Mem. Inst. Oswaldo Cruz, Rio de Janeiro, Vol. *87*, Suppl. IV, 153-161, 1992

SCHISTOSOMIASIS RESEARCH FUNDING: THE TDR CONTRIBUTION

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In spite of the recent decline in financial support on the part of some major donors, the overall international support for schistosomiasis research in current US dollas has been holding steady. However, when adjusted for inflation, a clear decline during the last decade appears and only in a few countries has this decline been balanced by increased national or bilateral funding. The prevailing level of support for schistosomiasis research is barely sufficient to maintain established laboratories and researchers, and highlights the need to attract young investigators. The important goal of bringing a new generation of scientists into the field of schistosomiasis can only be achieved by a considerable long-term increase in funding, both at the national and the international levels. A break-through in current research emphasizing improved techniques for control is needed to encourage donors and governments to improve the situation.

Key words: schistosomiasis – research funding – TDR

Science needs patronage and thrives on financial encouragement but ever since the emergence of scientific disciplines this support has taken on different forms. In the immediate past, research was carried out within the academic framework without external funds but the picture has changed dramatically during the last 20 to 30 years. Costs have increased at a speed much in excess of the growth of university budgets and modern scientific institutions are generally in no position to provide more than working space and marginal resources. This trend has continued unabated and some universities now even request their tenured staff to include part of their salaries when applying for research support. Consequently, the active scientist of today spends as much time on fund-raising as on actual research. The introduction of overhead costs, bench fees, etc. has not made things any easier, particularly in the field of tropical medicine where research has never been given priority.

In the industrialized nations, the levels of financial allocation for research in, and treatment of, various diseases provide an indicator of their perceived importance. However, the scale of human suffering and lost productivity associated with ill health in most developing countries, combined with the present, uneven distribution of the world's wealth, makes this desired relationship between need and resources a distant goal. Realizing the need to produce tools capable of controlling the great endemic diseases of the tropics, notably diagnostic assays, drugs and vaccines, donor agencies have initiated a number of programmes to strengthen neglected medical research. The amounts spent on tropical diseases have not been completely inadequate, e.g. at least US$ 100 million have been used for research on schistosomiasis and several times that sum has been allocated for the study of malaria over the last 30 years. It is ironic that, in the face of these efforts, the two most spectacular successes in this field, the drugs invermectin and praziquantel which have proved to be efficient and safe for the treatment of onchocerciasis and schistosomiasis, respectively, were first developed by industry without outside financing. On the other hand, thanks to interventions by the former Parasitic Diseases Programme (PDP) of WHO and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and their promotion of clinical trials, these drugs, initially intended for the veterinary field, are now widely available for human use.

TDR was initiated in 1975 as a WHO special programme with the possibility of raising funds and recruiting member countries on its own. Its activities and prospects have recently been reviewed by the current director, Dr T. Godal (1989). About one quarter of its financial resources is reserved

for training and institutional strengthening, whilst the remainder is used for research in sex tropical diseases, of which schistosomiasis is one. With more than 600 million people at risk and 200 million actually infected, this disease ranks high on the global public health agenda. The addition of praziquantel has already completed the arsenal needed for its control, so TDR's role in this case is to encourage the development of new tools that would attain control faster and/or at a lower cost. Workplans are prepared in close association with the WHO Division of Control of Tropical Diseases (CTD) which focuses on the same diseases targeted by TDR. The majority of grants for schistosomiasis are awarded after review by a Steering Committee constituted by a continuously changing board of renowned scientists but support also comes through other funding mechanisms.

STEERING COMMITTEE ADMINISTERED FUNDS

TDR is a goal-oriented programme and adherence to programme guidelines is as important as scientific quality. The proportional weight of these merits is carefully considered for each proposed project and even proposals of the highest scientific merit can be rejected if they do not clearly comply with the guidelines. On the other hand, scientifically inadequate projects are not accepted just by virtue of relevance. Thus, in order to be approved, proposed research must be deemed acceptable in view of both relevance and scientific merit.

A break-down of the funding resources reveals that the Committee has administered more than 70% of the total TDR financing of research on schistosomiasis (Fig. 1). This core support is normally awarded for three years in the form of disease-oriented (regular) projects which are reviewed annually. Due to a relatively long period of financial constraint, funding was depressed in the mid 1980s but after that a steady growth of financial resources ensued. However, the granting level of the early years will not be easily regained, particularly since inflationary pressures have made the recent nominal improvements illusory in many recipient countries (Fig. 2). Project budgets are not limited but, in practice, they seldom exceed US$ 60,000 per year and most of them amount to about half that figure. The average nominal cost of laboratory projects has been relatively stable over the years, in contrast to the varying budgets of field projects, but the size of the latter has consistently increased during the last five years leading to a convergence of the average cost of all project budgets of around US$ 30,000 per year (Fig. 3). Record numbers of proposals have been received during the last three years but, due to increased financial resources, the approval rate remains largely unchanged at 36% (Fig. 4).

