TDR—the Special Programme for Research and Training in Tropical Diseases—is a coordinated attack by the world’s scientific community upon diseases of the tropics, and is jointly sponsored by the UN Development Programme, the World Bank and WHO. TDR stimulates and supports research on new and improved methods to control six major diseases (malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis and leprosy) by funding research projects world-wide, and by giving special assistance to research institutions in tropical countries.
Towards a leprosy vaccine
by Barry R. Bloom

It began in a most inauspicious way, at a meeting in New Delhi in 1972. Although the leprosy bacillus was the first micro-organism associated with a human disease, it has remained the only major human pathogen that has not been cultivated in the laboratory. As a consequence, biomedical research into the causes, treatment and prevention of leprosy has remained far behind that of most other diseases.

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The meeting in India on the Immunology of Leprosy brought together, under WHO auspices, several distinguished leprologists steeped in knowledge of the disease, and a small band of immunologists who knew very little about leprosy. In addition, there was a young Norwegian, working in the Hansen Research Institute for leprosy in Ethiopia, Dr Tore Godal (later to become the first chairman of the IMMLEP Steering Committee), who was uniquely able to bridge the gap between the science of immunology and the disease.

For me the meeting was electrifying. For four days the immunologists fired questions at the leprologists about the nature and course of leprosy and the response to treatment of patients with the disease, and the experts provided many answers from their practical experience. As a result, the meeting formulated an overall immunological picture of leprosy, and generated two WHO Technical Reports fancifully outlining a great many scientific protocols that could perhaps provide important insights into the disease process, and provide information as to whether development of a vaccine was feasible. They were fanciful because there was very little support for embarking on such work. Yet they were published by WHO in the hope that investigators somewhere might regard some of them as worth pursuing.

Because the causative micro-organism has not been cultivated in the test-tube, it is difficult to study the organism and immune response to it. A key breakthrough made it feasible to begin a serious study of immunity to leprosy, namely the discovery that the leprosy bacillus could be grown in very large numbers in the nine-banded armadillo. But the number of scientists with relevant but specialised expertise was very limited. The solution, conceived of by Tore Godal and initially supported by the Norwegian Government, was to develop a small research programme under the auspices of WHO which would solicit cooperation from scientists with different kinds of expertise from many countries and direct it towards leprosy research. One initial aim was to provide leprosy bacilli to qualified scientists all around the world in order to make research possible. Thus, in 1975, began the programme on the immunology of leprosy—IMMLEP.

We had some funds in 1975, we had protocols and plans, but we had no leprosy bacilli, since it requires two to three years to harvest enough from the armadillo to begin research. At the very first meeting in Geneva, the two groups which had established the feasibility of growing large amounts of bacilli in the armadillo, and which had been keen scientific rivals, both gener-
Towards a leprosy vaccine

ously volunteered to provide a large part of their accumulated stocks of the leprosy bacillus to IMMLEP. So now we could study its chemical composition and the nature of the immune responses of animals to it.

A remarkable network developed. Armadillos in Louisiana in the United States were inoculated with live leprosy bacilli from patients in India and South America. The tissues were harvested and sent to London where a group developed great expertise in separating and purifying the bacilli free of contaminating host tissues. The organisms were then sent to Sweden and Norway for an analysis of the number and kind of antigens which they possessed. From there they were sent to New York and Atlanta, Georgia, where the killed purified organisms could be tested for the ability to engender the kind of immune response in guinea pigs and mice which is thought to be associated with protection. In the competitive world of science, the degree of exchange of materials and information as well as critical analysis and encouragement was truly extraordinary.

Thus was developed a “laboratory without walls,” from which rapidly emerged a strategic plan for developing diagnostic tests and possible vaccines. Further, there was a commitment to add many more scientists whose expertise might advance the cause of leprosy research.

IMMLEP, in a fashion unsuspected in 1972, became the prototype for the entire Special Programme for Research and Training in Tropical Diseases (TDR). There is a Steering Committee composed of scientists chosen for their special expertise; for example, in the clinical aspects of the disease, its epidemiology, understanding of bacterial biochemistry, immunology, or animal models. This group came together once or twice each year to evaluate the status of leprosy research, identify needs and draw up plans for future actions. But the continuity and overseeing of this programme depend crucially on the support and commitment of WHO’s disease units and the TDR Secretariat.

How does it work?

Research proposals submitted by scientists all over the world are evaluated by every member of the Steering Committee, and a secret ballot is taken on scientific merit and relevance to the strategic plan of each proposal. Of those grants approved on scientific grounds, funding occurs by order of scientific priority, until the limited funds available are exhausted. We are all well aware that the funds actually allocated by TDR represent only a fraction of those required to get the work done, and there is little question that all the scientists in the programme have to beg, borrow or steal additional funds to enable them to fulfil their scientific obligations. Yet they do it, and progress has been enormously rapid.

The IMMLEP Steering Committee has established another unusual scientific policy. All unique reagents produced with support from WHO go into an IMMLEP “bank”—bacilli, skin test antigens, monoclonal antibodies, and most recently genes of Mycobacterium leprae. The material in the “bank,” when available, is distributed without charge to qualified investigators all over the world.

How well are we doing in leprosy? Two of the overall aims have already been achieved, namely to attract to the field of leprosy research some of the most able scientists and to apply the most modern techniques of biomedical research, including monoclonal antibodies and recombinant DNA technology, to the problem of leprosy.

Our sister panel, on the chemotherapy of leprosy (THELEP), identified the emergence of dapsone-resistant leprosy bacilli as an important and threatening problem. It recommended combined chemotherapy to minimise the possibility of organisms emerging that would be resistant to drugs, and it is currently testing a variety of drug combinations to find the most effective, least expensive mode of treatment.

As far as the immunology of leprosy goes, there are prospects for simple, new diagnostic techniques, perhaps using only finger-prick blood, which could indicate which individuals in any population have recently been infected with the leprosy bacillus. It would have been inconceivable ten years ago that WHO is now testing a candidate leprosy vaccine in a large study in Venezuela to see if it can prevent leprosy in a population of known contacts of leprosy patients, who are at higher risk of contracting the disease. The vaccine developed by Dr J. Convit in Caracas consists of killed purified leprosy bacilli obtained through WHO from the armadillo and mixed with the BCG vaccine used against tuberculosis. Two other exciting vaccine candidates, based on cultivable organisms, have recently been identified by Indian scientists. On the
A little girl receives her dapsone dose. But will the bacillus become dapsone-resistant?

possibility that one or more of these vaccines may be effective, IMMLEP has already begun examining the possibility of using recombinant DNA technology to make a second generation of vaccine for which specific antigens may be introduced into an organism which can be cultivated. We hope this might produce a vaccine much more cheaply than through the production of bacilli from armadillos. No one can guarantee that any or all of this enormous effort will be successful; but if not, it will not be from lack of commitment, imagination or effort.

From ancient times and in virtually every culture, leprosy has evoked singular images of horror and fascination. Fear and stigma have historically been associated with this disease. Will it be possible, through the application of modern scientific approaches, to develop vaccines and diagnostic tests to change social attitudes, so that people will come forward earlier to be treated for their disease or will ultimately agree to be vaccinated to prevent leprosy?

Why is there a general lack of commitment to the concept of international cooperation in health? It is profoundly sad and humiliating for a chairman of the Steering Committee, after successfully recruiting good scientists into the field of leprosy research, to have to tell an increasing number of them that their proposals for research in leprosy have been approved with good priority at the scientific level, but that there are insufficient funds to support the research project. This at a time, when a single jet fighter costs more than the entire WHO Programme for Research and Training in six tropical diseases. Why do the developed countries not make a greater commitment to the present and future health needs of the people of the developing countries?

I am equally perplexed as to why leaders in many developing countries do not place a greater emphasis on the health of their people relative to other priorities.

Finally, why is there so little awareness that prevention of disease, and the research which may be required, can prove infinitely less costly than the expense of treating or suffering the human consequences of disease? It is always easier to seek funds for drugs to treat illnesses than it is for supporting research to develop vaccines that will perhaps prevent disease. It may be worth mentioning that 12 years of operations and research for the eradication of smallpox cost approximately 46 million dollars, and that the United States saves 500 million dollars each year in not having to vaccinate overseas travellers. The analogy with smallpox is germane to leprosy in another sense as well; in both cases, the major source of disease transmission is from man to man. By eliminating transmission from man to man, there is the potential to eliminate the disease from the face of the earth.

Why would any first-rate scientist want to become involved in research on a tropical disease like leprosy? Clearly, anyone interested in fame and glory, or perhaps winning Nobel prizes, could find much easier and more tractable subjects for rapid recognition. Yet with virtually no exceptions, every scientist who has been asked to become involved in research for IMMLEP has agreed to do so. In part, this has to do with the intrinsic fascination and complexity of leprosy as a disease. Partly there is a kind of honour in being asked to participate in a WHO programme. Partly, there is the satisfaction of applying basic scientific knowledge to the very urgent and practical problem of human disease. But mostly, I think the reasons why so many of my colleagues have committed such an enormous part of their lives, and have required sacrifices from their families as well, were best stated over 200 years ago by the English writer John Donne:

“No man is an Island entire of itself; every man is a piece of the Continent, a part of the Main; ... Any man's death diminishes me, because I am involved in Mankind.”
Mefloquine and its allies
by Michel Fernex

Two new antimalarial drugs were registered in 1984. Mefloquine (with the trade name Lariam) and the same generic drug in combination with two others (under the trade name Fansimef) were the end-products of a research project conducted by TDR, research institutions and a Swiss pharmaceutical company.

