Final Statement of the Working Group on Perspectives of Immunization in Parasitic Diseases

a) Rationale for Development of Vaccines

With a national commitment to achieve control of parasitic diseases, presently available tools and strategies for control are effective but have limitations which require further field and laboratory research and constant surveillance in the endemic areas. Even when applied, the repeated failure to achieve control has been due to insufficient national resources and failure to implement sustained efforts. Development of vaccines for parasitic diseases offers potential for protection of the affected populations which could be attained within national capabilities. Recent biological technological developments applied to parasitic diseases show encouraging results toward achieving this goal.

b) Characteristics of Vaccines for Parasitic Diseases

The epidemiological characteristics of the parasitic diseases will influence the type of vaccine to be developed. A vaccine may create a sterilizing immunity by eliminating the existing infection and providing protection against new infection. Another type of vaccine may provide only protective immunity with some beneficial effect on the existing infection. A third type of vaccine may desensitize the immunized person so that the existing or new infections do not cause pathological changes.

c) Evaluation of Safety of the Vaccine

Prior to administration of a vaccine for parasitic diseases to human populations thorough evaluation of their safety by national regulatory agencies will be required. The effect of the vaccine

on existing parasitic infections, the occurrence of cross reactions with host tissues and the degree of protective immunity are among the aspects to be carefully investigated, before field trials can be ethically undertaken.

d) Evaluation of Efficacy of Vaccines for Parasitic Diseases

The design of field trials and evaluation of the efficacy of a new vaccine will require quantitative base-line demographic, parasitological, immunological and morbidity data to accurately assess the efficacy of the vaccine in human populations and to monitor other possible unforeseen effects. Close international cooperation will be required to undertake the field trials in endemic areas.

II. Recommendations for Specific Parasitic Diseases

a) Malaria

Malaria is the most widespread among the parasitic diseases causing very high mortality and morbidity rates. Presently the incidence of malaria is increasing alarmingly in a number of developing countries in spite of the availability of control methods such as insecticide application and drug treatment, which were successfully applied in a number of areas. This increase in malaria, which frequently occurs in the phase of agricultural and economic development, is due to the non-existence or inadequate application of the available control measures and is aggravated by the spread of insecticides as well as drug resistance. The development of a malaria vaccine, combined with the available control measures, would contribute significantly towards the achievement of malaria control. The potential of this approach is supported by the clear evidence of natural resistance to malaria, which, however, takes many years to develop in the inhabitants of the endemic areas. Within the past few years considerable progress has been made in the research aimed at developing a malaria vaccine and potential for further advance towards this goal is greater than at any time in the past. Complete protection against malaria has been obtained upon vaccination of laboratory animals.

Three types of vaccine based on the use of different development stages of malaria parasites have experimentally been shown to have protective value. They are based on the use of the infective mosquito stage, namely sporozoites, and on the use of free asexual blood stages and gametocytes as immunogens (sexual stages). They induce very diverse specific immune mechanisms and possibly will satisfy different needs, besides having different shortcomings. Attenuated sporozoites do not require the use of adjuvants, induce complete protection but their protective effect is rather short-lived. The merozoite vaccine at the present stage requires the use of rather toxic adjuvants in order to be effective and results primarily in considerable diminution of disease manifestation of malaria. Finally, the gamete vaccine has a rather peculiar prophylactic effect by interrupting malaria transmission without affecting the course of the disease in the vaccinated individual. However, the recently developed successful approach of identifying and characterizing specific protective parasites, components for their eventual use as immunizing agents might change some of the presently recognized characteristics of these potential vaccines

and reduce the potential undesirable side effects.

The past inability to obtain sufficient amounts of parasites or their components, for the development of a vaccine, might now be overcome by improved culture methods, the recently developed methods of genetic engineering combined with hybridoma technologies and possibly even by chemical synthesis. The application of this technology to malaria research is also leading to the development of more sensitive methods to measure malaria incidence and monitor the protective effects of immunization procedures. Broad international support of this research effort as well as of other control methods, combined with the creation of adequate conditions for the future administration of a vaccine are essential for achieving malaria control on a world-wide basis.

b) Schistosomiasis

Schistosomiasis is one of the most common parasitic infections in the world. Over 600 million persons in the developing countries are exposed to the risk of Schistosome infection and over 200 million persons are currently estimated to be infected. The prevalence of this infection is increasing rapidly within endemic areas where water resources for agricultural and economic purposes are being developed.

