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Report on the review of

UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES

conducted by

The Swedish Agency for Research Co-operation with Developing Countries (SAREC)

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REPORT ON THE WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES

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1 BACKGROUND

1.2 General

The World Health Organisation's Special Programme for Research and Training in Tropical Diseases was initiated in 1975. Its purpose is to develop methods for controlling a number of tropical diseases and to strengthen the research capability of the countries affected. From its inception, Sweden has provided extensive support to the Programme. SAREC has disbursed a total of MSEK 102 from its budget, and in 1985 appointed a special working group to review and follow up the Programme's activities.

The review was aimed, with SAREC's goal of supporting research in developing countries as a starting point, to take up various issues in order to assess how far the Programme corresponded to SAREC's requirements. The issues selected for special attention were:

(a) The intradisciplinary quality of research activities.

(b) The orientation and results of research, and its utility in relation to existing health problems, resources, priorities and health care policy in developing countries.

(c) The Programme's potential in strengthening research capability (institutional support, research training, etc.).

(d) The timescale of the Programme and its position in relation to WHO's regular activities.

(e) The social-scientific and epidemiological components of the Programme and their integration with research activities; efforts to promote popular participation in control programmes.

(f) Collaboration with industry and issues concerning patents. The position of the Programme in relation to other donors.

(g) Funding channels, including earmarked grants e.g. for field studies.

1.2 Outline of SAREC's review

The Terms of Reference for SAREC's review of the Special Programme for Research and Training in Tropical Diseases in 1985 are enclosed (App. 1). The evaluation was conducted as follows:

(a) A systematic review of Programme documentation was conducted by the SAREC Secretariat and members of SAREC's advisory scientific consultant group (App. 2).

(b) Working group members paid visits to several developing countries, in order to try and assess how the Programme helps these countries, against the background of existing health problems and resources.

Large-scale reviews were conducted in Ethiopia and Zambia; in Somalia, Nicaragua and Cuba small-scale surveys of current research on tropical medicine took place (Apps. 3, 4, 5, 6, 7).

(c) Several members of the SAREC working group and representatives of the SAREC Secretariat visited the Programme's Geneva headquarters in June to obtain up-to-date information (App. 8).

(d) A draft report was discussed at a meeting of the working group at the end of August 1985. A joint meeting with members of SAREC's working groups for two other SAREC-supported research programmes in WHO (research on human reproduction and primary health care) took place on 16th September 1985. SAREC then produced reports on the three research programmes and proposals for joint support to health research under the aegis of WHO, for presentation to the SAREC's governing board in the autumn of 1985.

2 THE SPECIAL PROGRAMME - DESCRIPTION AND COMMENTS

2.1 Origins of the Programme

During the 1960s and '70s, the severe health problems posed by infectious tropical diseases in many developing countries became increasingly apparent. It was realised that existing methods for controlling these diseases were inadequate and that the accelerated progress of medical research since the Second World War had not had any appreciable impact on this group of diseases. This realisation was one of the points of departure for the discussions leading to the inception of the Special Programme for Research and Training in Tropical Diseases in the mid-1970s. The

Programme should, it was agreed, concentrate on the following six diseases: malaria, schistosomiasis (bilharzia), filariasis (including onchocerciasis, "river blindness"), trypanosomiasis (African sleeping sickness and Chagas' disease), leprosy and leishmaniasis. Of these diseases, malaria, schistosomiasis and filariasis are estimated to have at least 200 million human victims each. In Africa alone, malaria causes about one million children's deaths annually. About 10 million people are infected with trypanosomiasis, the same number with leprosy and a slightly smaller number with leishmaniasis. Apart from leprosy, all these diseases are spread by vectors.

(årligen?)

In 1974, the World Health Assembly adopted a resolution requesting WHO to establish a programme for research and training in tropical diseases. Planning work and a pilot project conducted by a scientific working group were initiated simultaneously. A first donors' meeting was held in October 1975. Planning continued in an informal working group in which Sweden was also represented. Recommendations on the Programme's organisation and content, scrutinised by a special Technical Review Group, were presented at the next meeting, in December 1976, when it was decided that scientific activities should commence on a full scale. Certain questions on the administrative nature of the Programme were settled at a subsequent meeting in February 1978. The Board selected - on which Sweden has been continuously represented - was first convened in December 1978 and has met annually since.

2.2 Objectives of the Programme

The Programme has two mutually dependent objectives:

- research and development to create new and improved methods of controlling tropical diseases;

- reinforcement of national institutions and national education to raise research capability in the tropical countries affected by these diseases. According to Programme policy, the bulk of development work on new tools and methods must take place in the countries where the diseases in question are endemic.

The Programme covers the six diseases mentioned in the introduction (2.1). It includes field studies of an epidemiological and operational nature, to map disease incidence and devise control strategies using new or existing methods. The Programme also funds socio-economic research relating to the six diseases.

The Programme component for strengthening the research capability of the developing countries gives long-term support to national institutions in the developing countries, and has thus laid the foundations for a network of research and training centres.

2.3 Modus operandi of the Programme

The Programme is incorporated in WHO, which is its executive authority. WHO, UNDP and the World Bank have assumed special responsibility as sponsoring agencies. The Joint Co-ordinating Board (JCB), which meets annually, comprises 30 members, 12 of whom are appointed by the donor countries, 12 by WHO's regional offices and 3 by JCB. Members are appointed for three-year periods and may be re-elected. In addition, the three sponsoring agencies form a joint Standing Committee which reviews the Programme, has some responsibility for allocating grants during the financial year and submits proposals to JCB on general policy and financial and administrative questions. JCB also appoints an external Scientific and Technical Advisory Committee (STAC), which reports annually on the Programme's scientific and other activities and formulates criticism and proposals for changes.

The Secretariat is located in the Geneva headquarters of WHO. The Director of the Programme since its inception has been the Nigerian Professor A. Lucas. Work is organised in Scientific Working Groups (SWGs), each of which has a small Steering Committee to draw up its work plans, assess applications and distribute grants. In addition there is a working group, the Research Strengthening Group (RSG), which co-ordinates funding to institutions and education in developing countries.

2.4 Supervision and review mechanisms of the Programme

The central organ of control is the Scientific and Technical Advisory Committee (STAC). Every year, this body reviews all the subject areas of the Programme, simultaneously monitoring the Steering Committees for the various SWGs and the RSG; otherwise, these bodies are autonomous as regards planning activities and the distribution of funds within established financial limits.

According to the Programme's Terms of Reference, STAC's 15-18 members must represent medical, biomedical and other disciplines. WHO selects new members in consultation with the Standing Committee, subject to the approval of the annual meeting. Members are selected in a personal capacity for a three-year period, and may be re-elected.

The task of STAC is to assess the content, orientation and scope of the Programme from a scientific and technical standpoint, to recommend priorities - including the formation and dissolution of SWGs - and to report annually to

WHO and the Standing Committee. The latter must submit a report containing its own and WHO's comments well in advance of the annual meeting. Through smaller groups (Scientific and Technical Review Committees, SRTCs), STAC also conducts special in-depth annual reviews of certain subject areas.

The Programme thus incorporates wide-ranging evaluation activities. An appraisal of its first five years was conducted by an External Review Committee, whose members included Professor Henry Danielsson of the Swedish Medical Research Council. With the assistance of the STRCs, the social and economic research component of the Programme was evaluated in 1983, followed by the malaria, filariasis and epidemiology components in 1984. The SWG on Biomedical Research has recently been dismantled at the behest of STAC.