Fansimef is now being deployed in malaria clinics established in the field in Thailand, in areas where multi-resistant strains of the causative protozoan Plasmodium falciparum have probably reached the highest prevalence in the world. This new drug is a combination of mefloquine—a quinolone-methanol derivative related to quinine, developed primarily by the Walter Reed Army Institute of Research (WRAIR)—and sulfadoxine plus pyrimethamine, two synergistic antimalarials which themselves were introduced as a fixed combination under the trade name of Fansidar in 1970.

Since the late 1960s the malaria situation has deteriorated in most tropical areas. This was not only as a consequence of technical, administrative and financial difficulties encountered, especially in controlling the mosquito vector of malaria, but was also due to the emergence and spreading of strains of P. falciparum resistant to the standard anti-malarials. So in 1975 the TDR programme accorded the highest priority to research in the field of malaria control.

The corresponding Scientific Working Group for the Chemotherapy of Malaria (SWG CHEMAL) decided to coordinate and complete the development of the most active schizontocidal compound against chloroquine-resistant strains of P. falciparum. Discovered in 1971 through a gigantic malaria screening programme of the WRAIR, this drug, mefloquine, proved to be both effective and safe.

At the first meeting of CHEMAL, representatives of the Swiss company Hoffmann-La Roche offered to contribute to the development of mefloquine. The decision was based on two main factors; highly active and analogous compounds developed by Roche were at least one year behind the development of mefloquine; and, being more closely related to quinine, they would probably also have been more difficult to synthesise and more expensive to produce. It was agreed that mefloquine should be developed jointly by CHEMAL, WRAIR and Roche.

The company synthesised large amounts of mefloquine, developed adequate pharmaceutical formulations and completed the necessary preclinical, pharmacological and toxicological studies. Most of the pharmacokinetic studies were performed in Basle, Switzerland, and in the United States. The clinical development was shared by CHEMAL and Roche, both of which drew up suitable clinical research plans for highly qualified investigators to undertake in Asia, Africa and Latin America.

Centres in Ndola (Zambia), Belém (Brazil) and Bangkok (Thailand) sponsored by the TDR programme were able to perform the necessary trials, with 63-day follow-up periods. Further trials are still progressing. In Thailand, the WRAIR carried out one of the most sophisticated and precise field trials ever conducted, using different dosages of mefloquine for the chemosuppression of malaria caused by both the falciparum and vivax parasites.

This study in 600 Thai farmers showed that the drugs were well tolerated and proved the remarkable prophylactic efficacy of mefloquine. Roche has subsequently undertaken therapeutic trials in nine different countries, involving more than 600 patients.

Sooner or later...

Studies in animal models, confirmed by clinical experience, showed that the malaria parasites sooner or later develop resistance to all blood schizontocides. Resistance to mefloquine itself was easy to induce in rodent malaria, and in human malaria has been observed in parts of Asia and in Tanzania.

Two years ago, WHO decided that, in order to protect populations against the development of mefloquine-resistant parasites, it was important for the drug to be introduced in a rational and deliberate manner. Appropriate precautionary measures included the development of mefloquine combinations.

Experimental work indicated that simultaneous administration of mefloquine, sulfadoxine and pyrimethamine delayed considerably both the time of emergence and the level of resistance to all three combination partners in the experimental models. Furthermore, there is an additive anti-malarial effect among the components. Fansidar was found to be the most appropriate partner for mefloquine because all three compounds remain in the blood for long periods in con-
The face of malaria. A Mexican woman shakes with the all too familiar fever.
Photo WHO/P. Larsen

Mosquito vector of malaria. Original drawing — and those on pages 10, 14, 19 and 22 — by Jacqueline Bradshaw-Price.

Below: No transport is scorned by the spraying teams battling against mosquito larvae.
Photo WHO/P. Sharma

centrations sufficient to destroy the parasites.

The development of the combination is a triumph both for the preclinical work and for the complicated pharmacokinetic studies which were needed to detect any negative interference regarding absorption, elimination, metabolism, activity or toxicity in different animal species and, finally, in man.

Radical cure

Single doses of two to three tablets of the triple combination achieved a radical cure of falciparum malaria in more than 95 per cent of adult patients from several tropical areas. Consequently, the dose proved more acceptable and more easily tolerated. One tablet contains 250 mg of mefloquine, 500 mg of sulfadoxine and 25 mg of pyrimethamine.

This new anti-malaria drug has been deployed in Thailand since early 1984, and is widely used in hospitals and in the decentralised malaria clinics of that country. The drug constitutes a new tool for controlling malaria, as a complement to other control measures.

So as to avoid misuse of this new drug, and in an attempt to delay the emergence of resistance to mefloquine, CHEMAL has recommended guidelines for its future deployment, and WHO's specialists have prepared recommendations as to where and how the drug should be introduced in endemic areas.

The triple combination Fansimef will be launched in countries where chloroquine resistance is a problem. However, it will not be distributed through pharmacies but only through channels designated by the national health authorities, for instance through hospitals and malaria clinics or bodies responsible for national malaria control programmes. As a rule, the drug will be used for therapy, but it may be associated with a single dose of primaquine to prevent transmission. The Swiss company has accepted these unusual restrictions in order to protect this anti-malarial compound, which is considered an essential weapon against malaria for many tropical countries.
The Danish connection

by Inge Jespersen

Denmark has been actively involved in WHO's Special Programme for Research and Training in Tropical Diseases since the programme started in 1975. It has been one of the major contributors to the programme's financial resources, and since the beginning has been a member of the Joint Coordinating Board, the programme's highest decision-making body.

Why should a small country with no special experience in tropical diseases support this programme in such a substantial way? This can be seen as indicating the Government's appreciation of the very thorough planning and efficient administrative and technical structures of the Special Programme. The Memorandum of Understanding in 1978 endorsed that appreciation.

In addition, it was felt that the goal of controlling the six diseases which the programme covers was not too ambitious, yet was a very important step towards solving some of the health problems in developing countries. While WHO's overall objective of Health for all by the year 2000 is much more ambitious and depends heavily on general development of the economic and educational status of different countries, Denmark felt that if a major impact could be made in the field of the six main tropical diseases, then an important part of the overall goal would be reached.

To start the ball rolling, Denmark decided to contribute a substantial amount of money at the beginning of the programme in the hope that, when it was on its way, other contributors would be encouraged to join in. Then perhaps, after some time, Denmark could transfer some of the resources from this programme towards helping to initiate other programmes of WHO.

This hope has been fulfilled only to some extent. New donors have joined in the support of the programme. But as a result of the programme's success—that is to say, in starting more and more research, in creating opportunities for the development of new technologies and in supporting the actual development of dozens of potential new tools for the control of the six diseases—there is a growing need for funds. This is a natural and positive development, not least because much of the new research these days is taking place in the developing countries themselves.

Many of the old research institutions in industrialised countries have traditionally been the ones who have investigated tropical diseases. But it is reasonable that today much of this research should be carried out in the areas suffering from these diseases.

On the other hand, it is also extremely encouraging that many more scientists in countries outside the tropical area are now interested in, and actively participating in, research concerning many aspects of tropical diseases. This is one of the signs that the whole world these days recognises a mutual interest and common responsibility for conditions in other countries.

In Denmark, there has been an increasing amount of work done, especially in schistosomiasis and malaria research. Several Danish scientists have participated in workshops and technical meetings sponsored by TDR, including those of the steering committees which manage the activities of different Scientific Working Groups. Denmark also has two members on the Scientific and Technical Advisory Committee which currently reviews and evaluates the different activities of the programme and makes recommendations to the Joint Coordinating Board. The many scientific publications produced under the umbrella of the Special Programme have increased the Danish public's interest in tropical diseases. The Society of Tropical Medicine has increased its memberships, and more doctors and nurses are becoming interested in post-graduate education in this field. The TDR newsletter and other sources of programme information have greatly helped to promote this interest.

As the main financial contributor to TDR, Denmark has, of course, closely followed the results of various evaluations of the Programme, and has noticed with satisfaction the very positive reviews. It has also been very satisfactory to note the flexibility with which the WHO Secretariat has responded to the points mentioned in the evaluations whenever a change was recommended, such as the need to keep a steady turnover of the members of the Scientific Working Group steering committees or to increase the percentage of resources going to research institutions in the developing countries.

This is not to say that the programme cannot still improve in certain areas. The Joint Coordinating Board has repeatedly stressed the need for more research in the social and economic aspects of the diseases and much more on-the-spot field research is needed. We must hope that a response will come from the developing countries themselves to these needs, and it is encouraging to observe the experience in these and other fields reported by the very efficient and distinguished Thai researchers at the session of the Joint Coordinating Board in Bangkok in 1984. It is also very encouraging to be able to anticipate a leprosy vaccine in the not-too-distant future and, let us hope, a vaccine against malaria—one of the single most damaging diseases in the world.
Denmark is satisfied that WHO is increasingly able to collaborate effectively with the pharmaceutical industry. New technologies emerging from laboratories in the developed world must be so deployed that the cost of scientific progress does not prove prohibitive for the poorer populations. As the work develops and the network of scientific collaboration extends to cover more and more countries, it is obvious that tasks of administration and coordination will become more difficult. So far it seems that the management structure established by WHO is well able to cope with this expansion.

