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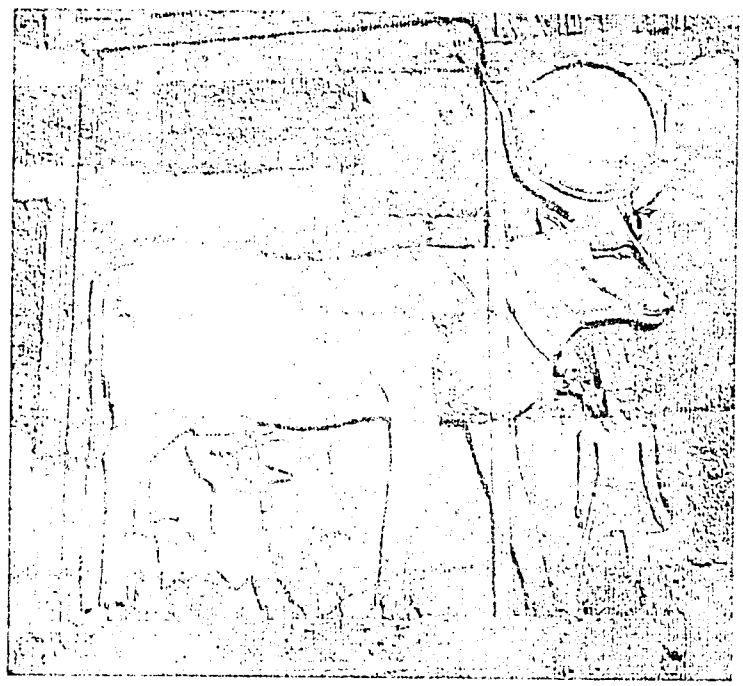
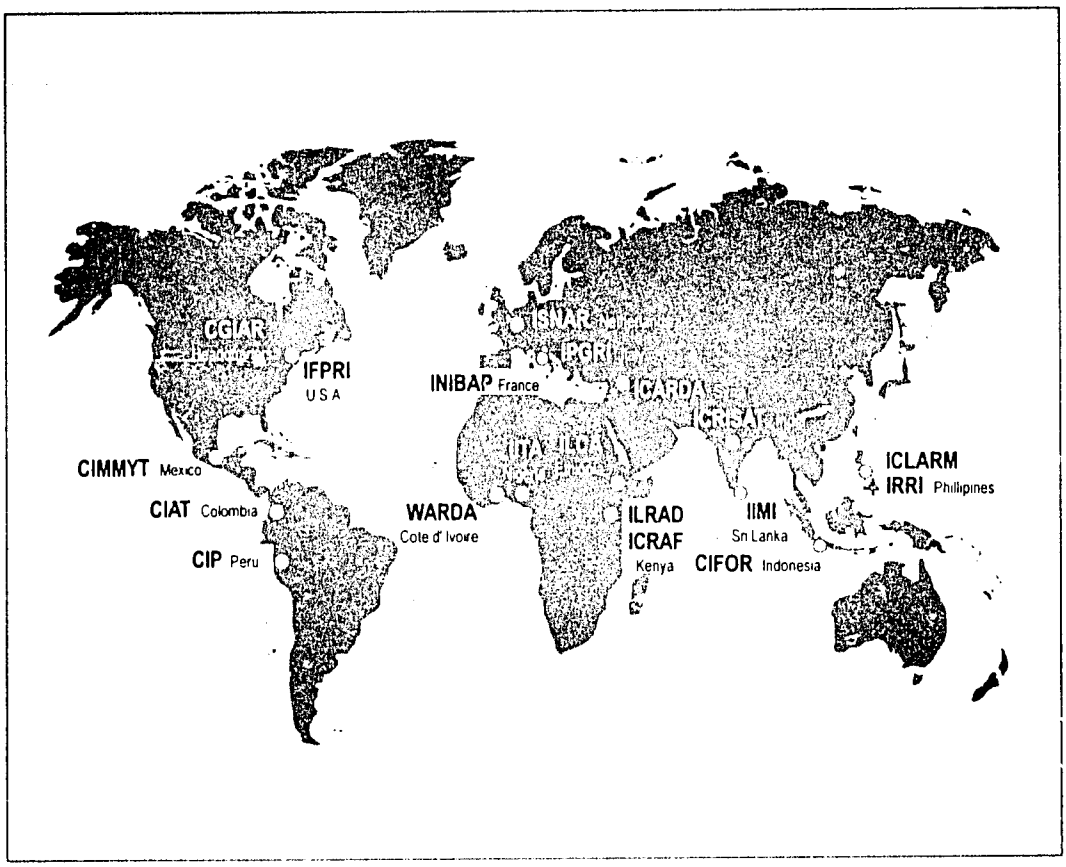


ILRAD 1992 ANNUAL REPORT



Locations of the 18 institutes that belong to the Consultative Group on International Agricultural Research.

CIAT	Centro Internacional de Agricultura Tropical, Cali, Colombia (International Center for Tropical Agriculture)
CIFOR	Center for International Forestry Research, to be located in Asia
CIMMYT	Centro Internacional de Majoramiento de Maiz y Trigo, Mexico City, Mexico (International Maize and Wheat Improvement Center)
CIP	Centro Internacional de la Papa, Lima, Peru (International Potato Center)
IPGRI	International Plant Genetic Resources Institute, Rome, Italy
ICARDA	International Center for Agricultural Research in the Dry Areas, Aleppo, Syria
ICLARM	International Centre for Living Aquatic Resources Management, Manila, Philippines
ICRAF	International Centre for Agroforestry, Nairobi, Kenya
ICRISAT	International Crops Research Institute for the Semi-Arid Tropics, Hyderabad, India
IFPRI	International Food Policy Research Institute, Washington, D.C., USA
IIMI	International Irrigation Management Institute, Colombo, Sri Lanka
IITA	International Institute of Tropical Agriculture, Ibadan, Nigeria
ILCA	International Livestock Centre for Africa, Addis Ababa, Ethiopia
ILRAD	International Laboratory for Research on Animal Diseases, Nairobi, Kenya
INIBAP	International Network for the Improvement of Banana and Plantain, Montferrier-sur-Lez, France
IRRI	International Rice Research Institute, Manila, Philippines
ISNAR	International Service for National Agricultural Research, The Hague, Netherlands
WARDA	West Africa Rice Development Association, Bouaké, Côte d'Ivoire

Cover photograph: A relief carving taken from the Mortuary Temple of Queen Hatshepsut, a monument cut out of sheer limestone cliffs about 1450 B.C. in the necropolis of ancient Thebes, on the west bank of the Nile at Luxor, Egypt.

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ILRAD

ILRAD 1992 ANNUAL REPORT

The International Laboratory for Research on Animal Diseases (ILRAD) was established in 1973 with a global mandate to develop effective control measures for livestock diseases that seriously limit world food production. ILRAD's research program focuses on African animal trypanosomiasis and tick-borne diseases, particularly East Coast fever, a virulent form of theileriosis.

ILRAD is one of 18 centres belonging to a global agricultural research network sponsored by the Consultative Group on International Agricultural Research, whose headquarters are located in the World Bank, Washington, D.C.

In 1992, ILRAD received funding from the United Nations Development Programme, the World Bank and the governments of Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Norway, Sweden, Switzerland, the United Kingdom and the United States of America. ILRAD's total operating budget for 1992 was US $13.7 million.

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CONTENTS

Foreword 1

Tick-Borne Diseases 9

PARASITE CHARACTERIZATION AND DISEASE DIAGNOSIS 11
SUPPORT FOR TICK-BORNE DISEASE CONTROL 12
CHARACTERIZATION OF THE *THEILERIA PARVA* GENOME 12
IMMUNIZING CATTLE WITH *THEILERIA PARVA* ANTIGENS 13
VACCINE DEVELOPMENT 14
CELL-MEDIATED IMMUNE RESPONSES 15

Trypanosomiasis 19

CURRENT CONTROL METHODS 20
ANTIGENIC VARIATION 22 EPIDEMIOLOGY AND DIAGNOSIS 22
TRYPANOSOME DIFFERENTIATION 23 DRUG TREATMENT 24
TRYPANOSOME ANTIGENS 24 HOST IMMUNE RESPONSES 25
BOVINE GENETICS 26

Socioeconomics and Environmental Impact 29

PRODUCTION, DELIVERY AND ADOPTION OF IMPROVED DISEASE CONTROL MEASURES 29
EPIDEMIOLOGICAL ASPECTS OF APPLYING IMPROVED DISEASE CONTROL MEASURES 30
SOCIAL, ECONOMIC AND ENVIRONMENTAL IMPACTS OF APPLYING IMPROVED DISEASE CONTROL MEASURES 31

32 Cooperative Programs, Training and Information

COOPERATIVE PROGRAMS 32 TRAINING 33
INFORMATION 35 LIBRARY 36

37 Research Support

TSETSE UNIT 37 TICK UNIT 38
LARGE ANIMAL PRODUCTION 39
LABORATORY ANIMAL PRODUCTION 39

40 Publications

45 Board of Directors

46 Senior Staff

51 Financial Statements

COSTS OF OPERATIONS 52
UNRESTRICTED AND RESTRICTED FUNDS 53
SOURCES AND APPLICATIONS OF FUNDS 54
ASSETS AND FUND BALANCES 55

FOREWORD

THE INTERNATIONAL LABORATORY FOR RESEARCH ON ANIMAL DISEASES (ILRAD) was established in Nairobi in 1973 and the institute's first laboratories were built in 1975. ILRAD's objective was to exploit new knowledge and research techniques then emerging from the field of immunology to find better ways of controlling fatal livestock diseases endemic in developing countries.

Tick-transmitted East Coast fever and tsetse-transmitted trypanosomiasis are diseases of cattle and other domestic ruminants caused by protozoan parasites. These two diseases have been largely responsible for retarding the development of livestock production and mixed livestock/crop farming in Africa throughout this century. Related tick-transmitted diseases and other forms of trypanosomiasis debilitate and kill domestic stock throughout the tropics and subtropics. To address these pressing animal health problems, representatives of several donor agencies and African governmental organizations together brought about the establishment of ILRAD.

ILRAD is governed by an international Board of Directors comprising 12 members. In 1992, Professor O. Nielsen, from Canada, continued to serve as Board Chairman. Professor I. Månsson (Sweden) and Professor P. Doherty (Australia) retired after completing two terms of much-appreciated service to the Board. Dr. M.J. Turner (UK) and Dr. C. de Haan (Netherlands) were elected to fill the vacant Board positions.

At the end of 1992, ILRAD staff in post comprised 42 senior scientific and administrative personnel, 9 long-term visiting scientists, 12 post-doctoral fellows, 22 research associates, 56 technical support staff and 276 general support staff. Staff turnover was balanced, with the departure of four core scientific staff and four long-term visiting scientists and the arrival of the same number of scientists. Two post-doctoral vacancies were still under recruitment at the year end and several new positions

ILRAD's two broad objectives are to develop and apply
(1) technologies that will strengthen and sustain existing livestock disease control measures for as long as possible, and
(2) new, more sustainable methods of disease control, such as genetically resistant livestock and vaccines.

ILRAD's general approach has been to develop through laboratory research a thorough, deep knowledge of the immune responses of livestock, to support epidemiology and immunization procedures, and to dissect the target parasites to the level of their molecules and genes to identify potential materials that can be used as the basis of vaccines.

Vaccines are a more sustainable method of controlling disease than vector control using insecticides or parasite control using drug treatments, which have contaminative, drug residue or drug resistance side effects.

Women's concerns must be addressed in research on livestock diseases because much of the farmwork in developing countries is done by women and also because women are usually the first members of a farm household to notice degradation of their environment. The expertise and opinions of women farmers are thus essential to any research designed to increase agricultural production while maintaining or enhancing the resource base on which agriculture rests.

approved by the Board remained vacant due to a reduction in funding. The Rockefeller Foundation and the governments of Belgium, France, Italy and Japan provided special support for the salaries of long-term visiting scientists at ILRAD.

ILRAD congratulates Dr. John Lonsdale-Eccles (UK) on his election to the Fellowship of the Royal Society for Chemistry, Dr. Tony Musoke (Uganda) on his award of a CIBY-GEIGY Prize for research on immunization against parasitic diseases, Dr. Hiroyuki Hirumi (USA) on his appointment to the Board of Editors of the *Journal of Protozoology Research*, and Dr. Onesmo ole-MoiYoi (Tanzania) on his appointment to the Steering Committee of the World Health Organization Special Program for Research and Training on Tropical Diseases. Drs. Lonsdale-Eccles, Jan Grootenhuis (Netherlands), Denis Grab (USA) and Ronald Kaminsky (Germany)—each having given many years of valued service to the Laboratory—left ILRAD this year. Seven ILRAD Research Fellows—from Benin, Canada, Italy, Kenya and Nigeria—completed their studies and were awarded M. Phil. or Ph.D. degrees.

The main text of this annual report summarizes progress made in 1992 in ILRAD's research programs on animal trypanosomiasis and tick-borne diseases and the socioeconomic and environmental impacts likely to result from improving their control. The report also describes ILRAD's research support activities and its cooperative research links and published communications with scientists working in national agricultural research systems in countries where these diseases are endemic. This report supplements information given in the ILRAD *1992 Annual Scientific Report* and *Highlights*, which appeared earlier in the year.

TWO MAJOR SERIES OF EVENTS required additional attention from the Directors and staff of the Laboratory this year: the outcome of the Third External Program and Management Review of ILRAD, organized by the Consultative Group on International Agricultural Research (CGIAR, USA), and preparation of the Laboratory's program and budget proposals for the 1994–1998 five-year period.

The External Program and Management Review team, commissioned by the Technical Advisory Committee (TAC, Rome) of the CGIAR and led by Dr. John Vercoe (Australia), presented its report to the Chairman of ILRAD's Board of Directors in April. ILRAD management discussed its response to the report with TAC members in June. In October the full report was presented to members of the CGIAR at its annual International Centres' Week meeting in Washington, D.C.

The report was generally highly supportive and favourable. It complimented much of ILRAD's work and predicted a productive future for the institute. Changes in the structure of ILRAD's research management—which the institute introduced in response to

an internally commissioned review conducted early in 1991—were judged effective in reinforcing staff productivity and accountability.

The review panel commended the persistent high quality of ILRAD's research and management. It emphasized that ILRAD's scientific achievements have contributed much to understanding the nature and complexity of the agents that cause theileriosis (East Coast fever) and trypanosomiasis. Mention is made throughout the report of the range of materials and methods developed at ILRAD that will be essential for the ultimate control of these two important diseases.

The review team expressed confidence that ILRAD will remain at the forefront of global livestock disease research. Nevertheless, to ensure continued strong support for the Laboratory as donor funding for research on Third World agricultural problems is declining, the panel recommended that ILRAD expand its research activities most likely to generate outputs that can be used in the near future by developing country scientists, policymakers and disease control agents. The panel stressed, however, that this move towards shorter-term, client-oriented research should not compromise ILRAD's long-term strategic research nor its responsibilities as an exceptional scientific resource for global and strategic research on tropical animal diseases.

In a transmittal letter to the CGIAR, TAC expressed pleasure with ILRAD's strategic orientation and scientific achievements, while cautioning donor agencies against holding unrealistic expectations that ILRAD can find quick immunological solutions to controlling theileriosis and trypanosomiasis. TAC recommended that the CGIAR continue to give ILRAD strong support, particularly as the Centre already has many of the attributes TAC believes are necessary to conduct global and strategic research to improve livestock production.

