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International Collaboration in Health Research

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One of the most remarkable achievements of the 20th century has been the enormous health gains that have occurred throughout the world. Most of these advances resulted from the application of new knowledge that was generated by scientific research. The discovery and development of new technologies for the diagnosis, prevention and treatment of diseases have expanded the range of medical and public health interventions.

Although health research is mainly organised through national institutions, there is a growing appreciation of the value of international collaboration. . This paper reviews the various models of international collaboration and analyses lessons that have been learnt from them It attempts to answer three key questions:

A. WHY international collaboration in health research?
B. WHAT experience has been gained so far?
C. HOW can the lessons learnt be applied to expand and optimise international collaboration?

A. Why international collaboration in health research

Cross-border collaboration expands the opportunities for scientists to pursue their research interests. Beyond the satisfaction gained by individual scientists, both the public sector and private industry sponsor international research as a mechanism for achieving specific goals. The motivations for international collaboration in health research can be briefly summarised:

- Scientific talent that produces creativity and innovation is widely distributed around the world; international collaboration expands the pool of talent that is available for tackling research problems;
- Because the research facilities in individual countries, especially in developing countries, are limited, it is often not possible to generate in one country the critical mass of talent and physical resources to tackle a research problem effectively. Cross-border collaboration offers the opportunity of generating this critical mass.
- Unique opportunities for collaborative research occur in some specific locations. For example, the investigation of Kuru in Papua New Guinea by a team of American scientists led by Dr. Gadjusek, gave the first clues about slow viruses and opened the way to a better understanding of scrapie in sheep, Creutzfeld Jacobsen disease in humans and bovine spongiform encephalopathy (BSE) in cattle;
- International collaboration facilitates the exploration of shared features in biological systems; this sometimes leads to unexpected discoveries. Cross-national comparative

studies by revealing similarities and differences, broaden perspectives and concepts beyond the narrow findings in individual countries; and

- International collaboration offers the opportunity for strengthening the research capacity of less developed countries and institutions as well as facilitating the transfer of technology.

The case for international collaboration is particularly strong in dealing with the health problems that affect poor populations in developing countries. Research on problems affecting poor people in developing countries has been relatively neglected. According to the Global Forum for Health Research (1999), only 10% of $50-60 billion that is spent every year for health research is used for research on the health problems of 90% of the world's people – the so-called 10/90 disequilibrium. Several reasons account for the relative neglect of research on these problems:

- Developing countries lack the research capacity to tackle their priority health problems, a picture which is still heavily dominated by communicable diseases including malaria and other classical tropical infections.
- It is not commercially attractive for research-based private pharmaceutical companies to invest in research and development on diseases which mainly affect the poor;
- Many governments in developing countries do not adequately finance their own research institutions and scientists. Although some of the more advanced developing countries --- Brazil, Mexico, Thailand -- are rapidly acquiring the capacity to do world class research, in many developing countries, research is still relatively neglected.
- The rising cost of developing new health technologies requires massive investments. In developed countries, research-based pharmaceutical companies are dealing with this challenge by merging to form larger and larger conglomerates thereby mobilising a wider operational base to absorb the high cost of research and development.

Conclusion

There is a geographical dissociation between the distribution of diseases and conditions that occur largely in developing countries ("the south") and the scientific expertise that is required to tackle them, capacity that is largely in the developed countries ("the north"). The present situation will not reverse itself spontaneously. Rather, there is a need for strategies that will help correct the 10/90 disequilibrium. The expansion of international collaboration in health

research should be an important element of the new strategies coupled with mechanisms for strengthening the research capacity of developing countries.

B. WHAT experience has been gained so far? A review of models of international collaboration in health research. What lessons have been learnt?

International health research occurs in many different forms ranging from the casual, opportunistic interaction between two scientists on a small limited project, to more extensive formal programmes involving many institutions and covering large research programmes. This section classifies and reviews models of international collaboration in health research. Analysis of each model shows lessons that have been learnt from previous experience and how these can be used to optimise future collaboration.

1. **Bilateral programmes (Table 1)**
    - 1.1 Scientist to scientist
        - 1.1.1 Public sector
        - 1.1.2 Public/private collaboration
    - 1.2 Institution to institution
2. **International networks (Table 2)**
    - 2.1 Interactive networks
    - 2.2 Multicentric studies
    - 2.3 Integrated networks
3. **Research Institutes (Table 3)**
    - 3.1 Bilateral
    - 3.2 Multilateral
    - 3.3 National centres of excellence serving regional functions

The analysis will present the experience derived from each type of model. It will identify the strengths and weaknesses of each one, identify the lessons learnt and suggest how to optimise the value of each approach.