What Denmark would like to see is more countries contributing financially to this very important Programme, whose activities should not be held up just as it is gathering momentum and bringing important results to light. It is a proof of the programme's efficiency that many more diagnostic tools for controlling these diseases and many more treatment methods have been developed more rapidly and at lower cost that was ever foreseen. This ought to increase the obligation of potential donors to ensure that this "snowball effect" is not wasted.

My own view is that it would perhaps be better to concentrate on a programme as successful as TDR instead of starting out on a number of ventures of unknown quality. But this, of course, must remain a question of priorities both within and outside WHO.
From the outset of the Special Programme for Research and Training in Tropical Diseases (TDR), it was evident that the research institutions of the countries where these diseases are endemic must be fully involved. Moreover, even if the new drugs, vaccines or diagnostic methods were mainly developed in industrialised countries, they would have to be deployed and put to the test where the diseases occur.

Alongside the various Scientific Working Groups (SWGs), the Research Strengthening Group (RSG) was therefore charged with the job of strengthening selected research institutions in the Third World. Unlike the SWGs, which could adopt long-tested models from many research grant-awarding bodies, the RSG was venturing into unexplored territory and had to develop its policy and procedures from scratch.

From the beginning it recognised that the time scale of institution-strengthening demanded a perspective of at least 20 years. It decided to strengthen existing institutions (of which there were many), not to create new ones. And it chose as the keynotes of its activities: to strive to make its contributions to strengthening institutions self-sustaining; to help institutions to become self-reliant - that is, capable of exercising independent judgment about problems and solutions, and of taking appropriate action through making optimum use of available resources; to encourage a network of collaboration between institutions throughout the world in research and training; to identify potential leaders of research, providing them with appropriate and flexible training and support, and ensuring that they would have satisfactory careers; to consider the needs of an institution broadly and flexibly, particularly as regards needs unlikely to be met from other sources; to use its limited funds as "seed-money" whenever possible by maximising collaboration with all other available sources of research funding.

The vast majority of Third World research institutions are dependent for core funding on their governments, whose continuing interest and support are vital to their long-term success. Thus governments should be involved in the negotiation of long-term support and must be persuaded to under-

Bloodsucking bug which transmits Chagas' disease.

...take the payments of such recurrent elements as salaries and local research expenses, as well as the maintenance costs of capital items provided. Institutions must make every effort to ensure that their governments can perceive the value of their research and benefit from its implementation. Fruitful relationships must therefore be developed with national research councils (or similar bodies) and with disease control organizations. Efforts are also made to strengthen such councils by offering to their staffs opportunities for training and for gaining experience elsewhere.

Not all institutions require, or can justify, long-term support; provision is therefore made for capital grants and shorter-term support. In order to free money for the support of further institutions, long-term support grants are limited (at least in the first instance) to five years.

Since few, if any, institutions will be able to sustain an effective volume of research based solely on funds available from their governments, they have to be able to seek and obtain research grants from wherever they are available. Indeed, an important index of success will be their ability to do so. Their research plans are judged by their appropriateness to the overall TDR programme, by the extent to which they exploit unique opportunities for research, and by their feasibility in the light of the intellectual and physical resources available.

The RSG collaborates with SWGs to identify fruitful research projects which they could support. Small research grants are available for the early stages of research, and so are re-entry grants to help trainees who have returned to their institutions to demonstrate their ability to do research.

The strategy for selecting institutions aims at a geographical network which will be representative of the distribution of the six diseases and of their different epidemiological/ecological patterns; it must also meet the long-term needs of the SWGs. However the RSG decided from the outset that the most effective way to proceed would be, first, to support mainly those institutions which were already engaged in tropical disease research and appeared likely to achieve self-reliance relatively quickly, and then to charge them with the responsibility of helping to strengthen neighbouring institutions.
Research Strengthening Group

Examples of institutions where long-term support programmes have been completed include FIOCRUZ (Rio de Janeiro), which has doubled the number of active research projects on Chagas' disease and leishmaniasis (some in collaboration with a national disease control organization, others with institutions elsewhere). The number of Brazilian scientists involved has increased from three to ten, and technicians from six to 14. The Faculty of Tropical Medicine at Mahidol University, Bangkok, was strengthened to tackle epidemiological and socio-economic aspects, particularly of malaria. Eight scientists have been trained and Thai staff numbering 16 in all have been recruited; many of them are now paid from local sources. And in Nairobi, the Clinical Research Centre has increased its complement of Kenyan scientists from six to 19 (11 of them trained by the Programme), and has published 37 papers in scientific journals over the past three years.

The RSG regards research training as the keystone of institutional strengthening. During an initial period, applicants for training fellowships were considered on individual merit and on the resources of their institutions to support their future research. Now institutions are required to submit nominations for training fellowships in the context of staff development plans which have already been approved by TDR.

Institutions are also actively encouraged to train and develop supporting staff of all sorts—particularly those required to maintain scientific equipment—and, when appropriate, training is made available in other (particularly neighbouring) developing countries. The proportion of such training has steadily increased as the Programme advanced, and between 1976 and 1984 represents 22 per cent of all training grants provided. The RSG also provides assistance in establishing new training courses at appropriate Third World institutions in subjects where the numbers of trained personnel are inadequate.

The RSG has undertaken a serious evaluation of its activities. The first step was to introduce self-evaluation into the institutions being strengthened, with the principal objectives of generating self-criticism within them and providing them with data for future planning. Internal evaluators selected by the institutions are provided with training. External evaluation is made annually by matching progress reports against approved plans, the funding of long-term support being reviewed annually. At longer intervals there are visits from the Secretariat.

Some lessons can already be drawn. Firstly, successful strengthening depends most on stable, strong and intelligent leadership which recognises the need for effective inter-institutional collaboration, not only within the TDR network, but also within the country and the Region, and particularly with relevant disease control organizations. Next in importance, whether in research or the development of training courses, is the creation of a viable mass of research or teaching staff of quality, with good interdisciplinary collaboration so that the many facets of the diseases can be taken into account in developing effective means for their cure and control.

At this still relatively early stage of the RSG programme, it has had more successes than failures. Provided that its activities can be maintained, there is reason for considerable optimism that at least a major part of its objectives can successfully be accomplished.
Malaria has plagued mankind since prehistoric times, and continues to hinder social and economic progress in the developing countries. In 1982, more than six million cases of malaria were reported from around the world.

The Shell Film Unit, with the technical cooperation of WHO, has just released a film on this important subject.

What is malaria? Malaria is a very widespread and debilitating disease which particularly affects the rural areas of tropical countries and is a common cause of death, especially among children. It is normally carried from person to person by a mosquito. There are over 2000 different kinds of mosquitoes but only about 60 can carry malaria. Immunity can build up after long exposure to the infection but this is a slow process and is seldom totally complete.

It was hoped at one time to eradicate malaria altogether, and large areas of the globe were cleared of the disease through the use of DDT against mosquitoes. But now, malaria is returning to many of them, and in some areas mosquitoes have become resistant to DDT and the parasites are becoming resistant to the drugs that are being used.

The film presents important aspects of the malaria problem and its control in Sudan, India and Thailand. The Blue Nile Health Project in the Sudan has developed a self-help programme to improve health education and facilitate community participation. Village committees are involved and the people are taught how malaria is transmitted and what part they can play in breaking the cycle of infection as a contribution to the regular control measures applied by the project. They are encouraged to protect themselves against the mosquitoes, by putting gauze at the windows of their homes and using bed nets. The behaviour of the mosquitoes is constantly assessed and the flow of water in the irrigation canals controlled so that the mosquito larvae are not given time to hatch before the water they are in is flushed out. The ditches also have to be kept clear of weeds, and this is often done by hand. Sometimes a fish is used that eats enormous quantities of weeds.

Controlling malaria in cities such as Bombay is another problem. Hundreds of new families arrive daily, many of them carrying malaria. The mosquitoes breed in any fresh water they can find. In Bombay, specially trained pest control officers check every potential mosquito breeding place. Water tanks are inspected regularly and no new building can be connected to the water mains unless the water tanks meet the proper requirements. Clinics are set up all over the city to give treatment to patients who develop fever. Blood tests are made and every care is taken to avoid the outbreak of an epidemic.

Thailand has been battling against malaria for the last fifty years. Considerable progress was achieved, but now malaria is on the rise again in some parts of the country, and resistance to antimalarial drugs represents a serious problem. Improvements in communication and transport have, ironically, aggravated the situation, and infected people now travel easily, bringing malaria with them. Isolated groups of people such as gem miners and rubber tappers are particularly vulnerable. A network of clinics has been set up by the public health service where diagnosis and treatment is free. The Ministry of Public Health encourages communities to help themselves. In some areas, villages have established their own clinics. Volunteers are trained by the health services to take blood samples and give treatment. Villagers, trained and supervised, are also participating in the spraying of their homes.