The external reviews of ILRAD and ILRAD's sister institute, the International Livestock Centre for Africa, based in Addis Ababa, contributed greatly to TAC's development of priorities and strategies for future CGIAR livestock research. In a draft statement to members of the CGIAR at International Centres' Week, TAC proposed an expanded global role for ILRAD, that is, to continue to conduct strategic research on the epidemiology and control of livestock diseases and on livestock genetics and to initiate research on livestock physiology and nutrition. The Chairman of the CGIAR subsequently established a donors' working group to consider the group's livestock research arrangements further and TAC revised and completed its draft strategy statement. Both planning groups are expected to produce reports and recommendations for discussion at the May 1993 meeting of CGIAR representatives.

This year the CGIAR required ILRAD and the 17 other international agricultural research centres it sponsors to review their long-term strategic plans and to prepare medium-term (five-

A special relationship exists between the CGIAR's two main livestock research institutes. ILRAD has a global mandate for research on animal diseases; ILCA has a regional mandate focussing on livestock production problems in Africa. Both the research programs and the governance of these two institutes are integrated to a degree. ILCA's success depends in part on ILRAD's strategic research to develop the disease control technology required to support its adaptive and applied research. ILRAD's success depends in part on technology transfer through the research networks across Africa that have been established by ILCA and the national agricultural research systems on the continent.

MEDIUM AND LONG-TERM PLANS

ILRAD has continuously maintained links with advanced laboratories in industrialized countries to identify new research methods and important findings and to apply them directly to problems affecting livestock in developing countries, thus adding greatly to the rate of progress permitted by direct donor investment in the CGIAR institutions.

year) program and budget projections for review in 1993. To help prepare for these tasks, senior ILRAD staff beginning in 1991 helped to conduct a major review by Winrock International (USA) of the contributions livestock make to agricultural productivity and development in Africa. In the same period, ILRAD staff undertook reviews of advanced methodologies employed in research and control programs dealing with the parasite species *Trypanosoma evansi* (the cause of trypanosomiasis in camels), *Theileria annulata* (the cause of tropical theileriosis), *Babesia* (the cause of babesiosis, also known as redwater and tick fever), *Anaplasma* (the cause of anaplasmosis, or gall sickness) and *Cowdria ruminantium* (the cause of cowdriosis, or heartwater).

This series of preparatory reviews was continued in 1992 to help determine future research priorities in the analysis and mapping of parasite genomes, in the development of computer models to predict the economic impacts of livestock diseases and use of alternative methods of controlling them, in development of computer-based decision-support systems to help researchers and disease control workers determine which disease-control strategies are optimal in given areas and conditions, and in studies of the biology of disease-causing parasites and the epidemiology of vector-borne livestock diseases.

In an effort to match projected donor funding with the costs of research programs anticipated by each CGIAR centre, the CGIAR gave the centres target budget figures early in 1992. With input from ILRAD's senior scientific staff, the ILRAD administration prepared program, staffing and budget proposals at four levels, starting with the prescribed target of 11.1 million US dollars and including ambitious plans for new research initiatives and a funding request to pay for the building of an improved facility for research on novel vaccines based on genetically modified organisms. The Board of Directors approved the plans this year and the CGIAR will consider them for funding in 1993.

THE TRYPANOSOMIASIS PROGRAM

IN THE NEARLY ONE YEAR that has passed since completion of the External Program and Management Review, ILRAD has adjusted emphases in program areas where this was recommended by the Review team. In the Trypanosomiasis Research Program, a recently appointed epidemiologist will coordinate the application of ILRAD tests by national agricultural research organizations in Third World countries where trypanosomiasis occurs. These tests include assays to diagnose trypanosomiasis, to determine the sensitivity of parasites to trypanocidal drugs and to detect the occurrence of genetic recombination in trypanosome populations. These improved tests will be used in development of computer-based models of trypanosomiasis and in the design of improved strategies for control of this disease.

Other program staff continued in 1992 to search for biological weaknesses in the parasite that may be exploited in interven-

tions designed to enhance the immune responses of host animals to trypanosome infection. In this area, studies were made to locate and identify trypanosome antigens that provoke immune responses, to discover the processes by which these antigens induce protective immune responses in the host, to locate the genes in trypanosomes that control the processes of cell division and differentiation, and to determine the parasite-host interactions that lead to the development of anaemia in the host.

In research comparing the molecular genetics of cattle that are resistant and susceptible to trypanosomiasis, good progress was made this year in producing resource herds of second-generation N'Dama (resistant)-Boran (susceptible) crossbred cattle that segregate resistance genes and in identifying DNA markers to support the production and use of a map of the bovine genome. Substantial collaboration in trypanosomiasis research continued in 1992 with the International Atomic Energy Agency (Vienna), the International Livestock Centre for Africa (ILCA, Addis Ababa), the African Trypanotolerance Livestock Network (Nairobi) and Africa's universities and agricultural research institutions.

THE TICK-BORNE DISEASES PROGRAM

In the Tick-Borne Diseases Research Program, which is an expansion of the former Theileriosis Program, ILRAD continued to provide support to national disease control programs in Kenya, Tanzania, Zambia and Zimbabwe in the use of live vaccines—which employ sporozoite forms of the *Theileria parva* parasite—to protect cattle against theileriosis. Research agreements with American and Australian laboratories to pool characterized materials derived from *Theileria*, *Babesia*, *Anaplasma* and possibly *Cowdria* parasites for use in diagnostic tests are under discussion. Such agreements open opportunities for further collaboration in research on parasite antigens that induce protective immune responses in their hosts and thus are candidate antigens for use in sub-unit vaccines. ILRAD scientists made major progress in 1992 in determining the molecular structures and bases of polymorphism of several previously isolated molecules of *T. parva* that offer promise as antigens for novel vaccines. Other members of this program are investigating optimal vaccine formulations and are designing strategies for the most effective presentation of the parasite antigens to the host immune system.

THE SOCIOECONOMIC AND ENVIRONMENTAL IMPACT PROGRAM

Research activities in ILRAD's Socioeconomic and Environmental Impact Program were reviewed and restructured in response to suggestions by the External Program and Management Review Team. Three topics are now the main focus of this program: identifying constraints to the application of new disease control technology, determining the likely socioeconomic and environmental impacts of implementing improved livestock disease control, and making economic assessments of research areas likely to yield the greatest productivity returns. ILRAD's socioeconomic studies involve collaboration with ILCA and Africa's

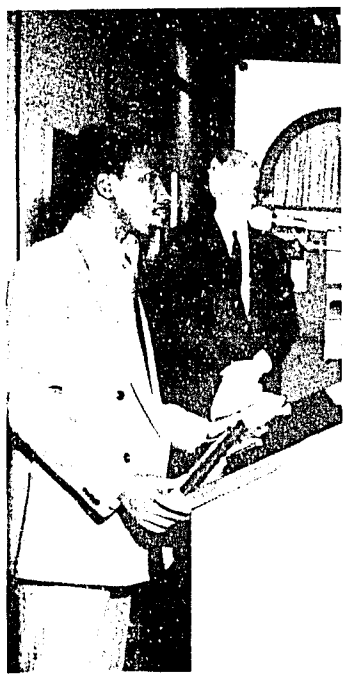
national agricultural research systems. A pilot study conducted in collaboration with Colorado State University and funded by the Rockefeller Foundation was initiated this year to investigate the ways in which improved control of trypanosomiasis is likely to affect different environments and the sustainability of small-scale livestock production systems.

OUTREACH ACTIVITIES

The Department of Cooperative Programs, Training and Information this year undertook a major review of its strategy and work plans to improve its capacity to support the transfer of technology from ILRAD to the national agricultural research systems of Africa and other developing regions. A major focus of this program's institution-strengthening was Sokoine University, in Tanzania, where a group of scientists is collaborating closely with ILRAD staff in several areas of research in tick-borne diseases and animal trypanosomiasis. The training courses this department supported in 1992 included two on use of advanced techniques for diagnosing trypanosomiasis, one given in French in Burkina Faso and the other in English at ILRAD. A third course on the Biochemistry of Protozoa was organized jointly with the University of Nairobi for participants from South America, Asia and Africa. Training activities at ILRAD are now more focussed under a recently appointed Education Officer. A record number of 40 Fellows undertook research at ILRAD during all or part of 1992 towards doctoral or masters' degrees.

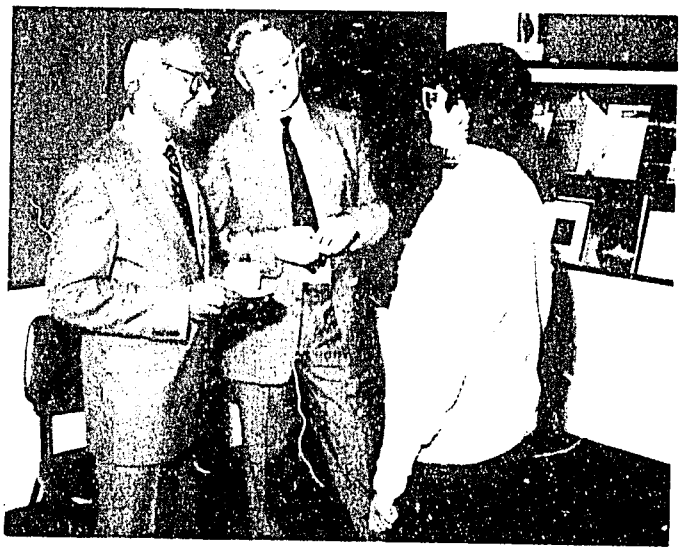
UNCERTAIN FUNDING ENVIRONMENT

FUNDING FOR CGIAR research was considerably reduced in 1992, particularly in the research centres that focus on livestock. Program activities were maintained at ILRAD substantially through the availability of staff seconded from donor nations and through favourable exchange rates in the host country. The financial outlook for 1993 shows little prospect of improvement, however, and future reductions in the research programs are anticipated. ILRAD appreciates the financial support the donor nations have given and will continue to explore new funding opportunities.



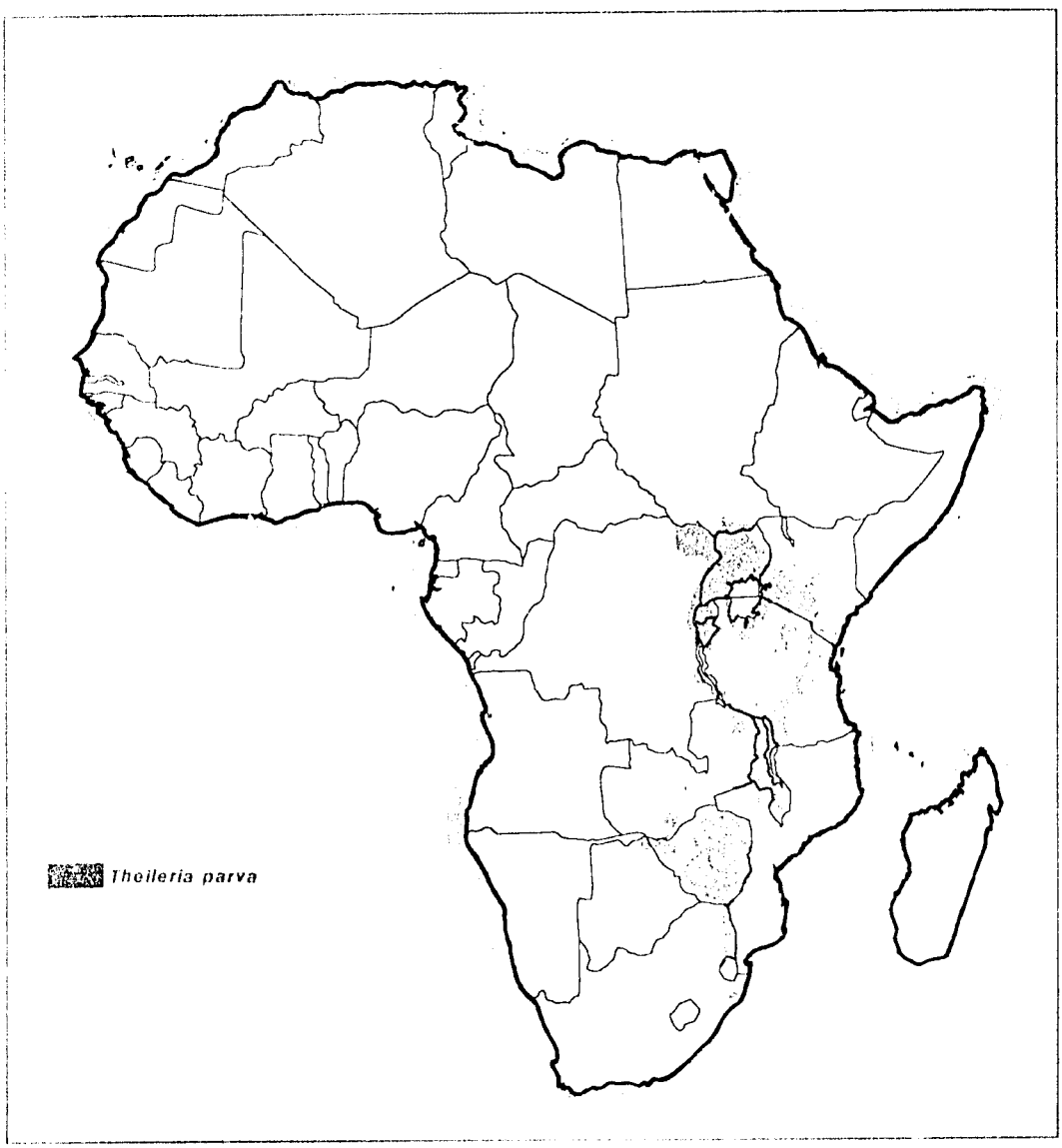
ILRAD is also grateful for the interest in its work expressed by visits to the Laboratory from distinguished donor agents, policymakers and scientists. The Honourable K. M'Mukindia, Kenya's Minister for Research, Science and Technology, was guest of honour at a reception for ILRAD's Board Members in April. In his speech and in discussions with Dr. Ole Nielsen, ILRAD's Board Chairman (pictured at left with the Minister), the Minister praised the institute's excellent educational program, which since 1978 has trained nearly 700 individuals from Africa and other developing countries. Of these, about 80 students conducted several years of advanced laboratory research towards M.Sc. or Ph.D. degrees under the guidance of ILRAD's internationally recruited scientists, who together represent more than a dozen biological and socioeconomic disciplines.

Dr. Visvanathan Rajagopalan, Vice President of the World Bank and Chairman of the CGIAR (pictured below, left), visited ILRAD in August. In an impromptu talk with 20 African Research Fellows working at ILRAD for their M.S. or Ph.D. degrees, Dr. Rajagopalan urged the students to 'stay in science': 'In the short term, many things will be more attractive; you must make a commitment to science. The spirit of enquiry is indispensable in science; it is even more indispensable to progress.'



The erosion in core funding to ILRAD and other CGIAR centres is due to several factors, including the world recession, concerns other than agriculture taking first priority in many development agencies, and the opening of eastern Europe and the former Soviet Union. Support for long-term basic research aimed at finding solutions to tropical agricultural problems is thus facing increasingly stiff competition. In spite of this, ILRAD and its many collaborating institutes in Africa and around the world remain committed to finding new ways of keeping tropical livestock—and the farm households that maintain them—healthy and productive.

A.R. Gray
Director General


Theileria parva

TICK-BORNE DISEASES

TICK-BORNE DISEASES of livestock cause economic hardships throughout the tropical and subtropical regions of the world. The major tick-borne diseases are caused by protozoan parasites: theileriosis is caused by *Theileria parva*, anaplasmosis by *Anaplasma marginale*, babesiosis by *Babesia* species, cowdriosis by *Cowdria ruminantium* and tropical theileriosis by *Theileria annulata*.