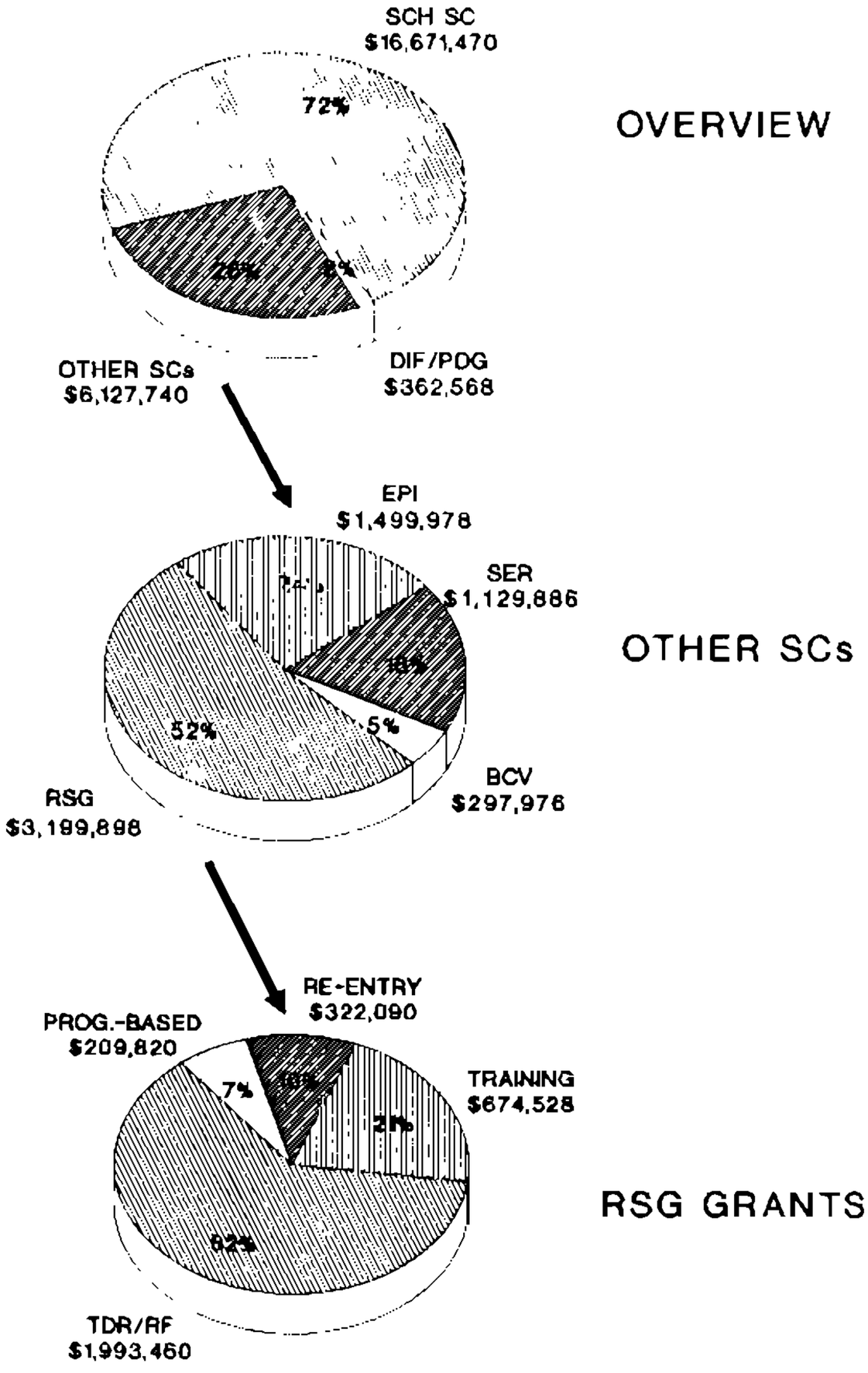

Fig. 1: sources of TDR funding for schistosomiasis research (disbursements 1977-1991).

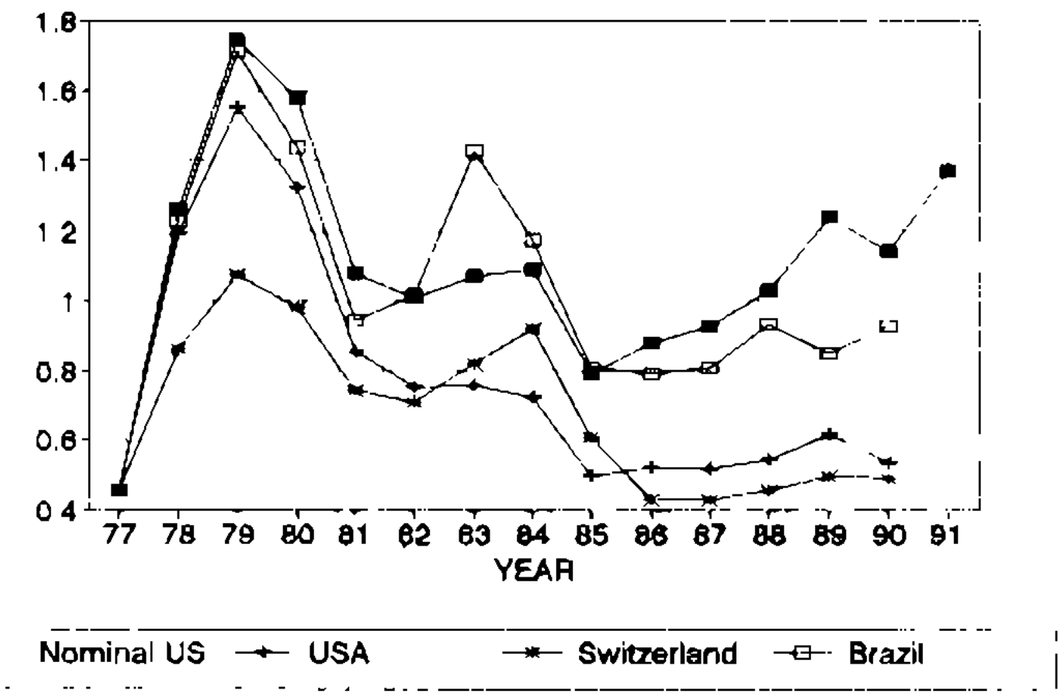

Fig. 2: buying power of TDR support of schistosomiasis research in selected countries.