The constant fight against malaria must go on since eradication will not be possible in the foreseeable future. New tools are being developed, and there is much hope of a vaccine, but the application of this or any other tool requires that each country should have the political will, a well-trained staff, and the economic resources to keep people healthy.

The film lasts for 29 minutes and is available in 16 mm and 35 mm colour. Videocassettes on VHS, Betamax, JVC and U-matic can also be supplied. The film will be produced in English, French, Arabic, Russian, Spanish and Chinese versions and copies can be obtained on request from Shell Centres worldwide. A booklet has been produced in support of the film.

World Health, May 1985
On this page we offer a sampling of the publications produced by or with the support of TDR.

**Malaria**
- Applied Field Research in Malaria in Africa. 1983. (English only).

**Schistosomiasis**

**Filariais**

**African Trypanosomiasis**

**Chagas’ Disease**

**Leishmaniases**

**Leprosy**
- Protocol for a Trial to Determine the Capacity of Several Vaccines to Produce Skin-Test Reactivity to a Soluble M. leprae Antigen in Treated Smear-Negative Patients with Lepromatous Leprosy. 1983. (English only).

**Vector Biology and Control**

**Epidemiology**

**Social and Economic Research**

**Science at Work**
- This brief description—based on Special Programme reports and on reports of scientists doing research under the auspices of the Programme—describes the origins, objectives, modus operandi, and achievements of the Special Programme, from its inception to the end of 1982.

**BROCHURES:**
- Venture for Health
- With the exception noted below*: all these publications are available from the Special Programme and briefly describes progress made on tropical diseases. It also includes a special form with which readers can ask to receive Scientific Working group reports regularly.

**TROPICAL DISEASES RESEARCH SERIES:**

**QUARTERLY BIBLIOGRAPHY OF MAJOR TROPICAL DISEASES:**
- Vol. 7, No. 4, Fourth Quarter 1984. The result of collaboration between the US National Library of Medicine (NLM) and TDR. (English only).

**NEWSLETTER:**
- The Newsletter informs scientists of the latest documentation and publications available from the Special Programme and briefly describes progress made on tropical diseases. It also includes a special form with which readers can ask to receive Scientific Working group reports regularly.

**MANUAL:**
- Genes and Antigens of Parasites: This practical manual of over 30 modern molecular biology techniques is based on the international laboratory course held in Rio de Janeiro in 1983, sponsored by TDR. (English only).
- With the exception noted below*: all these publications are available from: The Office of the Director, Special Programme for Research and Training in Tropical Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

*Scientists not in tropical countries should request copies of the Tropical Diseases Research Series directly from the publisher, Schwabe AG, Basel, Switzerland.
We at The World Bank are delighted to be co-sponsors, with the World Health Organization and the United Nations Development Programme, of the Special Programme for Research and Training in Tropical Diseases (TDR). TDR’s goal of finding effective tools to control the six major tropical diseases represents an important element in the Bank’s efforts to promote social and economic development in the Third World. We believe that the toll exacted by tropical diseases in suffering and lost production is a key constraint in our efforts to spur economic growth and improve human welfare.

TDR has a solid record of accomplishment in promoting, catalysing and supporting the scientific advances that must form the basis for control of the six diseases. It has succeeded in its efforts to harness the talents of outstanding scientists around the world to the vast potential for new breakthroughs provided by recent advances in biotechnology. TDR has also succeeded already in making available badly-needed improvements in drugs and diagnostic techniques.

We are confident that the Programme will continue to provide a steady stream of new weapons—vaccines, drugs, diagnostic methods and new control measures—with which to combat the scourge of tropical disease. The World Bank is proud to be associated with this important enterprise.
If the diseases affecting tropical countries are to be fully understood and if vaccines, drugs and diagnostic tests are to be used most effectively, research must be conducted "on the spot", in the tropical countries themselves. One of TDR's objectives is to help developing countries to build up the resources they need to conduct their own research, with their own researchers, among their own people. TDR's Research Strengthening Group seeks out institutions in developing countries which might benefit most from such help and become more able to meet their country's research and health needs.

Scientists and institutions of developing countries have risen to meet this challenge and are participating in research that is being conducted in laboratories, in hospital wards and in the community. Significant advances that have been made by researchers from developing countries include test kits for measuring the drug sensitivity of malaria parasites, a molecular biology technique for studying differences between the species of parasites causing Chagas' disease, and a method of growing filarial worms in the laboratory.

TDR—the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases—is a response by the world's scientific community to the long-standing, long-neglected needs of nearly a quarter of the world's population burdened by sickness. Until recently, too little was known about the diseases, and they appeared as dauntingly complex as they were geographically and culturally remote. Now, ten years after the creation of TDR, more than 4,000 researchers from over 125 countries (including around 2,000 scientists and 400 institutions in tropical developing countries) are producing new drugs, vaccines, diagnostic tests and other weapons. Backed by TDR's worldwide network of scientific experts and institutions, these weapons will be pitted against six of the most devastating tropical diseases: malaria, the trypanosomiases, leprosy, filariasis, schistosomiasis and leishmaniasis. Studies are also being conducted "on the spot" to identify risk factors for infection, and to determine how people's reactions to a disease affect efforts to control it. Through TDR's efforts, scientists can now work together in a rational, coherent way that may, for the first time, give mankind an even chance of holding its own against these diseases.

Throughout the ages

Some of the diseases which we classify today as "tropical" were once much more widespread. Malaria, for example, was well known far outside the tropics, and derived its name from the Italian words for "bad air" because of its association with fetid swamps. Tradition held that the Roman dictator Julius Caesar was himself a victim of malaria. In the 16th century, William Shakespeare described the symptoms of the disease in this speech by Cassius, one of the conspirators who were presently to murder Caesar:

He had a fever when he was in Spain,  
And when the fit was on him, I did mark  
How he did shake. 'Tis true, this god did shake.  
His coward lips did from their colour fly,  
And that same eye whose bend doth awe the world  
Did lose his lustre. I did hear him groan.  
Ay, and that tongue of his that bade the Romans  
Mark him and write his speeches in their books,  
Alas, it cried 'Give me some drink, Titinius,'  
As a sick girl!
Malaria

Malaria is one of the world's most widespread, devastating diseases. More than half of the world's population lives in endemic areas, and an estimated eight to nine million people die from the disease every year. Earlier hopes of eradicating malaria with drugs and insecticides were dashed by the development and spread of drug-resistant malaria parasites and of insecticide-resistant mosquitoes carrying the parasites. Now the emphasis is on control, rather than eradication. Strong hopes are pinned on new drugs, vaccines and novel vector control methods, many of which are being developed with TDR support.

Filariasis

Some 300 million people suffer from the different forms of filariasis. One of the most serious is onchocerciasis (river blindness), which affects about 40 million people, mainly in Africa, and blinds up to one-third of the population in some areas. TDR supports research on drugs that would be both effective and safe for large-scale treatment (several promising compounds are now being tested), diagnostic tests that would detect infection and permit early treatment, and natural pathogens of flies and mosquitoes that could be used to control these disease vectors. One such pathogen, Bacillus thuringiensis H-14, is already being used in West Africa against river blindness.

Schistosomiasis

Around 90 per cent of the population of developing countries live in areas endemic for schistosomiasis (bilharziasis), the most widespread waterborne infection in humans, currently affecting 200 million people. Blood in the urine, kidney damage, bladder cancer and liver failure are some of the effects of the disease. Targets for TDR-supported research include parasite biochemistry, the search for simple field tests of infection, and natural "ways of controlling the water snails which carry and spread the parasite.

Leprosy

Still an endemic disease today in many tropical countries, mainly in Africa, Asia and Latin America, leprosy affects nearly 11 million people. Of these, only one-quarter receive effective medical treatment. TDR is tackling leprosy on several fronts: a search for new drugs and shorter treatment schedules, to combat the spread of drug resistance; vaccines to prevent the disease; and tests for early infection.

Schistosomiasis

A new antimalarial drug, mefloquine, (diagram, left) has been developed with TDR support. Resistance to standard drugs, in particular chloroquine, first appeared in Asia and South America and has now spread to Africa (below). Research supported by TDR on schistosomiasis focuses on three stages of the parasite (drawing, right): the sporozoite, the merozoite and the gamete.
Tropical Diseases Research (TDR)

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Map shows the regions where malaria is endemic and, in red, the areas where malaria parasites have become resistant to chloroquine and related drugs.
Leishmaniasis

Large areas of Asia, Africa and Latin America are affected by the leishmaniasis, which are transmitted by sandflies and cause a range of illnesses, from skin sores to life-threatening kala azar, which affects internal organs. TDR's research has shown how widespread these diseases are (infecting about 12 million people), and includes the search for less toxic and more effective drugs, and for ways of detecting early infection. One new drug is already being tested in humans.

Kala azar—one form of the disease

Leishmaniasis sores can be destructive and disfiguring. The sloth (left), is one animal reservoir of Leishmania.
TDR: A very “Special Programme”

by Dr Adetokunbo O. Lucas

Director of the Special Programme for Research and Training in Tropical Diseases

The long struggle against malaria and other tropical diseases is taking a new turn. It has been a see-saw battle, with periods of high hopes and great expectations yielding to moments of despair and despondency. Time was when malaria retreated under the pressure of chloroquine and DDT; when dazzling successes in some parts of the world generated the hope that this infection could be totally eradicated from the globe. But malaria fought back: drug-resistant strains of the parasite emerged, in collusion with insecticide-resistant vectors. Much ground was lost, but some of the gains were consolidated.