The most economically important of these species in Africa is *T. parva*. The disease this parasite causes, commonly known as East Coast fever (and in some regions as Corridor and January disease), occurs in eastern, central and southern African countries. Most cattle that are susceptible to East Coast fever die from infection if not treated. Of the 63 million cattle raised in this region, an estimated 24 million are at risk from the disease.

The brown ear tick, *Rhipicephalus appendiculatus*, is the organism that transmits *T. parva* parasites between cattle as the tick feeds. The tick also takes up parasites from infected African Cape buffalo and passes them on to domestic cattle. Like several other wild species that are hosts to *Theileria* parasites, most infected buffalo show no signs of clinical disease.

Most domestic cattle, on the other hand, suffer from infection with *T. parva*. The cattle most severely affected are highly productive taurine *(Bos taurus)* breeds from Europe, animals crossbred with these, and genetically improved indigenous zebu *(Bos indicus)* cattle moved from areas free of East Coast fever into endemic areas. Among indigenous cattle where the disease is relatively endemically stable, up to 50% of the calves exposed to *T. parva* die; in livestock herds first introduced to the parasite, 80–100% of animals of all age groups may die. ILRAD scientists estimated that East Coast fever killed 1.1 million cattle and cost the agricultural industry a total of US $168 million in 1989.

The most common method used to control East Coast fever is the regular application of acaricides to keep cattle free of ticks.

(Opposite) The protozoan parasite *Theileria parva* causes severe and often fatal disease in cattle in eleven African countries: Burundi, Kenya, Malawi, Mozambique, Rwanda, Sudan, Tanzania, Uganda, Zaire, Zambia and Zimbabwe.

A brown ear tick *(Rhipicephalus appendiculatus)* on a blade of grass questing for an animal host on which to feed. This tick transmits *Theileria parva* parasites to cattle. Most cattle that become infected with these parasites develop East Coast fever and—if left untreated—die within a few weeks. The chief habitat of the brown ear tick is the savannah. Where climate, vegetation and host density suit their development, these ticks will heavily infest pastures and animals.

The practice of regularly dipping or spraying cattle with acaricides to prevent tick infestation generally has proved effective in preventing the transmission of tick-borne diseases in Africa.

The main disadvantages of this control method are its dependency on water, which is often scarce, the rising costs of acaricides, the difficulty in maintaining dip and spray infrastructures, the development of acaricide resistance in ticks, contamination of the environment and food by acaricides and their residues, and adverse effects of intensive tick control on endemic stability for tick-borne diseases. These problems have stimulated research into new and innovative disease control methods.

This control method, however, is costly and potentially damaging to the environment. An alternative, 'live vaccine', control method was developed several years ago. Cattle are infected with a stock of *T. parva* while simultaneously treated with an antibiotic drug to lessen the severity of the infection. After receiving this 'infection-and-treatment' immunization, cattle are protected against subsequent infection with that parasite stock.

This immunization, although a useful control method in many circumstances, has several drawbacks, in particular its use of live parasites, which must be frozen in liquid nitrogen to remain viable. In addition, immunized animals are generally protected only against the stock of the parasite used in the infecting dose. The focus of ILRAD's strategic research on tick-borne diseases is to develop improved control methods, especially a safe, relatively cheap and broadly effective vaccine that will protect cattle against East Coast fever and lay the groundwork for better control of related tick-borne diseases.

THE LIFE CYCLE of the *T. parva* parasite is complex. In both the tick vector and the mammalian host, the parasite develops through a series of different stages. When feeding on an infected animal, the *R. appendiculatus* tick ingests parasites of a form known as piroplasms, which infect bovine red blood cells. In the gut of the tick, the piroplasms undergo differentiation to sexual forms that fuse to form zygotes, which then differentiate into kinete forms. The kinetes migrate to the tick's salivary glands, where they differentiate into sporozoite forms. As the tick prepares to take a blood meal, these sporozoites are injected into the cattle along with tick saliva.

In the animal host, the sporozoites attach to and enter lymphocyte cells of the bovine immune system. Within two to three days of invading the lymphocytes, the sporozoites develop into forms called schizonts. The infected lymphocytes grow larger and begin to divide. As each lymphocyte divides, the schizont inside it also divides, ensuring infection of each of the two daughter cells produced by the lymphocyte.

In this manner, the lymphocytes that were initially parasitized expand rapidly and spread throughout the lymphoid system of the animal, giving rise to widespread destruction of cells of the host animal. In untreated, susceptible cattle, this usually results in an overwhelming infection of the lymphoid system and death within three to four weeks of infection.

In the later stages of infection, some of the schizonts differentiate into merozoite forms. Upon rupture of the lymphocytes, the merozoites are released into the bloodstream, where they invade red blood cells. In the red cells, the parasites change into piroplasms, which are able to infect ticks, and this completes the life cycle of *T. parva*.

PARASITE CHARACTERIZATION AND DISEASE DIAGNOSIS

ILRAD's development of standardized diagnostic ELISAs for tick-borne diseases will facilitate epidemiological studies and disease surveillance in tropical countries. Use of the assays will also help scientists define disease challenge environments before testing novel vaccines in the field.

ILRAD SCIENTISTS have spent considerable time over the last several years developing increasingly sophisticated laboratory procedures for identifying different species and stocks of *Theileria*, which are often indistinguishable when viewed using a light microscope. Success in protecting cattle in a given area against East Coast fever by administering the infection-and-treatment method depends on accurately identifying the parasite stocks that predominate in that area. Furthermore, by determining which *T. parva* strains occur in each area and how often the parasites infect their tick and mammalian hosts, epidemiologists are gaining a better understanding of how East Coast fever is spread and in what areas livestock are at risk.

The tests developed at ILRAD include DNA-based diagnostic technologies and enzyme-linked immunosorbent assays, known as ELISAs, that identify parasite antigens or antibodies made against the parasites. ILRAD's diagnostic and epidemiological work has been greatly advanced in recent years by use of the polymerase chain reaction (PCR) technique to amplify defined stretches of DNA, as well as use of a variation of this technique known as the RAPD method (the acronym stands for 'random amplified polymorphic DNA').

In 1992, ILRAD staff sequenced the gene from different *T. parva* stocks that encodes the major surface antigen of sporozoites—a protein designated p67. The sequence appears not to vary among cattle-derived parasites, confirming that a vaccine based on this parasite antigen would be broadly effective. The sequencing work also revealed a 129-base-pair insertion in the gene encoding the antigen in two buffalo-derived stocks; the insertion is not present in cattle-derived stocks. Results of amplifying parasite DNA by PCR suggest that the additional DNA sequence in buffalo-derived *T. parva* may prove a valuable marker in epidemiological studies.

In collaboration with Washington State University (USA), antigen- and antibody-capture ELISAs were developed at

The African Cape buffalo is probably the definitive host of the most important *Theileria* species found in Africa. These animals invariably survive primary infections with *Theileria parva* and become carriers of this parasite.

As a result of a reduction in buffalo and expansion of cattle populations on the continent, the latter are now the main domesticated hosts of the pathogenic *Theileria* species found in Africa.

ILRAD this year to detect infections with *Anaplasma marginale*. The two types of assays will prove useful in determining the true prevalence of the parasite in endemic areas. Similar assays are being developed for identifying *Babesia bigemina* infections in cattle.

SUPPORT FOR TICK-BORNE DISEASE CONTROL CARRIED OUT BY NATIONAL AND REGIONAL PROGRAMS

STAFF MEMBERS conducting epidemiology studies of tick-borne diseases continued to help Africa's regional and national tick-borne disease control programs to determine the prevalence of East Coast fever in their countries and to immunize cattle using the infection-and-treatment method. ILRAD has provided most support to control programs on Pemba and Unguja islands of Zanzibar (Tanzania), in Zambia and in Zimbabwe, where good progress is being made in implementing the infection-and-treatment method of immunization.

As part of an epidemiological study of theileriosis in Zimbabwe, 30 parasite isolates from different areas were characterized at ILRAD in 1992 using a panel of monoclonal antibodies and four DNA probes. *Theileria taurotragi* isolates were distinguished using an extrachromosomal element probe and a monoclonal antibody specific for *T. tauratragi*. Primers for PCR amplification, DNA probes and monoclonal antibodies were transferred to Zimbabwe during the year and staff from the Veterinary Research Laboratory in Harare were trained in the use of these reagents.

With colleagues at Imperial College (UK), two mathematical models were developed in 1992 to investigate the dynamics of *T. parva* transmission to cattle by *R. appendiculatus* ticks. The impacts of two disease control methods—infection-and-treatment immunization and acaricide application—on the rate of transmission of infection were evaluated. In addition, criteria were developed for determining under what conditions control by vaccination should be implemented.

CHARACTERIZATION OF THE *THEILERIA PARVA* GENOME

A MAJOR ACHIEVEMENT at ILRAD in 1991 was the completion of a physical map of the total genetic material of a stock of *T. parva* made using *Sfi* I linking clones. The map locates all the genes isolated from *T. parva* to date. Several of these genes are of major significance because their protein products may provoke protective immune responses in cattle. The map was used this year in molecular experiments to confirm earlier evidence that a sexual cycle—and thus genetic recombination—occurs in *T. parva* and helps to generate the wide variety of parasite strains found in the field. A variation of this linking clone strategy is being used to construct comparative physical maps of *T. parva* Boleni and buffalo-derived stocks. Such maps will give the researchers fingerprints of the different parasite stocks and disclose information about the relationships among closely related parasites.

ILRAD's map of the genome of *Theileria parva*, completed in 1991, was the first complete restriction map made of the genome of a protozoan parasite.

A VACCINE STRATEGY designed to protect cattle against *T. parva* must address several kinds of complexity: that of the different life cycle forms of the parasite, the different responses to the parasite made by the two main branches of the immune system—antibody and cell-mediated (T lymphocytes) responses—and the different abilities of individual animals to mount an immune response to infection.

In light of so many variables, ILRAD scientists have adopted a rational approach to development of a vaccine against this parasite. This involves reproducing the disease experimentally in cattle, dissecting the immune responses to the parasite and identifying the parasite antigen(s) that induce 'protective' responses. Genes encoding these antigens are cloned and sequenced and expressed in bacterial or mammalian cells to generate large quantities of recombinant protein. Alternatively, the gene may be incorporated in recombinant viruses or bacteria that can be used as live antigen delivery systems. The final strategy for expression will depend on the nature of the immune response to be generated by the candidate vaccine.

ILRAD scientists have developed two strategies for controlling *T. parva* infection in cattle. They are investigating ways of blocking the entry of sporozoite forms of the parasite into bovine lymphocyte cells to prevent the infection from taking hold and they are exploring ways to stop the rapid proliferation of schizont forms of the parasite that have invaded the lymphocytes.

The *T. parva* antigen found to be the most promising candidate for vaccine material—designated p67 because its molecular mass is about 67 kilodaltons—occurs on the surface of sporozoites and has been found to be the same in all stocks of cattle-derived *T. parva* tested. This molecule is able to generate antibodies against it that prevent all or most parasites from entering lymphocyte cells.

It is believed that the severity of East Coast fever depends largely on the numbers of sporozoite parasites that infect an animal. If the numbers of sporozoites are sufficiently reduced, the immune system of most animals is probably able to clear the infection with little trouble through activation of T lymphocytes that specifically recognize and cause the destruction of parasite-infected cells. The vaccination strategy being developed at ILRAD using the p67 molecule thus may not have to depend on complete elimination of sporozoite challenge, because a limited establishment of schizont parasitosis will generate T cells against schizont-infected cells (see below for further discussion of these T-cell responses).

IMMUNIZING CATTLE WITH *THEILERIA PARVA* ANTIGENS

The immune system has evolved in vertebrate animals to protect them from invading pathogenic microorganisms. The extraordinary complexity of the immune system is rivalled only by that of the mammalian nervous system.

By designing vaccines against important parasites such as *Theileria parva*, ILRAD is aiming not to devise new ways of attacking the parasites, but rather to enhance an animal's immune responses to them—to give the immune system a small push in the right direction.

These electron micrographs show a sporozoite form of the *Theileria parva* parasite (top cell) attaching to and then entering a T cell of the animal host. As soon as the parasite has invaded the cell, a race begins between infection and host immune response. Domestic livestock usually lose the race because they cannot mount an immune response fast enough to control the parasites. Within three to four weeks, infected bovine lymphocytes proliferate abnormally, like the expansion of white blood cells in leukaemia. This kills the animal.

Despite the complexities of the *Theileria parva* parasite and the immune responses of cattle to it, with ILRAD's demonstration that cattle can be protected against sporozoite forms of the parasites, a subunit vaccine for this parasite is now on the horizon.

In previous years, a recombinant form of the p67 antigen, NS1-p67, was expressed in *Escherichia coli* and produced in bulk quantity in collaboration with SmithKline Beecham (USA). The recombinant antigen was then inoculated into cattle at ILRAD and shown to protect them against subsequent challenge with *T. parva*.

The recombinant protein gave rise to protective immunity in about 70% of immunized animals when administered in a saponin adjuvant. In 1992, a new adjuvant was evaluated that appears to enhance protective bovine immune responses to the p67 antigen.

The gene encoding p67 has also been expressed in the baculovirus expression system. This insect cell system carries out post-translational modifications on the introduced gene product. In 1992, cattle were experimentally immunized with this recombinant p67 antigen, BEVp67, and subsequently challenged with a *T. parva* stabilate. The protection this immunization gave animals was similar to that provided by NS1-p67 using saponin.

It appears from these results that the adjuvant augments the induction of protective immune responses to recombinant p67 in cattle. Future studies will focus on determining the minimum quantity of NS1-p67 required to induce protection against challenge both with stocks of the parasite used in the immunizing dose and with different parasite stocks.

VACCINE DEVELOPMENT

This light micrograph shows fibroblast cells infected at ILRAD with a recombinant vaccinia virus that gives rise to the expression of the p67 gene of the *Theileria parva* parasite. This virus construct has been modified to optimize the expression of p67 on the surface of infected cells. When inoculated into an animal, such infected cells should be able to provoke protective responses from an animal's immune system.

A SUCCESSFUL VACCINE must deliver parasite antigens to the immune system of the animal host in such a way that it stimulates protective immune responses. Delivery vehicles based on recombinant organisms have several advantages over conventional antigen delivery systems. Recombinant vaccinia viruses have been shown in several experimental systems to give rise to potent antibody and cytotoxic T-cell responses. A recombinant vaccinia virus was constructed in 1989 that incorporates the gene encoding the p67 sporozoite antigen of *T. parva*. In 1990, the recombinant virus was shown to produce neutralizing responses in rabbits, guinea pigs and cattle. Experimental results obtained in 1991 showed that neither the virulence of the parent virus of the recombinant nor the virus dose significantly affected the outcome of immunizations.

Results of several experiments conducted in 1992 indicate that the available construct for the expression of *T. parva* p67 gene in cells infected with vaccinia virus is unsatisfactory. The antigen is expressed poorly on the cell surface. This may in part explain the low antibody levels generated in immunized animals. In 1992, an effort was made to generate new constructs to favour antigen-processing mechanisms that would generate either antibody or cytotoxic T-cell responses. ILRAD scientists employed two strategies to induce antibody production, both of which involved constructing chimaeric (hybrid) p67 genes designed to give rise to expression of the antigen on the cell surface.

