT 1 - VACCINE DEVELOPMENT

1. Problem and Background

Epidemiological studies in various endemic foci in the world, including regions of Egypt, have consistently provided data which were interpreted to detect age-dependent immunity to schistosomiasis. Mechanisms involved, however, have not been precisely determined. Nevertheless, the consensus among most active workers in the field is that over a number of years, humans can develop specific resistance to reinfection. This occurs, apparently after repeated exposures and infections.

The specific induction of immunity has been attempted for decades in a variety of experimental models, but with unimpressive results. In the past 25 years, however, the application of radiation-attenuation methodology has resulted in a wealth of compelling data indicating that of significant resistance to infection may be achieved.

2. Current Status

Successful vaccination against schistosomiasis has resulted most successfully from the use of irradiated cercariae of S. mansoni or from inoculation of non-living schistosomula larval worms. Ionizing radiation from ^{60}Cobalt, X-rays, or ^{137}Cesium at high levels of 20 KRad-50 KRad has been the most commonly used method. In this form, irradiated cercariae applied directly to the skin or mechanically transformed irradiated schistosomula inoculated parenterally readily engender resistance within one week with the optimal response frequently resulting 4-5 weeks post-vaccination.

Significant literature has been published on various parameters of the vaccination, such as dose of inoculating organisms, number of inoculations, duration of resistance, strength of resistance and putative sites of attack on organisms entering a resistant animal. All of these studies have been predominantly performed in various strains of outbred and inbred mice with some variations in outcomes attributed to host genetic differences. Much more limited studies have been performed with several non-human primate species with generally significant resistance demonstrated.

Concurrent studies have implicated specific antibodies of the IgG and IgE isotypes as being important mediators of eosinophil and other cellular helminthotoxic attack on schistosomula as the primary mechanisms of resistance. Tlymphocyte cell-mediated immunity also plays a significant role in resistance. A single study has shown that passive transfer of vaccine-induced antibodies will confer immunity.

Aside from attenuation of the lifespan of irradiated schistosomula, no other parameter of the vaccine's antigenic mosaic or morphologic development has been identified as a unique property of the irradiated organisms.

The other modality of vaccination that has been successful is the inoculation of non-living schistosomula (S. mansoni) either with a bacterial adjuvant or alone. In the former case, a specific protein antigen of 97,000 molecular weight has been identified as the primary immunogen. Through recombinant DNA technology the cDNA coding for this protein has been cloned and the bacterial fusion product identified as paramyosin, thus describing a functional property of a significant protective antigen in S. mansoni.

Several laboratories have identified a number of monoclonal antibodies directed against S. mansoni that are protective by passive transfer, that identify apparently different protein antigens, and that have been used to affinity purify antigens which in turn protect animals upon active vaccination, usually in combination with an adjuvant. Here too, DNA cloning techniques have been utilized to produce the antigens in question, in considerable quantities for detailed studies. These studies are all being actively pursued with the likelihood that several further candidate vaccine antigens may become available for in-depth study.

The complex mosaic of antigens that the schistosome possesses indicates that these studies are far from being successful with respect to the identification of a molecularly defined vaccine. It has been suggested that a combination of critical antigens may be required to obtain optimal resistance from vaccination, an area of endeavor yet to be systematically approached.

3. Description of the Component

Goal - The primary aim of this development effort is identification of a candidate molecularly defined vaccine or set of candidate molecularly defined vaccines for human schistosomiasis.

Purpose - Develop a highly structured, detailed operational plan that will have candidate vaccine development as the core activity with specified and integrated tasks to be assigned individual institutions or laboratories.

Activities - a. Seek institutions or laboratories that have the capacity to develop a strong program in vaccine model development in schistosomiasis. The university departments in Medical Parasitology or Tropical Medicine such as at Cairo University, Alexandria University, Ain Shams University and Mansoura University are just some of the capable sites.

b. Ascertain institutions or laboratories that have the capabilities to develop active programs in immunological research in experimental schistosomiasis with particular orientation to the ability to identify and characterize specific antibodies and schistosome antigens. At present, the institutions named above as well as the Theodor Bilharz Research Institute, and NAMRU-3 are some of the capable sites.

c. Seek institutions or laboratories that could develop a significant capacity for research in molecular biology of schistosomes, particularly as focused on recombinant DNA technology. In this new area it may be of immediate concern to identify units committed to developing in this direction and units with the capability to train selected individuals in certain aspects. Organizations that may be able to offer direction in this area are NAMRU-3, Mansoura University and the Biochemistry Unit of the National Research Center.

d. Identify institutions and laboratories that will be able to develop strong research capabilities in the isolation and characterization of potential candidate molecular vaccines for schistosomiasis.

Management and Participants - This component of vaccine development should be evaluated and formulated by the design team's consultants in immunology and molecular biology. One immunologist experienced in schistosomiasis vaccine research and one molecular biologist working in schistosome antigen identification would work as a team to complete this task. They each should have significant work experience in Egypt. In some phases of this design the epidemiologist will be able to contribute insights into identifying the realistic levels of protection to be sought in vaccine development in order to aid in the reduction of clinical morbidity.

4. Issues

Supply of schistosome materials - a successful research endeavor in vaccine development will require a constant and large supply of schistosome larvae for vaccine preparation and for antigen tests. This will require an Egypt-based facility whereby the short-lived life cycle stages will be readily available. There is little doubt that all of the laboratories involved in this component area of vaccine development as well as those participating in the component on diagnostics development will need a constant source of schistosome parasite materials. The most basic and critical issue to be resolved is the potential assignment of one laboratory to devote its entire activity to this end. The nature of this core facility, its location, management and specific mechanisms for supply of snails, infected snails, parasites, species and strains to be maintained must be carefully planned and integrated with the other component activities. The model of the NIH supply contracts for parasite materials (schistosomes and filariae) is a useful reference in this consideration.

Supply of commercial biologicals, consumable supplies and experimental animals - While it is recognized that most of the required biologicals (antisera, restriction endonucleases, radioisotopes, etc.), chemicals and specialized consumable supplies (culture-ware, plastic-ware, etc.) are not manufactured in Egypt but may be purchased through local agents, their constant availability will remain an important issue. The supply of experimental animals, especially various inbred strains of mice, is another major issue since no significant supplier is available in Egypt. The project design team may find it useful to consider whether a mouse-breeding core facility may also be cost-beneficial for the various units that will be participating in these component areas.

Vaccine model development - In the identification of institutions and laboratories where the vaccine development program may be situated, the project design team must ascertain the available radiation source (^{60}Cobalt or ^{137}Cesium) that will be used for all studies oriented to the establishment of the irradiated vaccine model.

Technical support staff - A primary focus of the activities carried out by the immunologist and molecular biologist must be directed at identifying the sources for highly trained research technicians and the mechanisms by which training in schistosome immunology and molecular biology training can be imparted to candidate technicians.

5. Summary Statement

Control strategies in schistosomiasis have traditionally been focussed on mass chemotherapy, molluscicide application, improvement of safe water supplies, environmental modifications and school health education. While significant advances have been made in these areas, schistosomiasis continues to be a public health problem. The spectacular advances in immunology and biotechnology in recent years indicate that a concerned, major effort for development of a vaccine for schistosomiasis is a viable and realistic strategy. Current studies have shown that a vaccine is feasible. It would be expected that a major, coordinated, multi-disciplinary research and development program focused on identification of candidate, molecularly defined vaccines will succeed in a limited time period.

B. COMPONENT 2 - DIAGNOSIS AND DIAGNOSTIC DEVELOPMENT

1. Problem and Background

Schistosomiasis or Bilharziasis signifies the occurrence of infection by any of the schistosome species and implies that the individual so affected must have been diagnosed by some modality. This in no way denotes the presence of clinical disease or sign or symptom of morbidity. In countries such as Egypt, in order to prevent the development of clinical disease, the individual must usually submit a fecal or urine specimen to be microscopically examined for the presence of characteristic *Schistosoma mansoni* or *S. haematobium* eggs, respectively, and then appropriately treated. Although the most reliable test available, this process is time consuming, requires trained microscopists and is relatively insensitive. These drawbacks are most glaring in the face of performing community-wide evaluations, particularly in the assessment of post-control measures.

Improvement in the sensitivity and rapidity of the identification of schistosome eggs in excreta has occurred in recent years. A number of alternative methods, such as serodiagnosis and detection of urine protein or hemoglobin have had limited applications although they have either lacked in sufficient specificity or were of decreased sensitivity.

2. Current Status

The identification of schistosome eggs and excreta unequivocally establishes the presence of an active or patent infection. It does not provide a measure of clinical disease,

however. For this, the precise quantitative enumeration of eggs per gram of feces or per unit volume of urine is the only widely applicable laboratory test. Nevertheless, in certain stages of clinical schistosomiasis, egg counts may not be reliable correlates. In acute schistosomiasis or Katayama Syndrome, egg excretion is not always evident and thus the clinical evaluation and specific schistosome antibody assays become essential for diagnosis. In this situation, the application of the Enzyme-Linked Immunosorbent Assay (ELISA) has advanced serodiagnosis immeasurably. Specificity is not always acceptable as the schistosome antigens used are not standardized nor molecularly defined. At the opposite end of the clinical spectrum, in severe chronic hepatosplenic schistosomiasis with extensive portal fibrosis the egg counts do not always correlate with the severity of the pathophysiologic dysfunction. A seroassay that correlates with this complication will be most useful but to date, none with reliability is available. A major advance in the identification and provision of more specific antigens for serodiagnosis will no doubt come from the application of recombinant DNA methodology. Work along these lines is progressing in a number of laboratories which will require thorough evaluation, particularly in endemic countries.

No less important is chronic urinary schistosomiasis haematobia with obstructive uropathy. It will be of great benefit to have a rapid field assay to identify this complication because egg excretion is not always consistently correlated. In Egypt, the development of urinary bladder cancer can further complicate the situation, making diagnosis difficult.

