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COUNTRY AND INTERCOUNTRY PROGRAMMES AND PROJECTS

CONSIDERATION AND APPROVAL OF GLOBAL AND INTERREGIONAL PROGRAMMES AND PROJECTS

Project recommendation of the Administrator

Assistance for a global project

International Laboratory for Research on Animal Diseases (ILRAD):
Research and Training on Animal Trypanosomiasis (Phase II)
(GLO/82/003)

Estimated UNDP contribution:	US\$3,800,000
Duration:	Five years
Executing Agency:	UNDP

I. Background

1. The International Laboratory for Research on Animal Diseases (ILRAD) was established in 1974 by the Consultative Group on International Agricultural Research (CGIAR) to assist in the development of effective controls for two major livestock diseases: trypanosomiasis and theileriosis. Together, these two diseases prevent livestock production in vast areas of some 50 developing countries in Africa, Central and South America, the Middle East, the Indian subcontinent, and Asia. The total loss in human and economic values - not only in milk and meat, but also in leather, wool, fertilizer, animal power, and other animal by-products, and in potential capital resources - is incalculable. Hundreds of millions of people, among them some of the world's poorest, are seriously affected. Ruminant livestock produce these materials from vegetation that man cannot eat, often on land that man cannot use for crops. In other areas, integrated livestock and cereal production are

desirable. Trypanosomiasis is a disease complex which affects both man and his livestock in Africa, Asia and South America. Especially in Africa, it is one of the major constraints of rural development and is a serious disease of man. The disease in cattle is caused by three species of trypanosomes: Trypanosoma brucei, Trypanosoma vivax and Trypanosoma congolense. The transmission of these trypanosomes is done mainly by the tsetse flies. Trypanosoma evansi may be important in camels; the transmission of this species is achieved mainly by bites of bloodsucking flies other than tsetse flies. T. gambiense (West Africa) and T. rhodesiense (East Africa) are well-known human pathogens, also transmitted by the tsetse fly. Most of the countries south of the Sahara are affected and large areas which are potentially capable of raising large and small domestic ruminants are not used or only sparingly used for animal production. It is known that Africa harbours about 170 million head of cattle, and even more sheep and goats; specialists estimate that these figures, especially those concerning cattle, may be doubled and in some cases even tripled, providing trypanosomiasis can be kept under permanent control or eradicated. Cattle, sheep and goats as well as other domesticated and wild animals may be infected by one, two or three trypanosome species. The animals develop an acute or chronic disease showing anaemia and weakness and death occurs very frequently. In any case, productivity is seriously affected and the economic losses are very heavy. This correspondingly influences human welfare and health.

2. Some effective methods for control of both animal and human trypanosomiasis and their vectors are available and it is known that in some areas chemotherapy and insecticides have been successfully implemented. Nevertheless, except in rare areas where success has been obtained after great and expensive efforts, trypanosomiasis still constitutes a major hazard for man and his livestock: neither chemotherapy nor prophylaxis, nor the use of short-acting or residual insecticides can be considered as yet economic, effective and environmentally safe methods against the disease or its vector. The use of the sterile male technique with tsetse flies is still uncertain and costly. For some years, both national and international authorities have become conscious of the potential importance of the phenomenon of trypanotolerance which is known to be prevalent in some breeds of cattle and small ruminants and in many species of wild herbivores as well. Moreover, some trypano-tolerant animals and maybe human beings are capable of self-curing a trypanosome infection. Despite the fact that trypanotolerance has been known for nearly 80 years, very little is known of its mechanism: only recently have modern techniques provided some hope for the study of this phenomenon. Its understanding could provide an opportunity for the development of many areas of Africa.

3. In view of the above-mentioned constraints, ILRAD's research programme has focused predominantly on investigating host/parasite/vector relationships which may prove susceptible to immunological control techniques. Unlike other diseases where effective vaccines have been produced, there was little evidence from the field to suggest that animals could develop a significant immunity to trypanosomiasis under natural conditions. The reason behind this failure to

develop a significant degree of acquired resistance was held to be the fact that the trypanosome has evolved a sophisticated process termed "antigenic variation". This allows its successful survival in, and onward transmission from, livestock which were inherently capable of mounting protective immune responses to the parasite. The process of antigenic variation is simply a means by which the parasite, throughout its life in the animal, continuously changes its surface molecules so as to avoid the lethal effects of the host's immune response to previously displayed molecules.

4. ILRAD, therefore, developed an institutional framework which provides a multidisciplinary approach to investigate the problems involved in analyzing the major areas in host/parasite/vector relationships which could be relevant to the possible development of practical immunological control measures for this disease. This approach involved the following disciplines: parasitology cell biology, biochemistry, molecular biology, immunology, pathology and entomology.