Other tropical parasitic and infectious diseases have similarly resisted efforts to bring them under control. In some cases, as urban areas became free of schistosomiasis, for example, there was an increase in the prevalence and intensity of the disease in rural areas, where irrigation schemes and new intensive farming methods expanded the breeding sites of the water snails that transmit the infection.

The toll on human life and the debilitating effects of these diseases strengthened the resolve of governments to improve control efforts. A two-pronged strategy was evolved, entailing vigorous application of existing technology and the search for new powerful remedies for prevention and control.

At the 27th World Health Assembly in May 1974, the Member States passed a resolution calling on the Director-General to intensify WHO’s activities of research into tropical diseases, with the stipulation that such research was to be carried out as far as possible in the endemic countries.

Thus was born the Special Programme for Research and Training in Tropical Diseases (TDR), initiated by WHO and co-sponsored by WHO, the UN Development Programme (UNDP) and the World Bank. The diseases—malaria, schistosomiasis, filariasis, the trypanosomiasis, the leishmaniaises and leprosy—were the prime targets, firstly, because of the suffering and death they cause but also because of their adverse effects on development. Furthermore, paradoxically, the projects designed to promote development—the creation of man-made lakes, irrigation schemes and similar agro-engineering projects—tended to increase the distribution and the intensity of some of these infections. Putting a dam on a river in Africa may increase snail breeding and schistosomiasis around the shores of the lake behind the dam, while in the fast-flowing spillways below the dam the blackflies that spread river blindness find ideal breeding grounds. A no-win case!

Exploiting a revolution

The past forty years have witnessed a major revolution in the biological sciences. New methods of studying living creatures and their products now make it possible to find out a lot more about the parasites—how they live, grow, multiply, enter and leave the human body, and their specific vectors—and thus to identify and exploit their weaknesses. Now that some of the parasites can be grown in test-tubes, we can study them more closely, test directly the effects on them of potential drugs and discover their responses to a variety of changes and challenges in the environment.

The information from this research is being used to design and fashion new, powerful weapons against these diseases. Many of the existing control tools are not highly effective; in some cases their effectiveness has been blunted by use and abuse; and diagnostic methods are often antiquated and not suitable for use outside specialised laboratories. Some drugs and insecticides have too narrow a margin of safety for the individual and the environment, and hence require high levels of technical experience and supervision to use them safely. Some require complex, long-drawn out schedules which cannot be conveniently administered on a mass scale for the control of community-wide diseases. We need new, highly effective tools which can be safely administered with minimal skilled supervision, which can be applied in simple schedules (single-dose regimes for drugs, single applications of biological agents to control vectors), and which the communities and the governments can afford to acquire and maintain.

As the executing agency of the Programme, who has mobilised resources and expertise from academia, industry, public health departments and other institutions from all over the world. The strategy of the Programme has been to use the scientific resources of existing research institutions rather than to create new ones. Scientists from all over the world have helped to identify needs and opportunities for research, to establish realistic goals and to plan as precisely as possible the specific steps that should lead to attaining these goals. They are then funded to do the work, mainly in their own institutions. So the very best scientific minds in the world are addressing the complex technical problems posed by these diseases. By having the tasks performed in existing institutions, results have been achieved more rapidly and more cheaply than if
new institutions had been established and fresh scientists recruited. So far, more than 4,000 scientists from 125 countries have participated in the planning, execution and evaluation of the Programme's activities.

The Programme's scientific networks are operating efficiently and its results have been reported in some 4,000 scientific publications. More significantly, there is now a steady stream of new products ready for use in the control of these diseases, and many more are in the pipeline. Some of these products originated from work supported by the Programme. Others stemmed from research conducted outside the Programme and were then "adopted" by TDR-supported investigators and further developed into usable or potentially usable products.

Some examples of the new products which have resulted from TDR support:
- Mefloquine—a new potent antimalarial drug discovered in 1971 by the Walter Reed Army Institute of Research in Washington, DC, in the United States, and effective against chloroquine-resistant malaria parasites—has been developed by the Programme in collaboration with industry and registered for human use in several countries.
- Bacillus thuringiensis H-14, a bacterium discovered outside the Programme in 1976, has been developed with the collaboration of industry into an effective biological larvicide for the control of blackflies, and is now used as an alternative larvicide in the Onchocerciasis Control Programme in West Africa.
- Multidrug regimens for the treatment of leprosy, based on a combination of existing drugs, have been carefully evaluated within the TDR network and shown to be more consistently and more rapidly effective in healing patients than the standard regimen using dapson alone.
- Test kits have been devised to measure the sensitivity of malaria parasites to chloroquine and other drugs in common use. They are helping malaria control programmes to use drugs more rationally, based, that is, on precise knowledge of the areas affected by the new epidemic of drug-resistant malaria.
- A simple card test for African trypanosomiasis, ideally suited for use at dispensaries and health centres, and in the field, gives reliable results within a few minutes; a drop of blood is placed on the card and the reaction examined with the naked eye.

New and exciting scientific discoveries already in the pipeline are being processed into usable tools for disease control. Vaccines are under development against malaria and leprosy. New drugs are being developed. Some were identified through the traditional screening of large numbers of compounds but, increasingly, new agents are being "hand-picked" or "tailor-made", using clues from studies on the chemical processes within parasites. Innovative vector control methods are being tested from mechanical traps to the use of the vectors' natural enemies and diseases.

Even with new tools, however powerful, the Programme could fail to achieve the desired objectives unless the tools are used in ways appropriate to the local situation. It is therefore important to study the distribution of infection and disease in the population, to determine the most important factors which influence occurrence of the disease and to design a strategy geared to the circumstances of the local community.

The role of human behaviour, of the social and cultural factors which influence the patterns of disease, must not be forgotten. Control measures must be socially acceptable and should involve to the fullest extent the people they most affect, who can participate, not as objects of outside measures, but as subjects sharing in the efforts to deal with their own disease problems. This is the rationale of the Special Programme's epidemiological and social science research activities.

If TDR has achieved nothing else, it has demonstrated the value of international collaboration in tackling a common threat to humanity. Scientists have collaborated in this venture across barriers of race, language, politics and geography. Many of TDR's activities have, in addition, been conducted with the collaboration of other agencies, including the Edna McConnell Clark Foundation, the International Laboratory for Research on Animal Diseases (ILRAD), the Onchocerciasis Control Programme (OCP), the United States Agency for International Development (USAID), the Walter Reed Army Institute of Research (WRAIR), the Wellcome Trust, the Swedish Agency for Research Cooperation with Developing Countries (SAREC), the Office de la Recherche Scientifique et Technique d'Outre-Mer (ORSTOM), the South-East Asian Ministers of Education Organization—Tropical Medicine and Public Health Project (SEAMEO-TROPMED), and the Rockefeller Foundation.

Who offers a neutral platform where exchanges of ideas and resources can take place. A chemical compound, synthesised in Europe, tested in laboratories in the United States, the United Kingdom, the Federal Republic of Germany and Australia, is subsequently tried in man in West Africa and Mexico, and may turn out to be a powerful drug for the treatment of onchocerciasis. Nine-banded armadillos are caught in Central America and infected with leprosy bacilli; the bacilli are harvested two years later and the products banked in deep-freeze storage in London; specimens are then distributed to scientists all over the world and some are used to make a vaccine, evaluated first in Norway and now being tested in Venezuela and in Africa.

As Rudyard Kipling might just have written:

"East is East and West is West
And never the twain shall meet:
But there is neither East nor West, Border, nor Breed, nor Birth
When two TDR scientists stand face to face, though they come from the ends of the earth."

Photo WHO/P. Pittet  
Spraying against mosquitoes in West Africa. Control measures must be socially acceptable to local communities.
TDR and the drug industry

by John Vane and Win Gutteridge

ew treatments are desperately needed for tropical diseases. The rapid spread of chloroquine-resistant malaria from East to West Africa, for example, highlights the requirement for new antimalarials. Other examples include the need for a less toxic replacement for melarsoprol to treat African sleeping sickness, a more effective drug for Chagas’ disease, an orally-active antileishmanial drug, a cheaper replacement for praziquantel for schistosomiasis, and safer and more effective therapy for filariasis, especially onchocerciasis. Furthermore, there are still no vaccines available to protect against any of these diseases.

The process of discovery and development for any one drug is expensive (between US $50 and $100 million), time-consuming (eight to ten years) and speculative (only one of 10,000 compounds synthesised empirically may finally reach the market). New drugs for tropical diseases are especially problematic. This is because parasite life-cycles are complex, knowledge of sensitivity to a whole range of current drug-resistant lines, the understanding of the biochemical and molecular biological mechanisms is inadequate, and there are few in vitro systems for primary evaluation. The parasites are dangerous pathogens and so need careful handling, clinical trials are logically difficult because they need to be carried out in the tropics, and the ideal drug (active in a single oral dose with no side-effects against all strains and species which cause disease) is unlikely to be found without extensive molecular manipulation. These additional burdens are particularly unfortunate because the extra expenses are coupled with other discouraging factors, including the poverty of the people and governments that need the drugs. Consequently, it takes a stout business heart to maintain faith that an adequate return on research and development investment in this area will be achieved.