While the Kato-type thick smear method or the modified-formalin-ether method for feces and the membrane filtration method for urine remain the current standards for quantitative recovery of eggs, innovative alternatives are needed to improve sensitivity and ease with which the assay can be done. The initial approaches will be to develop sensitive methodologies to detect schistosome egg antigens in fecal extracts or urine samples. The quantiative assay of such egg antigens may eventually supplant egg counting, especially in population-based samples.

An exciting application of molecular biology can be envisaged in this area. It is not unreasonable to expect the construction of egg-specific DNA probes that can then be used to identify, by hybridization, egg DNA extracted from eggs voided in excreta. The high degree of sensitivity and specificity and the ease of quantitation make this approach a compelling application.

Finally and of no less importance is the possible application of new immunoassays utilizing sensitive chemiluminescent and bioluminescent reactions such as with an acridinium ester and luciferase, respectively. Methodologies to enhance these reactions are becoming available and should be readily adaptable to schistosome antigen-antibody systems.

The combined application of these various appoaches may renew the modality of diagnosis by identification of specific schistosome antigens circulating in blood. While this modality had some initial success, the lack of correlation of specific antigens with infection intensity diminishes its appeal. However, the continued exploration of such antigens may in the future provide a useful tool for specific diagnosis.

3. Description of the Component

Goal - Identification of alternative methodologies for the quantitative diagnosis of schistosome infections by either new seroassays or molecular probes to identify schistosome eggs in excreta.

Purpose - Develop a focus for a program that incorporates and integrates the applied immunologic and applied biochemical expertise in Egypt. The program should target development of innovative, rapid, field-adaptable diagnostic tests for schistosomiasis.

Activities - a. Identify institutions and laboratories that have demonstrated competence and research productivity in the use of state-of-the-art immunoassays for diagnosis of schistosomiasis. Such sites are to be evaluated in terms of capabilities of developing innovative methodologies or biochemical (molecular biologic) modalities.

b. Ascertain from in-depth discussions with clincial experts in schistosomiasis in Egypt the need for development of better indirect assays (immunologic or biochemical) to specifically diagnose the various clinical complications of schistosomiasis. The major university-based medical centers, particularly the Tropical Medicine and Urology departments will form the primary resource for this information.

c. Ascertain from in-depth discussions with experts in schistosomiasis clinical epidemiology that institutions such as Cairo University Tropical Medicine Department and Qalyub Center for Basic and Applied Field Research the specific needs for better diagnostic tests for epidemiologic studies. This should

include not only improvement of the sensitivity and specificity of tests to diagnose infection but also the need for further tests to establish morbidity patterns.

d. Further determine the relative role of potential new assays in the assessment of control strategies that can be applied broadly and rapidly and that can establish on a quantitative basis changes in infection intensity and in morbidity patterns.

Management and Participants - Analysis and design of this component will depend upon the broad expertise of the specialist in diagnostics. This process requires intensive consultation with the immunologist and molecular biologist in phases of the project design related to development of innovative and model diagnostic approaches for schistosomiasis. The epidemiologist will be important in contributing information on the desirable goals of diagnostic tests for application to field epidemiologic programs. The diagnostics specialist should be well-experienced in all laboratory diagnostic methodologies for schistosomiasis, with particular expertise in the application of immunologic methodology (immunoassays and immunochemistry). The individual should have experience in Egypt and should be familiar with the spectrum of expertise currently available in this area.

4. Issues

Schistosome materials are the most important non-commercial supply needed to effect the development of new diagnostic methods for schistosomiasis. As clearly indicated in a previous annex, the supply of schistosome life cycle stages must be available on a constant basis. The plan for a core facility to provide this should thus be a primary item in the analysis and design.

In the drive to develop new and innovative approaches to schistosomiasis diagnosis, it is clearly evident that some overlap and duplication of effort may be involved. Here, this may be beneficial to more rapid development of a test. The project analysis and design team, nevertheless, will need to develop an excellent integrated organization that will allow for a free exchange of data and information between laboratories.

While most laboratories in Egypt involved in use of schistosomiasis diagnostic tests, especially immunoassays, are associated with clinical departments or are part of an institution with patient resources, some potential collaborators in this new initiative may be affiliated with "basic" science organizations. It is important for the team to devise a plan

whereby these basic scientists who may contribute greatly to the development of innovative immunological and biochemical diagnostic approaches are able to obtain readily sufficient samples (sera, excreta, biopsies) from well-documented schistosomiasis patients covering all stages of clinical morbidity.

As iterated in other portions of this document, the supply and availability of perishable biologicals and specialized consumable supplies (plastic-ware, culture-ware, microtiter plates, nitrocellulose paper, etc.) will remain a persistent issue to be addressed and resolved throughout the project period.

5. Summary Statement

Despite a number of direct and indirect diagnostic tests for schistosomiasis (Bilharziasis), those that result in the actual identification of eggs in excreta or biopsies are the most specific, but lack sensitivity. The indirect tests are primarily serologic and all are hampered by the lack of molecularly defined antigens.

It is thus important that the means are available for developing defined schistosome antigens for diagnosis and for developing new immunologic and biochemical diagnostic tests using the newest methodologies of protein analysis and molecular biology.

C. COMPONENT 3 - EPIDEMIOLOGY

1. Problem and Background

Present information regarding prevalence, incidence and distribution of schistosomiasis mansoni and schistosomiasis haematobia in both humans and snails in Egypt is limited to a few geographical localities. Basic information on the distribution and intensities of infection by *S. mansoni* and *S haematobium* in other regions in Egypt, particularly among various age cohorts, is not available. Such data will allow for a contemporary assessment of the intensity of transmission, seasonality of transmission, incidence of infection, morbidity patterns, and for an evaluation of various past and ongoing control programs. This type of data also will be of great importance in the impact assessment of future application of vaccines, chemotherapy, and vector and environmental control measures.

As a result of numerous and country-wide schistosomiasis control programs in Egypt in the past 50 years, the epidemiologic pattern of infection for the two species of schistosomes has changed markedly. This, in combination with the extention of perenniel irrigation practice, population dynamics, and changes of prevalence of vector snail populations, has resulted in increased presence of S. haematobium in Upper Egypt and in dominance of S. mansoni in the Nile Delta. The impact of this dynamic change in schistosomiasis epidemiology on morbidity patterns has not been fully assessed.

2. Current Status

An estimated 20 million Egyptians are at risk of infection by either S. mansoni or S. haematobium. While children from age 5 to 15 years are the high risk group for acquiring the heaviest infection rates and infection loads, the risk of developing critical morbidity is clearly high if left untreated but precise risk assessments have been difficult to ascertain. The current widespread availability of anti-schistosomal drugs from a variety of sources in recent years has no doubt perturbed the epidemiologic patterns of schistosomiasis.

Almost all of the early studies on schistosomiasis epidemiology were conducted with imprecise and less than ideal methodologies for case detection, i.e., identification of eggs in excreta which resulted in varying sensitivities. While of value, all of these studies lacked the most important correlate of morbidity -- quantitative egg excretion. With the general recognition that based on population-based studies, the level of morbidity correlated positively with the level of egg excretion, it is now important to obtain such quantitative data to obtain a more meaningful assessment of disease in schistosomiasis as opposed to infection. Historical prevalence data do not provide unequivocal evidence of the extent of morbidity, although it is generally assumed that in areas of very high prevalence, the proportion of the population with high infection intensities was most clearly significant. In this context, various reported cross-sectional village prevalence rates of from 40 to 70% suggest significant morbidity levels. It is only in recent years that host genetic susceptibility patterns are being sought and possibly identified which in the future will have much greater relevance to our understanding of village morbidity patterns in schistosomiasis. Schistosome genetic strain variation as a further variable in the production of disease has yet to be clearly established.

The integration of human water contact behavior patterns with quantitative cercarial exposure is now being sought, and studies already completed have pointed to complex interaction in transmission dynamics. These studies have clearly shown the need to integrate social/cultural parameters in the assessment of schistosomiasis epidemiology, and the essential requirements for community participation, particularly in intervention strategies.

Central to all epidemiologic studies is the ability to detect cases as well as to be able to classify individuals into morbidity categories. In schistosomiasis, the distinction between infection and disease is critical to the understanding of the public health impact of the problem. Thus, improved and innovative methodology is surely needed to improve the sensitivity of case detection or diagnosis. This approach is thoroughly discussed in a previous annex. Innovative methods to ascertain clinical morbidity in population-based studies are clearly needed. One of these in current use is the portable ultrasound diagnostic apparatus that is identifying severe periportal fibrosis due to S. mansoni, and various stages of chronic urinary schistosomiasis haematobia, such as obstructive fibrosis and urinary bladder mucosal lesions. The use of this instrument is now providing incisive analyses of village schistosomiasis morbidity patterns previously measured with poor sensitivity and precision.

3. Description of the Component

Goal - Provide a contemporary epidemiologic assessment of schistosomiasis representative of the endemic areas in Egypt using state-of-the-art methodologies.

Purpose - Develop a plan of epidemiologic research in schistosomiasis that will provide an up-to-date knowledge base for continued assessment of current and future control measures.

Activities - a. Identify institutions and epidemiologically oriented research units that have demonstrated competence and research productivity in the sound application of epidemiologic principles and quantitative methodology to population-based schistosomiasis studies. In this analysis, the capabilities for longitudinal cohort studies and sound state-of-the-art data management are essential.

b. Identify institutions and units that have demonstrated competence and research productivity in schistosomiasis clinical epidemiology that have particular expertise in establishing contemporary morbidity patterns in community-wide or population-

based samples.

c. Ascertain the deficiencies in current epidemiologic knowledge of schistosomiais in Egypt with particular focus on the impact of control programs on prevalence, incidence, and morbidity patterns.

d. Ascertain the operational inefficiencies in schistosomiasis control programs in Egypt.