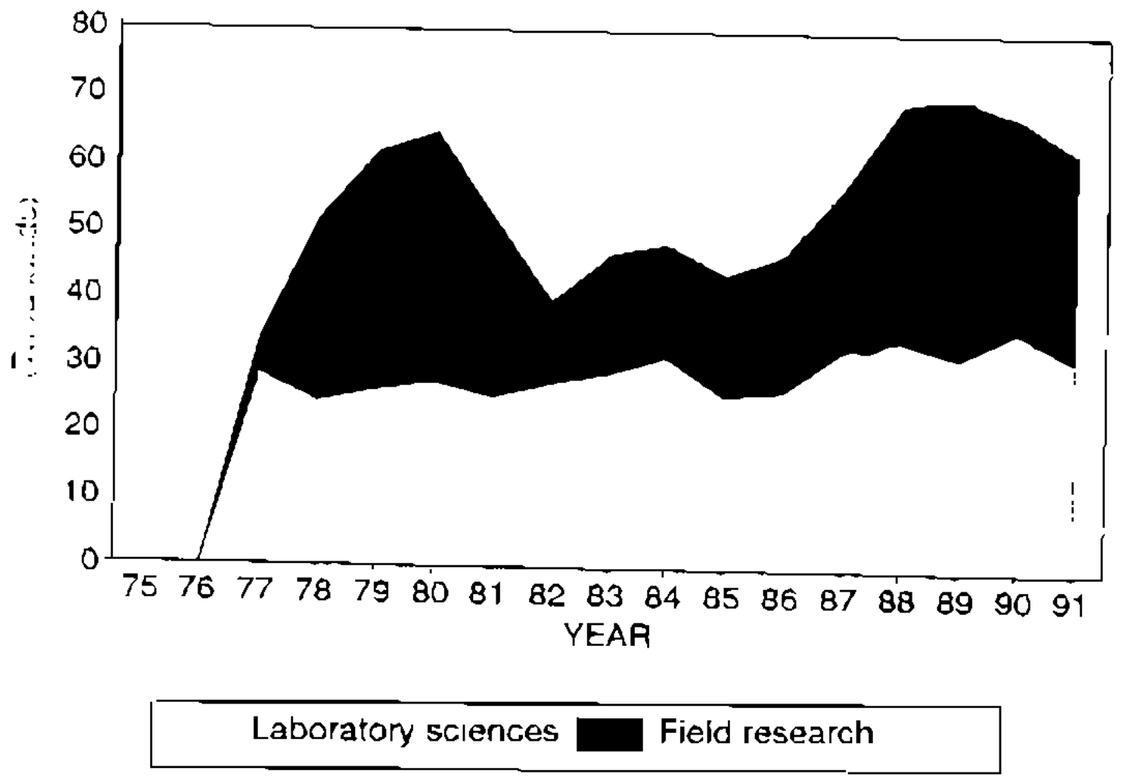

Fig. 3: average project size for different types of research (nominal US$).

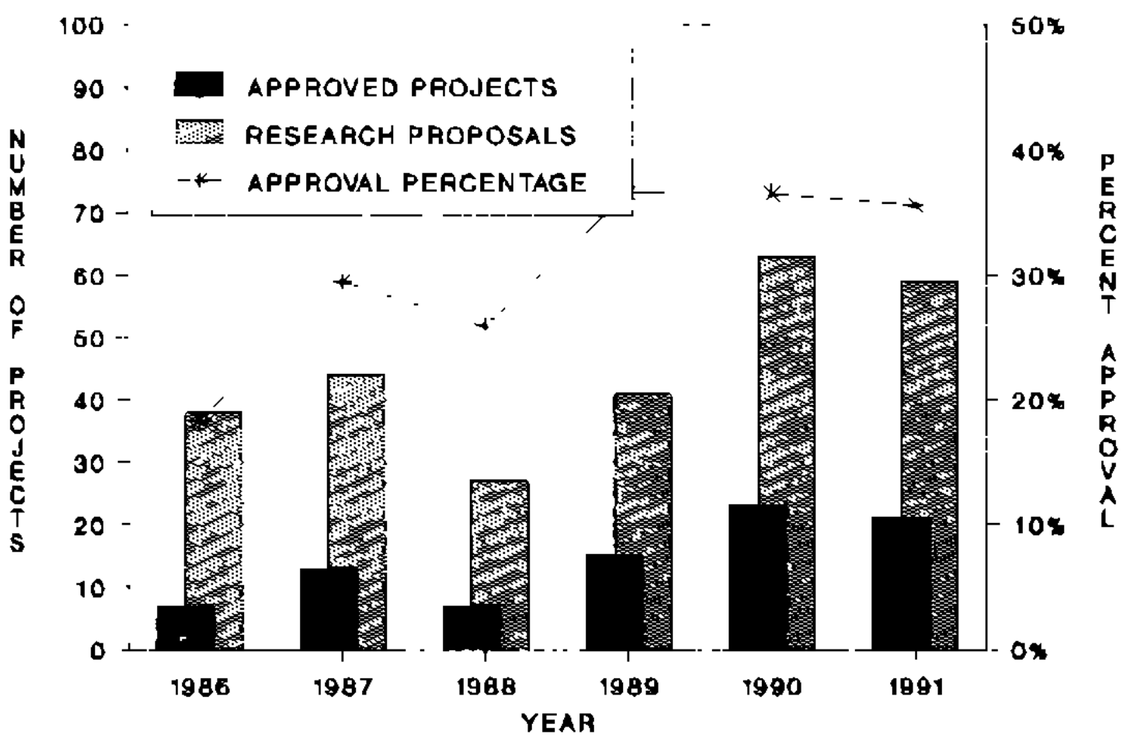

Fig. 4: project aproval rates 1986-1991.

An overview of approved new projects in relation to developing and industrialized countries in the three main areas of supported research: immunology and basic sciences, biochemistry and chemotherapy, and applied epidemiology and snail control (field research) is shown in Fig. 5. This account of the total regular schistosomiasis projects funded by TDR, 267 projects in all, highlights the dichotomy between basic and applied research. Although the number of field projects is more or less equally divided between institutions in industrialized and developing countries, the vast majority of resources for immunological and biochemical research has been invested in American and European laboratories. However, in recent years, a growing trend of project allocation to institutions in the developing countries is taking place which becomes visible when viewed on an annual basis (Fig. 6). Although lower in 1991, the number of active projects in developing countries actually surpassed that in industrialized ones last year. This development stems from a deliberate effort by the Steering Committee to encourage research by national scientists. For example, in 1987, prompted by the drastic reduction in field projects, outline proposals on specific topics of operational research were invited with the aim of developing these with the aid of experts. Out of 60 outlines, eight were selected according to originality, quality, priority of subject and geographical provenance. During a three-day workshop held in Leiden, The Netherlands, seven proposals were produced, six of which were finally approved. In some cases, however, the proposed investigations were not accepted until further improvements had been made, delaying the actual research for up to two years.