1. Bilateral programmes

The bilateral model of international collaboration involves partnerships between scientists from two institutions located in two countries.

1.1 Scientist to scientist collaboration

In one form, both scientists are in academic institutions or other public establishments – Model 1.1.1. In another form, one partner, usually the scientist from a developed country, represents a pharmaceutical company or other for-profit private entity – Model 1.1.2.

1.1.1 Scientist to scientist partnerships in the public sector

This common model of international collaboration involves partnerships between scientists from two institutions, one or both located in developed countries or in developing countries; but often, the research project links scientists from a developing country to partners in developed countries.

The most successful examples of such partnerships confer clear benefits to both contracting parties, and eventually to scientific progress in general. In an ideal case, the partnership produces a smooth dovetailing of skills and expertise. The partner from the developed country or from a more advanced institution in a developing country contributes sophisticated laboratory and other special resources that are not available in the less developed institution. Their peers in the developing country or in the less developed institution contribute local clinical and other contextual knowledge.

Such bilateral collaborative programmes provide opportunities for international comparative studies in which the same phenomenon is examined in different countries and among subjects from different social, cultural and genetic backgrounds. Such studies can be very useful in unravelling the complex aetiology of chronic diseases such as cancers, heart diseases and diabetes. For example, a Nigerian team collaborated with scientists in the USA in comparative analysis of prostatic cancer. (Jackson et al., 1975.1977). (See also Box 7)

BOX 1 gives an illustrative example of such collaboration between a British scientist and Nigerian partners who collaborated in the study of cyanide metabolism in the one case, in patients with a hereditary defect and in the other case, from high intake of cyanide in the local diet!

Features of scientist to scientist relationship could include:

- Joint planning of projects including the statistical design
- Mobilisation and management of financial resources;
- Two-way exchange of visits;
- Strengthening of the research capacity of the weaker institution and transfer of technology; and
- Joint publication of papers with appropriate recognition of all the contributors.

Forward planning of such collaborative projects can increase the likelihood of successful collaboration. As far as possible, there should be prior agreement on the allocation of specific tasks (clinical, field and laboratory), data handling and processing and drafting reports and formal publications. There should also be agreement about the sharing of the rewards (intellectual property, authorship of publications, etc.) as well as arrangements for future negotiations, and in complex projects, for arbitration mechanisms.

Less attractive is the so-called "SAFARI" model of international research in which a foreign investigator lands in a developing country, with minimal involvement of scientists from host institution, collects specimens - clinical, biological (parasites, vectors, etc.) and returning home after a few weeks stay. Usually, the host institution hears no more until a paper appears in a scientific journal. In the so-called courier model (DHL/Fedex), the investigator in a developed country requests a scientist working in a developing country, usually a former student, to send specimens from patients or some other biological materials. The 'safari' and 'courier' models are exploitative and unacceptable. Such practice has occasionally led to strange conclusions. A foreign investigator who has no understanding of local health problems may draw strange conclusions from the few patients encountered during the whirlwind tour or from laboratory specimens that are examined out of context of the local situation. Some of the major controversies in tropical medicine have occurred between scientists with long acquaintance with the problem in an endemic area and scientists who pay brief visits to the area. In one classical debate, clinical and epidemiological evidence had previously established onchocercal infection as the cause of the posterior lesions (choroido-retinitis) of the eye in endemic areas of Africa. After a brief visit to a site in West Africa, a distinguished European ophthalmologist concluded that the lesions were not related to onchocerciasis but were due to a genetic disorder in a community, which practised consanguineous marriages. After a long and acrimonious debate, the role of onchocerciasis was confirmed. (Budden, 1963; Choyce, 1964; Hissette, 1938; Rodger, 1971).

Fragmentation of national research programmes

Strong bonding with foreign partners sometimes inhibits collaboration with national colleagues. This sometimes leads to irrational fragmentation of effort within the country. For example, in one African country, there was a well-designed longitudinal epidemiological study of HIV/AIDS but with relatively little information on behavioural aspects. In the same country, another team studied the behavioural aspects in detail but in a different site; apparently, each donor insisted on having a separate, discrete project!

Medical Research Councils in Developed Countries (MRC)

MRC's in developed countries should intensify their support for their own nationals who wish to engage in international research. The MRC should earmark 5 % of its budget for such projects. Such support would enable the scientists to use modern sophisticated biomedical techniques in addressing problems affecting developing countries and the resources would also enable them to engage in fruitful partnerships with scientists in developing countries. The availability of resources would also encourage young scientists to seek careers in international health.