Management and Participants - The epidemiologist will be the central participant in the design of this project component with considerable contribution from the data management specialist. In some phases of the design, the specialists for diagnostics, chemotherapy, and anthropology and social science all will be essential. The key individual is the epidemiologist who must be conversant in all phases of epidemiologic research and must have had previous significant working experience in Egypt on schistosomiasis.

4. Issues

The analysis and design of epidemiologic studies will require a careful evaluation of the research sites with preference given to thoroughly monitored communities that are stable with respect to population composition and thoroughly representative of the endemic areas for schistosomiasis in Egypt.

A critical component will be the identification and recruitment of a cadre of well-trained epidemiologists at both Master's and Doctorate levels. It would be advantageous to identify the professional with both clinical training (for morbidity studies) and quantitative epidemiologic training.

Sampling frames - In the past, the sampling sites used in Egypt have been either too large for the study locale or poorly selected, resulting in a non-representative sample for the governorate or region. The analysis and design of the epidemiologic component should be concerned with rational, cost-effective, representative, precise sampling programs, perhaps through specification of cluster size and numbers of individuals to be subsampled from clusters to obtain the maximum statistical precision at the minimum cost.

Water-contact behavior is recognized as an important determinant of infection but may not be the sole or primary factor in regulating the human parasite burden. Host immune responsiveness and chemotherapy are the other determinants of

infection and infection-intensity. The design of this component should clearly integrate the contribution of water-contact behavior (and other social parameters) to the study of schistosomiasis epidemiology.

Environmental/vector parameters must be carefully selected for inclusion for study into the epidemiologic component. The issue that must be resolved is how to ascertain to what degree malacological studies can be integrated with the epidemiologic component to provide more incisive information on the actual dynamics of transmission at selected, representative water contact sites.

e. Summary Statement

In the past 50 years, the epidemiology of schistosomiasis in Egypt has undergone dynamic changes due to changes in irrigation practices, drug availability, country-wide control strategies and population dynamics of the snail vectors. Concurrently, the morbidity patterns for schistosomiasis mansoni and haematobia have also varied. The present situation with respect to prevalence, incidence, infection-intensity and morbidity is known for a few well-defined geographical areas in Egypt, and even this body of information is scant. In order to have a better assessment of the epidemiologic pattern of schistosomiasis and for impact assessment of current and future control strategies, more representative, quantitative epidemiologic data are needed not only of the infection but of the morbidity patterns caused by the two schistosome species. This information base also will be available for the rational application of schistosomiasis vaccine trials and trials of new potential drugs in the immediate future.

D. COMPONENT 4 - CHEMOTHERAPY

1. Problem and Background

Chemotherapy has become an important component in attempts to control schistosomiasis. This is due to the availability of a new breed of potentially safe, orally administered and effective drugs for the treatment of the disease. Some control interventions, are designed to interrupt the fragile interrelationship between the snail-intermediate host and the schistosome parasite, require detailed pre-control studies based on precise scientifically planned projects. In contract, chemotherapy requires a minimum of pre-control studies. When chemotherapy is used in control programs, however, clearly defined aims are required, and the appropriate antischistosomal

drugs, dosage and frequency of regimens must be selected as well as the most reasonable delivery system.

Other control interventions only reduce transmission and do not affect the worm load of infected individuals. On the other hand, chemotherapy can not only reduce the excretion of live ova from infected persons but also causes a reduction in transmission. In addition, when schistosomes are eliminated from the body of an infected person, the risk of morbidity and mortality due to schistosomiasis is reduced and the patient is able to recover from the pathological effects of the disease, mainly the lesions, which are reversible.

While both of these effects are beneficial, it is important to distinguish one from the other. The entire community benefits from the reduction in egg output and the subsequent transmission reduction, but only the treated individual benefits from reduction in the risk of morbidity and mortality and the resulting recovery from pathological lesions. In situations where there is only partial reduction, a considerable decline in the risk factor may also occur. Thus, chemotherapy can be used as a tool for both primary and secondary control purposes.

The aim of primary control is to eliminate egg excretion, especially among those persons who are most likely to contribute to the pollution of transmission sites. There are situations in which egg excretion is not reduced to zero, and it is not known exactly at which level persisting egg excretion ceases to be a major problem for the health of any particular population. Nevertheless, the major goal of primary control efforts should be reduction of the egg excretion of as large a part of the population to as near to zero as possible within the constraints of cost, toxicity, and potential effects on immunity in infected individuals.

Secondary control aims to treat all infected individuals. However, in situations where operational constraints exist, priority should be given to treating the most heavily infected or individuals or high-risk groups as school children.

The earliest use of chemotherapy for large scale control purposes occurred nearly 35 years ago. Tartar emetic and fouadin were used in Egypt in 1953 and 1959 in a compulsory treatment project. Astiban was used in a mass suppression management treatment regimen in 1964-1965. In 1968-1971, a project in Fayoum used niridazole and tartar emetic in conjunction with the molluscicide Bayluscide. Niridazole was used in Tanzania in 1972, and in the Malagasy Republic in 1973, it was used in

conjunction with the molluscicide Frescon. Prevalence of infection was reduced, but not to expected levels in any of these projects. Major constraints were toxicity and multidose regimens which resulted in incomplete coverage of the target populations. In addition, the cost of the drug administration was high.

2. Current Status

During the past five decades there has been a steady introduction of new antischistosomal agents. The regimen of treatment for most of these drugs was as a single dose regimen. Hycanthone, the first of these compounds, gave promise of adequate population coverage, improved therapy, and the promise of enhancing the success of major control schemes. Major control schemes were initiated in Egypt, Brazil and St. Lucia using this drug but because of toxicity encountered the drug became unacceptable. Use was abandoned after nearly one million persons were treated.

Only three of the drugs developed during the past 20 years and presented clinically are recommended by the World Health Organization (WHO) for treatment of human schistosomiasis.

Metrifonate, formerly known as trichlorphone, and trichlorofone is an organic easier that is active against *Schistosoma haematobium*. Tolerance of this drug is good. Cholenergic side-effects have been observed, but are rare and mostly mild disappearing within a few hours. No mutagenic, carcinogenic or teratogenetic properties have been reported. Cure rates in control programs range from 40-80%. Individuals who were not cured experienced an approximately 90 percent reduction in egg counts.

Oxamniquine is a tetrahydrophenoline that is only active against *Schistosoma mansoni* infection. There are distinct differences between South America and Africain the responses of schistosomal strains to therapy with oxamniquine. The drug is also well tolerated, especially when given after meals. Side-effects such as dizziness, drowsiness and headaches usually occur 1-2 hours after administration and persist for 6 hours or less. Vomiting and diarrhea are infrequent, but halluccinations, psychic conditions, and epileptiform convulsions following treatment have been observed. Fever 24-72 hours following treatment has also been observed.

After the appropriate therapeutic dose of oxamniquine has been administered, cure rates of 60-90% can be expected. For persons who are not cured, reduction in egg excretion of 80-90%

can be expected. This drug has been used to treat several million persons thus far.

Praziquantel is a heterocyclic pyrazino-isoquinoline with broad spectrum activity against trematodes and cestodes. It is effective against all species of schistosomes which infect humans. No mutagenic, carcinogenic, embryotoxic or teratogenic activity has been reported for this compound. This drug is well tolerated; major side-effects include abdominal discomfort, diarrhea, dizziness, and sleepiness. Less frequent side effects such as fever and skin rash have been also reported. Successful treatment of advanced hepatosplenic schistosomiasis, without any apparent adverse side-effects, has been reported. For Schistosoma haematobium infections, the cure rate in the field is between 80-90%. Reduction in egg excretion for those who are not cured is approximately 90-95% at one year after therapy. For Schistosoma mansoni infections, a cure rate of 60% is reported at one year after treatment, and a 95% reduction in egg excretion is reported for those who are not cured. Approximately one million people have been treated to date with this drug.

The use of drugs in combination has been recently reported for treatment of schistosomiasis. Use of a combination of praziquantel and oxamniquine for human therapy and experimentally in mice infected with schistosomiasis has been reported in the literature. This approach was carried out to try to improve drug delivery and overall efficacy of treatment regimens, as well as to reduce the length of treatment.

Amoscanate, a new isothiocyanate, has broad spectrum activity against infection in man by all species of schistosome as well as against some nematodes. Phase I. clinical trials in human volunteers have been completed in the United States. Use of the precise formulation appears to be related to efficacy and reduction of toxicity. Nevertheless, hepatotoxicity, dizziness, dreaming, anorexia, and abdominal pain have been reported, especially in the Peoples Republic of China where hundreds of thousands of people have been treated.

RO.13-3978 is an oral drug which has shown marked antischistosomal activity against three species of schistosome infection in humans. Laboratory tests are continuing for this compound.

3. Description of the Component

Several areas of research are relevant to chemotherapy and should be included as components of a multifaceted program designed to eventually control the disease. These include the following:

- Continued research for new and improved antischistosomal drugs should be encouraged. The capability to conduct precise and well-planned chemical trials at both phase I and phase II levels should be established within the framework of the overall program design.

- Development of feasible strategy for morbidity control, including monitoring, evaluation, methodology, development and standardization of procedures.

- The design of new, cost-effective delivery systems.

- Pharmacokinetic and biochemical studies of existing and new antischistosomal compounds.

- Combinations and/or synergistic drug studies to improve efficacy and reduce treatment costs.

- Monitoring for occurrence of drug resistance, and development of laboratory studies and a field test for resistance.

- Development of community participation and drug distribution programs, taking into consideration that each community is a separate cultural entity (see operational research section).

4. Issues

The potential problem of drug resistance in schistosomiasis therapy has been recognized. Strains resistant to oxamniquine and hycanthone have been isolated and confirmed in mice studies in Brazil. Recent reports indicate that oxamniquine resistance is occurring in Kenya. It appears that resistance to metrifonate may also be occurring in Kenya. Praziquantel is effective against the drug-resistant strains isolated thus far.