STAC appears to have performed its tasks hitherto in a firm and independent manner. Its interdisciplinary composition is not entirely convincing since, for example, no social scientists are included. SAREC's working group considers that JCB should play a more active role in the appointment of members of the central organs of control, and obtain more information on their working procedures.

2.5 Research and development

2.5.1 Organisation

Activities are conducted by Scientific Working Groups (SWGs) and Steering Committees (SCs) as follows.

Malaria	SWG on Chemotherapy of Malaria (CHEMAL) SWG on Immunology of Malaria (IMMAL) SWG on Applied Field Research in Malaria (FIELDMAL)
Schistosomiasis	SWG - General Research Three sub-groups with joint SC: Immunology and Basic Sciences Chemotherapy and Biochemistry Epidemiology and Snail Control SWG - Applied Field Research
Filariasis	SWG on Filariasis
African trypanosomiasis	SWG on African Trypanosomasis Three sub-groups, each with its own SC: Chemotherapy and Drug Development (CHEMAF) Immunology and Pathology (IMMAF)

	Epidemiology, Vector Biology and Control (EPIAF)
Chagas' disease	SWG on Chagas' disease Three sub-groups, each with its own SC: Chemotherapy and Parasitology (CHEMCHA) Immunology (IMMCHA) Epidemiology, Vector Biology and Control (EPICHA)
Leishmaniasis	Two sub-groups with joint SC: Chemotherapy (CHEMLEISH) Immunology and Biochemistry (IMMLEISH) One sub-group with its own SC: Epidemiology (EPILEISH)
Leprosy	SWG on Immunology of Leprosy (IMMLEP) SWG on Chemotherapy of Leprosy (THELEP)
"Trans-disease" groups	SWG on Vector Biology and Control SWG on Epidemiology SWG on Social and Economic Research SWG on Biomedical Research (dismantled at the end of 1985)

Short descriptions of and comments on activities in these different spheres are given below.

2.5.2 Malaria

(a) Immunology

Developing vaccines against malaria and improved and/or new immunodiagnostic methods has continued to be the main objective of immunological research on malaria, both within and outside the Special Programme. Progress to date, primarily in solving vaccine-related problems, has well exceeded expectations, owing to the very rapid development of techniques used in immunology, molecular biology and biochemistry for identifying, characterising and producing the plasmodium antigens which may confer protective immunity.

Vaccine development

Research on the development of vaccines has been conducted both within and outside the Programme. Nonetheless, it may be noted that a substantial number of

results have been achieved in projects either wholly or partially financed, or at least initiated, by the Programme. This fact is important for several reasons, not least because it entitles Programme personnel to take part in negotiations concerning the large-scale vaccine production that must precede future mass-vaccination programmes.

IMMAL therefore has close contact and collaborates with other international and national agencies which are deploying heavy resources in the field. In addition to giving direct financial support to research projects, it has performed important co-ordinating functions, for example arranging several annual conferences at which various projects have been discussed by researchers within and outside the Programme and in industry. Co-ordinating activities have been of prime importance for the rapid development of this field. Liaison has also begun with the pharmaceutical industry and biotechnology enterprises, whose collaboration in developing and producing vaccines is essential. Following an introductory conference in October 1983, regular consultations have been held with representatives of a number of companies which have shown an interest in collaborating on vaccine development.

Full implementation of the Programme will require considerable financial and personnel resources in the next decade. These investments are required for continued work on gene-cloning and the characterisation and synthesis of antigens to combat both the asexual blood stages and the sexual forms of the parasite. In addition, major investments are needed for vaccine production and vaccination campaigns, including preparatory testing of vaccines, field trials and in-depth epidemiological studies. A major international conference in February 1985, at which guidelines were laid down for future vaccine development and the evaluation of vaccine trials, paved the way for the above-mentioned activities. Since then, there has been a conscious effort in the malaria component of the Programme to facilitate vaccine production by funding research in institutions where the necessary technology is available. Admittedly, research has involved massive participation by researchers and grant recipients, but the institutions are for the most part located in the industrialised countries. Progress to date could not have been achieved otherwise. While these efforts should continue for a further five years or so it is nonetheless also obvious that massive resources will be needed to transfer the new expertise to countries where malaria is the outstanding health problem. This will involve, for example, investments in existing centres in countries where malaria is endemic, and the establishment of

new centres for clinical evaluation of vaccination campaigns. In this connection, the Programme has a unique organisational potential for making a vital contribution under the aegis of WHO.

Immunodiagnosis

Improvements in existing diagnostic testing systems and the development of new methods must parallel vaccine development. IMMAL has financed a number of projects yielding important results, for example the development of a new and highly sensitive test for detecting sporozoites in infected mosquitoes. Existing radioimmunoassay and enzyme-linked immunoassay techniques have been improved and are partially ready for use in connection with vaccination trials and for certain epidemiological field studies. A register of monoclonal antibodies against the parasite's asexual blood stages has been started in Geneva and is accessible to researchers both in and outside the Programme. Tests for the detection of protective antibodies are being devised in several projects.

Immune mechanisms and immune pathology

Hitherto, investigation of humoral immunity has predominated; research under other headings has therefore been overshadowed. The rapid strides of the vaccine programme have made it clear that better insight is now required into the cellular mechanisms conferring effective protection against the disease. At a conference in the autumn of 1984, attended by researchers in and outside the Programme, a report was compiled on the current situation. The Programme is now funding an increased number of projects involving investigations of, for example, cellular protective mechanisms and immune pathology in cerebral malaria. An intensification of efforts in this field is planned for next few years.

(b) Chemotherapy

Several weapons in the battle against malaria were developed at the end of the 1940s, including new drugs such as chloroquine and insecticides such as DDT. Attempts to eradicate malaria were thwarted, however, partly by the development of resistance to DDT and other compounds among mosquitoes and partly by a rapid development of resistance to drugs in current use by Plasmodium falciparum, the parasite causing the most serious form of malaria. Although 300,000 substances were tested for their antimalarial effects in the 1970s, only a few compounds were produced which were conceivable for human use. In the field of bacteriology, by comparison, numerous

antibiotic derivatives were launched on the market in the same period.

Mefloquine is the first compound for 30 years to undergo clinical trials. The drug was originally produced outside the Programme, by the Walter Reed Army Institute of Research. Fruitful co-operation between the manufacturer, Hoffman-La Roche, and the Programme has resulted in the compound now being registered in Switzerland for prophylaxis and treatment among certain demographic groups. Clinical trials (phases 1, 2 and 3) are being conducted in Brazil, Zambia and Thailand. Owing to the risk of resistance arising, a combination anti-malarial (mefloquine, sulphadoxine and pyrimethamine) is also being tested in Thailand. Negotiations are also under way with five pharmaceutical companies on several new substances acting on the asexual blood forms (sporozoites and merozoites). The most interesting are derivatives of the Chinese drug Qinghaosu (artemisinine), which has a chemical structure entirely unlike that of anti-malarials in current use. Primaquine, which also acts on the tissue forms (gametes), is now the subject of intensive research, especially into its metabolism and mechanisms of action. One important step forward is the success achieved in cultivating P. vivax gametes: this now makes it possible for in vitro tests to be devised to ascertain the effect of primaquine on the tissue stages of P. vivax.

The Programme has actively collaborated in the production of test kits for in vitro trials of several drugs in current use against P. falciparum, and tests have been standardised in multi-centre studies in Switzerland, Thailand and the USA. Field trials have taken place in several countries where malaria is endemic.