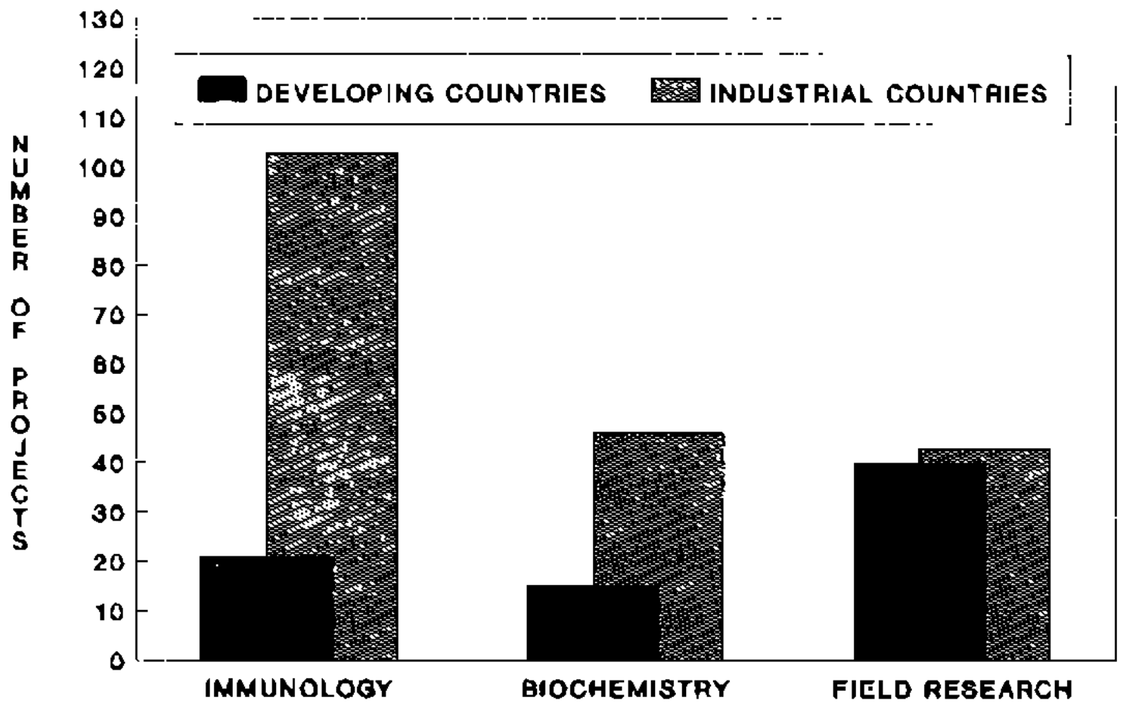

Fig. 5: number & distribution of projects 1977-1991.

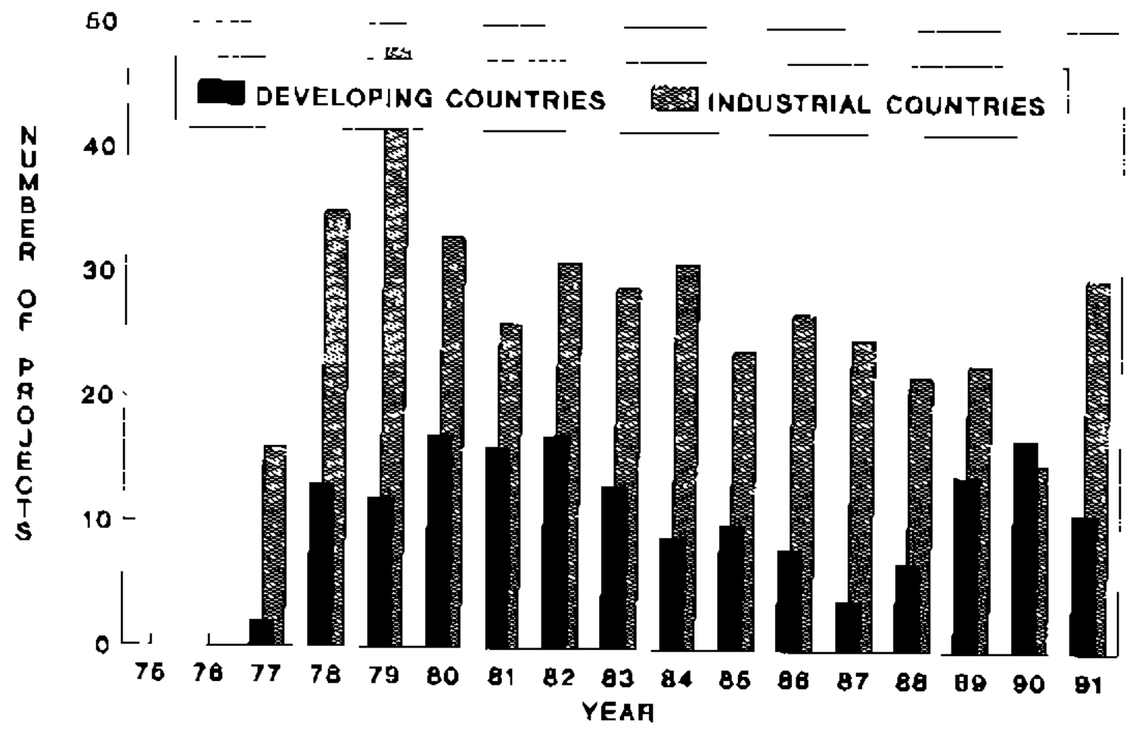

Fig. 6: distribution of supported projects 1975-1991.

CONTRIBUTIONS THROUGH OTHER STEERING COMMITTEES

Interestingly, as depicted in Fig. 1, more than one-quarter of the total TDR financing of schistosomiasis research has been awarded through the "trans-disease" Steering Committees on Social and Economic Research (SER), Biological Control of Vectors (BCV) and Epidemiology (EPD). These Committees, rather than focussing on a specific disease, are responsible for research topics which are com-

mon to several of the TDR target diseases, e.g. the role of vectors and human behaviour. The EPD annual grants related to schistosomiasis used to be substantial, as is reflected by the fact that its contribution is still one of the largest in spite of the phasing out of this Committee which has not been operational since 1987.