An additional strategy to improve the immunogenicity of recombinant p67 vaccinia viruses has been to incorporate genes that encode immunomodulating molecules. The nature of immune responses is determined by the T-cell subpopulations involved and by the types of cytokines they produce. Cytokines are soluble factors that act as chemical messengers. Recent reports suggest that incorporating certain cytokine genes in the recombinant vaccinia constructs can influence the nature of immune responses to recombinant antigens. In 1992, a recombinant vaccinia was made that incorporates the bovine gene for interleukin 4, a cytokine that drives the immune response towards antibody production. This construct is being evaluated. Similar constructs will be made with the bovine genes encoding the cytokines interleukin 2, interleukin 6 and gamma- interferon.

CELL-MEDIATED IMMUNE RESPONSES IN CATTLE

IT IS THE SCHIZONT form of *T. parva* that parasitizes host lymphocytes and causes them to proliferate excessively, leading to the development of disease. The death or recovery of an animal depends greatly on its ability to control the rapidly dividing infected lymphocytes. Several features of immunity to *T. parva* infection suggest that protective host responses mounted against challenge are directed largely at the schizont form of the parasite. Over the past decade, scientists at ILRAD have determined that these responses are probably mediated by T lymphocytes. Identifying the components of the parasite that induce these responses is a major area of research at the institute.

ILRAD scientists have determined that the main 'effector' in cell-mediated immune responses against *T. parva* is likely to be a subpopulation of T lymphocytes known as cytotoxic T cells. Parasite-specific cytotoxic T cells cultured *in vitro* have been shown to kill schizont-infected lymphocytes.

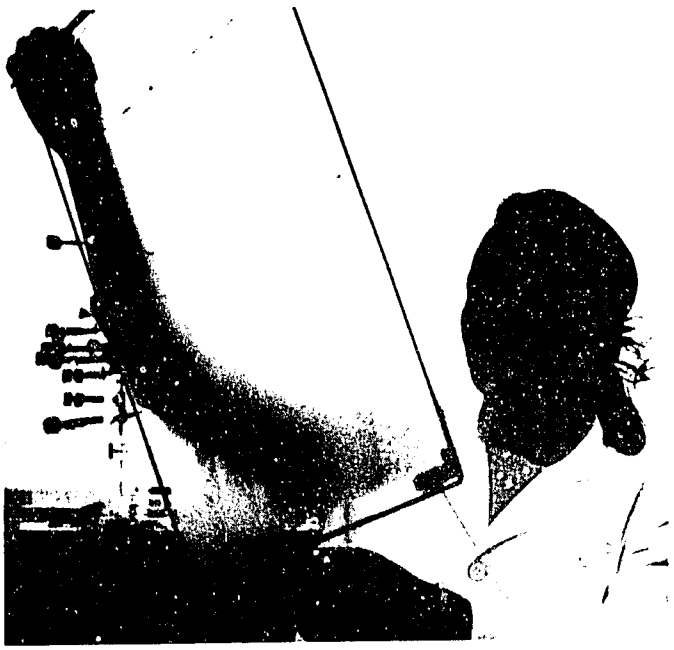
To define what factors are important for the generation of primary and secondary responses by bovine cytotoxic T cells, highly purified populations of T cells were employed in 1992 in co-culture experiments with *T. parva*-infected lymphoblasts. The analyses indicate that another subpopulation of T lymphocytes—helper T cells—play an important role in generating primary and memory cytotoxic T-cell responses. Future experiments will be conducted to define the signals that helper T cells give to cytotoxic T cells. These observations have highlighted the requirement for additional components in a cytotoxic T lymphocyte vaccine that will provoke helper T-cell responses.

Despite the evidence that parasite-specific cytotoxic T cells can clear *T. parva* infections in cattle, observations made in 1992 indicate that some immune cattle are protected against challenge with *T. parva* through use of other mechanisms. Lymphatic cannulation experiments were performed in the year to investigate the nature of these alternative immune responses to the parasite. The experiments confirmed that a significant proportion

Immune events are small events, occurring at the molecular level. Their power lies in their orchestration. Because mobilization of cytotoxic and helper T cells would greatly enhance a vaccine against *T. parva*, ILRAD scientists are searching for the parasite antigens that provoke these responses.

of cattle immunized by the infection-and-treatment method do not deploy parasite-specific cytotoxic T cells upon challenge with the parasite. This phenomenon appears to occur most frequently in young cattle. These alternative mechanisms have become the focus of much research effort in the program.

ADVANCED MOLECULAR and other biological techniques and much of the knowledge and expertise modern biological science has to offer will be needed to bring ILRAD's vaccine development research to fruition. The rewards will be lasting. Development of a novel vaccine against East Coast fever will lift a burden of animal disease from African farmers, enabling them not only to produce more food for themselves but also to generate more cash that can be used to improve their farms and lives. And because no broadly effective recombinant vaccine against a protozoan parasite has yet been developed, such an achievement would also be a major biological breakthrough, ushering in a new stage of human as well as veterinary preventive medicine.



An ILRAD technician examines an autoradiograph of a DNA sequencing gel. Each lane of the gel corresponds to one of four bases that make up DNA (deoxyribonucleic acid).

The gene being sequenced here encodes a protein molecule of *Babesia bigemina*, a tick-borne parasite that causes the disease babesiosis (redwater) in Africa, Asian, Australian and South American cattle.

This DNA sequence will be used to produce large quantities of the parasite protein it encodes. The protein will be employed in assays whose use will improve both the diagnosis of babesiosis and our understanding of how the disease is spread.

TRYPANOSOMIASIS

TRYPANOSOMIASIS occurs across more than a third of Africa. It is arguably the most important livestock disease on the continent. Like East Coast fever, trypanosomiasis is caused by infection with a protozoan parasite. In Africa, trypanosomes are usually transmitted to domestic and wild animals, as well as to people, by tsetse flies as they feed on mammalian blood. The wide occurrence of this disease in people and their livestock continues to retard agricultural and economic development on the continent.

The tsetse fly occurs only in Africa. It transmits at least four parasite species—*Trypanosoma brucei brucei, Trypanosoma congolense, Trypanosoma simiae* and *Trypanosoma vivax*—that cause serious forms of trypanosomiasis in cattle, sheep, goats, pigs and horses. The fly also transmits two parasite species—*Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*—that cause human trypanosomiasis, commonly known as sleeping sickness.

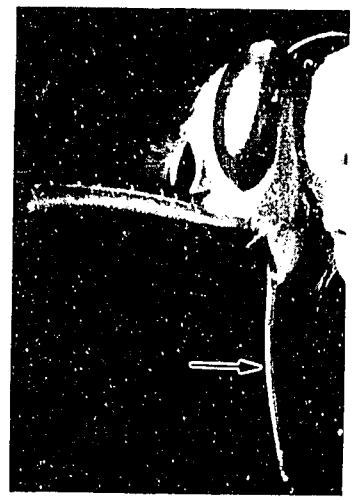
In parts of Africa and Asia, camels suffer from disease caused by *Trypanosoma evansi*, a trypanosome transmitted by biting flies other than tsetse. In large areas of Asia and South America, *T. evansi* also poses a threat to cattle, domestic buffalo and pigs. *Trypanosoma vivax*, which in Africa is transmitted by the tsetse fly, also exists in the absence of this vector in the Caribbean and South America. Non-tsetse-transmitted trypanosomiasis is a potential threat to livestock in many parts of the world.

Thirty percent of Africa's cattle population, estimated to be 160 million, and comparable numbers of small ruminants are at risk from trypanosomiasis. Losses in meat production, milk yield and tractive power and the costs of running programs to try to control the disease are estimated at US$500 million each year. If

(Below) The head of a tsetse fly showing the proboscis (arrow) through which the fly feeds and transmits trypanosome parasites to an animal.

(Opposite: top) Low-magnification electron micrograph showing a cross-section of the proboscis with trypanosomes *(T. congolense)* that have developed to the metacyclic stage and are ready for transmission to an animal host when the fly next feeds.

(Opposite: bottom) Higher-magnification electron micrograph of the same specimen.



lost potential in livestock and crop production is considered as well, the disease is estimated to cost Africa $5 billion a year. In addition, 50 million people are exposed to the risk of contracting human trypanosomiasis.

An unfed tsetse fly *(Glossina morsitans centralis)* resting on a twig of a tree.

Tsetse flies occur across 36 countries and 10 million square kilometres of Africa. This tsetse belt includes regions with great potential for agricultural production on the continent. The risk of trypanosomiasis in much of this area precludes farmers from keeping cattle and small ruminants. This fact largely accounts for the continent producing only one-seventieth of the animal protein produced per hectare in Europe.

The trypanosome parasites that cause disease in livestock and people also infect wildlife species, which are a source of infection for tsetse, which then infect domestic animals and people. Many wild animals tolerate trypanosome infections with no apparent ill effects. In humans and domestic livestock, however, such an innocuous relationship with the parasite has not evolved, and the pathogenic effects of infection are severe.

For several days following infection with trypanosomes, animals show no signs of disease. One to two weeks later, susceptible animals develop intermittent fever and anaemia. In most endemic areas of Africa, cattle must forage daily for food and walk long distances for water. Bitten repeatedly by tsetse flies, they are also commonly infected with different kinds of trypanosomes. Under these stressful conditions, infected animals continue to deteriorate for months before dying.

The life cycle of the trypanosome, like that of the *Theileria* parasite, is complex. In both the tsetse fly vector and the mammalian host, trypanosomes undergo a series of transformations into different forms. The tsetse fly ingests trypanosomes when it feeds on an animal infected by the parasite. In the fly, the parasites differentiate into several forms, culminating in the metacyclic form, which is able to infect mammalian hosts. When the infected fly next feeds, these metacyclic trypanosomes are injected into the skin of the host along with tsetse saliva. In the animal, the parasites differentiate into a form specially adapted to live in mammalian blood. These bloodstream parasites multiply by binary fission and enter the animal's lymphatic and blood circulation. As flies feed on animals infected with the parasite, the flies may take up blood containing trypanosomes, thus completing the parasite's life cycle.

CURRENT CONTROL METHODS

NONE OF THE METHODS now available to control trypanosomiasis is ideal and no combination of methods is sufficiently efficacious and cost-effective to sustain small-scale livestock raising in much of the tsetse belt without close supervision. Drug treatment is the most widely used means of controlling the disease, but the drugs available are relatively expensive; furthermore, widespread use of the few drug compounds developed for trypanosomiasis has led to increasing parasite resistance to them.

The disease can also be controlled by reducing populations of the tsetse vector. Infested areas may be sprayed with insecticides to kill the flies, but this pollutes the environment. Habitat hospitable to tsetse may be destroyed to rid areas of flies, but regeneration of vegetation frequently favours reinvasion of re-

claimed areas. Fly populations may be reduced to acceptably low levels by deploying tsetse targets and traps, but this control method is successful only in some ecological environments and only for some species of fly.

The other main method used to control trypanosomiasis is to keep cattle of a few ancient African breeds, such as the West African N'Dama *(Bos taurus)*, which are innately able to tolerate infection with trypanosomes. Use of these 'trypanotolerant' animals is perhaps the most attractive of the control methods available and has made livestock rearing possible in tsetse-infested areas. However, this disease control method also has important drawbacks. Levels of trypanotolerance are reduced in animals under stress, the amount of milk trypanotolerant cattle produce is relatively low and trypanotolerant animals raised in traditional farming systems are typically small and are therefore not ideal for draught work. Most importantly, few such animals are available. In spite of their importance in tsetse-infected areas where other livestock cannot survive, trypanotolerant cattle constitute only 5% of the cattle raised in countries where tsetse flies occur. In contrast, the humped zebu *(Bos indicus)* cattle, which are widespread in Africa, are susceptible to trypanosomiasis, and highly productive, genetically improved European *(Bos taurus)* cattle are extremely susceptible to the disease.

The humpless N'Dama first appeared in Africa about 7,000 years ago. The innate ability of this breed to resist trypanosomiasis probably evolved during the long association between these cattle and trypanosome parasites.

ANTIGENIC VARIATION IN TRYPANOSOMES

TRYPANOSOME POPULATIONS avoid elimination by the mammalian immune system by employing a defence mechanism known as 'antigenic variation'. Most animal hosts make immune responses to the first wave of invading trypanosomes by producing antibodies against antigenic protein molecules displayed on the surface of the parasites. The antibodies bind to these antigens, and this initiates a series of immune events that ends in the rupture and death of the parasites. However, before all the parasites can be eliminated, trypanosomes bearing a new surface molecule appear. While the immune system begins to produce antibodies against the new antigen, the second wave of trypanosomes multiplies rapidly, and before all parasites in the second wave can be destroyed, parasites appear displaying yet another molecular surface. This process continues, with the parasite population always keeping a step ahead of the host's immune system. Unable to keep pace, the animal's immune system becomes exhausted and the animal eventually succumbs. This remarkable parasite defence mechanism makes it unlikely that a conventional vaccine, which primes an animal's immune system against just one or a few antigens, will be broadly effective. With this in mind, ILRAD scientists are investigating other strategies for controlling the disease.

EPIDEMIOLOGY AND DIAGNOSIS OF TRYPANOSOMIASIS

CHARACTERIZING AND DIAGNOSING trypanosome infections is complicated by the existence of many species and subspecies of the parasite. More efficient systems for identifying trypanosomes are needed to make accurate diagnoses, to obtain sound epidemiological data and to optimize use of chemotherapy for trypanosomiasis.

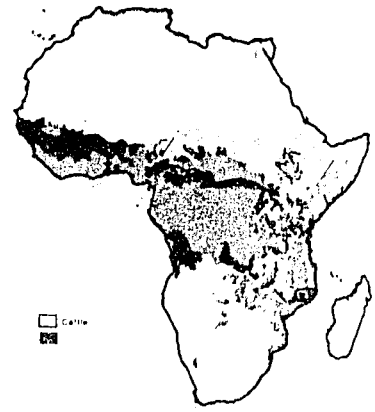
In 1992, ILRAD scientists cloned and sequenced the gene encoding an antigenic molecule used to diagnose *T. congolense* infections. To make improved diagnostics available for wider use, staff examined ways of labelling DNA probes that do not require use of radioactive materials. These probes are used to identify trypanosomes in the blood of mammalian hosts and the saliva of tsetse flies. Commercial kits for the non-radioactive labelling of DNA were evaluated for their ability to reveal trypanosomes present in crude samples prepared from infected tsetse and livestock. A kit using a digoxigenin/LumiPhos combination proved best able to detect the parasites. Once labelled with digoxigenin-11-dUTP, the probes are sufficiently stable to be used repeatedly for a year or longer. Protocols that employ locally available reagents and methods for linking this assay system with diagnostic PCR are now being investigated.

Staff also successfully used the RAPD technique—which employs single short oligonucleotide primers of arbitrary sequence to amplify parasite DNA in the PCR—to generate genomic 'fingerprints' that will enable them to distinguish among

and within species of trypanosomes. One of the primers tested this year, ILo 525, distinguished the three important trypanosome subgenera and produced identifiable fingerprints for the different parasite populations within each subgenus.

Individual isolates of the economically important and heterogeneous group of *T. vivax* parasites are known to differ in important respects, particularly in the severity of the diseases they cause, in their ability to infect laboratory rodents, in their requirements for cultivation *in vitro* and in their reactivity with repetitive DNA sequence probes. In a quest for simple and direct diagnostic methods with which to identify and characterize *T. vivax* parasites, the PCR method using arbitrarily selected oligonucleotides (AP-PCR) was employed this year. This relatively rapid and sensitive technique, which requires only small amounts of DNA, successfuly identified and discriminated among *T. vivax* parasites: three experimental primers gave polymorphic and reproducible DNA fingerprints for all 13 isolates tested.