Priority research fields for the immediate future are further clinical trials of new preparations and both field and laboratory studies of the development of resistance. Laboratory research to develop active anti-malarial substances must continue, as must attempts to devise simple and reliable methods for determining drug concentrations in the blood and urine.

Owing to the considerable risks of resistance to mefloquine appearing, a group of WHO experts have recommended that the drug should not be employed alone except to treat acute, multi-resistant malaria, and that in other cases combination preparations should be used.

(c) Field studies

The Programme has supported research in the field in certain areas in particular: surveys of the development of resistance in the malaria parasite, field trials of drugs, chemoprophylaxis and vector control.

A global system for surveying the emergence of resistance in P. falciparum has been developed and to a certain extent integrated with national health-care programmes in parts of South-East Asia, Africa and Latin America. Special kits for in vitro testing of resistance are manufactured in the Philippines and distributed jointly by WHO and the Special Programme.

Attempts to bring the pharmaceutical treatment of malaria into line with needs and opportunities in individual regions are under way in Central America (Guatemala), Africa (Kenya and Tanzania) and South-East Asia (Thailand). Chemoprophylactic models have been tested in several parts of Africa and Thailand. Malaria morbidity has been shown to decline sharply with a monthly anti-malarial intake in a controlled investigation in Liberia, in which Swedish researchers took part, whereas in wide-ranging, uncontrolled programmes in Kenya and Upper Volta, for example, the impact was small.

Some research on vectors has been done, and the research results obtained by IMMAL have also been useful. Our skill in identifying vectors which can transmit malaria to human hosts is now greatly improved and, using immunological techniques, it is possible not only to detect infection in a mosquito but also to identify the plasmodium species causing the infection.

Surprisingly good results have been obtained in vector-control experiments in Somalia, using larvivorous Oreochromis fish. In one study area in northern Somalia, the incidence of malaria declined significantly with the introduction of such fish in reservoirs. The species reproduces rapidly and is also suitable for eating. However, the method is probably viable only in certain ecological conditions. Promising trials with a special insecticide-spraying device have also been reported.

Future plans primarily concern the continuation of ongoing epidemiological projects on treatment, prophylaxis, the development of resistance and vector control. A heavy workload for this component of the Special Programme may be expected, in connection with planned field trials of vaccines and new drugs. It is therefore essential for the resources available for field studies to be built up in malaria-endemic

countries, and this includes the promotion of personnel training at various levels. Close co-operation with the Programme components for epidemiology, social and economic research and resource build-up, as well as with other components in the field of malaria, appears to be an essential precondition of success.

2.5.3 Schistosomiasis

Of the diseases covered by the Programme, schistosomiasis (bilharzia) is that which, after malaria, is considered most serious from the world health standpoint. The disease is caused by a worm (schistosoma) and is widespread in tropical and subtropical regions of South America, Africa and Asia. The number of individuals currently infected is estimated at 200 to 300 million. Since the disease spreads via infected water, children are particularly susceptible; about 90 per cent of infections are probably acquired by the age of 10 or 15.

Three species of Schistosoma are pathogenic to humans. Where geographical incidence and localisation in the infected organism are concerned, they are mutually distinct: S. mansoni (South America and Africa) is localised in the blood vessels in the portal system, while S. haematobium (with the same geographical distribution) inhabits the blood vessels surrounding the bladder. S. japonicum is restricted to Asia, including the Philippines, and localised in certain blood vessels connected to the intestinal canal. S. mekongii and S. intercalatum are two other species with a relatively small geographical range.

One phase in the parasite's reproduction is the formation and excretion of eggs via the infected individual's faeces or urine. Dead eggs deposited in the tissues during the excretion phase give rise to a chronic inflammation which, if sufficiently prolonged, leads to the transformation of connective tissue in the tissue in question (intestinal or bladder wall, liver or spleen), with resulting functional defects. The disease thus tends to be chronic, and its major significance as a world health problem lies in the enormous number of infected individuals, whose work capacity is diminished. However, schistosomiasis not infrequently takes an acute, more serious course, and may be fatal; according to estimates, it causes about 750,000 deaths annually.

Effective chemotherapy has gradually become available in recent years. The advantage of effective drugs such as oxamniquine (for S.mansoni) and metriphonate (for S. haemotobium) is that they are relatively cheap, while one drawback is that doses often

need to be repeated. Praziquantel, one of the latest drugs to appear, is effective in a single dose against both S. mansoni and S. haemotobium, but is about 5-8 times more expensive and therefore impracticable for widespread use in countries with hard-pressed economies. It may briefly be mentioned that the intricate interplay between the parasite and the infected host organism is one reason why an effective vaccine has been so elusive. In experiments on animals, a protective effect has been attainable from certain types of vaccine, but there is no current likelihood of a vaccine for human use being produced in the near future.

The Programme's efforts in research on schistosomiasis have, in short, concentrated on "identifying and developing new scientific methods for more effective, cheaper and simpler disease control". Control measures may in theory be oriented towards both parasite stages in the intermediate host - various freshwater snail species - and stages in the definitive, human host.

The efficacy of chemicals against snails has been investigated in projects funded by the Programme. Positive effects have been achieved where use is limited to relatively small, well-defined areas. Any large-scale use of molluscicides requires thorough evaluation and, above all, consideration of possible ecological side-effects. The potential of molluscicides of plant origin (such as Endod) is particularly interesting in this context, since such preparations can often be made from plants cultivated locally. However, molluscicides used as the sole means of intervention have had discouraging results where transmission is concerned.

To provide documentation for various health-care programmes, reliable, simple and cheap epidemiological methods are required to establish the range and prevalence of infection. With the support of the Programme, a simple and sensitive parasitological method has recently been developed for detecting eggs in the urine (S. haematobium). Since almost all children with massive S. haematobium infections have blood in their urine, the development of cheap test strips for haematuria detection is also being promoted. For the diagnosis of S. mansoni, its eggs must be detected in the faeces - a method which is arduous and time-consuming, and requires considerable experience on the part of laboratory staff. As an alternative to parasitological methods, serological methods have been developed. Their weakness, however, is that in their present form they cannot distinguish between active infections, i.e. those requiring treatment, and those which have healed.

Intensive research has been conducted, largely on Programme funds, to expose the mosaic of antigens in the various stages of the parasite's life cycle, in order if possible to find one or more "diagnostic antigens" which may permit a differentiation of the various stages of infection. The production of monoclonal antibodies, which may be used to engender these diagnostic antigens in pure form, is also of outstanding current interest. The Programme has also funded the development of simplified serological test methods.

The combination of a suitable diagnostic antigen with a cheap and simple serological technique may bring enhanced opportunities of large-scale epidemiological field studies which, in turn, can pave the way for further attempts at control, with correct and specific orientation.

The Programme has also co-operated in developing and studying various pharmaceuticals for the treatment of schistosomiasis; one example is the phase III studies of Praziquantel at the Tropical Research Centre in Ndola, Zambia. Large-scale chemotherapy has recently been applied in conjunction with the field projects in Burundi and Zanzibar. Initially, a striking reduction in the incidence of infection was noted. Since the studies conducted in other areas showed that a large segment of a treated population become reinfected relatively quickly, researchers prefer to await another evaluation before attempting to assess how long the effects of mass chemotherapy alone can last. Geographical and cultural divergences between different areas appear to play a major role in this connection. It should be emphasised that, for an optimal transmission-inhibiting effect, chemotherapy must be employed in conjunction with other measures such as the use of molluscicides, construction of latrines, removal of vegetation from beaches used for bathing and fishing, instruction on the spread of infection, etc. In this context, it is also worth mentioning that the Programme has initiated and stimulated research into the biochemistry and metabolism of the parasite, with a view to developing new, specific and selective anti-parasite compounds. The schistosomasis component of the Programme also offers numerous examples of fruitful co-operation between institutions in developing and industrialised countries.

