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RESEARCH AND TRAINING IN TROPICAL DISEASES (TDR)

Geneva, 28 August-1 September 1989

REPORT OF PROSPECTIVE THEMATIC REVIEW (PTR) ON DIRECTIONS AND ORGANIZATION OF TDR'S RESEARCH AND DEVELOPMENT RELATED TO DRUGS

CONTENTS

1. TERMS OF REFERENCE

The Committee met in Geneva from 28 August - 1 September 1989 to undertake a Prospective Thematic Review on Research and Development Related to Drugs. The first two days of the meeting were taken up by presentations by invited participants on current research topics pertinent to this Review. On the last three days, the PTR had discussions with Director, TDR. The objectives of the PTR as stated in the Terms of Reference were to:

a) Outline and assess briefly the present status and constraints of drug development in relation to TDR's target diseases.

b) Review and assess briefly TDR activities in the area of drug development.

c) Outline current thrusts and expected future directions of research and development in this area.

c) Make specific recommendations on (i) priorities for TDR in the area of drug research and development, and (ii) how TDR should organize the required activity.

2. COMMENTS AND RECOMMENDATIONS OF STAC SUBCOMMITTEE

General Recommendations

Two areas are in special need of evaluation (covered by two days of meeting):

a) Distribution and delivery of drugs already available (or to be developed in the future).

b) Improve the capability of TDR to carry out the development of potential new drugs.

Specific recommendations on these areas were made to TDR by the STAC subcommittee (in consultation with Director TDR).

2.1 Drug delivery

TDR to undertake "demonstration projects" to improve availability of drugs to underserved target populations, and study various mechanisms in different countries.

Three anthelminthic drugs, praziquantel, ivermectin and albendazole, were chosen as the first drugs to be tried in these projects.

Four potential models to be evaluated, in which the major criteria of success are that the drug reaches the target populations, and the system proves sustainable. Regional production of the chosen drugs would be encouraged.

Model 1. Traditional, in that TDR/WHO would, in consultation with the country concerned, develop a drug distribution programme which would be funded through normal aid channels.

Model 2. A novel approach in that the private sector would provide the drugs, funding and expertise in drug delivery. TDR/WHO and the countries concerned would provide guidance in this three-way partnership.

Model 3. TDR/WHO to fully sponsor the project in consultation with the country concerned.

Model 4. In countries where an infrastructure for drug manufacture exists (e.g. India, Thailand, Brazil), but delivery to the target population does not currently occur, TDR/WHO could provide technical assistance on improved delivery systems.

Identification of successful mechanisms for effective drug delivery would offer a model for other diseases, e.g. multidrug treatment of leprosy.

In order for STAC to evaluate the value and feasibility of the projects of drug delivery in developing countries, additional information will be required:

a) Determine possible countries where it would be of interest to set up such a delivery project, and recommend the models for implementation that would be most appropriate for that country.

b) Provide information on feasibility of linking the delivery of drug to existing programmes, e.g. EPI (which may be contemplating school vaccination in certain countries against tetanus), or CDD, and on involving UNICEF early on as a possible agency for maintaining successful programmes in certain countries.

c) Explore possible relationships with the private sector to enable Model 2 of drug delivery to be established and to facilitate cooperation in drug development.

d) Develop a plan for public information that will focus attention to the project and stimulate participation in the country.

2.2 Drug development

To improve the TDR programme in drug development, it was recommended that a special task force, representing all diseases of TDR, should be established. Members of the task force should be chosen from members of Steering Committees with expertise in the areas of drug development, with coopted outside experts. Selection of drugs for further development would be by the Steering Committees concerned.

A product manager, supervising several project managers, would ensure optimal progress of each selected product under development.

Finance for product development would come from a percentage of existing programme funds, or preferably by obtaining additional funds.

It is essential that the product development team have its own source of funding.

In the absence of suitable drugs, there is an urgent need to intensify drug research and development for leishmaniasis, Chagas disease and African trypanosomiasis.