THE ROLE OF THE RESEARCH STRENGTHENING GROUP (RSG)

The majority of RSG support concerns the bolstering of the research infrastructure of eligible institutions in developing countries but these grants are omitted in this review since several diseases are involved and the proportion going to each component cannot be separated. However, the fact that the combined support awarded to institutions where the objectives include research on schistosomiasis has now reached US$ 6,626,238 gives an indication of the extent of financing emanating from this source. The remaining resources are divided between special grants (see below) and different types of training (Master's and Ph.D. programmes, grants enabling scientists to visit laboratories abroad, career development grants, etc.) and re-entry grants which are one-time awards of a maximum of US$ 30,000 intended to facilitate the re-establishment of scientists in their home countries after training abroad. These grants constitute an important and growing resource (Fig. 7) representing almost one-third of the total RSG contribution to research on schistosomiasis (Fig. 1).

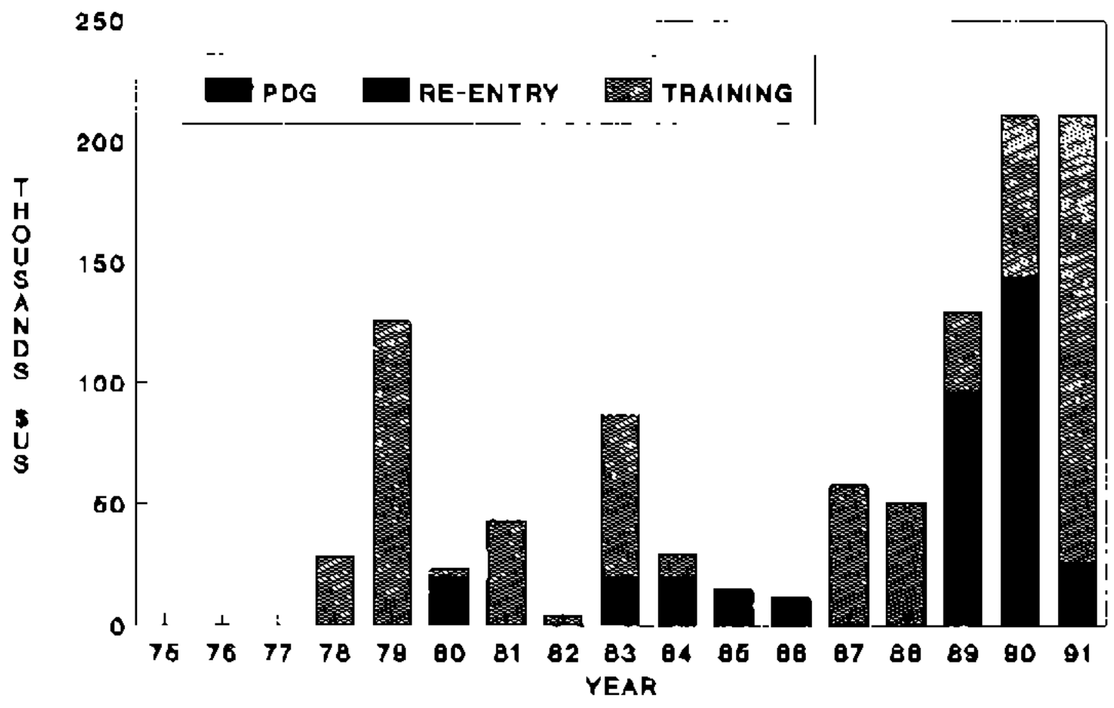

Fig. 7: funding mechanisms targeted for developing countries.

The programme-based grant is a relatively recent addition of follow-up financing aimed at bridging the gap between institutional strengthening and the regular grants administered by the Steering Committees. These projects generally include many scientists and are less focussed than disease-oriented projects and, although they frequently involve research on several diseases, the different parts can easily be identified. So far, US$ 209,820 have been allocated for schistosomiasis research through this mechanism (Fig. 1). In 1988, a twinning arrangement with the Rockefeller Foundation (RF) was introduced with the aim of initiating collaborative projects managed by scientists from both industrialized and developing countries. In this agreement, RSG supports the research carried out in the developing country and RF provides the rest of the money. The full funding for research on schistosomiasis from this source amounts to US$ 3,305,260 over the period 1989 to 1991 but the break-down in Fig. 1 includes only the TDR contribution (US$ 1,993,460) for the four current TDR/RF projects which, incidentally, constitutes the largest contribution to schistosomiasis research outside the Steering Committee domain (Fig. 1).

MISCELLANEOUS FUNDING MECHANISMS

Project Development Grants (PDG) and funds provided by the Director's Initiative Fund (DIF), although marginal in size and numbers compared with the regular grants, represent versatile mechanisms geared at initiating novel research. This "seed money" is limited to one year and US$ 10,000 and US$ 15,000, respectively, after which successful investigators are supposed to find other sources of support. The PDG formula, introduced in 1988, has been highly successful. Out of the seven applications received so far, five were approved and they have all been developed into active regular research projects. The grants for training, re-entry and project development constitute three different mechanisms which are open exclusively to scientists in the developing countries (Fig. 7).

The DIF mechanism has been utilized irregularly but on an even basis in relation to institutions in industrialized and developing countries (Fig. 8). Half of the applications received over the years, 44 in all, were approved but the success rate in terms of opening up new lines of research has been comparatively low. Out of 22 approved DIF projects only five produced preliminary results useful for attracting other TDR sources of funding.