In summary, it may be said that the Programme's schistosomiasis component has boosted, and been crucial for, the expansion of knowledge of this disease in recent years. As in other areas, the picture is one of contracting economic frames in an expansive development phase. It may also be pointed out that

previous major sponsors, such as the Edna McConnell Clark Foundation, have drastically cut their contributions to schistosomiasis, in favour of other fields. This being so, a concerted effort is essential to retain, or if possible reinforce, the role of the Programme in such research.

2.5.4 Filariasis

This group of diseases includes several infections caused by worms of the genus Filaria.

The two most important and commonest filarial diseases in human medicine are:

1. Onchocerciasis. This disease is most common in tropical Africa, but it also occurs in the eastern Mediterranean region and parts of Latin America. About 40 million people are estimated to have the disease. The infection is transmitted by black fly (genus Simulium), which contains the larva of Onchocerca volvulus. In humans, the adult worms collect in subcutaneous nodes or swellings. The symptoms of the disease are caused by the larvae - microfilaria - entering the blood stream. Victims suffer from intense itching and ocular symptoms, owing to the larvae damaging various parts of the eye. Onchocerciasis often leads to blindness. In endemic areas, blindness is therefore common in the adult population.

2. Lymphatic filariasis. This disease occurs in Asia, Africa and South America. It is estimated that about 90 million people are infested with lymphatic filariasis, which can be caused by three different species of parasite. The adult worms infest the lymph vessels and the microfilaria inhabit the blood stream. The disease manifests itself at an early stage as chronic swellings, above all in the lower extremities.

The Programme's efforts to combat filariasis have been concentrated primarily in two areas: the development and screening of filaricides, and immunology.

No satisfactory drug has yet been found against any of the filariases. Researchers are currently seeking a safe, non-toxic anti-filarial compound which can attack the macrofilaria or function embryostatically. Microfilaricides are transitory in effect; moreover, the majority produce severe side-effects in the form of the "Mazotti reaction", owing to toxic and allergenic substances released when the microfilaria disintegrate.

One problem connected with the drug trials has been that of finding suitable animal ~~subjects~~. The *Filaria* species which attack humans cannot infest animals, and work must therefore involve closely related *Filaria* species in experimental animals. An adequate animal model for *Onchocerca* species has now been found: cattle in Australia, after infection with *O. gibsoni*, exhibit symptoms closely resembling human onchocerciasis. However, owing to the animals' size, the model is not ideal.

Several thousand substances have been tested in experiments on animals, and two are now virtually ready for human trials. Ivermectin is a new anti-filarial compound now undergoing tests on humans, and it has yielded promising results. The compound affects adult female filaria, causing the larvae they bear to die. Only in exceptional cases does the Mazotti reaction occur.

There are close links between the Special Programme and the Onchocerciasis Control Programme in the Volta River Basin in West Africa. Collaboration consists of testing new filaricides and joint vector-control efforts.

In addition, the Programme supports research capable of elucidating immune reactions of importance for pathogenesis in natural infection or for drug reactions. Other activities conducted under Programme auspices are surveys aimed at exposing the antigen mosaic, and the design of simple, specific immunodiagnostic tests. The latter activity has been beset by problems owing to the occurrence in the *Filaria* parasites of antigens shared by, or cross-reactive with, antigens from other parasites. However, researchers have recently succeeded in developing specific methods of detecting filarial antigens in the blood stream, and an attempt is now being made to simplify these methods so that they are practicable in endemic areas.

2.5.5 Trypanosomiasis

Trypanosomiasis is an umbrella term for several diseases caused by flagellata belonging to the same family, but otherwise not very closely related. The diseases vary pathogenetically and clinically, and occur in different continents. African sleeping sickness occurs only in Africa south of the Sahara, and Chagas' disease is confined to the Americas, chiefly South and Central America.

African sleeping sickness

The disease is transmitted by the bite of the tsetse fly. The parasites first proliferate around the bite

and then spread to the nearest lymph-gland site. Reproduction proceeds apace, mainly in the lymph and blood, and the parasites are transported to all organs of the body. Parasitic infestation of the blood follows an undulating pattern: each peak corresponds to the appearance of a new surface antigen borne by the parasite. The central nervous system is invariably affected, and in the absence of treatment the disease culminates, as a rule, in death from chronic encephalitis.

There are two types of sleeping sickness in Africa. In East Africa, Trypanosoma rhodesiense causes a subacute infection, which may be fatal within a few weeks or months, whereas T. gambiense in West Africa gives a sub-chronic or chronic infection which usually lasts for several years.

Trypanosomiasis in Africa also poses a severe problem in veterinary medicine. The infection occurs in livestock and game, and may cause serious food-supply problems.

Around five million people in Africa inhabit endemic regions, and the known incidence is 20,000 cases annually. However, the true morbidity figure is probably a good deal higher.

The Special Programme has provided considerable financial support to research on sleeping sickness, but its most important contribution has been in drawing attention to this intractable - and, at the same time, scientifically interesting - disease, and co-ordinating research and trypanocide distribution.

Some of the most significant scientific results stem from research conducted outside the Programme. The identification and investigation of variant antigens borne by the parasite was first conducted outside the Programme and later received Programme support, though to a limited extent. Production of monoclonal antibodies, like the design of techniques for in vitro cultivation, previously took place entirely outside the Programme at ILRAD (the International Laboratory for Research on Animal Diseases) in Nairobi.

A few examples of Programme efforts in research and disease control are given below.

Under Programme auspices, a network of research groups working on various aspects of African sleeping sickness has been formed. Epidemiological work funded by the Programme is being carried out in several locations in Africa. Researchers are attempting to map the incidence and extent of the

disease. Related studies aimed at identifying vector species in the tsetse complex are under way. Simple aids have also been produced or developed and distributed by the Programme: examples are a simple agglutination test for the detection of antibodies in *T. gambiense* infection, a miniature anion exchanger which concentrates parasites in the blood (to determine parasitaemia) for *T. rhodesiense* diagnosis, and simple tsetse traps which, impregnated with insecticides and odoriferous substances resembling the host animal's smell, are highly effective.

The Programme supports the development and screening of trypanocides, and drug trials are conducted, for example, at a Programme-funded centre in Ivory Coast. The Programme has also initiated and funds post-mortem studies of sleeping-sickness victims. Investigations of this kind take place in Ivory Coast in collaboration with Glasgow University, and have yielded valuable information on the pathogenesis of the disease.

2.5.6 Chagas' disease

Chagas' disease is a chronic infection caused by *T. cruzi*, transmitted by blood-sucking triatomine bugs whose preferred habitat is poorly constructed and maintained dwellings. The infection thus has a clearly social background. Its onset is usually acute, with general symptoms of infection, and its subsequent course is subclinical, for a variable length of time - sometimes up to several decades. The manifest, chronic stage is characterised by irreversible changes in the peripheral nervous system, heart, oesophagus and large intestine. Patients often die of heart failure. The disease may be cured in the acute phase, but there is no effective therapy for the chronic phase.

In previous years, the Programme's Chagas' disease component failed to function satisfactorily, and difficulties were experienced in co-ordinating research, which was not always target-oriented. Since the Steering Committees were reorganised - they now chiefly comprise researchers from endemic countries - activities have developed extremely well.