REPORT OF THE MEETING

3. INTRODUCTION

The Special Programme for Research and Training in Tropical Diseases (TDR) was set up in 1977 with a mandate which includes the development of new and better technologies for the control of tropical diseases. In the twelve years of its existence, and with a modest budget ranging from US$ 20-30 million per annum, the TDR Programme has been associated with the development of over sixty such products. It has had a major impact on basic research, as judged both by scientific publications of research it has supported and by other criteria such as the number of parasite genes cloned. On the drug development side, it has done much to promote clinical work, especially regarding the standardization and vetting of protocols, post-registration field trials of drugs such as ivermectin, mefloquine and halofantrine and the evaluation of multidrug therapy for leprosy. It has tended, however, to leave preclinical development to the pharmaceutical industry and has not been directly involved in the drug distribution business. The former is becoming an increasing problem with the demise of the pharmaceutical industry's activities in this area; the latter is a continuing problem. The purpose of this meeting, therefore, was to review the current situation with regard to consumer potential, drug distribution

systems, drug registration, research and development strategies and current mode of operation of programmes dealing with tropical diseases, with particular emphasis on preclinical development, on drug distribution and on the way ahead.

4. DISEASE TARGETS AND POPULATIONS

4.1 Disease Targets

The exact numbers of individuals at risk from, infected with and suffering morbidity or mortality because of tropical diseases continues to be a matter for dispute. For example, estimates for malaria range from 500 000 to 2 300 000 deaths per annum and 100-489 million infections. What is clear, however, is that substantial numbers are involved, especially for malaria, schistosomiasis and the filariases. The numbers are readily elevated by economic activities, e.g., the building of a dam for irrigation purposes, mining or the provision of housing close to vector habitats. Economic development schemes and private industry often inadvertently create disease problems by their activities, and must be made aware that prompt treatment of these diseases gives economic benefits from increased productivity.

There is thus a substantial requirement for chemotherapy. For acute diseases such as malaria, this tends to manifest itself in terms of self medication with drugs purchased from a pharmacy. For more chronic diseases such as schistosomiasis, drugs tend instead to be provided by the public sector. Such chemotherapy for malaria is dominated at present by problems of chloroquine resistance since the alternatives are more toxic and/or more costly. Praziquantel is an excellent schistosomicide but under-utilized at present. Chemotherapy for leishmaniases is associated with serious adverse reactions; that for Chagas disease is also not very efficacious. The treatment of African trypanosomiasis has received a boost with the introduction of eflornithine for infections due to *T. gambiense*, and ivermectin has revolutionized the control of morbidity in onchocerciasis. Multidrug therapy is producing very encouraging results in leprosy.

4.2 Needs for New Drugs

For some diseases new drugs are urgently required; in other areas, they are highly desirable. Ideally, these should not only be highly efficacious, well tolerated and active by the oral route, but also active in a single dose. The priority for malaria is drugs to overcome the problem of chloroquine resistance but there are also other needs such as an alternative to primaquine. In leishmaniasis, a drug active by the oral route would be particularly valued. Chagas disease is still awaiting treatment for chronic cases. In African trypanosomiasis, the control of cases with neurological involvement is a continuing problem, especially in cases of *Trypanosoma rhodesiense*. Filariasis still needs a macrofilaricide; leprosy, a single entity treatment effective in a small number of doses.

4.3 Expenditure on Tropical Diseases

The need to attempt to control tropical diseases is recognized in most endemic countries but there are often no hard figures on what is actually spent. Government spending involves vector control, diagnosis and health

education, as well as drugs. Individuals spend mostly on drugs.

Government spending on health care varies from year to year, especially in oil-based economies. The variation is particularly marked in the spending on drugs which involves use of hard currency and therefore is subject to variations in the fortunes of the economy as a whole. Drug purchase does not involve fixed personnel costs and so it can be changed dramatically from year to year.

Data of spending by individuals is sparse but is considered to be small: to be measured in cents per annum, not dollars per annum. About 2-5% of family income tends to be spent on total health care, 30-50% of this on drugs. Since tropical diseases tend to inflict the poor, this means that total spending is very low. There could, however, be potential here for increased purchase of drugs: for example, spending on cigarettes is much higher. Clearly there is a market for drug sales to Third World countries.

4.4 Consumer Potential

Current usage rates of drugs in third world countries are low. In 1985, 79% of all drugs sold in the world were used by the 24% of the population living in the developed world. Up to 40% of the world's population (i.e., 2.3 billion people) have no access to a basic range of essential drugs.

Drug development is both an expensive and lengthy process. Current industry estimates put total development time and costs at 13 years and US$ 125 million per New Chemical Entity, respectively, and these are increasing.

Companies must obtain a return on this investment through sales of the product and all pharmaceutical companies assess sales potential prior to a compound entering clinical development - using arbitrary, actual and cumulative three- and five-year sales figures. Since there are both price and volume considerations, companies focus their R&D efforts on diseases which are prevalent in the first world where high margins can be achieved even if volume sales are lower than expected.