The use of chemotherapy in field programs can be limited by constraints such as toxicity, cost and effects on immunity. In some instances, the dosage of some drugs required to cure all of

the individuals treated produced side effects of varying degrees and occasionally caused death. Therefore, the dosages of those drugs were administered below the level considered to be clinically optimal for cure. The drugs available today are far less toxic than earlier drugs. The dosage for some of them, however, may have to be reduced below the optimal level to make them to be acceptable to the population.

The antischistosomal drugs currently in use, with the exception of metrifonate, are expensive in relation to the health budget of most countries where the disease is endemic. The costs of the drug and its administration are major constraints.

The effect of treatment on immunity should be assessed before treatment programs are initiated. The prevalence rate is of major concern. One may choose to treat only those persons found infected by parasitological examinations. Or, one may identify those high-risk groups with high prevalence of infection and then treat all members regardless of whether each individual is infected. These are major decisions which must be worked out individually for each program with regard to safety and cost of the regimen.

5. Summary

Chemotherapy is now considered one of the preferred interventions for use in the schistosomiasis control program, either alone or in conjunction with snail control and health education. There are, however, impediments to the overall effectiveness of the interventions. These are: (1) a need for more appropriate-delivery systems; (2) cost of drugs; (3) reinfection which necessitates repeated treatment; (4) lack of specific serodiagnostic tests to monitor cure and reoccurrence of the disease; (5) lack of health education programs concerning causes, modes of transmission, and presentation of the disease; (6) lack of community involvement; and (7) a new emerging problem -- the potential for schistosome drug resistance.

Despite the availability of three drugs which are relatively safe, highly effective, and easily administered as oral regimens, there are still shortcomings at the community level for each of these drugs that compromise their usefulness.

E. COMPONENT 5 - SOCIO-ECONOMICAL AND CULTURAL FACTORS

1. Problem and Background

In many instances, national authorities prefer to direct all of their available financial resources (national as well as external) to so-called economically important development projects such as irrigation schemes, dams, and man-made lakes. These kinds of projects are important, but unless transmission control and ecological, environmental, health, social, cultural, and economic impacts are first studied, the overall benefits obtained may be negated by their adverse effects. In some countries, because of the lack of foreign exchange, the government prefers to spend public funds on local manpower rather than on importation chemicals, drugs, equipment, and other commodities needed for disease control.

In many areas where schistosomiasis is endemic, fish are a source of protein. The use of molluscicides that may harm fish are prohibited or limited in use, thus preventing the potential control of the snail intermediate host. The establishment of large-scale fish farms to provide low-cost sources of protein as well as minimize human contact with the water has been suggested. They might also generate income.

The use of long-term intervention measures such as health education and local environmental improvements which are directed at the population at risk may not be successful without community participation. Sometimes, despite community participation, there are conditions which may impede progress of the control program. Examples include high illiteracy rates in local populations which lead to irrational opinions and/or concepts concerning the disease and its origin, local customs and/or taboos, misunderstanding or hostility between rural dwellers and local authorities, lack of trained personnel, and inability of the responsible local authorities to appreciate or understand the value of community participation.

Another important aspect is priority placed by the government on control of schistosomiasis. This can influence the budget and hence, the control policy which is ultimately adopted. Any progress in control, and the methodology used, may depend on this emphasis.

The introduction of new and innovative interventions which heretofore have not been experienced by a given population, especially in rural communities, will certainly interfere with routines that have been in effect for perhaps centuries and

practiced by untold generations. These routines can be a serious impediment to any control program. The use of a vaccine for mass immunization surely would have to be preceeded by a series of health education and public health interventions.

2. Summary

During the past five decades or more of schistosomiasis control efforts, the expenditure for control purposes has been disproportionally high in relation to the results achieved. One reason for this could be lack of consideration in the overall control design of social, cultural and economic parameters.

An important aspect of proposed S&T schistosomiasis program should be a fully integrated social, cultural, and economic component which will interact across all of the proposed applied and basic research sections of the program. Thorough social, cultural, and economic assessments should be made before the program is implemented.

F. COMPONENT 6 - OPERATIONS RESEARCH

1. Problem and Background

Operational research can be an important component of a multidisciplinary program designed to meet the objectives as envisaged by the science and technology program for critical childhood diseases including schistosomiasis. Such a component can be used to develop the necessary tools needed to achieve the objectives as set forth in this type of multidisciplinary program. In addition, operational research can be designed for the purpose of using the results to overcome certain constraints which stand to mediate against some of the program components. The overall characteristics of the operational research component should be evaluated in terms of the local conditions within the region where results from various other components of the multidisciplinary program will be used to achieve the objectives of the overall program. A comprehensive evaluation should include consideration of epidemiological, ecological, socioeconomic and cultural factors.

2. Health Education

Health education should be a continuous process where schistosomiasis is endemic. It should be initiated before the begining of any control operation and should continue well beyond the intensive plan of the control program, as well as becoming a more or less permanent component of the national health program.

Health education is essential from the outset, for example, in programs which are designed to achieve morbidity control. The same can be said for snail control, interventions related to safe water supply, and other control efforts. An important responsibility of control program field staff is to communicate health information as well as health education to the end-users.

a. Community Participation

Community-participation is an important aspect of health education. The success of chemotherapy and vaccine programs could depend on the extent that community inhabitants understanding their role in disease transmission and the resulting benefits that may result from their full participation. The importance of involving the entire community is increasingly appreciated now that chemotherapy, which requires cooperation of the community and its inhabitants, is being employed on a large scale. This is in direct contrast with minimal community involvement in snail control programs.

Regardless of whether a program is research - or control-oriented, community involvement should be planned. There are many semiformal contacts which can be used to inform community inhabitants of the nature of control programs. This can be done by presenting lectures in schools, adult meetings, films or other manual aids concerning the schistosome parasite, its life cycle, and the disease it causes. As they conduct their work tasks, survey teams, regardless of their assignment, can explain the program to community members. Individual home contacts are also a good way by which to inform people of health programs. The use of radio and television is recommended whenever possible. Some schemes have used information pamphlets, matchbook covers, and children's books. The teaching of personal hygiene courses in schools can be an effective method providing that there are properly maintained and adequate water and toilet facilities at the school to support and emphasise the classroom instruction.

b. Summary

Health education must be recognized by both technical, professional and management staff as an important and integral operational component of a program to control schistosomiasis.

Potential research efforts include the following:

- approaches which would modify knowledge, attitudes and practices with respect to transmission, diagnosis and control of schistosomiasis;

- o development and initiation of programs that promote full participation of women and the community in general;

- o determination of the utility of media campaigns and their effect on community participation in health education programs; and

- o development of innovative methods to modify attitudes towards water and water-borne diseases such as schistosomiasis.

3. Delivery System

a. Chemotherapy Delivery Systems

The use of an antischistosomal drug-delivery system should be based on a sound understanding of the epidemiology of the disease and the effectiveness of the drug to be used. Several basic elements exist for any chemotherapy delivery system. These are: diagnostic methods and associated materials, logistic support, data management, drugs and personnel.

There are systems which can be used such as mass treatment, selective approaches (selective population chemotherapy, selected group treatment, targeted chemotherapy, phased treatment) and retreatment schedules.

Mass treatment refers to the treatment of all members of a particular population without having conducted prior diagnosis of each subject. When the decision is made to use this system, adequate epidemiological data must exist that indicates that there is a high infection rate. The proper sampling frame and design of this approach are very important and are most often based on the involvement of the smallest administrative unit. Case detection costs for mass treatment are low in comparison to other systems, and are restricted to preliminary samplings. However, drug and delivery costs are high, and one can expect significant impacts upon morbidity and transmission.

A number of selective approaches to chemotherapy have been developed. These approaches are as follows:

- o Selective Population Chemotherapy

In this approach urine and/or stool specimens from the entire population of a particular area are examined and only persons passing schistosome eggs are treated. In this approach,

case-detection costs are high, but drug and delivery costs are lower than with mass treatment approaches. If the diagnostic tests used are sensitive enough, then a high level of morbidity control can be obtained and effects on transmission will be only slightly less than in mass treatment approaches.

- Selected Group Treatment

This is a variant of selective population chemotherapy. The highest prevalence, intensity and morbidity are usually found in the younger age groups. Thus, either the enitre group or all those found infected are treated. In selected group treatment, case-detection costs are low and drug delivery costs are lower than for other approaches. The greatest effect on morbidity and transmission will be in the age group at greatest risk among those persons who contribute most to contamination of the environment.

- Targeted Chemotherapy

This is a theoretical approach that has not been adequately tested on a large scale. Its method is to treat persons with high levels of egg passage who are at the greatest risk of developing disease.

- Phased Treatment

This approach uses various combinations of the above described approaches in sequence (phased treatment). This method may provide for the most economical use of drugs.

Using present strategies for morbidity control, it can be anticipated that transmission will continue after large-scale treatment programs are completed. Thus, further treatment will be required to maintain whatever level of control has been achieved. More information is required on this aspect of control from different endemic areas. It could be obtained by careful monitoring of the relationship between morbidity and infection intensity following chemotherapy programs.

This type of applied field investigation could be carried out by control program groups which are associated with research entities assigned to investigate any of these kinds of problems. The rate at which prevalence and intensity of infection increase will depend on factors such as: (1) the number of persons remaining infected after therapy, which is in turn dependent on pre-treatment levels of endemicity, operational approaches, cure rates, immigration in and out of the area, community cooperation

and case-detection; and (2) the rate of reinfection which depends on the extent of water contact, fecal or urine contamination, size of snail-intermediate host population, seasonality of transmission, possible animal reservoirs interaction, and availability of safe and adequate water supply.

b. Molluscicide Delivery Systems

The conventional means of molluscicide delivery include hand-operated or pressure sprayers, and automatic and semi-automatic dispensers.