After a developmental cycle in snails in water bodies of endemic areas, Schistosoma parasites infect man by penetrating the skin. Some species migrate to the blood vessels of the liver, and one species goes to the blood vessels around the bladder. In infections of long duration, the former parasites cause irreversible liver damage and the latter damage the urinary tract, particularly in children.

Presently available control tactics may be effective in most endemic areas, particularly by administration of new safe chemotherapy, to reduce prevalence, intensity of infection and the risk of development of disease. However, a vaccine administered during early childhood and conferring long lasting protection would be a more effective method of control and should remain the ultimate goal.

Current and past research has indicated that resistance to reinfection in schistosomiasis can be demonstrated in experimental animal models and the mechanisms of induction and expression of these forms of resistance are currently being investigated. Immune responses against schistosomes can be demonstrated in man but their relative roles in regard to protective immunity or to immunopathology are still unclear.

Experimental situations which have led to the induction of protective immunity include an active infection, immunization with attenuated (irradiated) cercariae (the skin penetrating stage of the parasite) and, in a few instances, immunization with non-living parasite-derived preparations. The resistance that develops during an active infection is closely associated with the disease process and is unlikely to provide a useful approach to vaccination. The attenuated live vaccine induces a high level of protection and holds promise for the elucidation of protective mechanisms. However, potential difficulties in production and logistical supply would seem to preclude large-scale use of this methodology. The use of non-living parasite preparations as a vaccine, while yet unproven, remains a highly desirable goal.

The development of a vaccine from non-living parasite material will involve the identification of the

immunizing agent, the determination of its structure, its synthesis, and the most efficacious modes of administration. It is anticipated that the development of such a vaccine will be greatly facilitated by the recent advances in biological technology, e.g., the production of monoclonal antibodies, peptide sequencing and synthesis, and recombinant DNA techniques.

c) Leishmaniasis

Leishmaniasis is a complex of diseases that can take different forms and are of worldwide importance. The relative toxicity of the drugs used to treat this condition, the resistance of certain forms of the disease to any kind of treatment, as well as difficulties inherent in vector control, render the search for vaccines a task of the highest priority.

Certain types of leishmanial infections, particularly the cutaneous disease known as Oriental sore, are self-contained and relatively benign: the only sequelae usually consist of unsightly scars. Vaccination against this infection is currently practiced in certain parts of the world by deliberately inoculating virulent parasites into inconspicuous sites, in order to protect against the disfiguring consequences of the naturally contracted disease. An effective vaccine other than the virulent parasite itself would undoubtedly be preferable.

Still far more important, however, is the requirement for vaccine development against the more severe forms of leishmaniasis, such as the visceral and the mucocutaneous infections. With respect to the former, it is almost certain that a degree of immunity develops in populations of endemic areas, presumably as a result of subclinical infections contracted naturally by exposure to parasite strains of low pathogenicity. In addition, clinical evidence suggests that many people who have recovered from the visceral infection by an appropriate course of therapy, are thereafter strongly immune against reinfection. The observation that immunity against visceral leishmaniasis does develop in these two situations makes it highly probable that a successful vaccine can be devised to protect against this condition. Equally important is the search for prophylactic measures against mucocutaneous leishmaniasis. In this case also, the finding that immunity against the causative agent develops in certain individuals, is a strong indication that appropriate vaccination procedures can be devised. In addition, since an effective vector control is at present unforeseeable, such a vaccine can be considered as the most effective way of controlling dissemination of the disease.

There are indications that dead vaccines may not be able to protect against visceral or mucocutaneous leishmaniasis. In view of the high morbidity and mortality associated with these two conditions, the use of a live vaccine that would produce a self-limited infection, even of some duration, confined to the skin, might be considered.