The industry conducts little research into third world specific diseases because the majority of individuals suffering from these conditions are both outside the economy and outside traditional distribution systems. For example, in 1986 there were only 26 antiparasitic drugs in development worldwide as opposed to over 500 in each of the eight major therapeutic areas.

These considerations may explain why Merck donated, rather than sold, ivermectin for use in filariasis and also explain the poor utilization of praziquantel in areas with a high prevalence of schistosomiasis.

Possible solutions to this problem relate to decreasing R&D costs (and therefore prices charged) and increasing volume (i.e., opening up of non-traditional distribution systems).

Ivermectin and albendazole were cheap to develop for medical use, for example, because they had already been marketed for veterinary diseases. This approach will not solve the problem when there is no large veterinary equivalent market and where existing drugs are of limited value, e.g., African trypanosomiasis, Chagas disease, leishmaniasis.

SK&F's recent approach to this problem has involved setting up a small dedicated management centre and promoting projects to international agencies which utilize their products, thus enhancing their total sales. These involve mass treatment for chronic infections in targeted populations (where preliminary diagnosis is not cost effective).

In the treatment of helminthiasis, for example, current programmes target the distribution of albendazole to school children, the drug being administered by teachers.

In acute diseases such as malaria and hepatitis B, the company searches for first world applications of, essentially, third world specific agents and operates a dual pricing strategy. For example, a presumptive emergency treatment pack for travellers to areas with multidrug-resistant malaria could be priced considerably higher than the same product sold in the visited area. Such an approach is being considered for halofantrine.

5. DRUG PURCHASE AND DISTRIBUTION

5.1 Essential Drugs Programme of WHO

The main objective here is to improve the accessability to key drugs in developing countries and to promote the rational use of drugs in general. The programme has comprehensive technical support programmes in over fifty developing countries, covering all steps in the selection, registration, supply, quality control, distribution of drugs as well as training in their management and rational use. The programme is in a position to advise governments on the selection of drugs and treatment guidelines for the public sector. As such, the programme can contribute to the early acceptance and adequate distribution and use of new drugs for tropical diseases in the field.

5.2 Role of UNICEF

UNICEF runs a programme which provides packs of essential drugs intended for children and pregnant women. Its budget last year was over US$ 50 million, about half of which goes on supplies and equipment. For example, in 1988, it spent US$ 35 million on six vaccines. Drugs (mainly generics) are purchased in bulk by international tender and shipped to Denmark where the packs are put together. The composition of these can vary not only from country to country but also by regions within a country.

5.3 Bilateral Agencies

In USAID, money is not used for research; some product development is supported but the principal activity is the implementation in developing areas of known technologies. However, it was suggested that some bilateral agencies might be interested in community Phase IV trials, and distribution of drugs, if TDR carried out trials to the Phase III level.

5.4 Private Sector

It was suggested that venture capital from the private sector might help the drug supply problem by providing a drug distribution system for Third World diseases, at a profit. Thus develops a niche not currently occupied by either

the larger pharmaceutical companies nor the international agencies. The principal partners would be the Third World countries, the industry and the aid agencies. Their basic strategy would be to ignore specific diagnoses and concentrate on the mass treatment market. To reduce overheads concurrent parasite chemotherapy (CPC), using albendazole, ivermectin, and praziquantel for helminth infections, could be practiced. Drugs would be ordered in bulk and therefore at minimal prices from the industry, using money provided by the donor agencies. Delivery and distribution would be organized and overall results of therapy monitored. For this service, a fee would be taken from donor agencies. Venture capital usually does not attract the high overheads of established companies. The Third World would gain from better drug availability; the industry from larger orders; the donors hopefully from lower unit prices as usage increases.

6. REGISTRATION OF DRUGS FOR THE THIRD WORLD

Most of WHO's work in this area is done by discussion with the national regulatory authorities. The advisory essential drugs list is regularly updated and new drugs for tropical diseases quickly enter this list. Inclusion leads to transfer to national drug purchase lists, and hence increased utilization. Model prescribing information is being prepared. There is increasing concern about false and substandard drugs. An annual list of compounds banned on grounds of safety is circulated. Drug registration in a wide range of countries could be speeded up if an international data file could be established and if WHO organized a meeting of the main regulatory agencies from the countries where registration was contemplated, immediately prior to registration.