It may be that, if significant new therapies or prophylactics are discovered, the international funding agencies will find a way to pay for them, and there may be an indirect but tangible commercial value to a company retaining an involvement in this area. However, many pharmaceutical companies over the last 30 years have completely given up research and development in tropical medicine and very few are still actively involved.

Sir John Vane, a Nobel laureate, was formerly Professor of Pharmacology at the University of London, and is now Group Research and Development Director for the Wellcome Foundation Limited.

Dr Win Gutteridge was Reader in Biochemical Parasitology in the University of Kent, and is now Head of the Department of Biochemical Parasitology, Wellcome Research Laboratories, at Beckenham, U.K.

The undp/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) was born in the mid-1970s in response to this situation. By judicious funding through individual research project grants, it rapidly stimulated basic biomedical research in academic fields both in the developing and developed worlds on problems pertinent to drug and vaccine discovery, their development and their application. However, it was apparent from the beginning that, although support of this kind would help to provide vital scientific background and understanding, the facilities to identify and especially to develop and market new drugs and vaccines would not be available unless the pharmaceutical industry became substantially involved.

There are four distinct areas in which the industry now collaborates with TDR. The activities of the Programme’s different components are controlled and coordinated by Steering Committees, Scientific Working Groups and review committees. One of the common objectives is the discovery and/or development of new drugs or vaccines. Scientists from the pharmaceutical industry are now members of many of these committees; for instance, scientists from the Wellcome Foundation in the United Kingdom are on the Steering Committees on Chemotherapy of Malaria, and of Chagas’ disease. This representation is of mutual benefit: not only is an industrial perspective added to the group but also the industrial representatives have their horizons broadened.

The pharmaceutical industry is skilled at manufacturing drugs and vaccines for commercial markets in the developed world right through to clinical trials, registration and marketing. But in the case of tropical medicines, it is not always easy to identify the centres best able to do clinical trials, and it is often difficult to reach agreement on methods. It is here particularly that the Special Programme can play a significant role, as Professor Fernex shows elsewhere in this issue in his article on the development of the antimalarial mefloquine.

Joint development, of course, is all very well if one is in a position to recognise that there is something worth developing. Tens of thousands of novel chemical structures are synthesised annually by the pharmaceutical industry, but few of these are normally the subject of screening to check their validity against tropical diseases. Random screening, if cheap,
The blackfly's bite transmits onchocerciasis — river blindness.

Left: Awaiting admission to a hospital in Thailand, this sick child wrestles with cerebral malaria.

Photo WHO/M. de Vreede

Right: For the pharmaceutical industry, it takes a stout business heart to maintain faith in adequate returns from investments in tropical disease research.

Photo WHO/A. Dorozynski

still has its champions and so we have sought to maintain primary screening facilities for the six parasitic diseases of TDR. Few companies do this, and it is here that the screening facilities sponsored by the Special Programme are of great value. We are currently making use of secondary and tertiary filariasis screens and for a number of years (1977–1982), we operated a primary filariasis screen on behalf of TDR.

This random screening approach to drug discovery has, in the past, led to the development of many of today’s antiparasitic drugs, but it is now superseded by a more rational discovery process which is based on biochemical differences between parasite and host. Certainly, during the time we ran the filariasis primary screen, no compound worthy of further development was discovered out of the many thousands tested.

The limitations of random screening, and the needs of the Onchocerciasis Control Programme (OCP) for new drug treatments, led to the setting up of the Onchocerciasis Chemotherapy Project (OCT), closely linked to TDR. In 1982 was established an ambitious research collaboration between WHO and the pharmaceutical industry — the OCT/WHO/Wellcome Onchocerciasis Programme dedicated to the rational discovery and subsequent development of a novel macrofilaricidal for onchocerciasis. The day-to-day costs of this programme (US $500,000 per annum) are paid for by OCT, while Wellcome provides the laboratories, insectarium, animal facilities, most of the capital equipment, a programme leader, the administrative and evaluative machinery and much additional experimentation. The programme has its own biochemists to do basic studies, as well as biologists and chemists, and is fully integrated scientifically with our other activities in the endoparasite chemotherapy area so as to maximise the chances of spin-off.

Working together

At the same time, OCT/WHO has stepped up the amount of biochemical funding in this area to academic laboratories, in order to develop further the data base. Our collaboration started over two years ago and is now in full swing. Two members of the WHO Secretariat attend the six-monthly meeting of the Wellcome onchocerciasis programme team, and Wellcome
sends an observer to present the results of the programme to the OCT Steering Committee. Wellcome organizes an annual Filaria Seminar to which all UK and some European filariais research workers are invited. We hope our successful collaboration with WHO will soon lead to at least one other such collaborative project between WHO and another pharmaceutical company.

In summary, four distinct types of collaboration now exist between the Special Programme and the pharmaceutical industry: membership of planning and review committees; collaboration over development of drugs; operation and/or use of screening facilities; full research and development collaboration.

A good start has been made on all of these, and further progress should be seen over the next decade. WHO and affiliated organizations have done much to maintain and increase the research base for tropical diseases.

But the fundamental problem remains that of ensuring an adequate research and development presence in the industry in the face of increasing commercial and other pressures to reduce investment still further.

Clearly, the international agencies can contribute some of the development costs, particularly in the clinical trials area, but new thinking is needed to find imaginative ways for further collaboration between them and the pharmaceutical industry.

One possibility would be to create an Institute for Tropical Medicine, dedicated to the discovery of drugs and vaccines for tropical diseases and funded by a once-and-for-all capital investment. Such an Institute should best be situated on the site of a major pharmaceutical company (where the buildings may even exist) so that the development machinery of that company is available to process any discoveries. Its activities would provide the focal point for collaboration between the Special Programme and the industry.

The capital funding could come from charitable trusts, international agencies or, perhaps best of all, the pharmaceutical industry itself. Kudos and profit (if any) would be shared equitably between contributors. A capital sum of the order of US $100 million could well fund such an Institute in perpetuity, and thereby guarantee a realistic and enlarged search for the new medicines so desperately needed for the tropics.
Schools and schistosomiasis

Photo story by Kenneth E. Mott

Blood in the urine is a common feature of life for schoolchildren in 53 countries of Africa and the Eastern Mediterranean area. In some places it is so frequent that the children and their parents think of it as a milestone in growing up. The blood results from damage to the bladder by the eggs of the schistosome, a parasitic worm transmitted from person to person via snails that live in fresh water (see World Health, December 1984).

At this school in Zanzibar, 10 per cent of the girls and boys had bright red bloody urine on the day the Health Ministry's flying PHC team came to visit. Using new rapid diagnostic tests and safe drugs, the team can "test-and-treat" several hundred children in one morning.
Each child takes a plastic cup—provided by UNICEF—and goes away to urinate into it. Returning with their samples, the pupils line up and register before passing to the urine filtration table where, in less than a minute per sample, the urine is passed through a small filter (inset, above left). In another 30 seconds the microscopist can scan the filter through the microscope.

*Dr Kenneth E. Mott is Chief of WHO's Schistosomiasis and Other Trematode Infections unit, Parasitic Diseases Programme*

If parasite eggs (inset, left) appear on the filter, the child is examined, weighed and treated at once with praziquantel or metrifonate tablets. Most of the infected children at this school will be cured with one or two treatments.

The children learn about their role in the disease from their teachers. It is *people* who cause urinary schistosomiasis by urinating in water—the snails can get infected in no other way. Treated children excrete fewer or no parasite eggs in their urine, and are less of a risk for others, especially if they learn not to urinate in or near water. In the long run, school treatment campaigns like this, with water supply and sanitation, can dramatically reduce the number of adult victims of this disease. So schools and schistosomiasis have a lot to do with one another.
A preventable bladder cancer

by Mahmoud Sherif and Amal Samy Ibrahim

In Egypt as in certain other Middle Eastern and African countries, most bladder cancer is of a type called squamous cell carcinoma, occurring almost exclusively in patients who have had severe and repeated infections with urinary schistosomiasis. Now, thanks to new drugs that cure schistosomiasis safely and effectively, and an early detection test that can reveal cell changes, doctors have a quite unique opportunity for preventing this kind of bladder cancer.

At the National Cancer Institute in Cairo, difficult cancer cases of all kinds are referred to us from many parts of Egypt. Among Egyptian men, bladder cancer associated with schistosomiasis is the most common cancer: it affects mainly agricultural workers who are exposed to schistosomiasis-infested water every day, and over many years. The symptoms of this cancer are the same as for the bladder infections that accompany it, which is misleading for the patient and even the doctor.

For sick farmworkers, a journey to the capital with relatives and friends for an examination is expensive and time-consuming; so they put it off until their disease is really advanced. Women get bladder cancer more rarely, being less exposed to schistosomiasis, but as patients they find it even more difficult to travel because of their heavy family responsibilities.

Due to these problems, two-thirds of patients arrive at the Institute so late that we can do nothing for them. We can treat the remaining third, but only by performing a complicated and expensive surgical operation. Thirty per cent of patients treated in this way will live for at least five years after the operation, but most will be severely incapacitated.