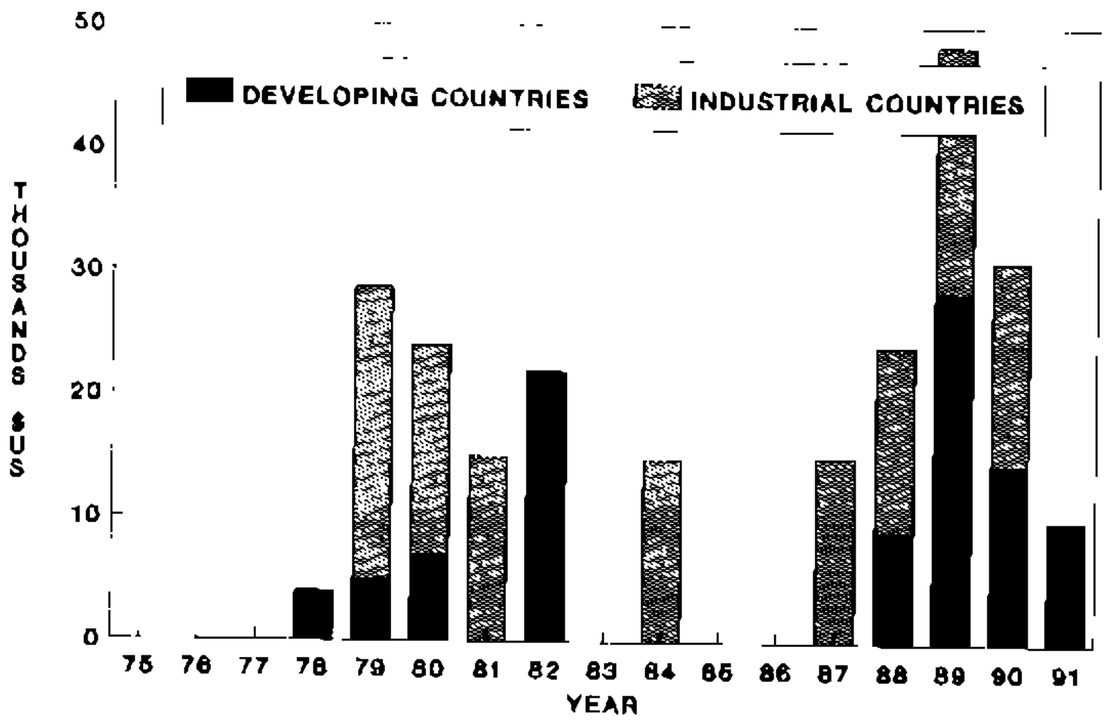

Fig. 8: the Director's initiative fund – schistosomiasis funding 1977-1991.

FUNDS PROVIDED BY OTHER DONORS

Although a detailed account of the global support of schistosomiasis research falls outside the scope of this communication a brief background summary is given. The declining level of funding from some donor agencies has fortunately been balanced by the advent of new ones and some have increased their contributions. However, the buying power of the US dollar has, due to the compounded rate of inflation, depreciated considerably more and, although the situation varies from country to country, the overall picture is one of diminishing support for schistosomiasis research.

Two private organizations, the Edna McConnell Clark Foundation (EMCF) and the RF, together have provided in excess of US$ 80 million for research on schistosomiasis; more than the combined contribution from other international donors. The RF's interest in this field dates back more than 30 years, whilst EMCF entered in the early 1970s but, a decade later, perhaps due to the great success of praziquantel, both shifted their emphasis to other subjects. These donor organizations remain, however, committed to schistosomiasis research and continue to provide funds for this purpose, albeit on a smaller scale. The EMCF has recently concluded an agreement with TDR channelling a first instalment of US$ 400,000 for the development of a schistosomiasis vaccine. The TDR/RF grants have been described above. The McArthur Foundation, another potentially important American contributor, has given some support, whilst the Wellcome Trust is the only British private institution showing any interest in this field.

The introduction, in the mid 1980s, of the "Life Sciences and Technologies for Developing Countries" (STD) Programme of the Commission of European Communities has been crucial for the survival of schistosomiasis research at the current level. The national funding agencies in countries such as Brazil and France remain committed to schistosomiasis research, whilst the Medical Research Council in the UK is currently reducing its emphasis on this disease. Incidentally, the substantially increased funding from the US National Institutes of Health (NIH) during the last few years suggests that the scientific standards of the schistosomiasis proposals are particularly good since, in contrast to the TDR procedure, NIH grant applications are reviewed in competition with applications in all fields of parasitic diseases.

Many governmental aid organizations and international donors such as WHO, the World Bank and UNICEF, finance national control programmes through activities which normally include research components, some of them substantial. The Schistosomiasis Research Programme (SRP), for example, manages an unprecedented US$ 40 million which have been allocated for US-Egypt collaborative research over a period of 10 years by the US Agency for International Development (USAID).

TARGETED RESEARCH

Although overall programme goals remain unchanged, the priorities of each Steering Committee are subject to variation. In the Schistosomiasis Component, drug development enjoyed a long period of preferential support but the need for a complementary means of control has now shifted the emphasis to vaccine development and improved immunodiagnostic assays which is reflected in the overview of allocations over the years (Fig. 9). Applied field research, on the other hand, has always been encouraged and the decrease in field research projects in the mid 1980s is related more to the reduced number of acceptable proposals than to a change in willingness to fund projects in this area. So far, a total of US$ 1,693,117 have been allocated for chemotherapeutic studies, US$ 2,145,004 for vaccine development and US$ 830,134 for improving diagnostic techniques (Fig. 10). In the latter field, the largest portion, US$ 596,537, was awarded for developing serologic assays, whilst the rest was divided between various other approaches such as improved parasitological diagnosis, DNA probes for application in the snail intermediate host, and assessment of morbidity using ultrasonography (Fig. 10).