7. ROLE OF DEVELOPING COUNTRIES IN DRUG DEVELOPMENT AND MANUFACTURE

Part of the solution to the problem of development of drugs for tropical diseases must come from Third World countries, though the process is probably too expensive and complex for them to do it alone at this time. Drug development to international standards in Third World countries is not easy, and it would not be sensible to duplicate all facilities for drug research and development in the developed and the developing worlds. There is a case to manufacture more drugs in developing countries, even though initially this will be more expensive. For example, the major site of manufacture of albendazole for SK&F is in China, with another plant in India. Competitive tendering when using aid agency money to buy drugs makes it difficult for companies in developing countries to make the initial breakthrough. At a recent UNESCO meeting, a proposal to establish a special programme in synthetic organic chemistry was made, with a view to doing more synthetic work in Third World countries. Synthetic chemistry work of this type might usefully employ venture capital. Synthesis of large chemical series for drug screening generally does not further the career of academic chemists in the developed world, so this is a useful development. It is clear that there are lots of ideas in academia, and in industry, on drug discovery for tropical diseases, but industry will not follow these up for economic reasons. Why not establish pharmaceutical industries in Third World countries where costs will be less? However, neither the government nor academic scientists in Brazil were interested in earlier Merck anti-Chagas compounds when these were offered for development.

Treatment of tropical diseases has gone out of fashion to some extent within international agencies. There is a case to re-establish control programmes using drugs and involving local governments to stimulate demand. Provision for drug costs to treat associated diseases should be included in all development schemes funded, e.g. by the World Bank. USAID is about to invest US$ 44 million on schistosomiasis research in Egypt. Would this not be better spent on purchase of currently available drugs? Most aid agencies think short term, i.e. 3-5 years. This is not helpful when drug development takes up to 15 years. Even successful programmes such as the Expanded Programme on Immunization (EPI) suffer from donor fatigue. One approach to solve this problem might be to extend the objectives after a few years.

Marketing information on Third World diseases needs updating. Could WHO help by supplying current data on disease incidence and impact of therapy to interested parties?

8. RESEARCH AND DEVELOPMENT STRATEGIES

8.1 New Approaches

The rational approach to parasite chemotherapy can readily accommodate academic/industrial/TDR collaboration. In essence, the approach involves five stages:

- identification of suitable biological targets
- isolation or expression of target receptor/enzyme
- analysis of structure and function of target
- molecular modelling
- chemistry/development

The first four of these can readily be done in academia with TDR support. The last one requires the involvement of the pharmaceutical industry.

As with any drug discovery strategy, the rational approach is expensive, time consuming and speculative. However, the chances of success and the unit costs can be reduced if targets such as dihydrofolate reductase (DHFR) and thymidylate synthase (TS) are chosen, since they are represented in a number of target parasites.

Recent work on the TS of bacteria, mammals and parasites, made possible by the cloning and expression of these enzyme proteins in *E. coli*, has indicated that TS is a relatively conserved protein, especially at the active site; however there is variation external to the active site which might be exploitable to provide inhibitor selectivity.

In contrast to TS, DHFR varies markedly with source. The leishmanial enzyme has been cloned and expressed in *E. coli* to the extent that 4 g of purified protein is now available. This has allowed the identification of novel 2,4-diaminopyrimidines which should have potent activity against intact organisms. The pharmaceutical industry has so far not shown interest in their development.

8.2 Drug Targets in Human Pharmacology as Leads

A number of chemical series made in recent years within pharmaceutical companies have potential activity in parasite chemotherapy. Two of these from Merck, Sharp & Dohme are used as examples.

1,2,3-triazoles and imidazoles are potent anticoccidial drugs *in vivo*, though potential problems with liver residues has meant that they are not being developed further. The latter are very active in the mouse model of acute Chagas disease, with activity titrating down to 3 mg/kg/day. Merck might have continued the development of the anti-Chagas imidazole if it was also being developed as an anticoccidial agent. Once the structural-activity relationships for the two parasites diverged, it was not economic to do so. They have not been patented and are available for TDR to develop, if they wish.

The second example relates to the inhibition of cholesterol biosynthesis and especially the synthesis of mevalonate by the enzyme hydroxy-methyl-glutaryl CoA reductase. Merck's inhibitor of this enzyme, mevinolin, marketed as a hypocholesteraemic agent, has been shown also to suppress egg production in schistosomes. Other inhibitors in this area of sterol metabolism are known, including imidazole 14-demethylase inhibitors which block the growth of *T. cruzi* epimastigotes. These could be made available to TDR screens.

8.3 Cross Disease Drug Targets

Parasites tend to differ from their mammalian hosts in key metabolic pathways. If these can be identified and characterized by conventional biochemical techniques, potential targets may emerge which can then be exploited using modern molecular techniques of drug development.