Whereas every effort should be undertaken to achieve this goal, great care has yet to be taken concerning the risks inherent in the permanent exposure of certain populations to the infection. In the case of cutaneous and mucocutaneous leishmaniasis of the South American continent, this refers particularly to new areas of settlement within forest regions. In this respect, it is recommended that migration programs, in countries where they exist, be accompanied and followed by sanitary measures aimed to guarantee proper surveillance and treatment of migrating populations.

d) African Trypanosomiasis

African trypanosomiasis is transmitted by tsetse flies and is usually a fatal disease in both man and domestic animals. Trypanosomiasis is a major barrier to stock rearing in Africa and is to a large extent responsible for the dietary protein shortage of man in that continent. Development of an effective vaccine against animal trypanosomiasis would therefore lead to substantial improvements in human health in an area, south of the Sahara, that corresponds in size to the United States of America.

The trypanosomes that cause human sleeping sickness can also live in cattle and game animals, but are confined to natural foci. The disease is contained in these foci by regular surveillance of the population by drug treatment of those at risk, and by anti-vector campaigns. When these measures break down, however, the disease may become epidemic and cause heavy mortality. This happens frequently following climatic changes, such as draught, and as a result of population movement. An increasing number of outbreaks have occurred in recent years, notably in Sudan, Cameroon, Angola and Uganda. These epidemics are difficult to control, and it is for such control that a vaccine is needed.

A major problem in developing a vaccine against both human and animal African trypanosomiasis has been the ability of the trypanosome to change its surface antigens and avoid the host's immune response. The repertoire of such changes for an individual trypanosome is likely to be large – amounting possibly to over 100 antigenic types. As it is likely that more than one serodeme or antigenic repertoire is circulating in a given endemic focus the number of antigenic types to be vaccinated against could be enormous.

One possible way of overcoming the difficulty posed by antigenic variation might be to vaccinate against only those antigenic types injected by the tsetse fly when it feeds. The metacyclic trypanosomes extruded by the vector appear to contain a restricted number of such antigenic types and immunizing potential hosts against these antigens should prevent infection. Determination of this number for each serodeme circulating in different foci would be a prerequisite for such a vaccine. The technology is now available, however, for filling these gaps in our knowledge, for producing the relevant antigens in bulk and for rapid identification of serodemes. Although it would be useless to pretend that a vaccine against sleeping sickness could be available within the next few years, research over this period should enable us to decide whether vaccination along the lines above will be feasible.

e) Chagas' Disease

Chagas' disease is closely related to the poor housing conditions prevailing in the endemic areas of the American Continent. Control of the disease depends upon the elimination of insect vectors which colonize human dwellings or such conditions and measures leading to housing improvement. Insecticide application drastically reduces intradomiciliary transmission and prevalence of the disease. It is therefore recommended that this method should be extended to all endemic areas. Housing improvement depends on social economic development. Transmission by blood transfusion is becoming an increasing hazard in endemic areas, and has both practical and ethical implications. It may be controlled by specific means such as serological screening of

donors and addition of sterilizing substances to banked blood, as well as by general measures to improve medical organization in developing countries.
The implementation of a vaccine still depends on basic research to elucidate important aspects such as efficacy and safety. The possible existence of cross-reacting antigens between Trypanosoma cruzi and host cells, as well as the practical logistical and ethical problems involved in the trial of a vaccine, makes this method at the time being more a subject of fundamental investigation than an immediate tool for the control of Chagas' disease. Nevertheless, since some problems may emerge in the future (such as vector resistance or other unpredictable factors which may handicap control programs), specific vaccination should be further investigated. In addition, this immunological approach may substantially contribute to increase knowledge on the immunopathology of the disease, the mechanisms of resistance and even on such practical aspects as diagnostic methods.