Scientists at Rockefeller University (USA) recently developed a technique for growing bloodstream and procyclic forms of *T. brucei* on agarose plates rather than in liquid media. This achievement promises to advance understanding of trypanosome genetics to a level comparable to that of yeast. After modifications were made to the system, ILRAD and Rockefeller staff this year successfully used it for maintaining bloodstream and procyclic forms of *T. brucei* and *T. congolense* stocks at ILRAD.



Little overlap exists between Africa's cattle-production and tsetse-infested areas except in regions of West and Central Africa where a few indigenous cattle breeds exist that are resistant to trypanosomiasis.

TRYPANOSOME DIFFERENTIATION

TRYPANOTOLERANT CATTLE may control parasitaemia through molecular signals that cause the parasites to divide relatively slowly or to differentiate into non-dividing forms. To test this hypothesis, the genes that control parasite differentiation and the rate of parasite replication must be isolated and characterized for monitoring the interactions of their products with the host. Identification of such genes may also make it possible to develop ways of interfering with the gene products so as to control parasite proliferation in susceptible animals.

Techniques currently used for identifying developmentally regulated genes incorporate several methods to enrich complementary DNA (generated from messenger RNA) specific to one life- or cell-cycle stage. All the techniques, however, have drawbacks. New systems have been developed for identifying these genes. The systems involve amplifying complementary parasite DNA in the PCR with short oligonucleotide primers of arbitrary sequence to generate fingerprints characteristic of the genes being expressed. When tested on *T. b. brucei*, this technique generated reproducible fingerprints with different primers; some primers, moreover, generated polymorphisms in the form of stage-specific amplifications. Using this approach, scientists this year readily identified genes expressed specifically in slender bloodstream, stumpy and procyclic forms.

DRUG TREATMENT FOR TRYPANOSOMIASIS

DRUG TREATMENT for trypanosomiasis relies on three closely related compounds that have been widely used for more than 30 years. This has led to the development of drug resistance in some parasite populations. The aim of ILRAD's chemotherapy program is to develop biochemically based diagnostics that will rapidly quantify parasite drug sensitivity in the field. Such diagnostics will help maintain the long-term efficacy of the trypanocides now in use.

African trypanosome populations are becoming resistant to the prophylactic drug Samorin®. Experiments conducted in 1992 in collaboration with the Technion-Israel Institute of Technology indicate that Samorin is taken up by bloodstream forms of *T. congolense* by a membrane transport molecule. Both fluorescence and radiolabel uptake techniques gave similar results, with levels of drug uptake showing marked and consistent differences between populations differing in resistance to the drug. These techniques might provide the basis for a practical test that can be used to detect drug resistance in field populations of parasites. The information obtained in these studies will lay the groundwork for devising better ways to use the drugs in the field and for developing treatment strategies that militate against the generation of drug-resistant parasite strains.

Transfection techniques now available allow foreign genes to be targetted to specific loci. This enables scientists to generate genetic crosses between trypanocide-resistant field isolates and laboratory generated transfected resistant parasites. This form of selection for recombinants offers new possibilitites in studies aiming to identify genes that control drug resistance. Because genetic exchange has already been demonstrated in *T. brucei* and because *T. brucei* transfectants can be selected *in vivo*, this parasite is being used as a model for the development of systems to select *T. congolense* recombinants.

TRYPANOSOME ANTIGENS

SEVERAL TRYPANOSOME MOLECULES with potential to protect cattle from trypanosomiasis were isolated and characterized in 1992. The gene for one of the most promising of the antigens, a 33-kilodalton enzyme (cysteine protease) of *T. congolense* associated with resistance to trypanosomiasis in cattle, has been cloned.

Among the other promising trypanosome antigens under study in 1992 were the vacuolar ATPase enzyme, a casein kinase II protein, cytoskeletal proteins and two chaperone-like molecules. A major invariant antigen in cattle infected with *T. congolense* is a 69-kilodalton heat shock protein. The gene encoding this protein was cloned and sequenced and its gene expressed in the bacterium *Escherichia coli*. The recombinant protein will be used to study immunological responses of cattle to the molecule.

ILRAD's trypanosome antigen studies have been partly supported by CIRAD-EMVT: the Department of Livestock and Tropical Veterinary Medicine at the Centre for International Cooperation in Agricultural Research for Development, France.

HOST IMMUNE RESPONSES TO TRYPANOSOME INFECTION

LEARNING MORE ABOUT the complex interactions between hosts and parasites and their relationship to the development of disease will help scientists better understand how cattle generate immune responses to trypanosomes. This information may lead to the development of methods to manipulate those responses in ways that will block or inhibit parasite proliferation.

Studies were continued in 1992 of the responses to infection made by bovine B cells, which produce antibodies against trypanosomes, and T cells, which effect and regulate various immune mechanisms, including aspects of antibody production.

To study B-cell activation, bovine cytokines, and in particular growth factors such as interleukin 4 (IL-4), are required. To provide the bulk quantities of this cytokine needed for these investigations, the gene encoding IL-4 was expressed in *E. coli* and the recombinant protein used as an immunogen to raise polyclonal and monoclonal antibodies.

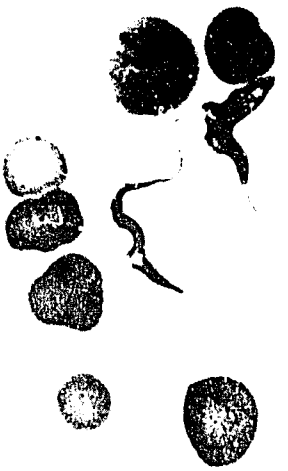
The gene encoding interleukin 4 was identified at ILRAD using a nucleic acid probe supplied by D.A.E. Dobbelaere, at the University of Berne, Switzerland.

Other bovine cytokine reagents important for the study of T- and B-cell responses—IL-1α, IL-1β, IL-2 and IL-6—have been obtained from outside sources. Some of these reagents were subcloned this year in riboprobe vectors. DNA probes, riboprobes and a set of specific primers for each cytokine were assembled to allow staff to study cytokine-specific gene expression.

The genes encoding another important cytokine, bovine tumour necrosis factor α, in both trypanosome-susceptible Boran and trypanotolerant N'Dama cattle, were cloned and sequenced this year. Sequence differences between the two breeds will be further studied to determine if they represent PCR errors or polymorphisms. Work is in progress to express the gene encoding tumour necrosis factor α in *E. coli* to produce sufficient quantities of this cytokine for biological studies.

Previous work has suggested that ineffective production of blood cells may be partly responsible for the development of anaemia in bovine trypanosomiasis. In 1992, ILRAD scientists examined bone marrow response during a *T. congolense* rechallenge infection in Boran cattle. The experiment produced quantitative evidence that there is a negative effect on erythroid development in the bone marrow of trypanosome-infected cattle.

The anaemia of *T. congolense* infection in cattle is associated with a poor erythropoietic response. Erythropoietin is a hormone that stimulates red blood cell production. Two assays used to measure erythropoietin in human plasma were assessed for their ability to measure bovine erythropoietin in the plasma of calves made anaemic either by sudden blood loss or by a natural *T. congolense* infection. From 76 days following infection with *T. congolense*, the erythropoietic response in the calves waned, suggesting that the bone marrow was unresponsive to observed elevated levels of erythropoietin in the plasma.



Light micrograph of slender and stumpy forms of *Trypanosoma brucei brucei* parasites in mouse blood.

BOVINE GENETICS

A DIRECT WAY to investigate the nature of trypanotolerance is to follow its inheritance in families of cattle for the purpose of, first, finding genetic 'markers' that are inherited with the disease-resistance trait and, ultimately, finding the gene or genes that control it. The breeding herd of trypanotolerant N'Dama available at ILRAD and the institute's unique ability to assess the responses of these cattle to parasite challenge under highly controlled and experimental conditions make such a genetic marker and mapping project feasible.

ILRAD's bovine genetics project was begun in 1990. The first two steps were to produce large families of cattle that segregate the trypanotolerance trait and to begin to identify some of the estimated 200 markers evenly spaced along the 60 chromosomes of cattle that will be needed to identify genetic markers associated with disease resistance. When developed, such markers will be a useful tool for breeders working to increase the numbers of trypanotolerant livestock and for researchers attempting to identify populations of animals to be targetted for germplasm conservation. Perhaps most importantly, the markers will also serve as starting points in a search of the bovine genome for the genes that control the trypanotolerance trait.

To produce the cattle needed for the mapping project, bulls from ILRAD's core herd of 10 trypanotolerant N'Dama were crossed with susceptible Boran cows in an accelerated breeding program that made use of embryo transfer expertise developed at ILRAD over the last several years. The cows were induced to produce more ova than normal. The ova were fertilized by artificial insemination and the embryos implanted in foster Boran mothers for gestation.

To investigate the mechanisms in trypanotolerant cattle that prevent development of disease, ILRAD has produced a resource herd of animals cross-bred from susceptible Boran and trypanotolerant N'Dama cattle. DNA from these animals is being used to develop a linkage map of the bovine genome that may reveal the gene or genes that control the trypanotolerance trait(s).

Below is a group of Boran surrogate mothers with their N'Dama × Boran offspring produced in 1992 using embryo transfer techniques on ILRAD's Kapiti Ranch.

For the purposes of linkage analysis of genetic markers and genes controlling the trypanotolerance trait, ILRAD has produced four full-sibling first filial generation (F_1) families of N'Dama × Boran cattle from which to breed an F_2 generation segregating trypanotolerance. Two of the F_1 families were completed in 1991, with 29 and 36 animals born. At the end of 1992, the remaining two F_1 families comprised 11 and 9 calves, with five calves *in utero* in each family. Construction of the 160-member F_2 generation was begun in 1992. By the end of this year, a total of 38 F_2 animals were *in utero* and the first F_2 calves were born.

A series of microsatellites—simple DNA nucleotide sequences that occur with a high frequency in the mammalian genome—and other genetic markers are being produced at ILRAD for the bovine genome map. A total of 16 microsatellite markers have now been characterized and their segregation followed in two large N'Dama × Boran families. No inconsistencies occurred in the pattern of inheritance. Polymorphic markers in specific genes were also generated in 1992.

To identify population-specific DNA markers rapidly, two pools of genomic DNA were made comprising equal proportions of samples from ten N'Dama and ten Boran animals. Each pool was amplified using the PCR. One of the primers produced a pool-specific product in all Boran DNA amplifications and none in the N'Dama amplifications. Using this approach and randomly primed PCR, ILRAD scientists were able rapidly to identify a bovine subspecies-specific DNA marker.

To make a consensus map of the bovine genome with sufficient marker density, the bovine genetic mapping community agreed at the XXIII International Conference on Animal Genetics to develop and test suitable markers using a common set of families. Two of these families, comprising 20 per cent of the global reference resource for the bovine map, are ILRAD's. The DNA obtained from these important resource herds is being made available to the international livestock-genome-mapping community.

A map of the bovine genome must be made before researchers can identify cattle genes that control resistance to disease, such as those that enable N'Dama cattle to tolerate infection with trypanosome parasites. ILRAD scientists are collaborating in the development of a bovine gene map with molecular geneticists worldwide, including staff at Texas A & M University (USA), the Hebrew University of Jerusalem (Israel) and the Commonwealth Scientific, Industrial and Research Orgnanization (Australia).

The first step in this project is to identify a set of a few hundred genetic 'markers' evenly spaced along the animals' chromosomes. Each marker is a fragment of DNA that varies in sequence among individual animals. The markers act as reference points in the genome: genes are inherited with markers that lie in their proximity; by following the inheritance of markers in families of genetically defined cattle, it is possible to determine what genes have been inherited in which animals. This information is used to develop a 'linkage' map.

The identification and subsequent dissemination of disease-resistance genes in cattle populations will provide the most robust and sustainable of disease-control options. After being introduced into a livestock population, the desired genes propagate themselves, thus reducing farmers' dependence on vaccines, expensive drugs and environmentally damaging insecticides. The international collaborative effort to map the bovine genome will thus greatly benefit livestock owners, consumers and the environment in developed and developing countries alike.

SOCIOECONOMICS AND ENVIRONMENTAL IMPACT PROGRAM

ILRAD'S DISEASE RESEARCH programs are supported by a group of scientists investigating the factors responsible for the successful application of improved livestock disease control methods, particularly immunization, and the likely social, economic and environmental impacts that will result from improving animal health in traditional farming communities. Focussing at first on East Coast fever, this program has now broadened its scope to include investigations of African animal trypanosomiasis.

PRODUCTION, DELIVERY AND ADOPTION OF IMPROVED CONTROL MEASURES FOR LIVESTOCK DISEASES

IN COLLABORATION with the Kenya Agricultural Research Institute (KARI) and the International Livestock Centre for Africa (ILCA), ILRAD staff conducted a study in 1992 to calculate the costs of immunizing cattle against East Coast fever by use of the infection-and-treatment method. This pilot study, conducted at the Kenya coast, showed that farmers would profit from immunizing their genetically improved 'grade' animals at a cost of US$25 for each animal. The benefits of immunizing indigenous zebu cattle, on the other hand, were judged insufficient to justify this cost. To make immunization of this dominant cattle type cost-effective, the immunization cost would have to be reduced or the farm-gate price of milk increased.

(Opposite) Livestock significantly improve the stability of small-scale farm enterprises.
On farms where both crops and livestock are raised, cattle supplement human muscle as power for pulling ploughs and transporting surplus produce to market. Cattle in poor countries exist on resources that cannot otherwise be exploited—they eat grass and shrubs and crop wastes rather than grain. Their dung is used as fuel, as building material, as fertilizer. Their milk is a major source of protein for the farm household. Hides and surplus milk are sold to buy clothes and seed, to pay medical expenses and school fees.

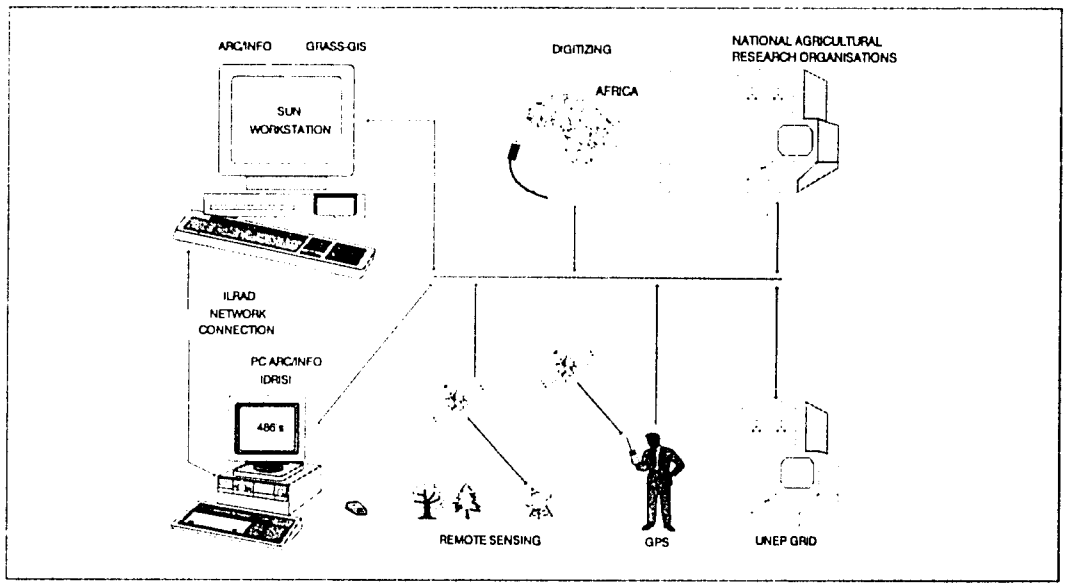
EPIDEMIOLOGICAL ASPECTS OF APPLYING IMPROVED CONTROL MEASURES FOR TICK-BORNE DISEASES

TO ASSESS THE ECONOMIC importance of a livestock disease and the probable results of bringing it under better control, researchers need to know where and how often the disease occurs and how it affects the economies of different livestock production systems. There is a paucity of such information regarding tick-borne diseases in Africa. The ILRAD program has thus investigated several computer models that might be used to predict the distribution and occurrence of tick-borne diseases in Africa. ILRAD staff and colleagues at the University of Oxford continued this year to develop models designed to predict the distribution of East Coast fever and its tick vector using discriminant analysis in a geographical information system.