5. At its January 1978 meetings, the UNDP Governing Council approved a five-year project at a cost of \$3,605,200 to enable ILRAD to carry out intensive basic research concerning the immunological and related aspects of controlling animal trypanosomiasis (DP/PROJECTS/R.9/Add.2). The overall objective of ILRAD's trypanosomiasis research programme is to develop economically effective means of controlling trypanosomiasis with a consequent increase in livestock production, improved human nutrition and better land use in affected countries. This will be achieved by possible development of new immunological control methods, utilization of resistant domestic livestock, improved use of available drugs and integrated programmes of vector control. Training of personnel involved in trypanosomiasis research and control in affected countries will be an essential component of ILRAD's trypanosomiasis programme.

6. ILRAD has, in a relatively short time, made significant progress in several important areas of trypanosomiasis research and identified new areas of importance for future studies. Significant progress has been made in elucidating the mechanism underlying the phenomenon of antigenic variation and its relevance to the development of effective immunological control measures for trypanosomiasis. Studies in this area necessitated the development at ILRAD of in vitro cultivation systems for the pathogenic bloodstream forms of the three trypanosome species important in animal disease. Long-term continuous cultivation was first achieved with Trypanosoma brucei, and similar culture systems for T. congolense and T. vivax are being established: the latter, in collaboration with the Swiss Tropical Institute. Research in other laboratories and at ILRAD has also provided in vitro systems for cultivation of the animal infective trypanosome stage which occurs in the tsetse (metacyclic trypanosome) of both T. brucei and T. congolense.

7. The availability of both in vitro and in vivo systems for analysis of antigenic variation in T. brucei has shown that the sequence of appearance of trypanosome populations carrying different surface molecules (variable antigens) is not as ordered, as thought previously, that the parasite does not change its variable antigens in response to the host's immune response as previously

suggested, but that new variable antigens appear with a frequency of one in ten thousand parasite divisions. Immunochemical studies on variable surface glycoproteins, mainly from T. brucei, have shown the presence of a common carbohydrate determinant, as well as common amino acid determinants (isotypes). The role of glycosylation reactions in the biogenesis and stability of the surface antigen coat is being determined. The steps involved in processing the variable surface glycoprotein will be analyzed. Work is being carried out on variable antigens of T. congolense and T. vivax.

8. A major achievement has been the isolation and characterization of genes coding for variable antigens in T. brucei and the demonstration that such isolated genetic material can be expressed in bacterial systems by recombinant DNA technology, thus providing an in vitro system for production of parasite antigens. This has important implications in the case of variable antigens of the metacyclic trypanosomes where, even with in vitro cultivation systems, very low numbers of organisms are available for variable antigen isolation.

9. The metacyclic forms of the trypanosomes have been intensively studied. It has now been shown that, while in the case of T. brucei and T. congolense the repertoire of bloodstream-form variable antigen types is large, the repertoire of variable antigen types of metacyclic trypanosomes of the same gene line (serodeme) is constant and characteristic for that serodeme in the situations studied. Serodemes constitute the range of different surface variable antigens expressed by the descendants of a single trypanosome.

10. It is possible to successfully immunize animals against challenge by tsetse flies infected with differing bloodstream variable antigen type (VATs) of the same serodeme using either active infection and drug therapy, or attenuated metacyclic trypanosomes which do not produce active infections. While such animals are resistant to homologous challenge, they are susceptible to heterologous challenge by tsetse carrying organisms of different serodemes of the same species of trypanosome. The site of an infected fly bite in the skin of a susceptible animal is characterized by the development of a raised lesion, the chancre. The immunological and pathological events leading to chancre formation in susceptible, but not immune, animals are presently being analyzed. This work is being carried out in cattle, sheep, goats and wildlife and confirms the results obtained earlier in mouse model systems.

11. Important work has been carried out in elucidating the mechanisms involved in the development of successful immune responses by the mammalian host to ongoing bloodstream infections with all three major pathogenic trypanosome species in both laboratory animals and domestic ruminants. In the case of T. brucei infections, experiments with inbred mouse strains have shown that parasite differentiation is required to initiate good immune responses and that this process is partly under parasite control and partly the result of host/parasite interactions. Similar experiments are being carried out with T. congolense and T. vivax. Analysis of the ruminant immune response to trypanosome infections has shown that, in contrast to findings in mice, a

chronic infection does not severely alter the animal's potential to respond immunologically to parasite and other antigens. The pathological changes induced by trypanosome infections in domestic animals have also been investigated and one of the major causes of death in such animals has been shown to be anaemia combined with severe damage to heart muscle resulting in congestive heart failure.