III. Conclusions

a) General Evaluation of the Present Situation

A general evaluation of the present vaccine situation in the diseases discussed reveals the existence of a considerable body of information regarding the immune responses during these parasitic diseases. It is thought that this information should and will continue to increase. This will greatly enhance the prospects for vaccine development. Currently, the only successful forms of immunization in these areas involve the experimental use of living, or attenuated, organisms. Indeed, the single vaccine now used in man is for the prevention of disfigurement in cutaneous leishmaniasis and this consists of actual localized infection by living virulent organisms.
In general, it is considered much more desirable to seek the utilization of non-living materials for immunization. This is based upon considerations of safety, production, and delivery.
It is toward this goal that most current research efforts are focused. The problem of the identification and large-scale production of parasite antigens for use in vaccination can now be approached with a series of new and powerful biological tools. These include monoclonal antibodies, new techniques for peptide sequencing and synthesis, recombinant DNA, and the induction of protective immune responses without antigen by the use of anti-idiotype antibodies.
It appears that the most progress toward vaccination against a major parasitic infection of man has occurred in regard to malaria. Currently, experimental immunity can be induced to 3 different life-cycle stages; sporozoites, merozoites, and gametocytes. The recent development of protective monoclonal antibodies against each of these stages should allow the isolation and production of protective antigens. This general approach is being used by several laboratories. In schistosomiasis, immunization with attenuated organisms has been demonstrated to be efficacious in experimental and domestic animals. These and other model systems, are expected to provide further information necessary for vaccine development.
Studies on immunity to leishmaniasis have emphasized the importance of cell-mediated immunity in the host control in all three major forms of this infection and the contribution of

immunoregulatory factors in determining the occurrence of disease. Existing evidence suggests that living attenuated vaccines, in addition to providing good immunization, may also be the most feasible for actual employment. The development of successful immunization against African trypanosomes is greatly complicated by the remarkable ability of the parasites to adapt to the immune response of the host by varying their surface antigens. However, recent work suggests that the naturally infective (metacyclic) forms of the parasite are more genetically stable and display less antigen heterogeneity and therefore may offer appropriate targets for immune attack. Both humoral and cellular immune effector mechanisms have been implicated in acquired resistance to the acute phase of Trypanosoma cruzi infection. Progress has been made on the isolation of protective antigens against this phase. Little is known about the immunological factors which lead to resistance against the chronic phase of the infection. Because of the possibility that disease may be attributed to autoimmune phenomena initiated by the parasite, caution must be exercised in future vaccine development.

b) Political Decisions

Recent progress in basic immunology and parasitology has made the production of anti-parasitic vaccines a realistic scientific goal. Therefore, further research on this subject should be encouraged and supported. However, since unforeseen problems may delay or even prevent the actual development of such vaccines, all available methods to control parasitic diseases should continue to receive proper attention. The fact that many methods available for the control of parasitic diseases which plague developing countries are not adequately implemented may be explained not only by social-economic factors but also because those diseases do not receive the proper priority by the governments of the affected countries. Vaccines may also have to face this problem. For this reason, whenever a vaccine would be available, it will be essential to ensure the fullest degree of approval and cooperation of country authorities with the immunizing program. It is equally essential that the population should be sufficiently educated to understand the need for vaccination and willingly agree to the procedure.

c) International Collaboration

International collaboration in the health field has achieved success in many instances, as for example in the control of yellow fever in Africa and South America and, most recently, in the smallpox eradication program. Support should be given to international efforts such as the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases, a joint venture of over 40 developed and endemic countries to stimulate and accelerate the development of human resources and improved tools for control of parasitic disease. These efforts must be urgently multiplied to face the challenges of global population growth, increasing poverty, urbanization and malnutrition.

All nations of the developing and developed world, notwithstanding their social and political status, must cooperate to achieve effective control of parasitic disease, even overcoming national rivalries and arbitrary political barriers. Collaboration between investigators and scientific institutions in

developing and developed countries in the research efforts towards vaccine development should be implemented.

Information on changing epidemiological patterns of parasitic diseases, particularly epidemics, should be communicated internationally. National pride should neither hinder the potential benefits of International Cooperation nor jeopardize the health of the affected populations.