A surprising number of such targets are common to more than one parasite. Examples include: purine salvage pathways (most protozoa, schistosomes); ornithine decarboxylase (kinetoplastida and malaria); glycosomal biogenesis and function (kinetoplastida); trypanothione (kinetoplastida); folate biosynthesis (sporozoa); cholinergic receptors (nematodes); chloride ion channels (nematodes and ectoparasites).

A target of particular interest in recent years is ornithine decarboxylase whose inhibition is exploited in trypanosomiasis by eflornithine (DFMO). One facet of the antitrypanosomal action of this compound is the question of selectivity. The mammalian enzyme in the test tube is in fact more easily inhibited by DFMO than is the isofunctional trypansome enzyme. Molecular studies have now indicated that the differential effect operates at the level of protein turnover. The mammalian enzyme has a sequence at the C-terminus missing from the trypanosomal enzyme. This difference makes the mammalian enzyme very unstable so that it turns over rapidly, thereby relieving the inhibition. Such a mechanism of selectivity is quite unique in parasite chemotherapy, and a search for examples of rapid turnover of mammalian proteins, relative to their parasite equivalents would be useful in identifying new drug targets.

Another target of current interest is the glycosome, an organelle which contains the trypanosomal glycolytic enzymes. Since these are synthesized on cytoplasmic ribosomes, they have then to be directed to the interior of the

glysosome. Such transport is thought to be related to the presence in the glycosomal enzyme protein of two "hot spots" of positively-charged amino acids which do not occur in the isofunctional cytoplasmic enzyme. It is possible that drugs such as suramin exert their therapeutic effects by binding to and cross-linking the hot spots, thus blocking the control of their transport to the glycosome.

9. MECHANISMS USED FOR DRUG DEVELOPMENT IN OTHER DISEASE AREAS WITH LIMITED FINANCIAL RETURN

9.1 Lessons from Orphan Diseases

The drug development programme evolved by the Multiple Sclerosis (MS) Society in the US illustrates what can be done with limited financial resources. There are <100 000 patients with MS in the US and thus the disease qualifies for orphan drug status. The MS Society has an annual budget of circa US$ 6 million, of which about 75% goes to support extramural research proposals. Good links are maintained with the NIH to avoid overlaps and duplication of funding. Initially, the Society supported the clinical trials of drugs developed for other purposes, e.g. methotrexate, but without success. It therefore sought to support the development of new pharmacologic agents.

To do this, it established a drug discovery unit. It obtained information on all relevant disease models and supported these operations to the tune of US$ 150 000. It went around the drug industry with a shopping list of compound types in which it was interested. Confidentiality of the results was maintained and the donor companies did not lose any commercial rights to these compounds. A screening committee reviews the compound evaluation data; a clinical committee deals with clinical trials. Preclinical development is sometimes paid for by the donor company; sometimes by the Society. Results to date have been very encouraging: 15 new chemical entities are in the pipeline, including one in the last stages of preclinical development and one in clinical trial.

It should also be noted that the proposed Infectious Disease Control Act of 1989, may soon be enacted in the US. This would establish a national programme for tropical medicine designed to achieve optimal prevention of human infectious diseases originating in the tropics and to plan and coordinate governmental and nongovernmental activities, including research, epidemiology, data collection and storage, drug and vaccine evaluation, licensing and distribution and professional training and public education.

9.2 Government-Industrial Collaboration for Orphan Diseases in Japan

The total market for pharmaceuticals in Japan is large. It represented about 22% of the total world market last year, with a value of about US$ 30 billion. Within this large market, the number of patients requiring treatment for tropical diseases is tiny. For example, malaria cases average <100 *per annum* in recent years. There is little incentive therefore for the industry to become involved with this market, when the home drug market is so large and profitable.

Thus in 1980, an orphan drug scheme was established, the aim of which was to simplify and thereby speed up the introduction of drugs intended for diseases involving small numbers of patients. The amount of clinical data required is much less and information on matters such as stability can be provided post-registration. As a result of this policy, a number of drugs for tropical diseases are now available in Japan, including pyrimethamine/sulphadiazine, praziquantel and pentamidine.

In addition, there is an Official Development Aid (ODA) programme designed to help Third World countries in activities which are not commercially viable by the normal criteria. A recent example of its work is the development of a series of heat insensitive vaccines. Collaboration with developing countries is introduced at a very early stage of such developments.

Longer term and more economically risky activities are supported by the Japan Health Service Foundation which spent a total of US$ 6.5 million last year.