12. In view of the reported trypanotolerance of indigenous African breeds of ruminants and species of wildlife, studies have also focused on explaining possible differences in the immunological and physiological responses of such resistant animals to trypanosome infections. A collaborative study carried out in the Gambia confirmed that N'dama cattle were more resistant to the effects of trypanosome infections than Zebu cattle. Trypanotolerant N'dama cattle do not exist in Kenya where the indigenous cattle are Zebu. Domestic ruminants in Kenya are now being screened for possible trypanotolerant traits and preliminary results have shown that indigenous Red Masai sheep exhibit a significant degree of trypanotolerance. Wildlife species, available in limited numbers in a collaborative project with the Kenya Government, the Canadian International Development Agency and the Netherlands Government, are also being used in research on resistance to trypanosomes and in investigation of the mechanisms involved. Experiments also continue in laboratory animal systems.

13. A number of potential immunogens other than trypanosome variable antigens have been biochemically identified and purified but until now no significant degree of immunoprotection has been achieved against any of the three pathogenic trypanosome species with antigens other than variable antigens. The search for potential immunogens continues and trypanosome antigens recognized by resistant N'dama cattle, but not by susceptible Zebu cattle, will be investigated in this respect.

14. The results to date show, therefore, that development of sound immunological control measures for trypanosomiasis will require considerable further research effort. Because of this, other factors which could be involved in an integrated control method deserve attention: these include the role of acquired immunity to metacyclic trypanosomes in localized field situations, and the possible improved use of strategic drug therapy. The mechanisms and genetic basis of the trypanotolerant trait need to be identified, possible marker systems developed and the utilization of trypanotolerant animals under different field conditions investigated. ILRAD scientists have developed much of the required technology and laid the basis for future experimental work on trypanosomiasis, using both experimental rodents in the laboratory and domestic livestock in field situations.

15. The training component of the trypanosomiasis programme involves post-doctoral and doctoral students from developing countries working at ILRAD on various aspects of research, together with the provision of short-term training courses and the organization of international workshops and seminars. Six graduate students from African countries have carried out part or all of their studies at ILRAD and a further six students are presently working towards a higher degree. Thirty-one

scientists or technicians from African countries have visited ILRAD to learn specific techniques required in their own countries. Seven post-doctoral fellows have worked at ILRAD to gain experience in the application of modern technologies to the problems of trypanosomiasis. Eight workshops/seminars/courses have been held at ILRAD since 1977 attended by 260 participants from 28 African countries. These countries are Angola, Benin, Botswana, Burundi, United Republic of Cameroon, Congo, Ethiopia, Gabon, Gambia, Ghana, Guinea, Ivory Coast, Kenya, Liberia, Malawi, Mozambique, Niger, Nigeria, Rwanda, Sierra Leone, Somalia, Sudan, United Republic of Tanzania, Togo, Uganda, Upper Volta, Zaire and Zambia.

16. ILRAD collaborates closely with other United Nations system agencies such as the World Health Organization, the Food and Agriculture Organization of the United Nations, the International Atomic Energy Agency and others in the organization of workshops/seminars/courses for which funds have also been made available by foundations and Government foreign aid programmes. ILRAD staff have published over 100 scientific articles on trypanosomiasis since 1976. Scientific staff have contributed to 10 expert consultation publications for international agencies and are members of the Scientific Working Group and Steering Committees of the WHO/Tropical Diseases Research Special Programme in Trypanosomiasis and the FAO Panel of Experts on the Ecology and Technical Aspects of the Programme for the Control of Animal African Trypanosomiasis and related development.

17. The overall programme of ILRAD was recently evaluated by a panel of outstanding scientists on behalf of the Technical Advisory Committee (TAC) of the CGIAR. This panel was highly impressed with the rapid progress being made in building up a first-class research institute and the remarkable scientific advances being made in the knowledge of trypanosomiasis and theileriosis - two of the most difficult problems confronting veterinary sciences.

II. The project

18. The main purpose of the second phase project is to expand and intensify current research in animal trypanosomiasis with a view to the eventual development of a vaccine to immunize animals against trypanosomiasis.