A model developed in collaboration with Imperial College, London, to predict the dynamics of theileriosis under specific conditions, was completed in 1992. Based on a differential equation methodology, this model accurately predicts the relationships in a cattle population among antibody prevalence, incidences of theileriosis and case-fatalities. Given that in Africa reliable data are generally available only for antibody prevalence and that data on disease incidences and case fatalities are needed to assess the impact of a disease, this modelling approach may prove particularly useful for assessing African livestock disease.

ILRAD obtains digital data on important factors determining livestock diseases and their control (e.g., climate, vegetation and livestock and vector distributions) mainly from Africa's national agricultural research organizations, the United Nations Environment Program and satellites (the latter include remote sensing and geographical positioning systems). Information available only in map form is read into computers using a digitizer.

The digital data is manipulated in a 486 microcomputer using the geographic information system computer software program ARC/INFO. Another program, IDRISI, is used to analyse the data. To conduct large-scale analyses, the data is transferred to a SUN workstation, which can handle much larger data sets and at a much faster speed. All of ILRAD's data are made available to Africa's national and regional research centres.



TWO COMPUTER SPREADSHEET models are being developed by ILRAD, with consultancy input from A.P. Consultants of the UK, for assessing economic losses due to theileriosis and trypanosomiasis in African cattle and the economics of implementing alternative control strategies under different livestock production systems. One model provides analysis at a site/country level, the other at a regional level. The models were previously tested using theileriosis data from eastern and southern Africa.

In 1992, the site/country model predicted that immunizing cattle against East Coast fever at the Kenya Coast would reduce economic losses in that region by 24 to 40% in indigenous zebu cattle populations and by 40 to 70% in genetically improved grade cattle. The immunization would yield increases in net income of 24 to 103% depending on which of a variety of alternative control strategies were employed.

The two models were run to analyse the economics of trypanosomiasis in two countries, The Gambia and Zimbabwe. The site/country model estimated the annual losses in The Gambia and Zimbabwe to be US$400 thousand and 6.2 million, respectively. The models are being tested and modified further using data from three other countries: Côte d'Ivoire, Zambia and Central African Republic. On the basis of these analyses, ILRAD staff will develop inputs for the many other African countries in which the disease occurs. An estimation will then be made of the continent-wide economic losses caused by trypanosomiasis.

A whole-farm-level simulation model—designated the Technology Impact Evaluation Simulator, or TIES—was developed jointly by ILRAD and Texas A & M University (USA). This model was used in 1992 to simulate the economic impact of controlling East Coast fever in grade and zebu cattle using the infection-and-treatment immunization method in conjunction with different acaricide application strategies. The latter involved reducing acaricide applications from their current intensity by as much as 75% following immunization. The model was run with data from two contrasting areas and livestock production systems in Kenya: large-scale farms in Uasin Gishu District in the Kenyan highlands and small-scale farms in Kaloleni Division at the Kenya coast.

The results indicate that under all scenarios immunization is financially superior to applying present levels of acaricides. The most cost-effective control was gained by employing immunization while reducing present acaricide applications by 75%. In both areas, greater economic returns accrued from immunizing grade rather than zebu cattle.

TIES proved a flexible model for assessing the financial rewards and risks of adopting new technologies on smallholder farms. The model can also be used to make farm-level comparisons of the benefits of employing alternative methods for controlling other livestock diseases.

SOCIAL, ECONOMIC AND ENVIRONMENTAL IMPACTS OF APPLYING IMPROVED DISEASE CONTROL MEASURES

Studies of the social, economic and environmental impacts of improving control of livestock diseases in traditional farming communities helps to keep ILRAD's research targeted so that its outputs will ultimately produce the greatest benefits for small-scale farmers.

Towards the end of 1992, a project funded by the Rockefeller Foundation was started to determine how improving control of trypanosomiasis under a wide variety of situations will affect the environment. The aim of the project is to provide guidelines for evaluating where, when and how trypanosomiasis control measures should be applied. This work will be carried out in collaboration with ILCA, the Food and Agriculture Organization of the United Nations and national research centres throughout Africa.

COOPERATIVE PROGRAMS, TRAINING AND INFORMATION

COOPERATIVE PROGRAMS

ILRAD'S OUTREACH ACTIVITIES fall under the Department of Cooperative Programs, Training and Information. The broad aim of ILRAD's cooperative activities is two-fold: (1) to advance understanding of the nature of important tropical livestock diseases by employing biological, socioeconomic and environmental data as well as materials and expertise from the countries in which the diseases occur and (2) to enlarge the human and technical resources available for agricultural research and disease control in those countries.

Staff of this department and senior scientists from ILRAD's research programs make collaborative visits to Africa's national agricultural research systems to inform developing country scientists and policymakers of ILRAD activities and research results that might be exploited by national organizations responsible for livestock disease control. During these visits, collaborative research projects are initiated that accelerate research progress both at ILRAD and at the collaborating institutions.

The department also coordinates the transfer of ILRAD's research findings and products to the institute's stakeholders. The latter include national governments, universities and research institutes; regional and international research organizations; and funding agencies and other organizations involved in livestock disease control. The following are some of the technologies being developed at ILRAD that will benefit these stakeholders.

(1) New reagents for improved diagnosis of tick-borne diseases and trypanosomiasis.

(2) Improved methods for characterizing parasite strains for use in infection-and-treatment immunization against ECF.

(3) Improved procedures for breeding ticks and tsetse flies.

(4) New *in vitro* assays for determining levels of drug

resistance in trypanosome populations.
(5) Novel genetic techniques for identifying trypanotolerant cattle for conservation and wider exploitation.
(6) Computer-based decision-aids for research and disease control organizations produced using empirical data on the development and epidemiology of tick-borne diseases and trypanosomiasis and the comparative merits of applying different methods to control these diseases.
(7) Methodologies for identifying cattle populations that will benefit most from immunization against ECF.
(8) Computer models for predicting the outcomes of applying new disease control strategies and technologies.
(9) Economic models for assessing and comparing the costs and benefits of implementing various disease control methods.

ILRAD's major collaborative research projects with developing country institutes include those listed below.

- CIRDES (Burkina Faso) on the immunogenetics of trypanotolerant livestock, assays to measure drug resistance in trypanosome populations, and methodologies to assess the economic importance and epidemiology of vector-borne diseases of livestock.
- OAU/IBAR/ISCTRC (Nairobi) in defining optimal regional strategies for controlling animal diseases.
- ILCA (Addis Ababa), the African Trypanotolerant Livestock Network (Nairobi) and national agricultural research institutes in Ethiopia, Kenya and Zaire on aspects of genetic resistance in cattle breeds to trypanosomiasis.
- FAO, IAEA (Vienna) and national agricultural research institutes in Egypt, The Gambia, Ghana, Kenya, Mali, Senegal, Sudan, Tanzania, Zambia and Zimbabwe in evaluation of an ILRAD assay for diagnosing trypanosome infections.
- Sokoine University of Agriculture (Tanzania) in various research projects of mutual interest in tick-borne diseases and trypanosomiasis and the socioeconomic impacts of their improved control.
- The Kenya Agricultural Research Institute (KARI) and the governments of Tanzania (Zanzibar), Zambia and Zimbabwe in characterizing parasite stocks for immunization against ECF.
- KARI, ILCA and Zimbabwe in socioeconomic studies to determine the most appropriate strategies for controlling theileriosis in different areas.
- The International Centre of Insect Physiology and Ecology (Nairobi) on development of DNA probes to detect trypanosome infections in tsetse flies and animals in the field and research to improve laboratory rearing and management of tick and tsetse fly colonies.

TRAINING

IN 1992, 19 scientists and senior laboratory technicians came to ILRAD for periods of one week to six months to receive individual training in techniques or areas specified by their research institute or disease control project. Two group courses with a total of 19 participants were held during the year on use of advanced techniques for diagnosing trypanosomiasis. In addition, ILRAD gave financial support to 16 of 22 developing country scientists who attended a 'Biochemistry of Protozoa' course conducted jointly by scientists from ILRAD and the University of Nairobi.

Thirty-nine students—most of them from Africa and supported by ILRAD fellowships—conducted research at ILRAD during all or part of 1992 towards Ph.D. and M.Sc. degrees. ILRAD provided four additional fellowships to senior African scientists to do post-doctoral research at the institute.

ILRAD hosted two scientific workshops in 1929, which were attended by a total of 58 international scientists: 'Modelling Vector-Borne and other Parasitic Diseases' and 'Genome Analysis of Protozoan Parasites'. Discussions at these workshops served both to update ILRAD staff on current research in these areas relevant to the institute and to inform scientists working in developed countries about the current state of livestock disease control and research in Africa.

Individual training at ILRAD in 1992; number of participants in different types of training by country of origin. Nearly 10% of ILRAD's budget is spent each year on training and related outreach activities.

TT = technical training (individual and group)
RF = Research Fellows
SRF = Senior Research Fellows

Country	TT	RF	SRF
Benin	—	1	—
Burkina Faso	1	—	—
Cameroon	—	1	—
Chad	—	1	—
Ethiopia	1	—	—
Gambia	1	1	—
Ghana	1	1	—
Kenya	7	16	1
Mali	1	1	—
Mauritania	1	—	—
Nigeria	—	3	—
Senegal	1	1	—
Somalia	—	—	1
Sudan	—	2	—
Swaziland	1	—	—
Tanzania	4	2	1
Uganda	1	1	—
Zaire	1	1	1
Zambia	1	—	—
Zimbabwe	2	1	—
Belgium	—	1	—
Canada	—	2	—
France	—	1	—
Germany	1	—	—
Italy	—	1	—
Netherlands	—	1	—
Totals	*25*	*39*	*4*

INFORMATION

THE INFORMATION UNIT publishes an *ILRAD Annual Report*, an annual *ILRAD Highlights* and a quarterly scientific newsletter, *ILRAD Reports*, in French as well as English and—in English only—an *ILRAD Annual Scientific Report*, an annual list of scientific publications produced by staff, one or two proceedings of international scientific meetings held at ILRAD, an annual *Program and Budget* document and a weekly *Internal Newsletter* distributed to all staff members and to the Board of Directors. This year the unit in addition gave editorial support to ILRAD's *1994–1998 Medium-Term Plan*. All of the institute's publications are written, edited, designed and electronically laid out to camera-ready stage in-house using a personal computer and laser printer. Translation and typesetting of French publications is contracted to a biomedical translation company in the USA.

The annual report, annual highlights and quarterly newsletter are intended for a wide range of readers, with emphasis on scientists and policymakers in national agricultural research systems. ILRAD's annual scientific report comprises abstracts describing the aims and results of each research project conducted at the Laboratory during the year. This book and the annual list of staff publications are intended for scientists and highly technical staff working in areas related to ILRAD's research programs as well as for new ILRAD staff. ILRAD's readership comprises about 3,500 English and 500 French readers in developing and developed countries worldwide.

Proceedings of the institute's international workshops are also intended mainly for a scientific readership. In 1992, ILRAD published papers presented at its May 1991 workshop, *Recent Developments in the Research and Control of Anaplasmosis, Babesiosis and Cowdriosis* (181 pages, ed. Tom Dolan), and at its November 1992 workshop, *Genome Analysis of Protozoan Parasites* (189 pages, ed. Subhash Morzaria). This year ILRAD also published summaries of papers given at a September 1991 workshop on *Ticks and Tick-Borne Disease Control* held in Kampala, Uganda (49 pages, ed. Tom Dolan). The Kampala meeting was the fourth in a series of workshops held since 1984 to discuss recent research findings in tick-borne diseases and to address problems encountered in their control. The workshop was organized jointly by ILRAD, the Food and Agriculture Organization of the United Nations and the Inter-African Bureau of Animal Resources of the Organization of African Unity.

Research topics covered in the four 1992 issues of ILRAD's scientific newsletter, *ILRAD Reports:*

- Transfecting genes to understand the workings of protozoan parasites and the cells of their mammalian hosts in molecular detail.
- New tools for better diagnosis of African trypanosomiasis.
- Clearance of antibody-VSG complexes by trypanosomes.
- The role of T cells in the development of immunity to trypanosomiasis.
- Suppression of the immune system in trypanosomiasis.
- Multi-drug resistant trypanosome populations in cattle.
- Progress towards developing an improved East Coast fever vaccine.
- ILRAD's links with global animal disease research.
- Improved technology for labelling DNA probes.
- Identifying lethal components of the *Theileria* disease complex.
- The role of macrophages in development of anaemia in trypanosomiasis.
- How trypanosomes tolerate drugs that once killed them.
- Making genetic fingerprints of trypanosomes using the RAPD (random amplified polymorphic DNA) method.

LIBRARY

The heart of any program of basic research lies in the publication of its results in internationally recognized and refereed scientific journals.

A major activity of the ILRAD Library is to respond to requests for reprints of staff publications.

ILRAD's publication output this year retained its high standards in both quality and numbers: of the 88 total publications published in 1992, 62 (71%) appeared in refereed scientific journals, 17 in proceedings of international meetings, and 9 in specialized books.

A bibliographic list of the year's publications appears at the end of this annual report. As can be judged by the nature of these publications, ILRAD's research findings are of direct relevance not only to scientists conducting strategic research on specific animal diseases and their control but also to those conducting basic research in a wide variety of biological disciplines.

THE ILRAD LIBRARY provides fundamental support for the institute's research by acquiring, organizing and disseminating information, most of it in the form of printed books, scientific journals and computer databases. The emphasis of the collection is on the livestock diseases ILRAD focuses on, African animal trypanosomiasis and tick-borne diseases, as well as veterinary medicine and the biochemistry, chemotherapy, cytology, epidemiology, genetics, immunology, molecular and cell biology and pathology of these diseases and their causative parasites.

Journals form the main part of the Library's collection. In 1992, the Library subscribed to 162 specialized scientific journals, 25 monographic serials and 15 indexing or abstracting journals. A total of 261 books were received this year, bringing the total book stock to about 4,055 volumes. A *Weekly Alert* newsletter is produced and distributed to staff and other local libraries to highlight important new accessions in the Library.

The Library also introduced access to several international agricultural and biomedical databases stored electronically on CD-ROMs (compact disks-read only memory). These include Current Contents on Disk (Life Sciences: 1991–present), CAB International Abstracts (1984–1991), Medline (1966–present), Science Citation Index, SESAME and Veterinary Science and Animal Health (1973–1991). Use of a local area computer network (LAN) established in 1991 enabled scientists to conduct their own literature searches using office personal computers.

Because the Library's extensive, up-to-date and highly specialized journal collection is unique in Kenya, its services are extended to staff from a variety of other local research institutes and from government departments and universities. In 1992, the Library received 104 reprint titles and supplied over 760 copies of reprints to researchers who requested them. The Library also made thousands of photocopies of journal articles for ILRAD staff and other libraries and undertook over 151 internal and 112 external literature searches for users. Staff helped strengthen the information services of national agricultural research systems through exchange of publications and interlibrary loans and by providing short-term practical training to 15 library students from Kenyan universities and research institutes.