10. MODE OF OPERATION OF PROGRAMMES OUTSIDE INDUSTRY DEALING WITH DRUG DEVELOPMENT IN TROPICAL DISEASES

10.1 TDR

The strengths of TDR in the drug development process have historically been in the areas of basic research, drug screening, clinical and community trials in endemic areas, international coordination and the training of workers. Partners in drug development have always been needed by TDR, due to limited resources and expertise and these have in the past come from academic institutions, government agencies and, above all, the pharmaceutical industry.

Within the six diseases of the Special Programme, TDR has been or is still involved in several drug development projects:

- in malaria with mefloquine, halofantrine, arteether and the synthetic trioxanes; the reversal of chloroquine resistance by calcium channel blockers
- in schistosomiasis with praziquantel, and its wider utilization
- in filariasis, ivermectin for onchocerciasis and lymphatic filariasis; with a number of companies for screening, including Ciba Geigy, MSD, Lilly, WRAIR etc.
- in African trypanosomiasis, with eflornithine, some nitroimidazoles and purine analogues
- in leishmaniasis with allopurinol, various triazoles and imidazoles, along with some tricyclic antidepressants
- in leprosy with multidrug therapy and more recently with 4-quinolones.

The major lesson from the successes to date is that the important drugs have usually come from those series of compounds whose potential had previously been recognized by other groups, and whose development is then carried out in a collaboration between WHO and the pharmaceutical industry.

In some cases, e.g. leprosy and schistosomiasis, industry has provided efficient therapies unaided, and the major problem has been of clinical/community trials and drug delivery. For malaria, companies have been willing to take up for commercial development drugs whose efficacy and safety have been proven by TDR or WRAIR. For other diseases, e.g. the trypanosomiases and leishmaniases, further development of "proven" drugs has not been attractive to industry.

Industry increasingly does not wish to be involved in drug development for tropical diseases and opportunities for such developments are limited, particularly for a drug with a single disease indication. The way forward for TDR may therefore require that it becomes increasingly involved in the drug development area. This is already happening in CHEMAL, who are undertaking the preclinical development of arteether.

TDR must utilize its knowledge of drug targets in parasites, obtained from basic research projects, to find areas of mutual interest within ongoing drug development programmes in industrial laboratories. Exchange of information, biological reagents and novel chemical compounds, might allow development of parasitic drugs by TDR, based on ongoing, and profitable, programmes in industry.

An important consequence of such an expanding role in drug development would be that TDR would need to modify its organization. In particular, it would need to set up a drug development management team to oversee and coordinate all drug development.

10.2 Walter Reed Army Institute of Research (WRAIR)

An antimalarial drug development programme was established in 1963 at Walter Reed Army Institute of Research by the US Army Medical Research and Development Command. In subsequent years, the scope of effort has been expanded to include anti-filarial, antileishmanial, antischistosomal and antitrypanosomal drugs. Emphasis is on drugs for prophylaxis.

The drug research and development programmes involve the coordinated efforts of WRAIR laboratory scientists, contractor research laboratories in academic and industrial institutions, collaborating laboratories in other government and international organizations (including WHO/TDR) and WRAIR laboratories in Bangkok, Nairobi, Rio de Janiero and Kuala Lumpur. Formal agreements with pharmaceutical companies are developed for confidential exchange of chemical compounds and screening information in which rights are specified. For drug products in advanced development, specific codevelopment agreements with industry are sought.

The strategies for drug discovery and drug design have matured since 1963 to reflect emerging technology and available resources. Lead-directed synthesis based upon active lead compounds and/or upon biochemical rationale has continued as a dominant strategy. In recent years, synthetic approaches have been increasingly guided by computer assisted QSAR and 3-dimensional molecular modelling techniques. Large scale screening is not currently utilized, but selective off-the-shelf screening continues on a limited basis. Increasingly, parasite culture technology is utilized effectively in the early phases of drug assessment although rodent and primate models are indispensable.

Preclinical studies necessary to support the design of phase I clinical pharmacology protocols and to form the regulatory basis of investigational new drug applications (IND's) are planned and directed by WRAIR and are usually executed under contract to laboratories experienced and equipped to perform such studies in accordance with US Food and Drug Administration "Good Laboratory Practices" regulations. For each drug entering into preclinical development, a suitably trained WRAIR scientist is assigned as project manager, and progress is monitored by a multidisciplinary in-house review committee as well as by a panel of extramural scientific advisers which meets twice annually.

Phase I clinical pharmacology studies are performed under contract in the US; Phase II and III clinical studies are performed by WRAIR overseas laboratories, by WHO/TDR and by collaborating pharmaceutical companies.