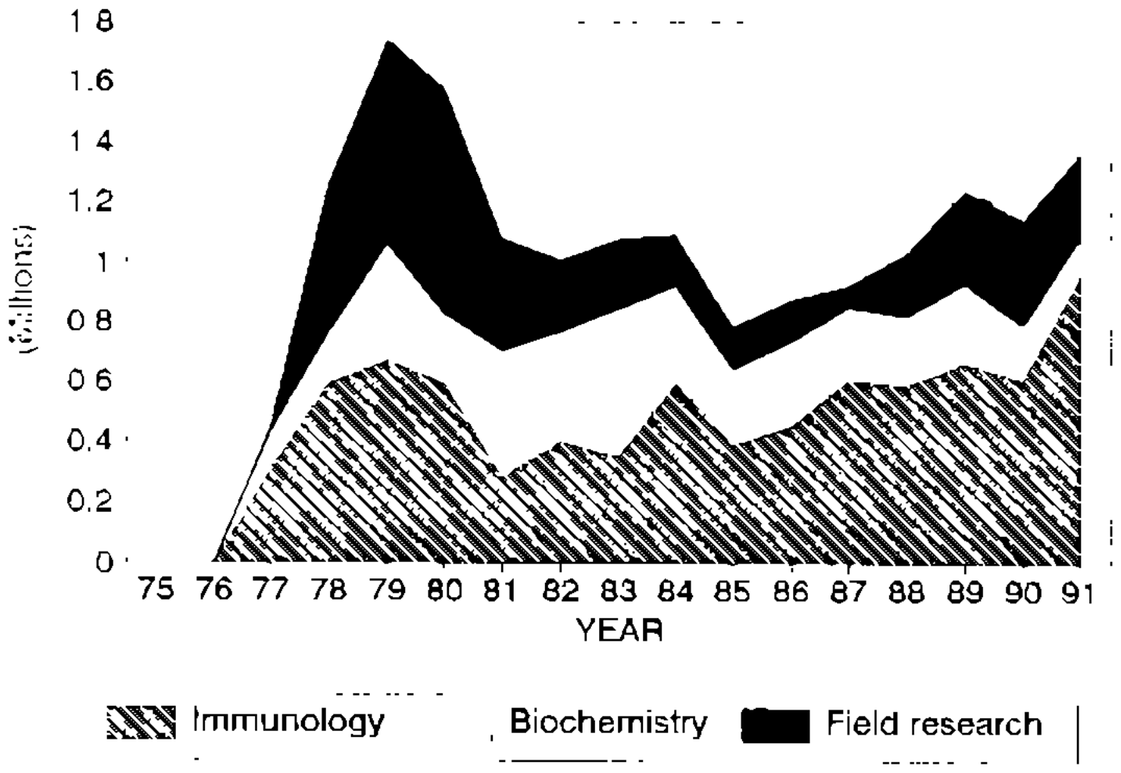

Fig. 9: allocation of funds to different research areas (nominal US$).

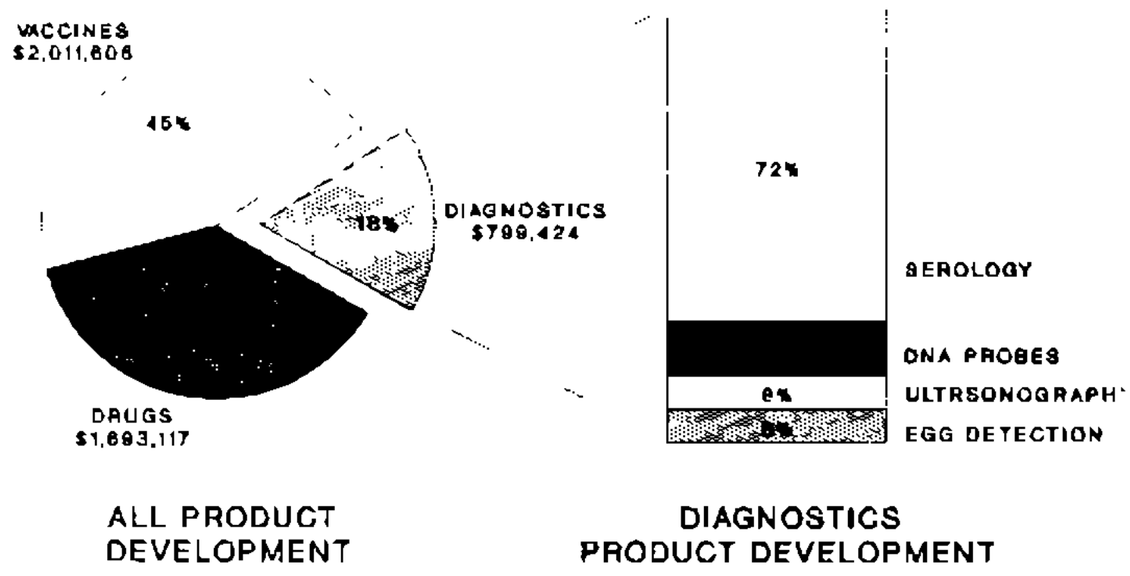

Fig. 10: distribution of funds for product development.

The outlays for each area of research should also take into account the costs of meetings devoted to the different subjects, which are held at irregular intervals in order to provide guidelines for decisions on long-term commitments. However, although meeting costs vary between US$ 30,000 and US$ 60,000, the total account of this expenditure in relation to grants provided for research projects is marginal. For example, in the fields of drug development, vaccinology and diagnostics these costs have not exceeded 1.5% of the expenditure.

EVALUATING FUNDING STRATEGIES

It is notoriously difficult to estimate the rate of return on nontangible investments such as expenditure on education and research. The link between activities aiming at improvement in the health area and reduction in mortality seems obvious but the role of funding of specific research topics cannot easily be isolated from other developments. Even in the most evident cases, e.g. the improved malaria control achieved in the years following the second World War, the true cause is hard to establish because broad economic advances occurred at about the same time. The widely held view that the substantial reductions in childhood diseases in Europe earlier this century were primarily due to vaccination has, for the same reason, been challenged by McKeown (1976). Efforts to separate the impact of general economic growth from the effect of specific support of education have been made by Schultz (1987, 1989).

The scientific literature provides one of the few ways of measuring the benefit of investment in a particular line of research. The number and quality of published papers emanating from approved projects are relatively reliable indicators which can be used for assessing performance in research centres, the effectiveness of research programmes and the utility of targeted grants. These questions have been comprehensively addressed in a review of methods and limitations in literature analysis (Van Raan, 1988).

A recent bibliometric study comprising 8,118 schistosomiasis articles published in the period 1966 to 1986 and funding data from 1970 to 1986 from the four most influential donors, EMCF, NIH, RF and TDR, concludes that research quality is closely correlated to funding policies (Pao, 1991). This author utilized the usual indicators such as publication counts for individual or group productivity and citation counts for influence of the scientific papers including an index based on the count of citations made by state-of-the-art reviews. In addition, she introduced a numeric value for quality incorporating the volume of relevant papers in a set of publications weighted with the impact factor of the journal in which the paper appeared. This was computed by taking the cumulative sum of the product of the number of relevant papers in each journal and its impact factor and dividing it by the total number of papers in each set. It was further reported that 3.5% of schistosomiasis researchers are associated with one third of the literature on this subject and that 16 of the 18 most productive authors, who also received 25% of all citations, turned out to be grantees. In fact, recipients of grants from the four donors were found to make up the large majority of scientists having published 30 papers or more.