Attempts have been made to co-ordinate existing resources by forming research-group networks. Activities have been primarily oriented towards mapping the incidence and extent of the disease in Latin America. Research groups in various endemic countries are now collaborating and carrying out parallel studies, using standardised protocols and methodology. Both prevalence studies and longitudinal projects are being conducted in this manner.

Ten diagnostic laboratories in Latin America and one in the USA (CDC) co-operate and exchange information. One of the South American laboratories serves as a reference laboratory. The Programme is also funding current efforts to prevent transmission via blood tranfusion and to control vectors by new insecticides and new methods of using them, for example incorporating them into indoor paint for dwellings. Finally, the Programme is funding ongoing efforts to produce and screen new drugs against Chagas' disease.

It should be pointed out that Chagas' disease receives considerably less financial support from the Programme than African sleeping sickness, although the former is at least as serious as and probably more prevalent than the latter, and although considerably less support for research on Chagas' disease comes from sources outside the Programme than for its immunologically more interesting African counterpart.

2.5.7 Leishmaniases

The leishmaniases are a group of diseases, all caused by species of the large Leishmania family. Infection is transmitted by sandflies. In the vector, the parasite is a thin, elongated flagellatum; in its warm-blooded host, it soon metamorphoses into a small, oval parasite ~~inhabiting~~ phagocytic cells, especially macrophages.

Leishmaniasis occurs in the Mediterranean region and large parts of Asia (particularly India), Africa and South and Central America. The disease may manifest itself as a general infection (visceral leishmaniasis, VL), with fever, anaemia and invasion of the liver and spleen. Untreated, VL is almost always fatal. Leishmaniasis may also appear as localised ulcers or lesions in the skin and/or mucous membranes. As in leprosy, the interaction of the parasite and the host's immune system may produce a gamut of symptoms, from a state characterised by virtually defunct cell-mediated immune defences and heavy infestation to a condition of excessive cell-bound immunity in which parasites are sparse. Neither of these extreme forms heal spontaneously. On the other hand there are self-healing, relatively benign forms halfway along the scale. Systematically and immunologically, the Leishmania species of the Old and New Worlds are related only distantly.

As with Chagas' disease, the leishmaniasis component of the Programme receives very restricted financial support. Nevertheless, the Programme has made substantial contributions to leishmaniasis research, particularly in the vital classification of infective

agents. Modern methods, such as isoenzym~~atic~~ determination, monoclonal antibodies and hybrid DNA technology, have been developed for the characterisation of species and strains. The establishment of reference centres in Europe, Asia and Central America is significant: these centres can classify strains ~~in isolation~~ from patients, which permits the incidence and range of various species to be surveyed. Individual laboratories can also concentrate on particular parasite strains. In addition, a serum bank is expected to be created shortly, and will be able to provide laboratories with reference sera. These measures will greatly facilitate research and development work at regional level.

The Programme is also carrying out important work in the vector-control research field, and has initiated and funded investigations of ~~infective agent~~ reservoirs. In spite of limited resources, drug research in the field is also receiving support.

2.5.8 Leprosy

Leprosy cases now number about 11 million worldwide, concentrated in Africa, Asia and South America. In Europe there are about 25,000 cases. The disease is caused by Mycobacterium leprae, which is related to the tuberculosis bacterium and gives rise to a chronic infection. Owing partly to the infected individual's lowered resistance to ~~disease~~, there is a broad spectrum of symptoms from a harmless, localised skin infection to one which has spread to several organ systems. In the latter case, the patient suffers serious damage to the peripheral nerves and skin in particular, which may lead to severe disablement. The disease is also problematic in that it has immense psychosocial consequences, often culminating in the individual's ostracism from society.

The Programme's leprosy research has focused both on immunology (IMMLEP) and on chemotherapy (THELEP).

Immunological research has included the following emphases:

(1) The development of sensitive and effective diagnostic methods to permit early diagnosis and the commencement of treatment at an early phase of the disease. Thus it has been possible to characterise and synthesise a diagnostic antigen (PGL-1), against which leprosy patients alone appear to have antibodies. Monoclonal antibodies are also being studied for use in immunodiagnostic methods.

(2) The development of an effective vaccine. This has involved particular difficulties, since leprosy bacteria cannot be cultivated in the conventional way. Vaccine development is still dependent on the production of ~~the raw~~ material from infected armadillos. Preliminary trials have shown that the vaccine is tolerated sufficiently well to permit large-scale field trials, and such trials have already started or are planned in India, Venezuela and Malawi. In connection with the WHO vaccine development programme, molecular-biological research is also being funded, to characterise and isolate protective antigens with the aid of hybrid-DNA technology for use in future vaccines. IMMLEP plays an important part in co-ordinating these research activities.

Under the auspices of THELEP, research is being conducted into the development of resistance in leprosy bacteria to drugs such as dapsone, a sulpha compound which has hitherto been the main form of treatment. Owing to dapsone resistance, the potential use of this drug is not as simple as it was formerly, and further agents of leprosy control are needed. Several projects are in progress or planned, for example in Mali and Malawi, to evaluate the effects of various drug combinations; such combinations have already yielded promising preliminary results in India. In another project in the Philippines, researchers are studying possible ways of using prothionamide without this drug giving rise to hepatic toxicity.

The chief importance of the leprosy component of the Special Programme lies in its information and liaison work, not least in promoting contacts between developing and industrialised countries and organising the exchange of material between researchers in the field. In the development phase the component has now entered, it appears particularly important for support to be maintained.

2.5.9 Epidemiology

Since its inception, the Programme has had an autonomous epidemiological component, with overall functions for all the diseases, to collaborate with the groups for individual diseases.

Epidemiological studies have been in progress in a number of areas where several of the six diseases occur simultaneously, such as Ndola, Zambia. These have permitted endemic-area surveys of disease incidence which, in turn, are valuable for the planning and implementation of future control programmes.

Analytical epidemiological methods may be used for investigation of the relations between infections and disease, and in studying effects of individual-related and environmental and/or hygienic factors.

Advances in epidemiological methodology have enabled surveys to be conducted more rapidly and efficiently than ever. Case-control studies have proved to be an important aid in the identification of risk factors, and also in assessing the impact of intervention procedures adopted. It has been possible for primary health care to utilise the simple epidemiological methods developed for diagnostics and the monitoring of disease. Further development of such methods should be feasible - for example, methods of measuring the incidence and prevalence of infections in areas of high demographic mobility.

The following measures are planned for the immediate future:

- Attempts to identify factors of potential significance for the courses of the six diseases.

- Cost-effectiveness studies of possible control programmes, taking into account the health problems posed by the infection concerned in an endemic area. This type of assessment is essential for the optimal allocation of available finance.

- Evaluation of current control programmes as a basis for future operational research.

It is vital for national and regional capacity to be strengthened in the epidemiological field. Educational programmes comprising both postgraduate courses and research studies for more advanced researchers from endemic countries, as well as workshops in epidemiological research methods, are therefore planned.

The epidemiological component of the Programme initially encountered certain difficulties in finding suitable projects to support. Its goals were revised in 1984, and the advisory scientific group was reorganised. It now co-operates both with the social and economic research component of the Programme and with other WHO programmes, and appears to be functioning well. During 1985, the Programme's STAC group will be devoting one of its recurrent reviews to this component.

2.5.10 Social and economic research

When the Special Programme was initiated, the consensus was that research on medical technology must be supplemented by research on the adaptation of this technology and efforts to get it accepted in developing countries. Programme policy in relation to the social sciences was revised in 1981. More attention began to be paid to social, cultural and economic factors in the spread and control of diseases; in addition, the importance of epidemiology as a tool for assessing the prevalence and incidence of various diseases was strongly emphasised.