10.3 Possible Mechanisms of Collaboration Between Industry and TDR

Especially on the helminth side, new drugs for tropical diseases have in recent years had their origins in chemical entities developed originally for veterinary purposes. To help foster this type of success, Ciba-Geigy proposed the following mode of collaboration with TDR.

Identification and selection of new compounds for development. Scientists in industry will periodically review compounds synthesized by their own companies that have an interesting anti-infective or biochemical profile, or are structurally related to known active principles. A selection of these compounds will be submitted to WHO-funded laboratories for further testing in different animal models and for investigation of their mode of action. From any promising compounds, the WHO Preclinical Drug Development Team (PDDT) will then select the candidate best suited for development.

Preclinical development. The WHO will request the company from which the compound originates to perform the necessary preclinical studies, including the preparation of the material needed. The request will be supported by a Development Concept for the compound, detailing the objectives and the strategy for their attainment. At the end of this first phase, on the basis of the experimental and preclinical data, TDR will decide whether or not development should continue.

Clinical development. Decisions relating to the initiation and conduct of clinical trials are the responsibility of TDR. The clinical investigators will draft a Clinical Programme Outline (CPO) and a Clinical Trial Plan and TDR will submit them to the company for comments. The company will reserve the right to veto the project at any time. Companies will provide the usual insurance coverage for patients and clinical investigators and their staff. As in the preclinical stage, the company will supply the trial material and perform the non-clinical investigations required for the conduct of the clinical studies in Phases I-III.

Marketing. If the joint project should ever reach this stage, industry and the WHO would need to negotiate in good faith to solve the many remaining issues in a way satisfactory to all parties, above all to the patients.

11. PROBLEMS OF DRUG DISCOVERY AND DEVELOPMENT FOR DISEASES OF THE DEVELOPING COUNTRIES

Astra has recently established a Biotechnology Laboratory in India which currently employs 60 persons; 25 with Ph.D.'s, of whom 15 were recruited in the US and Europe. The work of the Laboratory is reviewed by a Scientific Board, half of whose members are appointed by the Indian Government, the other half by Astra. The Indian laboratory works closely with Astra's R&D laboratories in Sweden but focuses on projects of special interest to Third World countries, e.g. diagnostic kits for P. falciparum and P. vivax malaria. Costs are less than half of those in Sweden. To date, the operation is judged to be very successful.

It is suggested therefore that a research-based pharmaceutical industry can be established in a country where tropical diseases are endemic. The Astra experience indicates that suitable staff can be recruited to do quality R&D in such an environment at reduced costs. Real progress in drug development should be possible because the pharmaceutical industry will be actively involved. WHO/TDR could participate as a partner to ensure that there is a balance between Third World needs and the priorities set by the Company.

The amount of money available to aid agencies is small (millions of dollars per annum) relative to the amounts spent by national research councils and the industry (billions of dollars per annum). The main donors for TDR are North America, Scandinavia and some EEC countries. There is an inequality in some cases between the amount donated and the amount received back in research grants, which tends to favour highly developed countries. If all countries could be persuaded to donate 1% of their GNP, TDR's financial problems would be over.

To allow real progress to be made in the development of drugs for Third World diseases there is a need for:

- a greater political commitment to provide drugs in endemic countries
- increased multilateral and bilateral agency support
- greater involvement of the global scientific community
  a proportion of all national research councils resources to be given to Third World countries
- a better understanding of the timeframe for drug discovery and development by donor agencies.

a) If the drugs are to be used for mass treatment, with minimal medical services, it is particularly important that they are known to be safe.

b) The industry and WHO would be wary of the risk of abbreviated preclinical toxicological studies for drugs for tropical diseases.

c) The contribution of TDR to clinical trials of drugs intended for tropical diseases is particularly valued by International Federation of Pharmaceutical Manufacturers Associations (IFPMA); and they are willing to inform their members of the opportunities for collaborative drug development with TDR.

d) The fact that representatives from the industry are present at the meeting

indicates there is still an interest in some quarters for continuation of drug development for tropical diseases. Senior personnel in WHO might capitalize on this and re-inforce it by direct dialog with senior industrial managers.