A concept which has been explored during the past decade is controlled slow-release application. This appears to be an attractive approach which may be more cost-effective, less labor intensive, of greater operational simplicity, less harmful to the environment, and effective in destroying schistosome larval stages. It can also be valuable in focal control, especially in static bodies of water. Despite these seemingly attractive features, no slow-release formulation is currently commercially available.

c. Summary Statement

The role of delivery systems for chemotherapy need further exploration for the purpose of devising new and innovative approaches for the control of schistosomiasis. More data is needed concerning reinfection potential and occurrence and means of drug resistence. Chemotherapy delivery systems must be investigated more fully to determine how they interact and impact on other operational research initiatives.

Research concerning the design and use of slow-release formulations should be addressed with the aim of ultimately employing this method in the field. Small scale pilot projects could be initiated to study the above possibilities.

4. Water Supply

Plans for interventions in the supply of safe water should be made on an intersectoral basis and should also include indigenous agencies responsible for water supply. Endemic areas where the prevalence and intensity of infection were initially high or remain high after direct intervention are ideal sites for provision of adequate, safe and reliable water systems. Other facilities such as showers and laundries which are maintained by the community are also important.

a. Summary

Efforts to provide safe water should be included in any control program. This requires full participation by the community members as well as integration into health education and public health programs.

5. Snail Control

The biological control of snail hosts is a relatively unexplored research area. In view of the need for effective snail control methods, rigorous laboratory and field research studies and training, often lacking in the past, are now required. Among major constraints on the use of biocontrol agents in endemic areas has been the lack of a balanced appraisal of safety factors and costs of potential agents such as microbial pathogens, parasites, predators, and competitors of snail hosts.

Of the three conventional control methods -- chemical, environmental and biological -- for snail host control, the greatest emphasis thus far has been given to the use of molluscicides and the least to biological control. While research on biological control has been neglected, recent appraisals indicate considerable promise for the cost-effective use of biological control of snail hosts in certain kinds of transmission sites. Similarly, encouragement has been drawn from the fact that in the last few decades, the biological control of agricultural pests has enjoyed significant success. For these reasons, biological control of snails appears to be timely.

During the past five years, overall strategy of schistosomiasis control, including the role of snail host interventions, has undergone significant change. Up to 1970, snail host control (mainly by mollusciciding) was the primary procedure used for schistosomiasis control. In consequence, it was, not surprisingly, given major support at both research and operational levels.

The present emphasis on control of schistosomiasis by chemotherapy must not be misinterpreted to mean that there is no longer a place in the strategies for snail control. At the present time, snail host control in most areas where schistosomiasis is highly endemic can best be viewed as an important supportive element (in contrast to its former pre-eminent role) in integrated schistosomiasis control activities. It is evident, for example, that where reservoir hosts or marked migration of people are important, population-based chemotherapy alone is unlikely to be satisfactory.

There is now a greater awareness that snail host control activities usually form part of a broad range of transmission site control operations. Identification of the most important potential transmission sites and of the main seasons of transmission is a crucial initial task. If snail control activities are to be initiated, careful consideration must be given to the basic options of desirability/feasibility. Should snail control (whether environmental, chemical and/or biological) not be excluded by these options, then plans for implementation must incorporate satisfactory solutions to the problems of where, when, how and by whom it should be implemented. In addition, the aims, costs and evaluation of results must be included in the provisional plans of action.

As part of the current strategies for control, potential snail control operations must be intimately associated with public health considerations and with the implementation of population-based chemotherapy schedules. In general, snail control operations are unwarranted in areas where there is no evidence that schistosome infection is giving rise to detectable morbidity. On the other hand, in areas of intense transmission, where chemotherapy is being applied, it is usually desirable that snail control activities be closely coordinated with the treatment regimen. In particular, snail host control activities, like other elements of control operations, must make a contribution to the reduction of transmission to levels which no longer give rise to significant disease in the affected populations. They must also be shown to be cost-effective and without adverse environmental impact.

Surprisingly, within each of the three areas (environmental, chemical and biological) of snail host control, no radically new, promising approach has been devised in recent years and, in fact, none can readily be anticipated, with the possible exception of biological control. In addition, among major constraints to snail host control approaches are high costs, relatively poor efficacy and lack of specificity.

a. Biological Control

1. Snail Host Antagonists

In spite of much interest in biological control, based partly on the successes of this approach in eliminating many agricultural pests and also, for example, on the possibility of considerable financial savings, its potential role in the control of snail hosts has not been rigorously investigated. This omission, certainly as far as research on the subject is

concerned, should now be rectified. Of all potential biological control mechanisms, intermolluscan competition is perhaps the most attractive at present.

Laboratory studies on biological control agents have ranged from relatively casual observations that snail colonies can be adversely affected by certain biological agents (e.g., microbial pathogens, ostracods, Helisoma, Bulinus tropicus, etc.), to rigorous investigations on the main biotic and abiotic factors governing the relationships between antagonists and their targets. It must be stressed, however, that even when excellent results are obtained in the laboratory, it is essential to perform carefully controlled field studies to confirm the true value of any potential control agent. It has been a common finding that some agents which have performed well in laboratory aquaria may not maintain their promise when tested under field conditions.

The effect of the predatory snail, Marisa cornuarietis under field conditions, was first observed in Puerto Rico in 1952 (Oliver-Gonzalez and co-workers, 1956). The snail was introduced in 1956 into 30 lakes and reservoirs containing populations of Biomphalaria glabrata. M. cornuarietis was re-seeded several times and, after 20 years, only five of the original reservoirs contained planorbid snails. However, M. cornuarietis was less successful in flowing water habitats in the Dominican Republic, Puerto Rico and St. Kitts.

Under tropical African conditions, there has been only one field investigation of M. cornuarietis. Following its release into a man-made pond in the north-west of the United Republic of Tanzania, three species of indigenous snails (Biomphalaria pfeifferi, Bullinus tropicus and Lymnaea natalensis) were apparently eliminated.

The thiariid snail Thiara (=Tarebia) granifera has also been reported to be an effective antagonist of Biomphalaria glabrata. It has been observed to replace a previously thriving population of B. glabrata in an extensive habitat on the island of Dominica (West Indies) and may have been responsible for severely restricting the range of the previously widespread B. straminea on the island of Grenada. It has also been reported to be an antagonist of B. glabrata on the island of Puerto Rico and, more recently, in a large area of the Dominican Republic. In contrast to these chance observations, T. granifera was released in limited areas of the island of St. Lucia in early 1978. In four separate field trials, B. glabrata was apparently eliminated from marshes and streams six to 22 months after the introduction of T.

granifera. The time at which the target population reached zero was dependent on the number of T. granifera introduced. When seeded in numbers approximating those of the target snail, dominance was quickly established. Observations made in 1983 showed that T. granifera had retained its dominance.

With regard to Helisoma duryi, although some successes have been reported from lentic environments, this competitor is unlikely to prove useful in streams because it loses its foothold in water velocities lower than those which can be withstood by various species of Biomphalaria spp.

H. duryi was first tried in the field, with some success, in Puerto Rico in 1958 and it was also successfully introduced into waterbodies at St. Croix. In St. Lucia, H. duryi was shown to compete successfully with B. glabrata in simulated field conditions, but when released into the environment it failed to become established. On the African continent, where it is now widely recorded, preliminary studies were carried out in small ponds in Egypt. At Moshi, United Republic of Tanzania, a field experiment in an irrigation system was started in 1973. The experiment failed because of flooding and H. duryi was found in all the furrows. However, after one year, members of H. duryi exceeded B. pfeifferi and constituted more than 95% of the snails collected. In 1975, H. duryi was seeded in the drains of the irrigation system. A snail survey undertaken in 1981 showed that H. duryi was still present in a few drains in which no B. pfeifferi snails were found.

In 1982-83, small-scale field trials were conducted in isolated areas of Saudi Arabia to test H. duryi against B. truncatus, B. arabica and B. beccarii. The preliminary results indicate that H. duryi supersedes B. beccarii.

Medical surveys recently carried out in the island of Martinique have all shown that the transmission of intestinal schistosomiasis has been largely or even totally interrupted. It has been impossible to find any child under 12 years of age positive for Schisotosma mansoni infection. This situation appears to be correlated with the replacement of B. glabrata by B. straminea, over a period of probably not more than 10-15 years. Whereas before 1967 B. glabrata was widespread, in 1983 it was restricted to only a few habitats; the converse is true of B. straminea, which has become widely distributed during the same period. Although other factors should probably be taken into consideration, replacement of B. glabrata by refractory B. straminea seems to be responsible for the almost complete disappearance of schistosomiasis transmission on the island. The

strain on Martinique of B. straminea could not be infected by Caribbean strains of S. mansoni, either by exposure to miracidia or by microsurgical transplantation of sporocysts.

In Guadeloupe, a similar situation of biological dominance has been observed. In the site of Grand Etang, fortuitous colonization by Ampullaria (=Pomacea) glauca resulted in the decrease of B. glabrata densities, while S. mansoni prevalence in rats dropped from 80% to about 5% in five years. However, in ponds in the low rainfall area of Guadeloupe, B. glabrata and A. glauca often coexist without any marked dominance by this snail.

At the present time, studies on intermolluscan competition are being carried out, in Brazil, Venezuela and certain Caribbean islands. In Africa, investigations on Marisa cornuarietis and H. duryi are being undertaken either together or separately, in Egypt, Niger, the Sudan and the United Republic of Tanzania.

There is no doubt that snail host population densities in certain kinds of habitats can be drastically reduced, even eliminated, by intermolluscan competition. However, if snail competitors are to be truly successful, they must also contribute significantly to control of the parasite populations which cause disease at levels of socioeconomic significance. With this objective in mind and in relation to the new strategies for schistosomiasis control, which distinguish between schistosomal infection and disease, absolute prevention of transfer of the parasite from snail to definitive host may not be strictly necessary. Unfortunately, snail host population density thresholds, permitting diverse (low, moderate, intense) levels of schistosome transmission, are still unknown. They are likely to be variable, depending on the complex interactions of physical, chemical and biological parameters. Despite their complexity, a good understanding of them would ensure a valid interpretation of the efficacy of biological or any other snail control procedures.

Our knowledge of snail host antagonists -- microbial pathogens, parasites, predators, and competitors -- is still rudimentary.