Only researchers in developing countries obtain Programme grants for social and economic research. The Programme is now funding descriptive and analytical research within the broad fields of social science, sociology, social anthropology, history and economics (e.g. cost assessments of adopting various disease-control strategies and developing different types of models). Some of these areas still need methodological improvement before their findings can be used in the Programme. Moreover, the component has an important role in field trials of various compounds.

The number of projects with social and economic aspects has been heavily increased in recent years, and 57 projects are now under way. As the Programme's social scientists see it, interest is growing among the researchers involved in control of the specific diseases. Each disease-oriented group has attempted to review the most promising control measures, and migration, for example, was found to be one of the factors influencing the spread of infections. Popular migrations affect the immunity situation in populations as a whole. Different groups' attitudes towards the diseases and towards methods of prevention and care play a major part in the successful implementation of control programmes. Popular participation in designing such programmes has often been neglected to date, and information programmes have not preceded start-ups. The Special Programme supports projects in these fields, and also studies to elucidate the integration of disease-control programmes with primary health care. The role of women in the prevention, diagnosis and control of tropical diseases, for example, has been underestimated in many health-care programmes.

One important issue is the recruitment of researchers from developing countries to work on interdisciplinary projects. Hitherto, Programme funding of such training has been limited, but possible M.Sc. courses in fields such as the social sciences and

public health are being investigated. One problem is career structure: in many developing countries, attractive promotion prospects are needed to tempt young researchers into these fields.

From the start, the Programme had set aside funds for two people to study the social and economic aspects of disease, but only one - an economist - had been appointed. For one year, a social anthropologist financed by Danida had assisted the Programme.

The programme of social and economic research on tropical diseases is of impressive quality, in view of the Special Programme's scarce personnel resources. The Programme has also prompted other WHO programmes to intensify their efforts in the social sciences.

It seems vital to point out the need for representatives of social sciences other than economics, not only among Programme staff but also in STAC and other groups. The current researcher in charge is an economist but has succeeded admirably in acquiring familiarity with other social sciences as well.

2.5.11 Vector biology
(see App. 9)

2.6 The balance between basic and applied research and between research based in industrialised and developing countries

The Special Programme supports a limited amount of basic research. It is above all in immunology, and especially the malaria and leprosy components, that it funds projects in the nature of fundamental research. An estimated 50 per cent or thereabouts of research grants disbursed in the immunology sub-components and 20-30 per cent of those in the chemotherapy sub-components are earmarked for basic research. The remainder are for applied research, but mainly in the laboratory sector. In connection with development work on vaccines against leprosy and malaria, experiments at molecular level are required, and the same applies to the development of modern techniques for identifying and typing several of the infective agents in question. The rapid development of biotechnology has greatly benefited the Programme. It may be said that the Programme's funding of basic research is well balanced against its aim of producing agents for controlling the six target diseases.

Table 1 shows the distribution, by country or continent, of research grants for immunology and chemotherapy in the specific disease-oriented components. The overwhelming proportion of grants have gone to the USA and a somewhat smaller proportion to Europe:

naturally, the grants go to institutions with the largest resources, and the majority of well-developed laboratories with the potential for high-tech research are in Europe and the USA. In Australia, highly skilled research on several of the target diseases has been built up, and an enhanced Programme commitment in this country should be considered. Another question is whether more use should not be made of the laboratory research expertise in several Programme-funded institutions in endemic areas, particularly South-East Asia and Latin America.

Table 2 shows the distribution of Programme grants among disease-oriented components and countries or continents. As mentioned above, most laboratory research grants go to the USA, and somewhat fewer to Europe; among European countries, Britain receives most. Other parts of the world obtain consistently few grants for laboratory research, except for Chagas' disease, on which most research takes place in Latin America. However, it is somewhat surprising that six Chagas' disease projects are under way in Europe, and also that eleven grants for research on African sleeping sickness go to the USA. Sleeping-sickness research is otherwise largely concentrated in Africa, with European scientific support. Research grants for field studies of the six target diseases have to a greater extent been disbursed in endemic countries, although 30 per cent have still gone to non-endemic countries.

As shown in Tables 2 and 3, the malaria component has the biggest share of the Programme's research grants for the specific disease programmes. This can be justified with reference to the extent and severity of malaria, as well as existing opportunities of producing an effective vaccine in the foreseeable future. These considerations, coupled with the fact that malaria can infect Western visitors, also enhance prospects of obtaining grants from funding research councils and institutions in industrialised countries. Such opportunities are hardly at the disposal of the disease components for Chagas' disease and leishmaniasis, which are only meagrely funded by the Programme. A certain redisposition of available research funds to the advantage of these two components should therefore be considered.

Nevertheless, it is clear that the major field trials planned for the evaluation of new vaccines against leprosy and malaria, as for new drugs, will not easily find grant donors outside the Programme, and that the Programme will therefore face major financial problems in the next few years.

2.7 The strengthening of research capability as a component of the Programme

Within the Programme, there is ample awareness of the problems which may arise in connection with attempts to build up or reinforce research capability in developing countries. Political instability may make activity in the study area difficult or even impossible. The Programme therefore often adopts a wait-and-see attitude when it comes to supporting institutions in countries where the political situation is unstable. A country should also be sufficiently developed economically to take over the costs of expanded research activities when the Programme grant period expires after 3-5 years. For funding purposes, the Programme as a rule stipulates a university organisation of fairly high standard, with good relations between the university, ministry of health and national health programmes. The Programme has also tried to obviate cultural and social problems by appointing experienced researchers (university professors) from each of the three disease-endemic regions (Africa, South-East Asia and Latin America) to work in the respective region. They all possess good local knowledge and often visit the institutions in their own areas.

Attempting to improve research capability in a country which has had a well-developed organisation led and administered by foreign researchers involves particular problems. In many countries, researchers have left their posts without rooting their activities in the localities concerned, to the extent which is desirable, by forming a national cadre of researchers. The results of much essential research on the endemic diseases of the developing countries are now to be found in the industrial countries' libraries. It is vital that past errors of this kind are not repeated.

About 25 per cent of the Programme budget goes on the component for strengthening the research capability of developing countries. Of this sum, half is used for institutional support, in the form of either capital grants or long-term institutional grants. The remainder is used for training. Research students, and in some cases institutional technicians, can obtain scholarships to study at other institutions. The Programme is increasingly trying to promote institutional training in other endemic countries, but the majority of research students are still sent to the West. On returning to the home institution, a young researcher may receive a re-entry grant to start his or her own research. Educational support is always given after application by the research student's institution, never to a

private applicant. The Programme continues to disburse grants to institutions it already supports, and sometimes tries to expand this activity with the help of other, smaller institutions in the same regions. Owing to limited financial resources, initiating new projects is feasible only to a small extent.

The Programme also includes other capacity-strengthening activities. Some training of researchers is built into the specific disease components; these tend to award research grants to groups receiving research students from endemic countries. Some courses are also held in conjunction with other Programme activities: the components for social and economic research and epidemiology, for example, have arranged their own seminars and workshops independently. The aim is for the component for strengthening research capability to take over responsibility in future for the educational activities now pursued by the biomedical sciences group.

The Programme is trying to create a network of groups involved in providing scientific information in the regions. In addition, grants to institutions always cover subscriptions to scientific journals. The institution must bind itself to retain the subscription even after the funding has ceased. Even so, many libraries in developing countries almost entirely lack journals and other scientific literature from the last few years, owing to the current economic crisis, especially in the African countries.