The operation involves taking out the bladder and doing a type of urinary diversion. One method is to divert the urine through the rectum and establish an artificial anus on the abdominal wall (stools cannot be evacuated through the same outlet as urine for fear of infection). Afterwards the patients can learn to control the flow of their urine during the day, but they are incontinent at night and must also be fitted with a colostomy bag to empty their intestines, which poses difficult problems of hygiene and sterility for them under village conditions.

Dr Mahmoud Sherif is Dean and Professor of Surgical Oncology at the National Cancer Institute in Cairo, Egypt, and Dr Amal Samy Ibrahim is Professor of Cancer Epidemiology and Statistics with the same Institute.

Most patients can never go back to their agricultural work, which entails a loss of income and other serious consequences for the whole family, especially in view of the relatively young age at which the disease strikes.

These stark facts have led the Cancer Institute to draw up a four-pronged plan of attack on bladder cancer based on the new possibilities we now have for prevention combined with early detection. Of course, if we could eliminate schistosomiasis, we could get rid of this type of bladder cancer altogether; but that will be a difficult and long-term job. In the meantime, we must intervene wherever we can in the natural history of bladder cancer, so interrupting its development.

The chain of events leading to a bladder cancer begins with severe and repeated schistosomiasis infections starting in childhood. We can now intervene at this first stage by treating infected children and adults with the drug praziquantel, repeating the treatment if necessary in order to reduce the severity and frequency of episodes of infection. People who are protected from severe schistosomiasis will have less chance of developing this type of bladder cancer later in life.

The next event in the chain follows on from schistosomiasis infection: the patient gets a secondary bacterial infection of the bladder, or cystitis. In time, the combined effect of these two infections brings about dysplasia, or abnormal changes in the bladder cells which are not malignant but pre-malignant. We can intervene at this second point by treating both the schistosomiasis and the bacterial infection effectively, so preventing dysplasia from developing at all.

Our third possibility for intervention lies in experiments now in course to find out whether very large doses of vitamin A or one of its synthetic derivatives, given alone or together with vitamin C, may also reduce the incidence of bladder-cell dysplasia. Although it is still too early for definite results, there is good reason to hope that vitamin therapy will indeed prove helpful.

Cells revealed

Both dysplastic and malignant cells can be detected in the urine by a cytological test simple enough to be performed in community health centres. In this test, urine voided by the patient in the normal way is collected and centrifuged. The cytologist puts a drop of the urine sediment on a slide, stains it, and looks at it under the microscope; any dysplastic or malignant cells are then seen and identified. This test is the fourth prong of our plan of attack. If it can be widely introduced for schistosomiasis patients thought to have cell changes, it will not only reveal treatable dysplasia, but enable us to detect and
Luckier than most

Mr Jamal Abul Maaty Ahmed, aged 36, is not an agricultural worker but a plumber, from a village 17 km from Mansourah. A couple of years ago he went to work in Saudi Arabia, where his contract entitled him to free medical care and sick pay. When he began to get loin pains and other symptoms, he was not reluctant to undergo tests and get prompt treatment.

He eventually came back to Egypt, where a Mansourah doctor, suspecting bladder cancer, referred him to the National Cancer Institute. Thanks to this perceptive doctor, Mr Jamal’s cancer was caught at an exceptionally early stage: it is still so small as to be invisible. He will have an operation shortly, but may need to have only part of the bladder removed and so will be less severely affected by the operation than most patients. At the moment he feels well, sleeps well and is not in pain.

Mr Jamal is an unusually fortunate man. Although he had schistosomiasis as a child, he did not get it again after his last treatment with tartar emetic at age 11, and he entered a profession where he was not occupationally exposed to the disease. He was also lucky to have the chance of a quick check-up in Saudi Arabia, and lucky that his Egyptian doctor suspected what was wrong. Early cases of bladder cancer like Mr Jamal’s are hardly ever seen at the Institute.

A classic case

Mr Mohammed Samir Marjalawi, aged 52, works on the land at Daha in Dakahlia governate, about 100 km from Cairo. He keeps buffaloes and two cows, and works in the fields with another man. He is married and has four children.

Mr Mohammed began to complain of urinary problems about eight months ago and came recently to the National Cancer Institute in Cairo by taxi with his son and some neighbours. His wife has not been able to visit him, because of the children and the expense.

Mr Mohammed has just been operated on for bladder cancer: in future, he will be incontinent at night, and will have to use a colostomy bag—difficult to keep clean in village conditions—to empty his intestines. He is worried that he will never be able to work again: his son, who has been replacing him, will soon have to go off to do his military service.

As a young man, Mr Mohammed was several times treated with tartar emetic (a toxic compound that can only be given under close medical supervision). This fact indicates that he had repeated schistosomiasis infections which, after about 20–30 years, finally led to his bladder cancer.

Introducing our new policy of prevention and early detection of bladder cancer associated with schistosomiasis in Egypt will not be an easy job. We are a developing country with only a limited number of treatment centres for cancer, and treatment naturally seems to most people to be the main priority. Nevertheless, we believe that by combining prevention, early detection and treatment we shall be able to keep up with the problem of bladder cancer, instead of lagging behind it—and above all we shall be able to prevent much unnecessary suffering on the part of patients and their families, both in Egypt and in other countries with the same problem.
Forty years have now elapsed since the end of the Second World War, the most destructive war in the entire history of mankind. Fascism, which unleashed it, saw its dreams of world domination and the physical destruction of entire peoples go up in flames and smoke.

Although decades have passed, the wounds and horrors of that war are not forgotten. Sombre memorials mark the sites of former concentration camps or commemorate the dead of burnt and devastated towns.

The Second World War was a cause of great bloodshed and severe hardship, and the harm it did is still reflected in health and population statistics. Between 1939 and 1945, the countries involved in the war lost more than 50 million dead, of whom some 40 million perished in Europe alone. Huge numbers were disabled by wounds, severe illness, harsh deprivations and famine. Entire towns and villages were wiped off the face of the earth.

Among the vast civilian losses, it was the children who suffered most of all—as usual—during the years of agony. Many forfeited their lives; many others were deprived of childhood, lost their home and parents, and forgot how to smile.

The sacrifices and deprivations undergone by the peoples of the Union of Soviet Socialist Republics during that war were without equal. More than 20 million Soviet citizens gave their lives as the aggressors ravaged 1,710 towns and cities and more than 70,000 villages, destroying 84,000 schools, colleges and research centres and 40,000 medical institutions.

I myself served in the Soviet army in the years 1941 to 1945, and witnessed the burning of towns and villages, the bombing of houses, schools and hospitals, and the destruction of old people and children. I remember how men and women perished in the first bloom of youth, and never knew the happiness of fatherhood and motherhood. How much creative potential and talent that could have become the pride of humanity was irretrievably lost!

In the post-war years, having completed my medical studies, I started work as a paediatric surgeon, and continued to be confronted for a long time by the scars and mutilations inflicted by war on humanity’s greatest resource—its young people.
The lessons of the Second World War are of lasting importance. The war showed the lethal and far-reaching consequences that may result from basing a policy on a position of strength and attempting to impose one country’s will on other sovereign states. At the same time, the victory of the progressive forces showed vividly that mankind’s aspirations for peace and cooperation in the name of humane goals are invincible, and that, once united, the peoples of the world can and must prevent a repetition of a universal tragedy by repelling the threat of a new and devastating war.

This is precisely why the United Nations Organization and its network of specialised bodies were set up immediately after the war. One of the largest of those agencies, the World Health Organization, was founded in 1948. The memory of what the war had cost in human lives, disablement and ill-health was still fresh, so a clause underlining the close link between health and international security was written into its Constitution from the very outset.

During its first ten years, WHO had to devote much of its efforts to helping countries that had suffered from military operations in restoring shattered health services and dealing with the adverse epidemiological situation created by the war. Consequently, the Organization knows from bitter experience what fearful wounds remain in the wake of battle.

The strengthening of peace and the limiting of the arms race have been reflected in many resolutions of the World Health Assembly—the forum of all WHO Member States. These include recent resolutions stressing that the role of physicians and other health workers in preserving and promoting peace was the most significant factor in achieving Health for all.

Since the development and manufacture of nuclear weapons, keeping the peace has become a principal concern of the modern era. At the end of the Second World War, the world shuddered to hear of the dropping of the atomic bomb on the Japanese cities of Hiroshima and Nagasaki, and of this weapon’s destructive force.

The long-term consequences of that tragedy in the history of humanity still persist.

Even so, there is no comparison between that device and the potential of today’s nuclear weapons. Their use would threaten the life and health of all peoples of the world without exception. This has been convincingly demonstrated in a report on the effects of nuclear war on health and health services produced by the International Committee of Experts in Medical Science and Public Health. The Thirty-sixth World Health Assembly in 1983 approved the Committee’s work and stressed that nuclear weapons constitute the greatest direct threat to the health and welfare of mankind. In a nuclear catastrophe, any health service would be powerless. The only reliable way of saving humanity from the horrors of nuclear war is not to permit it ever to happen.

In 1981, Soviet and American doctors combined forces in an effort to prevent nuclear war. This was the beginning of the broad international movement called International Physicians for the Prevention of Nuclear War, which now unites doctors in at least 54 countries. Last year this movement was awarded the UNESCO Prize “For Education in the Spirit of Peace.” Working contacts between WHO and this movement are now being widened.