2. Microbial Pathogens

It is reasonable to assume that host snails, like other organisms, may be attacked by a variety of microbial pathogenic organisms. Such pathogens must be capable of eliciting histopathological or degenerative biochemical alterations in the snail host. When possible, Koch's postulates should be demonstrated.

Snail hosts respond to injury by means of a variety of defence mechanisms, such as phagocytosis by haemocytes, encapsulation and pearl formation. Invading pathogens may cause atrophy of certain organs, aplasia, necrosis and tissue liquification, alterations in tissue enzymes and haemolymph components, metaplasia, hyperplasia and possibly neoplasia. Physiological changes in fecundity, growth, locomotion and feeding behavior may also occur in snails infected with particular pathogens.

To date, there has been very limited interest in snail host microbial pathogens. Not surprisingly, therefore, is that the number of microbial pathogens described from freshwater snails and is relatively small and includes mycobacteria and other bacterial agents, most of which have not been well defined. These include such protozoa as Hartmanella, Trypanoplasma, Dimoriopsis, Nosema, Plistophora, Unikaryon; and fungal organisms of unknown etiology. Viral and rickettsial agents have not, as yet, been described from freshwater snails. Several laboratories in Europe and North America offer services for the identification of microbial pathogens of invertebrates. No potentially useful pathogens have yet been identified.

3. Parasites

Parasites, including schistosomes, reduce the fecundity of snails. One field trial to prevent transmission of Schistosoma spindale failed to raise the infection rate with Echinostomum malayanum above 50%, despite the application of nearly 600 million eggs to a small pond containing an estimated 13,000 Indoplanorbis exustus. Over a seven-month period, there was no noticeable reduction of the snail population. Another trial gave more satisfactory results, but the method was still very inefficient. More recently, Ribeiroia marini, a cathaemasid trematode, eliminated Biomphalaria glabrata from a pond in Guadeloupe. Snail infection rates reached 85% after the addition of seven to nine million parasite eggs over a four-month period. As R. marini is a natural parasite of the little blue heron, Florida caerula, on the nearby island of St. Lucia its use might represent a threat to this and perhaps other water birds.

Along with competitor molluscs, studies on trematodes which do not infect humans have given rise to the largest number of field trials, mainly in Guadeloupe, Malaysia and, more recently, in the basin of the Niger River. The results indicate that while the approach may be effective, it will be rendered impractical by the need for repeated release of eggs. The cost of such operations and their evaluation is likely to be high, the

technology is not simple, and their efficacy is probably much lower than that of molluscicidng operations. Moreover, the analysis of effectiveness is the least satisfactory aspect of research on which trematode parasites which infect non-human hosts. The regulatory mechanisms of host populations involved in host/parasite systems undergoing increased parasite pressure should be noted. Moreover, because of the well-known phenomenon of overdispersion of the parasites, the great difficulty of reaching the whole of the target snail population, even when miracidia are very numerous, must not be overlooked. It has been argued convincingly that the castration effect of parasitic trematodes deserves further study.

Angiostrongylus cantonensis, a nematode which infects rats, has been proposed as a biological control agent, but it is known to cause serious human disease in the Pacific region and its use is, therefore, not recommended.

4. Predators

Little research has been carried out in recent years on the efficacy of vertebrate predators of freshwater snails. It has been noted that the fish Astatoreochromis alluadi had a significant long-term effect on snail populations in artificial dams in Kenya, and, in Zimbabwe, Khaki Campbell ducks have been reported to suppress effectively snail populations in fish ponds. The use of such predators is probably of value only in certain specialized habitats.

Sciomyzid flies are obligate predators of molluscs. The larvae of the 200 reared species of sciomyzid flies (of 600 described species) kill and feed only on aquatic and terrestrial snails, eggs of snails, slugs, and fingernail clams. Prey and microhabitat selection ranges from broadly distributed to highly specialized, with the greatest number of species preying on several genera of freshwater, nonoperculate snails. A Central American sciomyzid that attacks Lymnaea which transmit fascioliasis has been introduced and established in Hawaii, but the impact of the fly on snail populations has not been determined. The larvae of most of the reared, aquatic sciomyzids attack various genera of pulmonate snails in the top few millimeters of the water, or on exposed vegetation of shorelines. Although their effects will not be confined, therefore, to the sole target snail species, the larvae of aquatic sciomyzids are restricted to a specific range of aquatic microhabitats and could not pose a threat to terrestrial snails. Some sciomyzid larvae occupy intermediate microhabitats (shoreline situations) and introduction of programs involving such species would need to

determine their microhabitat range and potential impact on terrestrial molluscs. At the present time, there is little direct evidence for the success or failure of sciomyzids as introduced biological control agents under field conditions, primarily because there have been insufficient field studies or biological control attempts.

Some vertebrate predators, especially fish, can contribute to the suppression of snail host populations in certain specialized situations (e.g., fish ponds), but sound evidence of their efficacy is lacking. Their inability to respond appropriately to rapid changes in prey density may be a major constraint. A critical review of the role of fish in the control of snail hosts would be useful and might stimulate further field research. Search for sciomyzids with suitable predator properties with narrow prey ranges and with the ability to search for prey in deeper water, needs to be pursued among the two-thirds of the species of sciomyzids that remain biologically unknown. The many species of semi-aquatic sciomyzids that have larvae living in marginal aquatic situations, and those that inhibit small, dispersed bodies of water and headwater situations, need to be examined for their potential as biological control agents.

5. Competitors

In recent years, many reports concerning the results of intermolluscan competition involving either prosobranch or pulmonate species have been published.

Helisoma duryi, a New World pulmonate snail, was many years ago observed to displace *Biomphalaria* spp. in aquaria and has been transported, probably accidentally and mainly via the aquaria trade, to many parts of the tropics. Limited field trials in Egypt and the United Republic of Tanzania have not given particularly encouraging results and suggest that *H. duryi* may survive in certain restricted microhabitats which only partly overlap those of the target snails. The morphology of this snail, especially of certain ecophenotypes, may cause even experienced field workers to mistake it for *Biomphalaria*. It has been found that no trematodes of medical or veterinary importance have to date been reported to infect any species of this genus. *H. duryi*, in particular, is remarkably free of trematode parasites. Recent examination of a small sample from a population established for at least seven years in a Tanzanian irrigation scheme failed to reveal any trematodes.

Marisa cornuarietis, a South American ampullarid snail with a voracious appetite for higher plants, eliminates Biomphalaria and Bulinus spp. from laboratory tanks as well as from experimental and certain natural field sites. It acts primarily by competing for food, modifying the nature of the habitat and destroying the niches occupied by the target snails. A secondary effect is the predation, which may be accidental, on egg masses and hatchlings of the target snails. It is refractory to infection with Paragonimus westermani, Clonorchis sinensis and Fasciola hepatica and does not appear to transmit Puerto Rican avian schistosomes in the field, but it has been found to be naturally infected with strigeids in Venezuela. Some reports have incriminated Marisa as feeding on rice seedlings in the field and on snail of related genera. Pomacea lineata in Surinam and Lanistes spp. in Swaziland have been reported as pests of commercial (swamp) rice. Species of the latter genus are both common and widely distributed in Africa, and have never been incriminated as pests of rice. In addition, laboratory studies in Egypt and the United Republic of Tanzania showed that Marisa does not eat either young or old rice leaves, even if no other food is available.

In Brazil, the general absence of Biomphalaria spp. in habitats containing Pomacea australis stimulated laboratory tests of its competitive ability. The related species, P. glauca, was widely distributed in certain habitats on St Lucia, sharing sites with B. glabrata in areas where S. mansoni transmission was prevalent. Trials in simulated field habitats showed that a starting ratio of 3:1 of P. glauca: B. glabrata was necessary to eliminate the latter within a six-month period. With progressively lower ratios, B. glabrata populations declined remained steady, or even increased over the eight-month period, though less rapidly than a population of B. glabrata alone. A field trial revealed no significant effect when P. glauca were added to B. glabrata populations. Pomacea has been implicated in damage to swamp rice.

Thiara granifera has been introduced from South-East Asia to the Caribbean region, probably on aquatic plants through the aquaria trade. Its rapid natural spread in certain areas apparently coincided with the disappearance of Biomphalaria spp. This observation was confirmed when it was deliberately introduced into parts of the island of St. Lucia. It feeds on detritus, diatoms and algae, and, being ovoviviparous, it is a prolific breeder. It is not yet known precisely how it competes with Biomphalaria spp. T. granifera can transmit a variety of other trematode parasites of relatively minor socioeconomic importance. As Paragonimus and Metagonimus spp. may infect man,

the use of Thiara in the biological control of schistosomiasis has been viewed with some reservation. However, scientists have recently questioned this view and have called for more investigation into these interrelationships.

b. Summary

There are many aspects of biological control which are suitable for research and development. With adequate funding and proper laboratory and field research management, determination of the efficacy, safety and cost-effectiveness of this approach should be investigated. The most promising of the potential control methods is intermolluscan competition, and it should be given priority for operational research support.

6. Control by Plant Materials

There are more than 1,000 plant species, including nearly 600 in China, which have been tested for molluscicidal activity. A relatively high proportion of the active species investigated were selected on the basis of observed medicinal properties or general folklore regarding toxicity. The highest proportion of species showing molluscicidal activity is in the family Leguminosae, followed by the Euphorbiaceae, Rubiaceae, Polygonaceae and Compositae. A large proportion of the Phytolaccaceae is also highly active.

The most thoroughly studied of the plant molluscicides is one derived from the berries of Phytolacca dodecandra (endod), an aqueous extract of which has been used for snail control in Ethiopia. In the Sudan, a water extract of the seeds of Croton macrostachys was found to have high molluscicidal activity. In the Philippines, Jatropha curcas showed activity against Oncomelania snails. In Egypt, trials are in progress using Ambrosia maritima. The crushed shells of the cashew nut (Anacardium occidentalis) are currently being used for snail control in Mozambique.