The Programme is attempting to establish collaboration between the research institutions it supports and other institutions in the same regions with experience in the same research fields. This approach seems to have been particularly successful in South-East Asia, where there are now networks of co-operating institutions which can jointly tackle current issues on a broad base.

In connection with its capability-strengthening activities at various institutions in the developing countries, the Programme also collaborates with institutions in the industrialised countries, especially universities and tropical research institutes in Britain and the USA. Of a total of 36 institutions in developing countries which have received Programme support since 1983, nine are also supported by Britain and 13 by the USA. The Programme also collaborates with Sweden, via SAREC, and up to 1984 took part in organising a research training programme at the University of Ibadan, Nigeria, with the Department of Clinical Pharmacology, Karolinska Institute. Three physicians and a microbiologist from the Somali

National University are currently being trained at the Department of Parasitology of Sweden's National Bacteriological Laboratory. Activities of this kind constitute much-needed backing, both financial and scientific, for institutions in developing countries. However, there also seems to be a certain inherent future risk. Research groups from industrial countries who have formerly participated in research programmes in endemic countries, above all in Africa, without giving their activities firm roots in the respective institutions there, are now once more involved in co-operation with developing countries. One can but hope that the Programme will ensure that, this time, the co-operation will be of lasting value to the local institutions concerned. (Table 4).

Efforts to build up research capability in endemic countries are aimed at making meaningful research possible at various levels in areas where one or more of the six target diseases are endemic. Political, economic and cultural factors may greatly impede such attempts. The Programme appears to have achieved most success with its resource-strengthening activities in South-East Asia, where preconditions have also been most favourable. This region now has local research groups of a high standard, fully comparable with groups in the West. The Programme's activities in Latin America have also been successful. The most daunting problems have been those in Africa, where dependence on the institutions and researchers of industrial countries is still heavy and the future of even well-established institutions, such as the one at Ndola, Zambia, must be regarded as uncertain.

2.8 Collaboration with the pharmaceutical industry

2.8.1 Introduction

Major problems are involved in developing new drugs to treat parasitic tropical diseases. In general, such research and development work is costly: mefloquine - an anti-malarial compound - is estimated to have cost MSEK 1,000 to develop. It is a protracted business. Research is often more speculative in nature than for other diseases, i.e. relatively fewer preparations prove to be effective. Complex parasitic life cycles, the appearance of resistance to drugs, deficient background data (owing to previous neglect of these areas) and a lack of satisfactory in vitro and in vivo models are examples of other difficulties. Treatments must be simple (often single doses) and drugs cheap in order to be of practical importance in developing countries. The presumptive incomes of the pharmaceutical industry are therefore

small, for numerous reasons. According to one estimate, the world market for anti-parasite compounds is MSEK 30, whereas that for antibiotics is MSEK 3,000.

2.8.2 Collaboration with the industry

Collaboration with the pharmaceutical industry has grown considerably: the Programme considers this essential for the development, testing, manufacture and marketing of new compounds. Types of liaison vary. The Programme employs WHO model agreements. In developing drugs, informal co-operation is the rule. One example is the anti-malarial compound mefloquine, where the Walter Reed Army Institute, USA, the Special Programme and the Swiss pharmaceutical company Hoffman-La Roche co-operate in development and production. In addition, a compound for treating onchocerciasis has been developed and tested clinically by the firm Merck & Company Inc., USA, the Special Programme and the WHO programme for control of this disease. Thirty-seven industrial agreements have been concluded with enterprises in seven different countries, the overwhelming proportion in the USA. In 1985, co-operation was in progress with 20 companies. WHO has patent rights, and works generally to promote the interests of developing countries within the framework of industrial collaboration.

In brief, the Programme has a realistic attitude towards the need to collaborate with industry. The agreement with Hoffman-La Roche is considered to be a model of satisfactory collaboration of this kind.

2.9 Reports on the Programme

Prior to the annual meetings, the Special Programme issues both a comprehensive annual report describing activities in the different occupational spheres and a catalogue giving systematic accounts of grant allocation in the various Programme fields. The contents of the former were previously issued in a manner which made overview awkward, and delegates to annual meetings therefore found it difficult to obtain a clear picture of activities. Moreover, reports omitted to state whether the various projects were financed entirely or partially by the Programme.

The latest annual report - for the financial years 1983 and 1984 - is much clearer and more satisfactory where both content and layout are concerned. It presents an overview of the most important research findings in the various fields and a clear account both of Programme grants and of results and publications unconnected with the Programme. This change in Programme reporting corresponds to the desire for clearer presentation expressed in SAREC's 1981 evaluation report.

In addition, the Programme includes extensive publication activities - newsletter, bibliographies, etc. - and reports from SWG meetings and seminars are also available. One valuable series of publications contains lectures and comments from all Programme workshops. However, it would also be useful for donors wishing to obtain a thorough knowledge of the Programme to have access to Scientific and Technical Review Committees' reports, which are at present confidential.

2.10 Funds and budget of the Programme

Trends in Programme income and expenditure are shown in the diagram below, which is taken from the 1983/84 annual report.

Figure 1

To date, the Programme has obtained contributions from over 40 countries and organisations. Altogether, the largest amounts have been donated by Denmark, the USA (support was first given in 1979) and Sweden. Since 1981, the World Bank grant has corresponded to about 10 per cent of its budget.

Total Programme expenditure in 1983 was slightly over US $ 20 million. (Figure 2).

In the initial years of the Programme, Sweden's contribution represented 17 per cent of the total. This proportion declined to 10 per cent by 1981; in 1982 it was nearly 13 per cent and in 1983 slightly below 8 per cent of the Programme budget.

The Programme has stressed the importance of at least maintaining its activities at current levels, in order to preserve the operational efficiency now attained. Within a few years, further resources are expected to be required for expensive field trials of new drugs and vaccines. The Programme's financial prospects now appear somewhat brighter than they were, thanks to larger contributions from the USA, but its management points out that activities are already severely restricted by lack of funds. Promising projects cannot be supported in a desirable way, and as a result research results are delayed. Too many applications for research grants from institutions in developing countries have had to be rejected.

Where Programme finances are concerned, Sweden has urged that earmarked contributions be ruled out. This has become an established principle which, however, has recently been questioned, since earmarked grants are considered easier to obtain. The Swedish attitude up to now has been that this would seriously affect the Programme's independent priorities, and this view was discussed at the 1985 meeting with JCB. The Programme is currently studying the question.

The proportion of administrative costs in the total budget is shown in the figure below, from the latest annual report, to be less than 10 per cent.

Figure 2
Budget for various types of expenditure, 1982-83

3 SUMMARY: ASSESSMENT AND CONCLUSIONS

The Programme can now look back on almost a decade in operation. With some exceptions, activities have yielded good results, in some respects probably exceeding original expectations. The Programme has opportunely focused the attention of the international research community on six previously neglected diseases, all of which pose severe health problems in countries where they are endemic. Research on these diseases was to a large extent favoured by the rapid advance of biotechnology which took place shortly after the Programme's inception. With the exploitation of modern techniques, remarkably fast progress has been made in the development of vaccines against malaria and leprosy. Other effective compounds for controlling these diseases are being developed, and modern methods of identifying and typing infective agents greatly assist the work of surveying their incidence and extent. New drugs have emerged since Programme activities started and now await testing in field trials. Much of the rapid development of research relating to the six target diseases has come about outside the Programme, but the latter's catalytic and co-ordinating role is indisputable.