e) One suggested way to solve the drug development and supply problem for tropical diseases is to set up a private corporation in cooperation with TDR/WHO. The venture capital for this could come from the multinational pharmaceutical companies who could also be the major share holders. The corporation could consist of a series of interacting subsidiary companies to cover activities such as medicinal chemistry, animal toxicology and pharmacology (including primates), clinical trials and production, many of which could be located in Third World countries. A major activity would be the establishment of an efficient product distribution system. The private corporation would collaborate with TDR in research and development of drugs for tropical medicine. Roles for the latter would include overviewing the operation of the corporation, giving advice on priorities, resolving conflicts, providing public relations and making some funding available. Additional funding could come from multilateral and bilateral agencies, Foundations, the Industry, etc. In the long term, spin-offs into other more commercially viable activities could also generate revenue and allow full use of scientific resources. The proposed corporation could be set up by TDR alone, but there are administrative advantages in setting up a separate entity. Such a company should operate according to the procedures of the national health structures of the countries concerned.

f) To be successful, a pharmaceutical company has to be large enough to cope with its failures. It is not clear that the proposed corporation would be big enough to survive a sequence of failures. Doubts were also expressed both on the ability of the company to introduce and operate an efficient drug delivery system in developing countries, and on the dependence on aid agencies as the major source of finance for drug purchase.

12. SUMMARY OF DISCUSSIONS

a) The problem we have is essentially a conflict between the health needs of large numbers of patients with limited financial resources, and the economic considerations of pharmaceutical companies needing to be profitable to continue their activities. The problem for pharmaceutical development is essentially a vicious circle of no money/no markets/no R&D so no new drugs. Attempts should be made to break the cycle at any one or more points. The market for drugs for tropical diseases may not be profitable, but it exists and it is essential to supply its needs.

b) The problem is best tackled where possible by a collaboration between the public and the private sectors. It is important that any innovative developments in the private sector avoids expensive duplication and overlap with existing companies.

c) A first step might be to try and find more money in the public sector to make use of the know how in the private sector. Money from within the EEC, earmarked for medical research, is not being tapped as much as it might be for drug development. The key problem now is clearly the catalysis of drug development, based on existing and future knowledge. This could be helped by interactions at very senior level between WHO/TDR and the drug industry.

d) Drugs for tropical diseases must not be looked at in isolation. They are but one way of fighting tropical diseases. They are also only one component of an essential drugs list for developing countries.

e) There is a continuing need for TDR to stimulate innovative research into parasite metabolism, molecular biology etc. to allow exploitation of mainstream medical sciences.

f) It is clear that many ideas have come out of academic research in recent years which have real potential for drug discovery. It is important that TDR disseminates this information widely, particularly to the pharmaceutical industry. TDR could also act as a clearing house for relevant information from all sources.

g) WHO/TDR could also encourage governments to develop orphan drug policies, to simplify and standardize preclinical development requirements and simplify the documentation needed for regulatory purposes. This need not equate with lowered or double standards, which are clearly not acceptable to WHO or Industry.

h) Individual donors might be encouraged to "adopt" a drug worthy of development and directly cover its development costs, and TDR should examine this possibility.

i) On the distribution side, too few data on the potential size of target populations are available, and it is a responsibility of WHO to provide such information. When considering drug distribution, do not restrict this solely to drugs for tropical diseases, e.g. multidrug therapy for leprosy might be linked with tuberculosis therapy.

13. RECOMMENDATIONS

The following important points emerged which would appear to warrant further discussion and action by TDR and STAC. They are not ordered by priority.

13.1 To Improve Sales and Distribution

a) Persuade the Industry to extend the practice of dual pricing for the public and private sectors.

b) Extend the activities of agencies such as UNICEF which operate drug purchase and distribution services.

c) Persuade other companies to follow SK&F's lead in developing mass treatment projects, funded by donor agencies, which utilize their products.

d) Promote the activities of innovative, commercially orientated companies which seek to develop multiple therapy mass treatment projects to governments and donor agencies, and who provide and distribute drugs in developing countries and monitor their effects in accordance with the national health legislations and structures of the countries concerned.

13.2 To Improve Discovery and Development

a) Make industry aware of proven drug targets in tropical diseases and key information on them.

b) Set up facilities for chemical synthesis in the Third World.

c) Ensure that drugs developed commercially for other purposes, especially veterinary anthelminthics, are tested for possible utility in human tropical diseases.

d) Extend the role of TDR to do more drug development, and provide adequate resources for this.

e) Develop TDR/industry collaboration so that chemical series of current commercial interest to the Industry are tested for possible utility in tropical diseases.

f) Set up an international data file on new drug products to speed their registration in Third World countries.

13.3 To Improve Discovery, Development, Sales and Distribution

a) Promote the establishment of a corporation linked to TDR, dedicated to the discovery, development and distribution of drugs for tropical diseases.

b) Promote the establishment of a pharmaceutical company in a Third World country to discover, develop and market drugs for tropical diseases.

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