This year the Library borrowed 651 publications from libraries belonging to a cooperative research network in Nairobi, loaned out 759 journals to staff and 189 journals to outsiders and donated over 1,796 duplicate issues of journals and over 214 books to the network. More than half of the literature searches undertaken during the year were conducted for external users from African countries. ILRAD also supplied over 760 reprints or photocopies of scientific papers to scientists from all over the world, notably from India, the USA and countries of sub-Saharan Africa.

RESEARCH SUPPORT

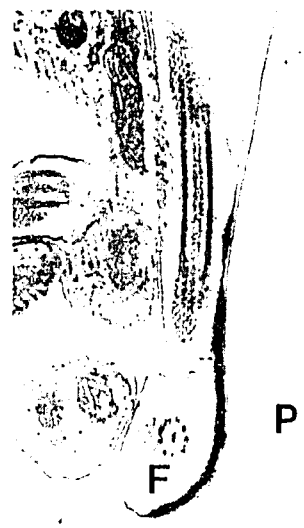
TSETSE UNIT

ILRAD'S TSETSE UNIT establishes and maintains colonies of tsetse flies for research on trypanosome parasites. Trypanosomes normally pass through several stages of their life cycle in the tsetse fly. Although it is possible to maintain trypanosomes *in vitro* and to infect laboratory animals and livestock by injecting parasites into the animals, trypanosomes maintained and transmitted artificially differ from those transmitted naturally through the bite of an infected tsetse fly. Thus, a great deal of the trypanosomiasis research conducted at ILRAD requires trypanosomes that have developed in tsetse flies.

Five tsetse breeding colonies were maintained at ILRAD in 1992. These were *Glossina morsitans centralis*, which originated from mainland Tanzania; two colonies of *G. pallidipes* obtained from different areas of Kenya; and *G. brevipalpis* and *G. longipennis*, also from Kenya.

The colonies were fed five days a week using rabbits. A colony of *G. fuscipes fuscipes*, initiated in January 1992 with 500 wild puparia from Rusinga Island, Kenya, is now in an expanding phase. The five production colonies provided all the tsetse required for trypanosomiasis research at ILRAD in the year. The unit also supplied tsetse puparia to other research groups in Kenya and abroad.

As well as maintaining tsetse colonies, staff members of the unit conduct research on tsetse flies as vectors of trypanosomiasis. Studies were conducted in 1992 to compare the rates at which two Kenyan populations of *G. pallidipes* are infected with *Trypanosoma simiae*: flies obtained from Nguruman, in the Rift Valley, were significantly more susceptible to infection than those from the Shimba Hills, at the coast. This difference in vector competence is likely to be partly responsible for differences in the epidemiology of *simiae*-trypanosomiasis in these two areas.



In this electron micrograph, a trypanosome has anchored its flagellum (F) inside the proboscis (P) of a tsetse fly. The parasite waits here while it matures before it is injected into an animal along with tsetse saliva as the fly feeds on its mammalian host.

Another study revealed that the virulence of *T. simiae* in pigs is not determined, as had been reported, by the species of *Glossina* transmitting the parasite. A study was also conducted to compare the rates at which *G. m. centralis* flies become infected when fed on trypanotolerant African buffalo and N'Dama cattle and trypanosusceptible Boran cattle, all infected with *T. vivax*. Infection rates in the tsetse were significantly lower when the flies were fed on the N'Dama cattle and buffalo than when fed on Boran cattle. Nevertheless, the trypanotolerant buffalo and N'Dama cattle, like the trypanosusceptible Boran cattle, may serve as reservoirs of *T. vivax* infection.

TICK UNIT

THE TICK UNIT supplies scientists with ticks and tick salivary glands infected with the sporozoite form of *Theileria parva*, which is infective for mammals. *Theileria* sporozoites can be obtained only by passage and development of the parasites in tick vectors.

Rhipicephalus appendiculatus is the most important tick species in East Africa, where it is the principal vector of *T. parva*. Stocks of this species maintained at ILRAD include those from Muguga, Kenya; Ol Pejeta, Kenya; McIlwaine, Zimbabwe; Chipata, Zambia; and Entebbe, Uganda. Colonies of other tick species maintained at ILRAD include other *Rhipicephalus* species—*R. evertsi*, *R. pulchellus* and *R. zambeziensis*—as well as *Amblyomma variegatum* and *Amblyomma gemma*, vectors of *Cowdria ruminantium*, which causes heartwater, and two relatively benign *Theileria* species, *T. mutans* and *T. velifera*, as well as *Boophilus decoloratus*, vector of *Babesia* and *Anaplasma*, which cause redwater and gall sickness, respectively.

Research was conducted in the year to optimize the feeding techniques used to produce infected ticks *in vitro*. The first report of feeding ixodid ticks to repletion *in vitro* was made by scientists at the Nairobi-based International Centre of Insect Physiology and Ecology (ICIPE) in 1991. They fed adult *R. appendiculatus* on an artificial Baudrache membrane to which tactile and olfactory stimuli had been added. In collaboration with ICIPE, ILRAD staff this year applied the technique to *R. appendiculatus* nymphs and succeeded in feeding up to 4,000 nymphal ticks on membranes in one experiment. The feeding apparatus was then improved; with further development, it may prove useful for maintaining and infecting ticks with pathogens. In another approach taken at ILRAD, skin membranes prepared from cattle and rabbits were used to feed all instars of *Amblyomma variegatum*. By providing the required stimuli, most species of ixodid ticks can probably be fed on membranes rather than animal hosts, thus saving both time and expense.

A major research effort of the Tick Unit is to determine the factors that influence infection rates in ticks in order to maximize infection levels. Studies were conducted in 1992 to investigate how the nature of cattle infections affect infection rates in ticks. A linear relationship was observed early in the infection of cattle between parasitaemia in the host and infection in ticks. Fifty-eight per cent of tick batches that became replete on days 17 to 19 after infection of the host reached a *T. parva* abundance of 80 infected acini or more per tick—the level required to harvest *T. parva* sporozoites efficiently.

This is a major improvement in tick infection rates: previously, only 5% of ILRAD's tick batches reached such high infection levels. It should now be possible to design a feeding system to produce large numbers of engorged ticks throughout the period in which cattle are most infective for ticks. This in turn should reduce the amount of work and numbers of cattle required to provide a continual supply of highly infected ticks for laboratory studies.

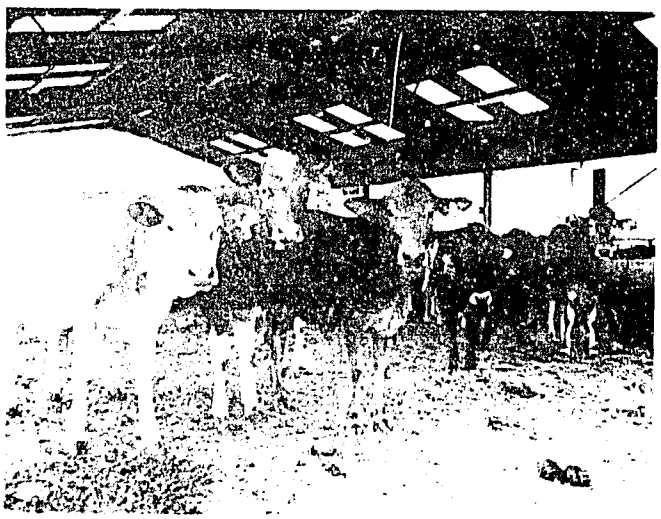
LARGE ANIMAL PRODUCTION

THE LARGE ANIMAL facilities on the ILRAD Farm, located next to ILRAD's laboratory, at Kabete, held about 350 head of cattle and 250 goats during 1992 that were allocated for research projects at ILRAD. Three rooms formerly used for maintaining small animals were converted in 1992 into a fly-proof isolation suite for cattle. A maximum of 16 calves under six months of age can be held in the new facility. The institute's ranch, Kapiti Plains Estate, located about 70 km from Nairobi, carried an average of 2,575 head of cattle during the year. The ranch supplied 385 cattle to the ILRAD Farm and sold 602 cattle to local farmers and butchers. Fewer calves were produced on the ranch this year due to withholding bulls from some breeding herds, which was necessitated by drought: 829 calves were born in 1992 compared with 1,061 in 1991.

ILRAD's embryo transfer program continued to do well this year, with 77 calves born from embryos implanted in 1992: 8 of these were pure N'Dama calves, 14 pure Boran (including four sets of identical twins needed for immunological studies), 14 first-generation N'Dama-Boran crossbreds, and 41 second-generation crossbreds. A total of 259 viable embryos were collected from 68 donor cows in 1992. The majority of these embryos were implanted into foster dams or cryopreserved.

LABORATORY ANIMAL PRODUCTION

THE SMALL ANIMAL UNIT provides ILRAD's research and training programs with regular supplies of mice, rats and rabbits. In 1992, ILRAD continued to be self-sufficient in the production of all of these laboratory animals. To maintain genetic purity, all the major colonies were renewed in 1992 from colonies reared in isolation in the UK. The breeding unit also supplied mice, rats and guinea pigs to other research groups in Kenya, particularly those in university faculties and in departments of the Ministry of Livestock Development.



All the experimental animals at ILRAD are housed and maintained according to international animal welfare conventions.

PUBLICATIONS

All the publications listed below were published in 1992. The numbers in parentheses are ILRAD Library accession numbers.

PUBLICATIONS PRODUCED BY THE INSTITUTE

ILRAD 1991 Annual Report. Nairobi, Kenya: International Labora- tory for Research on Animal Diseases, 84 pp.

ILRAD 1992 Annual Scientific Report. Nairobi, Kenya: International Laboratory for Research on Animal Diseases, 142 pp.

ILRAD Highlights 1992. Nairobi, Kenya: International Laboratory for Research on Animal Diseases, 4 pp.

ILRAD Reports. Nairobi, Kenya: International Laboratory for Research on Animal Diseases, 6 pp. each.

JANUARY ISSUE: *Transfecting Genes* and *New Tools for Better Diagnosis of African Trypanosomiasis.*
APRIL ISSUE: *Do T Cells Help Animals Develop Immunity to Trypanosomiasis?* and *Suppression of the Immune System in Trypanosomiasis.*
JULY ISSUE: *Towards an Improved East Coast Fever Vaccine: Evening the Odds* and *ILRAD's Links with Global Animal Disease Research.*
OCTOBER ISSUE: *How Trypanosomes Tolerate Drugs That Once Killed Them* and *RAPD Fingerprinting of Trypanosomes.*

ILRAD Publications 1991. Nairobi, Kenya: International Laboratory for Research on Animal Diseases, 6 pp.

ILRAD Research Updates. Nairobi, Kenya: International Laboratory for Research on Animal Diseases, 1 p. each.

NO. 4, AUGUST: *New Tools for Determining Optimal Livestock Disease Control Strategies for African Farmers.*
NO. 5, OCTOBER: *Mapping the Bovine Genome.*
NO. 6, DECEMBER: *Scientists Complete the First Map of a Protozoan Genome.*

ILRAD Program Plans and Funding Requirements for 1993 (Interim Year). Nairobi, Kenya: International Laboratory for Research on Animal Diseases, 25 pp.

Dolan, T.T. ed. *Recent Developments in the Research and Control of* Theileria annulata: *Proceedings of a Workshop Held at ILRAD, Nairobi, Kenya, 17–19 September 1990.* Nairobi: International Laboratory for Research on Animal Diseases, 125 pp. (1098).

Dolan, T.T. ed. *Recent Developments in the Control of Anaplasmosis, Babesiosis and Cowdriosis: Proceedings of a Workshop Held at ILRAD, Nairobi, Kenya, 13–15 May 1991.* Nairobi: International Laboratory for Research on Animal Diseases, 181 pp. (1234).

JOURNAL ARTICLES, PAPERS IN PROCEEDINGS AND BOOK CHAPTERS WRITTEN BY ILRAD STAFF

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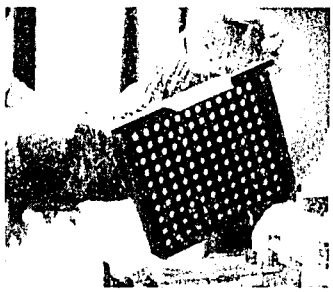
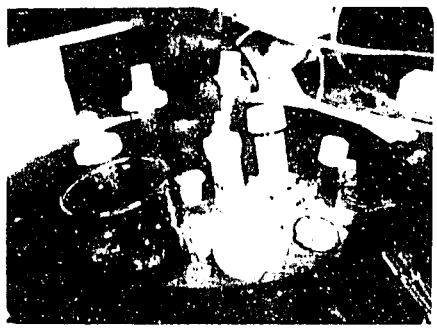
P.A.O. Majiwa
Scientist
N.B. Murphy
Scientist
V. Nene
Scientist
T. Urakawa [3]
Visiting Scientist
R. Pellé
Post-Doctoral Fellow
M. Macklin
Laboratory Superintendent
E. Gobright
Research Associate
N. Doshi
Research Fellow
W. Endege
Research Fellow
M. Hoeve [4]
Research Fellow
H.R. Jamnadass
Research Fellow
R. Janoo
Research Fellow
A. Kairo
Research Fellow
M. Kibe
Research Fellow
G. Ndoutamia
Research Fellow
M. Maina
Laboratory Technician
J. Osaso
Laboratory Technician
P. Pandit
Laboratory Technician
S. Wasike
Laboratory Technician



LAB 3 CELL BIOLOGY

H. Hirumi
Senior Scientist
W.R. Fish
Scientist
R. Kaminsky
Scientist
K. Hirumi
Laboratory Superintendent
W. Kitungu
Research Fellow
N. Wasike
Research Fellow
F. Chuma
Laboratory Technician
C. W. Muriuki
Laboratory Technician
A. M. Muthiani
Laboratory Technician
D. Ndegwa
Laboratory Technician
J.R. Wando
Laboratory Technician

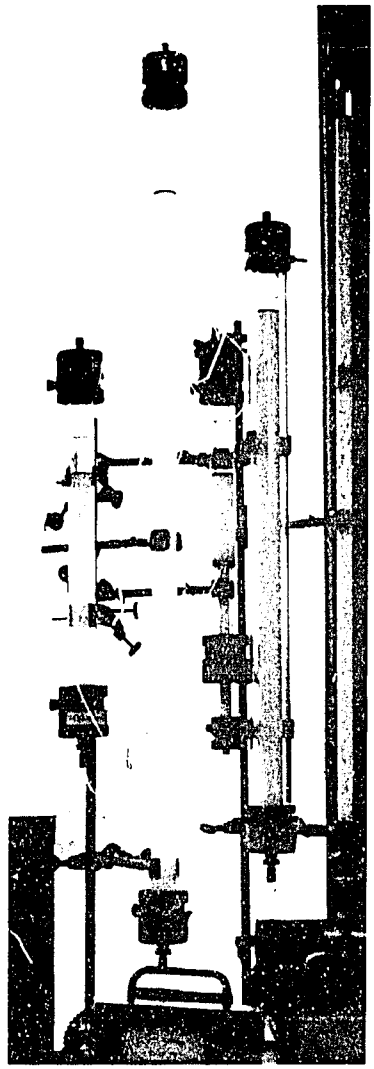


LAB 4 IMMUNOBIOLOGY

D.J.L. Williams
Trypanosomiasis Program Area Leader: Host Resistance
E. Authié [5]
Scientist
L.L. Logan-Henfrey
Scientist
M. Sileghem
Scientist
V.O. Anosa
Visiting Scientist
B. Mertens [6]
Visiting Scientist
J. Naessens [7]
Visiting Scientist
B. Wilkie [8]
Visiting Scientist
A. Andrianarivo
Post-Doctoral Fellow
V. Lutje
Post-Doctoral Fellow
A.E.M. Schutte [9]
Post-Doctoral Fellow
J. Magondu
Laboratory Superintendent: FACS
K.A. Taylor
Laboratory Superintendent
L. Gaidulis
Research Associate
A. Makumyaviri
Senior Research Fellow
A. Boulangé [10]
Research Fellow
B. Buza
Research Fellow
S. Mwangi
Research Fellow
D.C.W. Russo
Research Fellow
H. Suliman
Research Fellow
V. Taiwo
Research Fellow
F. Mucheru
Laboratory Technician
B.G. Muchiri
Laboratory Technician
P. Muiya
Laboratory Technician
D.K. Muteti
Laboratory Technician
J. Nthale
Laboratory Technician
M.O. Opollo
Laboratory Technician
R. Saya
Laboratory Technician