The build-up and continued evolution of the Programme correspond in many ways to SAREC's research-funding principles. Sweden has pressed for the extension of research activities to cover the ecological, social and economic contexts of the diseases. Sweden has also emphasised the value of initiating and supporting operational and epidemiological research within the framework of the endemic countries' own control programmes, especially in view of the consolidation of national research capability in this respect. Sweden has laid particular emphasis on the Programme's second major objective, which is in accord with SAREC's, urging that a large part of the budget should go towards capability-strengthening activities. This stand has involved controversy with certain other industrialised countries, which consider the first objective more important and believe any alternative policy will lower the quality of technical research. In certain fields, such as immunology, the bulk of research has been conducted in industrialised countries, and this has been conducive to rapid development. About 25 per cent of the Programme budget goes on strengthening the research capability of developing countries; a growing number of research projects are based in developing countries and run by indigenous researchers.

The latest annual report states that in the period 1975-1984 the Programme awarded grants to about 2,300 projects, of which just over 1,300 were conducted at institutions in endemic developing countries. One way of gauging the results of this research is to estimate the number of articles or reports published in scientific journals, monograph series, etc. By the end of 1984, more than 3,800 articles had been published and a further 420 were being printed. Of all the publications, half had appeared in 1983/84 - roughly the same number in industrial and developing countries. The estimated number of theses - Ph.D. and M.Sc. - backed by Programme grants in the period 1975-84 is 146. Since SAREC funds about 10 per cent of Programme activities, the result may be estimated at about 230 projects and 380 publications. These figures should be compared with the number of projects and publications relating to the six target diseases for which SAREC provides funds in the course of its other activities - direct, bilateral co-operation with individual countries and projects arising from Swedish applications. In that case, the cost to SAREC of administering these projects should be included.

Some critical views of Programme research may justifiably be expressed. The pace of research on the diseases caused by filaria has been markedly slow. However, this appears to reflect biological problems: the parasites in question are adept at evading the host organism's defence mechanisms and not easily neutralised by drugs. Nonetheless, there have been some recent successes, and there are solid grounds for continuing Programme activities in this field. There does not seem to be much potential for further development of the vector-control component, and the disease-specific components would probably perform its tasks better. (App. 9).

The second objective of the Programme has been to strengthen research capability in countries where one or more of the six target diseases are endemic. This objective has been more difficult to fulfil. A realistic view of the problems involved has been adopted and an effort made to approach them with an awareness of the cultural, social and economic features of countries obtaining Programme support. Increasingly, an attempt is being made to create regional networks of institutions with which co-operation is feasible; this appears to be a strategy yielding good results. The greatest difficulties have been encountered in Africa, while the Programme has achieved considerable success with its capability-strengthening activities in South-East Asia and Latin America. It is essential for institutions in endemic areas to be included at the earliest possible opportunity in international

networks and incorporated into the specific disease-oriented programmes.

Nevertheless, it is clear that the major field trials planned for the evaluation of new vaccines against leprosy and malaria, and of new drugs, will not easily find donors outside the Programme, and that the Programme will therefore be faced with financial problems in the next few years.

The importance of a coherent programme for tackling the target diseases - including socio-economic and epidemiological expertise - must be emphasised strongly, since research in the field of tropical medicine has neglected the latter fields. The epidemiological and socio-economic components are in need of further reinforcement. Both the Programme's objectives - basic and applied interdisciplinary research, and support to the strengthening of capability in developing countries - are unique, and its role in pursuing them would be hard to replace.

The chronological perspective of the Programme should be assessed for each of the various research fields supported. For the majority, termination of the Programme would mean serious setbacks to research on the diseases concerned. In recent years, the Programme has also acquired more of a co-ordinating and catalytic role, which is felt to be crucial. Its continuation as a united whole for a further ten-year period would appear to be a reasonable goal. The current capacity of the regular WHO organisation to take over Programme-backed research activities is extremely inadequate.

SAREC is justified in taking up discussions with WHO on a long-term schedule for the take-over of Programme activities. Certain elements of the Programme, for example leprosy research activities, are run jointly by the Programme and the regular WHO organisation. A gradual increase in WHO's financial and manpower responsibilities for the Programme should be possible. However, this presupposes expanded and modified WHO activities at central, regional and national levels. One reason why the special research programmes were established was that, as mentioned above, the regular WHO organisation lacked the capacity to assume responsibility for research programmes. A gradual take-over of Programme activities by WHO therefore presupposes both policy decisions by the World Health Assembly and time for WHO to alter its organisational structure. An expansion at regional and national level has begun, but is bound to take time. Another precondition is the transfer of extra funds to WHO's regional and national organisation.

For a number of years, SAREC has supported several different research programmes in WHO. The Special Programme, owing to its dual purpose - research and the strengthening of capability - has concentrated heavily on the implementation of research results in the endemic countries concerned. In recent years, owing to lack of funds, the Programme has been unable to support a number of institutions in more poverty-stricken developing countries. There is reason to stress the need for supplementary backing of research on tropical diseases. Such backing may comprise grants to national university and research institutions or to health care authorities' research programmes for the development, adaptation and exploitation of research results, and could be given as part of SAREC's direct, bilateral co-operation with other countries. By the same token, greater use may be made of Swedish, Scandinavian and/or other institutional resources. The potential for collaboration with Swedish foreign aid authorities - both SAREC and SIDA (the Swedish International Development Authority) - should be expanded.

One example of SAREC-backed co-operation of this kind is the Programme's grant - initiated by SAREC - to the medical faculty of the Somali National University. Experience from Programme-funded malaria research in several countries shows that there is a paramount need to build up resources for field studies in the endemic countries and also financial and other support, e.g. for personnel training. SIDA funds certain field research programmes on malaria and leprosy in India, but the Special Programme has found it difficult to devise channels of similar support in that country, although discussions with the Indian authorities are now under way. Increased co-operation between SAREC, SIDA and the Programme in India and, perhaps, other countries within the sphere of field studies, for example, is highly desirable. The Programme has concentrated on networks to strengthen contacts between research institutions in the same regions. These networks should be surveyed in the countries with which SAREC collaborates, so as to identify possible ways of further reinforcing and/or supplementing co-operation with the Programme. Contact with SIDA should be retained for the co-ordination of various efforts. Discussions must continue on the forms and content of any closer co-operation between SIDA and SAREC.

SAREC thus has reason to investigate more closely how the results of Programme-funded research in various fields reach the consumers concerned. The stage prior to local application of research results may be further exemplified with reference to malaria: here, the need is for continued testing of various

anti-malarial drugs and for vector-control measures, i.e. the introduction of special larvivorous fish and experiments with special insecticide-spraying devices.

In-depth knowledge accruing from the special epidemiological and socio-economic research components of the Programme where mapping, prevention and control of the six diseases are concerned must be adapted to local needs. SAREC should give particular support to these components, which have hitherto been weak elements of most national programmes in the endemic countries.

The annual Swedish contribution to the Programme in the last few years has been MSEK 13. An write-up to MSEK 16 annually for the next two years appears to be advisable owing both to the Programme's extensive needs for costly field studies in the years to come and to the decline in real terms due to the falling value of the Swedish krona. At the same time surveys should be conducted, in the countries supported by SAREC, of further resource requirements to permit exploitation and adaptation of the technology which has emerged under the aegis of the Programme. The SAREC-Special Programme co-operation model created in Somalia should serve as a lodestar for SAREC's continued studies of support at national level.