Some 42 molluscicidal compounds have been isolated from plants. In addition to saponins, thought until recently to be the major active molluscicidal constituents, flavanoids, alkaloids and terpenoids have shown encouraging results. The recent findings that bidesmotic saponins and some dammarane glycosides and alkaloid saponins are inactive and may help to explain variations in the results obtained by different investigators.

Further studies of other structure/activity relationships of compounds may result in the identification of plants with more selective effects. Molluscicidal compounds, like other phytotoxins, may be present and synthesized more frequently in some plant groups than in others, although many compounds do occur independently. Thus, sesquiterpene lactones are most common in the Compositae, but triterpenoid saponins are widespread in nature.

Successful and cost-effective cultivation of plants on a large scale, exclusively for snail control, remains to be demonstrated. The agonomic success achieved in the 1970s with Phytolacca dodecandra suggests that, at least in Ethiopia, such cultivation at the village level is feasible. The U.S. Agency for International Development is now implementing a project in Swaziland on this subject.

Successful cultivation of a "wild" plant requires careful breeding and selection for a high-yielding and high-potency type (strain) adapted to a wide variety of environmental conditions--soil, temperature, moisture, and shade. Differences in molluscicidal activity have been observed for the same plants grown in different environments. Evaluation can be accomplished only under strict supervision, preferably at agriculture research stations or in experimental plots in different geographical areas.

Plant propagation techniques will vary according to species and the plant's specific ecological requirements. Methods of breeding and cultivation should be well documented so that the information gained can be readily transferred to situations in other countries. After initial breeding and selection, cell culture techniques may play an important role in future research and development activities.

Ideally the plant would be intercropped with local crops, thereby promoting greater farmer supervision in regard to weed, pest and disease control. A self-help program should, if possible, be integrated into the daily activities of local farmers. This would produce opportunities for additional income generation.

Plant materials in their natural state are not generally molluscicidal. For the most effective use, minimal processing, such as grinding and crushing, is normally required.

Large-scale cultivation may or may not be feasible in some endemic countries, where the need for the recurrent use of machinery, fertilizers and possibly pesticides requires scarce hard currency.

a. Summary

The availability of safe, effective oral antischistosomal drugs and the high cost of imported synthetic molluscicides used in the control of schistosomiasis provide the incentives for examining the potential role of plant molluscicides. It is clear that an inexpensive and effective method of snail control in combination with chemotherapy is desirable. Although natural products have been used for millennia, their toxic effect on non-target organisms has rarely been evaluated. This is true also for plant molluscicides.

Phytolacca dodecandra, Ambrosia maritima and Anacardium occidentalis are several of the plants which have shown promising molluscicidal activity. Field trials of these species are currently being carried out in Ethiopia, Egypt, Mozambique and Swaziland.

Based on present knowledge of the distribution of recognized plant molluscicides, there is no justification for future "blind screening" of plants in order merely to identify new taxa. At present, certain saponins, specifically those with an aleonic acid derivative, seem to offer the greatest potential as molluscicides and should be studied.

There has been great progress in the development of extraction procedures for plant products. However, there is a need to standardize methods for phytochemical screening and bioassay to permit more comprehensive evaluation of plants and greater comparability of the results obtained by different investigators.

Phytolacca dodecandra provides a good example of the possible problems associated with different extraction methods and their relation to toxic effects. This plant has been reported not to be mutagenic when extracted in water, but the alcohol extract of the plant is mutagenic.

The success of the Phytolacca dodecandra breeding and selection program in Ethiopia clearly demonstrated that saponin quantity and potency, as well as its resistance to insects, can be increased over several years. The occurrence of varietal differences among plant species with promising molluscicidal

activity should be investigated - possibly using cell culture techniques. A long harvest period is preferred as this promotes more efficient processing, a ready supply of molluscicide, and reduced storage costs.

Probably the first criterion in assessment of any potential plant molluscicide is that it be water soluble. Such a property enhances biodegradability and reduces possible build-up of toxic residues in the environment.

Production of plant molluscicides by an inexpensive and efficient method may be best carried out at the village level. A self-help program, using a locally produced molluscicide and coupled with chemotherapy, should be investigated.

Safety factors (toxicity) should be studied for candidate plants as well as their biochemistry and mode of action.

7. Chemical Control

During the past decade numerous control projects in Brazil, Congo, Egypt, Jordan, Madagascar, Philippines, Zimbabwe, United Republic of Tanzania, Ghana and others have demonstrated that snail control by molluscicides, in combination with other methods, can reduce and in some instances eliminate transmission. There is however, a major need for development of new synthetic molluscicides in order to complement the impact of the other advances which have been made in schistosomiasis control.

Only one chemical, niclosamide or Bayluscide, has endured for use as a molluscicide. A similar chemical product is known in Egypt as Molluto.

Other compounds under development are organotins which have high molluscicidal properties and amide compounds which show some promise. The toxicological effects and environmental impact have not been ascertained.

a. Summary

Mulluscicides must be safe, that is, nontoxic for mammals and other aquatic organisms, they must not produce unacceptable adverse effects if they enter the food chain, and they must be stable in storage as well as cost-effective and available. They must have snail specificity, low-toxicity for non-targeted species, acceptable formulation, simplicity in application, and an easy and reliable method for field analysis. Research should be directed towards screening of any available compounds to meet

the above stated criteria.

8. Environmental Modifications

Environmental modifications can be an important component of a control program. Interventions such as filling in or draining all unnecessary water bodies, and/or reducing human contact with water sites by making them less accessible are practical approaches which can be used. Other interventions include the building of bridges to eliminate fording, and fencing off of popular areas where children play and have contact with contaminated water. Other measures include stream straightening, increasing velocity of flow, removal of vegetation, deepening of marginal areas, prevention of pollution, fluctuation of water level in dams, reservoirs, irrigation canals and water storage areas. All of these interventions are considered important adjuncts in any attempt to bring about control.

a. Summary

Environmental control requires changes in the environment of both the definitive and intermediate host of schistosomes. Prevention of contact with snail-infested water is the objective as regards the definitive host while for the intermediate host relatively drastic changes in ecology of the habitat are necessary to prevent further breeding of snails. In order to render the snail habitat unacceptable, data on the ecological parameters is required.

A major area of field research that needs to be addressed is the ecological profile of the various snail habitats in Egypt. This should include the chemical and physical profile of the water bodies in which snails reside. In addition, the roles of different habitats, either as active transmission foci or as reservoirs of snails for other active foci, should be known. This may be especially true in areas where fish farming or rice growing is an important local activity and the cooperation of the community is sought. Knowledge of the success and/or failures of water-management projects such as Lake Nasser, Lake Kariba, Yahara Bussa Dam and others may be helpful in the design of intervention for environmental modification.

9. Data Management

For all stages of operations, the schistosomiasis research program will require quantitative information on all of its components. A single index such as prevalence of schistosomiasis within a defined population is not sufficient for purposes of

monitoring or modifying the operations of a control program. Other indices are needed, especially those relating to in morbidity and intensity of transmission.

Modern statistical methods facilitate, to a large extent and on an objective basis, the interpretation of data in which variations may be due to the simultaneous action of many factcrs. These statistical methods should be used at all phases of a schistosomiasis control program in the establishment of the operational plans as well as in the monitoring of the operations and final evaluation of results.

Usually, considerably more data are accumulated by a research or control program than can be analysed correctly or used satisfactorily. Thus, rational planning should be flexible, adapted to local conditions, and practicable within the limitations of available funds and trained personnel.

The geographical area to be covered, the timing of the observations, the methods and frequency of intervention, and reasonable targets for achievement should be established. This requires that definitions be established and standardized classifications used. Questionnaires and record forms appropriate for use in the data-collection procedures must be pre-tested. It is important that the staff responsible for data collection be suitably trained and the procedures for their supervision and quality control established properly.

Appropriate statistical methods will be required to select appropriate sampling schemes. Evaluation of any pilot effort results, assessment of the statistical significance of the conclusions, timely preparation of progress reports on the progress of the program and dissemination to field workers are important activities of the statistical services.

A central statistical service should not necessarily be responsible for the analysis and interpretation of the data. Each operational level of the program may be capable of making specific judgements concerning the efficiency of the operations within its sector and able to pass essential information to the next level for further analysis.

a. Summary

Proper organization of the data management component of a multidisciplinary research program as proposed requires very sound and perhaps innovative logistical preparation. A system requiring all segments of the program to interact positively with

this component is essential. No component should be exempt from complying with the requirements for an orderly and consistent flow of data into this unit.

An important operations research entity could be a data management core unit to assist the various research programs in preparing statistical frameworks for analysis of data. Such a unit surely would result in considerable savings.

10. Training

Persons responsible for training should have in-depth knowledge of the control methods, investigational techniques, and epidemiology of schistosomiasis. Those trained should be prepared not only to perform their particular tasks, but also to train other staff.

Major changes are taking place in the training activities of successful public health programs of all types. The technology used in these training schemes is being critically evaluated in each country. It is being recognized that a thorough training of professional and technical personnel in epidemiology, vector biology, and other areas involved in control programs are needed in order to be able to develop rational operational approaches and to assess achievement. The reorganization of the managerial process and infrastructure to improve the efficiency of operations is another important sign of progress in national control programs.

The implementation of a strategy for morbidity control instead of transmission control or eradication requires a fundamental change in approach. This strategy must concentrate on specific quantitative goals and modification in approach must be made once these goals are reached.

In-service training as well as supervision of the personnel involved in a national schistosomiasis research program will be an important component. Periodic in-service training programs can be used to inform the staff of advances or changes in technology and methodology, review the standard operational procedures, and evaluate the implementation and progress of research and pilot control activities.

Regional training activities should be encouraged. The technical cooperation between endemic countries is increasingly important as they realize that different strategies are required for morbidity control in different situations. Exchange of personnel between countries involved in schistosomiasis control

would facilitate the transfer of knowledge and even of successful techniques.

a. Summary

There are urgent needs for training of technical personnel to staff the various applied, basic, logistical and operational research needs of this proposed program. Training should be considered as an integral part of the overall program at both technical and professional levels.