LAB 5 PARASITOLOGY AND EPIDEMIOLOGY OF THEILERIOSIS

T.T. Dolan
Theileriosis Program Head
A.J. Musoke
Theileriosis Program Area Leader: Antigens
S.B. Morzaria
Theileriosis Program Area Leader: Epidemiology
R. Bishop
Scientist
Y. Yagi [11]
Visiting Scientist
J. Syfrig [12]
Post-Doctoral Fellow
P.R. Spooner
Laboratory Superintendent
C. Nkonge
Research Associate
R.A. Skilton
Research Associate
M. Butera
Senior Research Fellow
I. Julla
Research Fellow
E.N. Kimbita
Research Fellow
N. Tabele
Research Fellow
T. Van de Putte [13]
Research Fellow
J.N. Gachanja
Laboratory Technician
L. Gichuru
Laboratory Technician
L.K. Juma
Laboratory Technician
J. Kiarie
Laboratory Technician
D.O. Lugo
Laboratory Technician
T. Ndolo
Laboratory Technician
R. Njamunggeh
Laboratory Technician
S. Njuguna
Laboratory Technician
B. Sohanpal
Laboratory Technician
S. Wanyonyi
Laboratory Technician

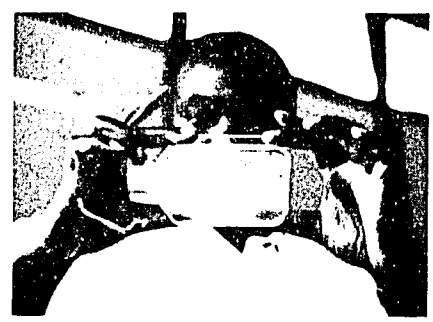


The following countries provided partial support to ILRAD scientists. The numbers are footnotes appended to names in this staff list.

1 Canada	11 Japan
2 UK	12 Switzerland
3 Japan	13 Belgium
4 Netherlands	14 Japan
5 France	15 Belgium
6 Belgium	16 Japan
7 Belgium	17 USA
8 Canada	18 USA
9 Netherlands	19 Canada
10 France	20 Netherlands

LAB 6 CELLULAR IMMUNOLOGY AND PATHOLOGY

D.J. McKeever
Theileriosis Program Area Leader: Vaccine Developent
P.G. Toye
Scientist
M. Kodana [14]
Visiting Scientist
C. Daubenberger
Post-Doctoral Fellow
M.G. Juarrero
Post-Doctoral Fellow
E.L.N. Taracha
Post-Doctoral Fellow
J.-P. Scheerlinck [15]
Post-Doctoral Fellow
G. Lamb
Laboratory Superintendent
R. Kennedy
Research Associate
N.D. MacHugh
Research Associate
A. Diaite
Research Fellow
H. Pereira
Research Fellow
E.O. Awino
Laboratory Technician
S.A. Kaushal
Laboratory Technician
J.K. Mburu
Laboratory Technician
F. Mbwika
Laboratory Technician
D.N. Ngugi
Laboratory Technician
J.K. Nyanjui
Laboratory Technician
M. Waithaka
Laboratory Technician



LAB 7 PARASITOLOGY AND EPIDEMIOLOGY OF TRYPANOSOMIASIS

A.J. Teale
Trypanosomiasis Program Head
S.J. Kemp
Scientist
P. Lessard
Scientist
R.A. Masake
Scientist
L. Brezinsky
Post-Doctoral Fellow
S.N. Minja
Laboratory Superintendent
J.M. Katende
Research Associate
S.G.A. Leak
Research Associate
M. Agaba
Research Fellow
K. Bosompen
Research Fellow
A. Jaye
Research Fellow
D. Kihurani
Research Fellow
R. Suzuki [16]
Research Fellow
E. Waithanji
Research Fellow
H. Gathuo
Laboratory Technician
J. Makau
Laboratory Technician
J. Mwakaya
Laboratory Technician
J.E. Ngatti
Laboratory Technician
J.T. Njuguna
Laboratory Technician
M. Omenya
Laboratory Technician
J.A. Sore
Laboratory Technician
J.M. Wambugu
Laboratory Technician

LAB 8 EPIDEMIOLOGY AND SOCIOECONOMICS

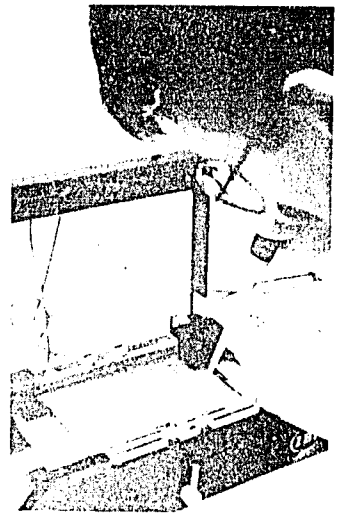
B.D. Perry
Epidemiology and Socio-economics Program Head
J.J. Curry
Scientist
A.W. Mukhebi
Scientist
J. Ellis [17]
Visiting Scientist
R. Reid [18]
Post-Doctoral Fellow
R.L. Kruska
GIS Analyst/ Laboratory Superintendent
I. Amadou
Research Fellow
H. Nyangito
Research Fellow
C. O'Callaghan [19]
Research Fellow
H. Ochanda
Research Fellow

ELECTRON MICROSCOPY

M.K. Shaw
Unit Head
L.G. Tilney
Visiting Scientist
C. Wells
Laboratory Superintendent

TSETSE LABORATORY

S.K. Moloo
Unit Head
N.N. Gitire
Laboratory Technician
F. Kaaria
Laboratory Technician
J. Kabata
Laboratory Technician
N. Kuria
Laboratory Technician
C. Lugonzo
Laboratory Technician
I. Okumu
Laboratory Technician



ICE LABORATORY

A.S. Young
Unit Head
F.N. Mwakima
Laboratory Superintendent
A. Djiteye
Research Fellow
M. Baya
Laboratory Technician
S. Mwaura
Laboratory Technician
G. Njihia
Laboratory Technician
P. Theuri
Laboratory Technician
M. Waithaka
Laboratory Technician

CENTRAL CORE UNIT

C. Hinson
Laboratory Manager

EXPERIMENTAL ANIMAL UNITS

R.C. King
Unit Head
J.D. Kennedy
Scientist/Veterinarian
Vacant
Farm Manager/Kabete
P.K. Ng'eno
Ranch Manager/ Kapiti Plains Estate

COOPERATIVE PROGRAMS, TRAINING & INFORMATION DEPARTMENT

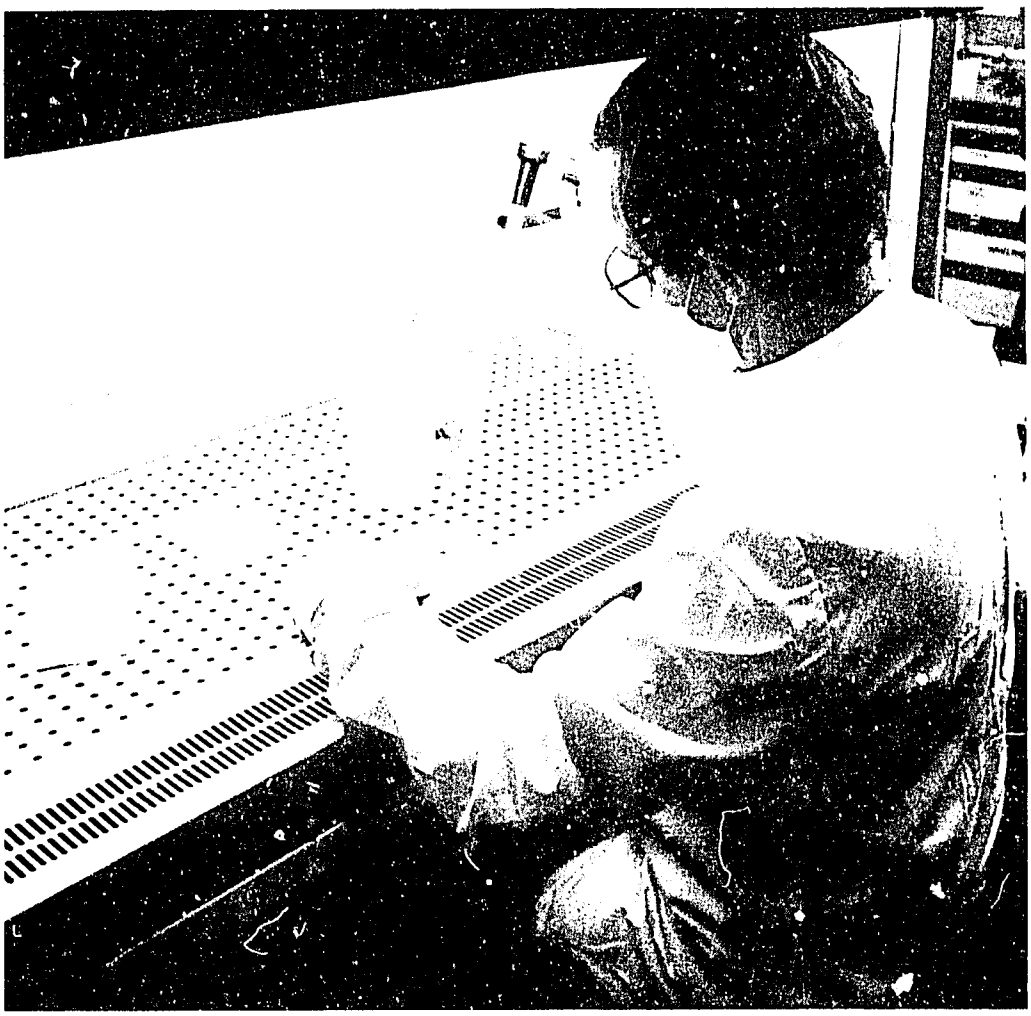
M. Touré
Department Head
R.M. Eley
Education Officer
S. MacMillan
Science Writer
W. Umbima
Librarian
D. Elsworth
Scientific Photographer/ Graphic Arts Supervisor
K.N. Nguli
Assistant Training Officer

BIOSTATISTICS AND COMPUTING SERVICES UNIT

J.R. Scott
Research Associate

WILDLIFE DISEASES PROJECT

J.G. Grootenhuis [20]
Senior Scientist



FINANCIAL STATEMENTS

Certified Public Accountants

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Cables PRICEWATER

Price Waterhouse

REPORT TO THE DIRECTORS OF THE INTERNATIONAL LABORATORY FOR RESEARCH ON ANIMAL DISEASES (ILRAD)

We have reviewed the abridged financial statements set out in Tables A1 to A4, which contain information extracted from the accounting records of ILRAD for the years ended 31 December 1991 and 1992.

We confirm that the information set out in the abridged financial statements is consistent with that contained in the audited financial statements for the years ended 31 December 1991 and 1992, on which we expressed an unqualified opinion.

Price Waterhouse

PRICE WATERHOUSE
Certified Public Accountants

1 November 1993

Table A1. Summary costs by program and activity (US$ thousands)

COSTS OF OPERATIONS	1992	1991
Research		
Parasitology—Trypanosomiasis	596	734
Biochemistry	706	767
Cell Biology	429	564
Immunobiology	814	638
Parasitology—Theileriosis	823	752
Pathology	675	465
Immunoparasitology	773	854
Tsetse Laboratory	236	235
Tick Laboratory	213	203
Electron Microscopy	152	162
Epidemiology and Socioeconomics	421	439
Research subtotals	5,838	5,813
Research Support		
Research Support	512	706
Farm Animal Production	431	509
Laboratory Animal Production	155	156
Radioisotope and Central Core Services	674	433
Research Support subtotals	1,772	1,804
Training and Conferences	748	1,267
Library and Information Services	459	642
Administration		
Board of Directors	178	152
Office of the Director General	795	599
Finance	364	379
Personnel	130	120
Purchasing	484	509
Administration subtotals	1,951	1,759
General Operations		
Engineering	889	863
Transport	210	187
Services	329	342
Food and Housing	4	(18)
Stores	57	55
General Operations subtotals	1,489	1,429
Quinquennial Review Costs	324	—
TOTAL OPERATIONS BEFORE DEPRECIATION	12,581	12,714
DEPRECIATION	1,146	1,157
TOTAL OPERATIONS AFTER DEPRECIATION	**13,727**	**13,871**

Table A2. Summary of core operating funds from donors (US$ thousands)

UNRESTRICTED AND RESTRICTED FUNDS FROM DONORS	1992	1991
Unrestricted Funds from Donors		
World Bank	3,240	2,524
United States Agency for International Development	1,975	1,900
United Kingdom	1,132	1,322
Canadian International Development Agency	839	964
Switzerland	670	792
BMZ Germany	664	872
Sweden	544	536
Japan	544	473
Norway	336	305
Belgium	290	293
Denmark	174	174
Netherlands	147	491
France	120	197
Italy	74	80
Finland	49	278
African Development Bank	—	250
India	—	25
Unrestricted Funds from Donors subtotals	10,798	11,476
Restricted Funds from Donors		
United Nations Development Programme	932	899
Italy	500	350
Belgium	290	293
Japan	125	150
Australia	116	77
Rockefeller Foundation	—	175
Restricted Funds from Donors subtotals	1,963	1,944
TOTAL UNRESTRICTED AND RESTRICTED FUNDS FROM DONORS	**12,761**	**13,420**

Table A3. Summary of sources and application of funds (US$ thousands)

	1992	1991
SOURCES OF FUNDS		
Core Operating Funds		
Unrestricted Funds from Donors	10,798	11,476
Restricted Funds from Donors	1,963	1,944
Earned Income Applied in the Year	1,059	359
Exchange (Loss)/Gain on Donations	(253)	100
Unexpended Balance from Previous Year	453	500
TOTAL SOURCES	**14,020**	**14,379**
APPLICATIONS OF FUNDS		
Core Operations before Depreciation	12,581	12,714
Capital Expenditure	588	236
Transfer to Working Funds	—	—
Transfer to Capital Replacement Fund	558	976
Unexpended Balance Carried Forward	293	453
TOTAL APPLICATIONS	**14,020**	**14,379**

Table A4. Balance sheet as at 31 December 1992 (US$ thousands)

ASSETS	1992	1991
Fixed Assets		
Land and Buildings	7,608	7,961
Research & Operating Equipment	2,484	2,666
Other Assets	371	456
Subsidiary Company		
Investment	1,786	1,786
Long-Term Loan	30	30
Fixed Assets subtotal	12,279	12,899
Net Current Assets	5,074	4,634
TOTAL ASSETS EMPLOYED	**17,353**	**17,533**

FUND BALANCES		
Capital Fund	12,279	12,899
Working Capital	2,813	2,813
Unrestricted Core Surplus	293	453
Revolving Fund	100	100
Capital Replacement Fund	1,868	1,268
TOTAL FUNDS	**17,353**	**17,533**