The humane goals of WHO oblige the Organization to speak out ever more decisively in defence of peace. The essential conditions for all peoples to cooperate in solving the global problems that face mankind, and for achieving Health for all by the year 2000—the noble aim set by WHO and its Member States—are: the relaxation of political tension, reduced military expenditure, quantitative and qualitative limits on nuclear weapons, the eventual prohibition of all weapons of mass destruction and the elimination of stockpiles, and prevention of the spread of the arms race to areas not yet involved in it.
**NEWSPAGE**

**who lends support to drought-hit Africa**

During 1984, who provided approximately US $3,500,000 in emergency health aid to 26 African countries struck by drought and famine. Two-thirds of this expenditure derived from the regular budget, while the rest originated from other sources, including the Arab Gulf programme for UN Development Organizations (Agfund), the Economic Commission for Europe (ECE), and the Canadian Government.

These figures refer only to direct material aid, which is not the principal aspect of WHO's contribution to such emergency situations. In fact, WHO's major task is to act as the "health arm" of the UN family, providing expertise and international coordination to Member States as well as to sister agencies in the UN family, and to other international organizations.

It was in response to the critical and unprecedented situation facing numerous African countries that WHO mobilized its resources, along with other UN agencies and international organizations, in order to bring immediate health-related aid to those most affected by famine and drought.

In January, Dr Farouk Partow, Assistant Director-General of WHO, told the Organization's Executive Board that, without being spectacular, the emergency operations were proving effective, and reflected the deep humanitarian concern underlying all activities undertaken by WHO. He said that WHO was active on all fronts where there was drought or famine, notably in Ethiopia, where a technical team had been sent to assess the magnitude of immediate resources needed in that critically affected country. WHO provided $600,000 in emergency medical supplies to Ethiopia in 1984.

In Western Africa, Mali and Mauritania also received emergency aid to combat the effects of the drought, which included the outbreak of a cholera epidemic.

In Chad, which allocated $200,000 to restore the functioning of its hospital services, and an additional $43,000 for diarrheal disease control.

Benin received urgently-needed laboratory supplies, while Mozambique was provided with about $700,000 in medical supplies and $20,000 worth of WHO emergency health kits. Similar kits were also sent to Swaziland and Zaire.

While the principal consequences of the drought are malnutrition and the infections it fosters, the situation has been further complicated by epidemics of cholera and acute diarrhoeal disease. Certain countries have, in addition, suffered outbreaks of yellow fever and cerebrospinal meningitis, as well as cyclones, earthquakes, and the massive displacement of refugees.

To control cholera and diarrhoeal diseases, WHO dispatched 200,000 urgently-needed packets of life-saving oral rehydration salts (ORS) to Botswana, 400,000 to Madagascar, and an additional 100,000 to Niger. Developed jointly by WHO and UNICEF, oral rehydration salts are simple solutions which can be easily mixed by mothers and given to their children.

Use of these salts can dramatically save the lives of thousands of children suffering from acute diarrhoea. To control yellow fever, WHO furnished 100,000 emergency doses of yellow fever vaccine to Benin, 600,000 doses to Burkina Faso, 200,000 doses to Cameroon, and 600,000 to Togo.

Angola, Burundi, Equatorial Guinea, Ghana, Guinea, Guinea-Bissau, the Ivory Coast, Kenya, Sao Tome and Principe, and Zimbabwe received emergency aid from WHO to fight renewed outbreaks of these communicable diseases. The Organization also provided medical equipment and drugs worth $50,000 to Somalia, and $100,000 to Sudan.

Beyond this immediate relief action, WHO is providing effective technical support to combat malnutrition in several projects initiated by the World Food Programme (WFP), WHO also collaborates with the Food and Agricultural Organization (FAO) and the World Bank to ensure that health needs are included in their nutrition programmes.

In the same field but on a longer time-scale is the special Joint WHO/UNICEF Nutrition Support Programme. A generous grant of $65.3 million provided over a five-year period by the government of Italy is enabling 17 countries to develop long-term national nutrition programmes. Eight of these countries are in Africa: Angola, Ethiopia, Mali, Mozambique, Niger, Somalia, Sudan and Tanzania. The overall thrust of this major programme is to strengthen the ability of national authorities to solve their own nutritional problems.

**Does smoking harm the non-smokers?**

Tobacco smoke has so far been found to contain nearly 6,000 different chemical substances, and their potentially damaging effects on the health of the active smoker are well-known. However, a large proportion of these substances are not absorbed by the smoker, but are disseminated into the atmosphere via the sidestream smoke and inhaled by non-smokers. So is the health of such "passive smokers" also at risk, despite the effects of atmospheric dispersion and despite the filtering effect of the nasal passages?

An international symposium on the subject of passive smoking took place in Vienna last year. It was organized by the Austrian Society for Industrial Medicine, the German Society for Occupational Medicine, the American Health Foundation and the Bavarian Academy for Industrial and Social Medicine, in conjunction with WHO and the International Green Cross.

Mr Martin Doell, vice-president of the International Green Cross, reported in the German edition of World Health what transpired at the symposium. For two days, he said, a group of internationally recognized experts in many fields discussed their latest findings in the field of passive smoking.

Dr T. Hiyama of the National Cancer Centre Research Institute in Tokyo described his long-term epidemiological study, which has been in progress since 1966. Having examined 91,540 Japanese non-smoking women married to smokers, he found that the risk of contracting lung cancer was...
higher for these women than for women who were married to non-smokers. He also found that the risk to the wife increased in proportion to the husband's daily cigarette consumption, that is, that there was a clear correlation between dose and effect. The findings would be broadly the same if the roles were reversed—if the husband was a non-smoker and the wife a smoker. But Dr Hirayama conceded that the sample was in this case too small for the findings to be regarded as scientific proof of his hypothesis.

Dr L. Garfinkel, vice-president of the New York-based American Cancer Society, said that, over a 13-year period, a total of 176,000 female non-smokers were classified according to whether they were married to a non-smoker, a smoker of up to 20 cigarettes daily or a smoker of more than 20 cigarettes daily. The relative risk of lung cancer was then compared for these three groups. It was found that the risk of lung cancer for the wives of smokers of up to 20 daily was 27 per cent higher than for the wives of non-smokers—but that contrary to the expected dose-response relationship the risk factor for the wives of the smokers of more than 20 daily showed a relatively small increase of only ten per cent. In neither case was the increase in the risk factor statistically significant.

But the participants in the discussion were unanimous in calling for more research. As far as preventive medicine is concerned, it was felt that measures to combat active smoking must be accorded first priority.

According to Mr Doell, who prepared a full report (in German) on the symposium, the participants concluded that if governments wished to legislate against passive smoking, such action could only be justified at present on the grounds that it is a social nuisance. Nevertheless special consideration ought to be given to people who are unusually sensitive to tobacco smoke—such as asthmatics, allergy sufferers, patients with chronic bronchitis and small children.

**Newsbriefs**

- **Welding hazards.** Industrial workers who spend their working days engaged in stainless steel welding may be subject to particular health risks. In February, WHO's European Regional Office in Copenhagen hosted an international conference on current knowledge of the chronic and delayed effects on human beings of exposure to particles and gases generated in welding processes. Measuring and predicting these effects, which may include cancer and respiratory diseases, is a principal aim of a who study now in progress. About one in ten of Europe's two million welders are engaged in this kind of work: the worldwide total of welders is estimated at around five million.

- **Routine vaccination.** A handsome handbook illustrating all aspects of immunization by means of easy-to-understand drawings and accompanying text has appeared from the presses of the Paris-based Agency for Cultural and Technological Cooperation. Produced at the request of the Ministry of Public Health and Social Affairs of Djibouti, the handbook is published only in French under the title "Vacciner au quotidien"—"Routine Vaccination". But the format lends itself to possible translation into any language.

  Produced in cooperation with WHO's Expanded Programme on Immunization, the handbook is intended to support long-term campaigns aimed at preventing several of the most important childhood diseases.

  Copies of "Vacciner au quotidien" may be ordered from: Agence de Coopération culturelle et technique, 13, quai André Citroën, 75015 Paris, France.

- **Slide-sets for health workers.** Tropicare, a three-year health care education programme for Africa, has produced two slide-sets—one on malaria and control of acute diarrhoea—expressly aimed at the training of health personnel. Available in both English and French, these audiovisual programmes last 30 and 26 minutes respectively, and each consists of a series of slides and a pulsed audio tape. Essentially they were made by local experts to suit local needs.

  For Europe and Africa, the sets may be ordered from: Dr M. Ogirizek, Warner Lambert France, Tropicare Programme, 11, avenue Dubonne, 92407 Courbevoie, Cedex, France; and for the USA, from: Mrs Aracelia Vila, General Coordinator Tropicare Programme, Warner Lambert International, P.O. Box 377, Morris Plains, New Jersey 07950, USA.

**In the next issue**

Medical technology has made incredible advances in the course of this century. Not all the progress is necessarily appropriate to the vast and pressing health needs of most people on this planet. The June issue of World Health examines some aspects of health technology which are truly appropriate.
A tropical paradise—but there are "serpents" in this Eden!