What has been achieved in the schistosomiasis field during the 15 years of TDR activity? Improved diagnosis of S. haematobium infection using urine filtration was introduced early on (Mott et al., 1982), as was the use of praziquantel where the role of the Special

Programme concerned the clinical trials which firmly established chemotherapy as the method of choice for control of morbidity (Davis, 1982). This is reflected in the comparatively large allocations to the fields of biochemistry and applied epidemiology in the early days of TDR (Fig. 9).

Research into immunological aspects has, from the start, commanded the largest part of available financial resources (Figs 5, 9). In fact, the proportion of immunological projects since 1981 has continuously increased due to a deliberate policy to invest more in this area. After all, immune reactions are the cause of morbidity associated with schistosomiasis and, in addition, serological diagnostic assays and vaccine research fall into this category. Although results, useful in practice, are not yet evident, some definite progress has been achieved, e.g. the existence of acquired human immunity against schistosomiasis has been established beyond doubt (Butterworth & Hagan, 1987), a number of cloned full-length antigens offering partial protection in experimental animals have been produced (Bergquist, 1990), immunoassays capable of detecting patent infection with great specificity and sensitivity have been developed (de Jonge, 1990) and standardization of ultrasound techniques for assessment of morbidity due to schistosomiasis has been initiated. This is the result of several decades of consolidated support from many donors confirming that the majority of the funds provided have served a useful purpose. It also signals the importance of a long-term outlook in financing medical research on a global scale with limited means.

DISCUSSION

Although a high proportion of grants has been awarded to research laboratories in Europe and the US, TDR encourages activities in the developing countries. The substantial sums provided for research strengthening have certainly had a positive effect on the activities of recipient institutions and there is no doubt that, due to re-entry grants, training grants and funds enabling scientists to visit institutions abroad, technology transfer is starting to have an impact. In fact, all immunology and biochemistry grants awarded to scientists in the developing countries (Fig. 5) have been allocated as a direct consequence of newly acquired abilities. The PDG initiative appears suitable in identifying interesting and worthwhile projects, whilst the expectation that the DIF would provide a prospective tool has not been borne out. The workshop in Leiden, on the other hand, was successful in that it resulted in a consistent rise in field projects over several years but the administrative procedures need to be improved to avoid delays. It is still too early to interpret the drop in 1991 but this may indicate that targeted actions such as specialized workshops should be a regular feature repeated every two or these years.

Effective yardsticks by which to measure the utility of research support are scarce and the outcome is not easy to assess. The finding that the most successful and productive researchers receive most of the grants is reassuring but hardly surprising. Although the retrospective view provided by bibliometric analysis is useful and necessary, a mechanism capable of identifying scientists and ideas of potential future importance is also needed. Lucas (1989), in this connection, envisaged a network including North/South partnerships and international institutes coupled with national research strengthening teams that would culminate in a tool of research capability transfer. On the other hand, a sobering discussion of the many factors that influence and actually determine the role of biomedical science in relation to the Third World health sector (Abel-Smith, 1989) reveals the difficulty in predicting the association between research and future developments.

Donor organizations, by virtue of their financial strength, are in a position to direct research, a responsibility requiring not only well-justified strategic plans but also correspondence with priorities set by society as a whole. This social accountability is particularly important in connection with long-term projects, where the ultimate outcome is uncertain. Fund-raising in the field of tropical medicine is meeting with increasing resistance since the public is wary about underwriting large and rising costs for research programmes with little hope of delivering tangible results in the short or intermediate term. This brings up the importance of reviewing research programmes in the wider context of general scientific and social developments. For example, vaccines against some of the important endemic parasitic diseases have been promised since the 1950s but only now, due to to advances in molecular biology and immunology, is this goal attainable in practice.

The recent stepped-up activities in the vaccine area espoused by TDR and EMCF are rooted in the conviction that a schistosomiasis vaccine would not only be beneficial for the individual but also have far-reaching propitious economic consequences. Vaccines against chronic infections associated with low mortality make sense since these diseases constitute a greater economic liability than those which kill rather than incapacitate. Morrow (1984) estimated that there is a significant social and economic impact of healthy days lost due to vector-borne diseases and high benefit/cost ratios for schistosomiasis control have been shown by several authors (Farooq, 1963; Chen et al., 1982).

If one believes that a protection rate of about 50% would reduce morbidity significantly, then trials with existing candidate vaccines can be considered. Since challenge infection cannot be ethically defended and since it would be difficult to find a sufficiently large group of healthy adults in danger of natural infection, such trials may have to target children. The thrust for developing a schistosomiasis vaccine is timely because the technical underpinnings for production are in place and safe and effective drugs exist with which to treat infections resisting vaccination attempts. Donors should make sure that this opportune opening is not ignored. The faster research moves, the smaller is the risk that drug resistance will become and obstacle to field trials.

The promoted goal can be reached with a dedicated and enthusiastic scientific community bolstered by access to preferential funding. The reality, however, is an overall financial reduction which has resulted in an intensified competition to attract a share of the available money leading to a concentration of support to fewer and more competitive research groups. Although this contributes to increased quality, e.g. as seen in the case of NIH-supported research, it is not an entirely desirable development since young scientists become increasingly dependent on an insufficient number of established scientists. For this reason the continuing real reduction of funds not only has a negative effect on current research but also makes it increasingly difficult to attract a new generation of scientists.

CONCLUSIONS

Bibliometric analysis is useful in evaluating research results but, for obvious reasons, cannot predict the future. Although donors clearly need a retrospective view of their activities, tools facilitating the search for winning strategies and promising young scientists would be of greater value. Continued reductions in real-term funding of research on schistosomiasis will ultimately reach breaking point as the base of experienced scientists becomes insufficient to maintain the current level of research production. The prospect of diminishing independent research in schistosomiasis is alarming and augurs ominously for the future. Consequently, a break-through providing new life and enthusiasm for tropical medicine research is urgently needed. Successful human trials of new diagnostic assays and vaccines could provide the impetus to boost public interest in research in the field of tropical medicine as a whole.

Applied research benefits from choosing goals in association with designers of national control programmes. The currently increasing share of research funds awarded to the developing countries is reassuring and it can be expected that, once new tools for control are available, intensified allocations in the form of field trials will foster a closer collaboration between field researchers and laboratory scientists.

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