19. Specific objectives of the Phase II project are to:

(a) Delineate and improve the role of the immune response of domestic livestock to both variable and non-variable antigens of the major species of African pathogenic trypanosomes. This requires identification of relevant antigens, their purification, characterization and production, further research on the immune response of domestic livestock and development of improved immunization procedures;

(b) Determine the basis for the reduced susceptibility to trypanosomiasis (trypanotolerance) exhibited by certain breeds of cattle, sheep and goats and some species of game animals with the aim of elucidating the immunological and genetic mechanisms involved, and identifying marker systems correlating with trypanotolerance which could be used to accelerate production of improved genetically resistant livestock:

(c) Identify and appraise the significance of factors which contribute to the epidemiology of trypanosomiasis in different regions. This project will produce information on the current prevalence of trypanosome infections and the productivity of domestic livestock exposed to trypanosomiasis under different management and ecological conditions. This information would be used in assessing the efficacy of new control methods developed from the preceding project: and

(d) Transfer information and technology developed at ILRAD and elsewhere to personnel involved in trypanosomiasis control at international, regional and national levels, by the issue of scientific publications, reports and newsletters, provision of technical training for both individual and course participants, and by organizing scientific seminars and workshops.

20. The benefits from this research programme on trypanosomiasis will include:

(a) Provision of essential scientific information and data relating to the biology of pathogenic trypanosomes, the diseases they cause in man and animals, and the immune responses of their vertebrate hosts;

(b) Introduction of improved and more specific diagnostic tests for trypanosomiasis and thus better case detection and disease control;

(c) Increased production with wider and more efficient use of trypano-tolerant varieties of domestic livestock for food production and general agricultural purposes, better land use, and more rapid economic development of rural communities in tsetse-infested areas of Africa;

(d) In the long term, the development of effective immunological methods for the prevention of trypanosomiasis, increased livestock productivity, improved meat and milk supplies, greater use of mixed farming enterprises, and a reduction in the costs of trypanosomiasis control; and

(e) Opportunities for continued training of scientific and technical personnel concerned with trypanosomiasis research and control in countries infested by the tsetse fly and advanced scientific training and the transfer of new technology to staff of African universities and institutions of higher learning concerned with training future generations of scientists.

21. Training under the project will include: post-graduate training leading to higher degrees, M.Sc. or Ph.D. for 4-6 national personnel in trypanosomiasis research; individual in-service training for scientists and technicians from developing nations for varying periods to work with ILRAD scientific staff to learn specific techniques and research approaches that are appropriate to the needs of their countries: one training course of 4-6 weeks duration for 15-20 scientists and high-level technicians from African countries each year; one workshop/seminar for up to 50 participants lasting 5 days; and special courses designed for franco-phone African countries to meet the French language requirements.
22. Information dissemination will continue by publication of scientific articles, reports and an English/French newsletter summarizing progress in trypanosomiasis research achieved at ILRAD and elsewhere.
23. ILRAD will work closely with the International Livestock Centre for Africa (ILCA) in a large-scale study of the productivity of trypanotolerant livestock in Africa. ILRAD provides training in animal health procedures for ILCA field staff. ILRAD scientists will take an active part in defining the tsetse-trypanosomiasis levels affecting the rearing of livestock under different management systems. Close collaboration will also be maintained with the International Centre of Insect Physiology and Ecology (ICIPE) in Nairobi on various aspects of trypanosomiasis and with national research institutions in African countries, as well as developed country laboratories. Project activities will also be co-ordinated with the WHO/TDR Programme.
24. The Programme Committee of the ILRAD Board of Trustees annually reviews research progress and policy. Provision also exists for the formation of a Scientific Advisory Committee comprised of eminent scientists in disciplines related to ILRAD's research programme when the Programme Committee and the Director-General require specialized advice outside the expertise of Programme Committee members. Representatives of UNDP, FAO and WHO/TDR will be invited to join the Programme Committee in 1984 and 1986 to review research progress and consider any project alterations required. In addition, representatives of major international organizations and donor countries are invited each year as observers at the Board of Trustees Meeting when the report of the Programme Committee is discussed. ILRAD staff also monitor the progress of each research project by twice yearly internal reviews. Towards the end of the project, UNDP, in consultation with ILRAD, will undertake an assessment of the research programme by a team of independent consultants. UNDP, however, will not field such a mission in the event the Technical Advisory Committee (TAC) of the CGIAR schedules an independent review of ILRAD at that time.
25. The Administrator intends, through contractual arrangements between ILRAD and UNDP, to entrust the implementation of this project to ILRAD, with the clear understanding that the Director-General of ILRAD will seek the advice of FAO and WHO when needed. As in the past, UNDP will follow closely all the developments in this global project and, together with FAO and WHO, will participate in the Programme Advisory Committee referred to above.

26. The expenditure components of the proposed UNDP assistance are:

	<u>\$</u>
Subcontract	3 500 000
UNDP direct costs	<u>300 000</u>
Total	<u>3 800 000</u>

The proposed UNDP contribution will be contained within the Global IPF established by the Governing Council for the current cycle.