ANNEX 2

RESOURCE MATERIALS FOR ANALYSIS AND DESIGN TEAM

A. Egyptian Universities

Institution	Investigators	Areas of Focus and Potential Collaboration
Cairo University	F. Abdel Wahab M. B. Tadros M. Kamel	Clinical Epidemiology
Ain Shams University	M. F. A. Saoud K. Makled M. A. Madwar H. M. Khalil M. A. Massoud M. E. Azab	Snail/Host-Parasite Research Immunology/Diagnostics Immunodiagnostics/Epidemiology
Alexandria University	N. H. Awadalla M. Y. Michel A. H. El Beheiry	Vaccine and Diagnostics
High Institute of Public Health, Alexandria University	R. M. Barakat	Immunodiagnostics
Mansoura University	M. A. Ghoneim A. F. Attallah	Immunology/Diagnostics Immunology/Molecular Vaccine/Biology
Zagazig University	M. Ismail	Immunodiagnostics
Canal University	S. Afifi	Immunodiagnostics
Al-Azhar University	A. M. A. El-Asfahani	Antigens-Immunology/Diagnostics
Assyut University		

B. Egyptian Institutions

Institution	Investigators	Areas of Focus and Potential Collaborations
Theodor Bilharz Research Center	Al El Garem	Clinical Application
	Z. A. Shaker	Immunology
	M. A. El Hassan	Socio-economic Factors Affecting Transmission
	M. A. Saber	Field Research Biochemistry
	N. El Badrawy	Electron Microscopy
	A. A. Metwally	Pharmacology
	F. Yousif	Malacology and Operations
	H. M. S. El Wabel	Parasitology
Qalyub Center for Field and Applied Research	M. A. El Alamy	Epidemiological Surveys
	M. Habib	Data Management
		Snail Surveys, Drug Trials
		Molluscicide Trials
Sera and Vaccine Development Center	A. M. El Kholy	Diagnostic Development
	N. N. Guirguis	Vaccine Development and Production
National Research Center	M. Kamel	Biochemistry Department
	R. R. Hamed	Molecular Biology
		Diagnostics
Institute of Research for Tropical Medicine		Clinical Drug Trials
Child and Nutrition Institute		Socio-economic Factors Affecting Health

C. U.S. Universities

Institution	Investigators	Areas of Focus and Potential Collaboration
Harvard University	J. David D. Harn F. Von Lichtenberg J. Byram	Clinical Pathology Immunology/Vaccine Production
Uniformed Services University of the Health Sciences	E. Michelson J. Cross G. Hayunga	Diagnostics Snail Population Dynamics Host Parasite Interactions
Lowell University	J. Bruce Y. Liang	Production of Biological Material Life Cycle Maintenance Chemotherapy Drug Resistance
University of Michigan	G. Higashi J. Burch S. Kunkel S. Chensue	Immunology Vaccine Production Immunobiotaxonomy of snails Snail Population Dynamics
Michigan State University	J. Bennett R. Pax	Pharmacology and Biochemistry
Tulane University	B. Cline E. Malek	Epidemiology Snail Population Dynamics Snail Biology Molluscicide Evaluation
John Hopkins University	M. Strand A. Buck C. Shiff E. Shapiro	Molecular Biology DNA Probes Environmental Factor Analysis Clinical Trials Epidemiology
University of Puerto Rico	G. Hillyer S. File	Antigen Identification Diagnostics
State University, New York (Buffalo)	P. LoVerde D. Rekosh	Molecular Biology
University of Pennsylvania	M. Phillips	Immunology

Institution	Investigators	Areas of Focus and Potential Collaborations
University of Illinois	B. Salafsky A. Fusco	Biochemistry of Cercarial Penetration
George Washington University	C. Tuazon S. James	Vaccine Development
Case Western Research University	A. Mahmoud J. Ellner R. Olds	Immunology Vaccine Development
Baylor University	M. Dresden C. Chappel	Biochemistry
Brown University	A. Senft P. Knopf	Molecular Biology
University of California, San Francisco Medical Center	C. Wang	Pharmacology Drug Interactions
Stanford University	P. Basch T. Mansour	Biology of Parasites Pharmacology
Oregon State University	C. Bayne E. Loker	Snail-Host Parasite Interactions
University of Hawaii	D. Miller	Epidemiology Data Management
South Carolina University	T. Cheng	Snail-Larva Interactions
University of Georgia	R. Damian	Immunology Animal Test Models

Institution	Investigators	Area of Focus and Potential Collaboration
Vanderbilt University	D. Colley C. Carter B. Bogitsh	Histochemistry Immunology Antigen Identification Molluscicides Biology
University of Massachusetts	G. Coles	Drug Resistance Biochemistry Physiology
University of California, Los Angeles	A. McGinnis	Molecular Biology
University of Cincinatti	F. Etges	Molluscicides Snail Biology and Physiology
Rensselaer Polytechnic Institute	G. Archer	Chemotherapy
Texas A. And M. University	M. Kemp	Biochemistry

D. U.S. Institutions

Institution	Investigators	Area of Focus and Potential Collaboration
U.S. Centers for Disease Control	V. Tsang S. Maddison E. Ruiz-Tiben B. Cline K. Walls	Immunodiagnosis Vaccines and Immunology Epidemiology Data Management Serology/Immunology
National Institutes of Health	A. Sher A. Cheever F. Neva T. Nash	Vaccine Immunology Pathology Clinical Schistosomiasis Immunodiagnosis
Biomedical Research Institute	F. Lewis M. Stirewalt	Vaccines and Immunology Snails/Host Parasite Interaction
Walter Reed Army Institute of Research	R. Miller W. Reid D. Davidson	Chemotherapy Parasitology Medicinal Chemistry Drug Development
Naval Medical Research Institute	D. Dean B. Mangold	Vaccines and Immunology

E. NAMRU-3

The position of NAMRU-3 as a potential collaborating center in the implementation of the schistosomiasis component of the S&T for Development Project is unique. It is an essential U.S. Institution which has been located on Egyptian soil since 1946. NAMRU-3 is undoubtedly one of the most sophisticated and well equipped facilities of its type in the world. The unit maintains an up-to-date technical library on subjects of interest to the project which it makes accessible to Egyptian students and scientists. The staff which is comprised of both U.S. and Egyptian scientists, are involved in research activities which are relevant to the project and conduct training programs for technical staff members of institutions in Egypt as well as other countries of the Middle East, Asia and Africa.

Staff Members	Research Priorities in Schistosomiasis
J. Woody, M.D., Ph.D.	Immunodiagnostics
K. Kamal, Ph.D.	Immunopathology, Vaccines
N. M. El-Ghorab, Ph.D.	Immunodiagnostics
N. S. Mansour, Ph.D.	Parasitology
M. M. Mansour, Ph.D.	Biochemistry
Z. Farid, M.D.	Drug Trials, Clinical
S. Bassily, M.D.	Drug Trials, Clinical
N. A. El-Masry, M.D.	Drug Trials, Clinical
K. Hyams, M.D.	Clinical

F. Literature

In connection with the development of scopes of work for the Project Analysis and Design Team, the SOW Team has collected a number of useful references which are available in the USAID/Egypt S&T Office. The list of holdings is as follows:

Note:

The Project Analysis and Design Team is advised that this is a highly technical undertaking and that reliance on finding key references and other resources in Egypt might be risky. Therefore participating specialists should plan on bringing reference materials with them. Funds will be provided to allow for transporting them to Egypt.

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ANNEX 3

SUGGESTED CANDIDATES FOR PROJECT ANALYSIS AND DESIGN TEAM

Epidemiologist/Team Leader	Barnett Cline	Tulane University
	Sten Vermund	Colombia University
	Joseph Cook	Edna McConnell Clark Foundatic
	Alfred Buck	Johns Hopkins University
Immunologist	Gene Higashi	University of Michigan
	Daniel Colley	Vanderbilt University
	Adel Mahmoud	Case Western Research Center
	John David	Harvard University
	Allan Sher	National Institutes of Health
Malacologist	John Burch	University of Michigan
	Edward Michelson	Uniformed Services University
	George Davis	Philadelphia Academy of Scienc
	Emile Malek	Tulane University
Diagnostics Specialist	Victor Tsang	Centers for Disease Control
	Shirley Maddison	Centers for Disease Control
	George Hillyer	University of Puerto Rico
	John Cross	Uniformed Services University
	Eugene Hayunga	Uniformed Services University
Environmental Specialist/ Engineer	Kaz Kawata	USAID/Cairo/Hopkins
	Victor Wehman	Wehman Associates
	DeWolfe Miller	University of Hawaii
Resource Development Specialist	John Bruce	University of Lowell
	Margaret Stirewalt	Biomedical Research Institute
Chemotherapy Specialist	James Bennett	Michigan State University
	Terry Shapiro	Johns Hopkins University
	Adel Mahmoud	Case Western Research Center

Data Management Specialist	DeWolfe Miller	University of Hawaii
	Ernesto Ruiz-Tiben	Centers for Disease Control
	Stanley Terrell	Tulane University
	Susan Raymond	Private Consultant
Health Education Specialist	Alton Wilson	Private Consultant
	Barry Karlin	Private Consultant
Molecular Biologist	Meta Strand	Johns Hopkins University
	Phillip LoVerde	S.U.N.Y. Buffalo
	Donald Harn	Harvard University
Project Design Specialist	Robert Emrey	Emrey Associates
	Veronica Elliott	Birch & Davis Associates
Anthropologist/Sociologist	Helmut Kloos	University of Addis Ababa
	John Thayer Scudder	Center for Developing Anthropology
Financial Analyst/Economist	Patricia Rosenfeld	W.H.O.
	Susan Raymond	Private Consultant
	Katerine Fort	Private Consultant
	Albert Farwell	Private Consultant