Comment and conclusions

International collaboration between scientists can be highly successful mechanism for advancing knowledge especially in situations in which peer-level relationships and complementary skills produce synergism. Such projects also offer the opportunity for training and capacity strengthening as well as the transfer of technology. There is however, the risk that foreign affiliations may inhibit local linkages by creating a local elite of scientists with strong loyalties to foreign partners.

The ideal set-up for scientist to scientist collaboration is a peer-level relationship that is based on mutual respect and reciprocal benefits. This is best achieved where the scientists in the developing countries have secure funding for their high priority projects and are not entirely dependent on handouts from their foreign partners. Poorly funded scientists, who are heavily dependent on resources provided by their foreign colleagues, are at great disadvantage in negotiating with their foreign partners. This weakens their ability to focus on high priority problems and induces them to accept projects that are dictated by foreign sponsors.

1.1.2 Scientist to scientist collaboration involving public and private institutions

Recent interest in promoting public-private partnerships has led to the expansion of linkages between scientists in academic institutions and pharmaceutical companies. These projects aim at accelerating the translation of research to usable products through innovative partnerships and collaborations with the private sector, e.g. the Medicines for Malaria Venture (MMV) and the Global Alliance for TB Drug Development.

Clinical trials of new drugs are the classical examples of projects involving pharmaceutical companies, mainly situated in developed countries, with research scientists in developing countries.

Why do pharmaceutical companies test their drugs in developing countries? The motives vary and may include some of the following:

- The disease is peculiar to geographical areas in the developing world e.g. tropical parasitic diseases like onchocerciasis or schistosomiasis;
- Peculiar clinical and epidemiological features of the disease in developing countries present situations that are significantly different from what is encountered in developed countries e.g. the massive epidemics of cerebrospinal meningitis are confined to certain parts of the developing world.
- The disease is of global distribution but the higher frequency of cases in developing countries makes it easy to accumulate information more quickly than if the study were done only in a developed country whe re the condition is relatively rare. e.g. tuberculosis.
- It may be easier to obtain ethical clearance in a developing country. This may be a cynical and unethical exploitation of less stringent requirements of the regulatory mechanisms in developing countries. However, there may be situations in which local conditions may justify ethical clearance of a study in one place that may be inappropriate and unethical in another place. For example, when treatment in a sanatorium was regarded as the gold standard of clinical practice for the care of tuberculous patients, studies on ambulatory care of tuberculosis would have been deemed unethical in a developed country. But with the limited resources in developing countries and the large number of active cases of tuberculosis, it was judged appropriate to conduct the study in India.

Clinical trials are absolutely essential for generating the scientific knowledge for improving the care of patients in developing countries. In many cases, the motives for conducting clinical trials in developing countries are legitimate and commendable. Even where the drug has been tested in other countries, local trials may be indicated because of the unpredictable effects of genetic variations, malnutrition and the existence of other underlying diseases and conditions. Such local studies have indicated the need for different dose schedules and other modifications of treatment regimes. For example, comparative studies in South Africa have shown that white and Indian hypertensive patients respond better than black patients do (Seedat, 2000).

Involvement in clinical trials can confer benefits to the clinicians and the host institution:

- The rigorous discipline imposed by drug trials may improve clinical care of the research subjects and other patients;
- For special studies, the host institution may acquire new equipment or upgrade existing ones. Often, sophisticated equipment that were acquired in the first instance for research

do eventually find other uses in routine care of patients. In some cases, the clinical trials are sponsored purely as a commercial undertaking in which an agency ion a developing country receives payment for conducting studies on behalf of drug companies.

- Intellectually, involvement in clinical trials puts the clinicians at the host institution at the cutting edge of the scientific developments in their special area of interest; it often expands their access to current scientific literature.

Ethical issues

In recent years, there has been increasing concern about some of the drug trials that pharmaceutical companies have sponsored in developing countries. Some of these studies have not met high ethical standards. There have been complaints about the exploitation of poor, uneducated individuals who have been exposed to drug trials without receiving full explanation of the procedures and without giving their informed consent.

Universal ethical standards

Debates about ethical standards for research involving human subjects have raised many contentious issues. A recent example is the controversy about the clinical trials of anti-retroviral drugs to control vertical transmission of HIV infection in pregnant women. Some commentators take up a rigid, absolute stance. They insist that there should be only one universal standard, both in ideals and in the implementation of projects. They support the wording of ethical guidelines that state that all participants in a study should be assured of "the highest standard of care". Such a stance protects vulnerable people from abuse and is ideologically comfortable but it may not always be realistic.

Ethical Progressive Improvement

It is possible that the strict imposition of these universal standards may work against the interests of poor people in developing countries. An alternative viewpoint is that all research involving human subjects must give the highest level of protection to all the subjects but that it is ethical to explore the development of cost-effective options that offer ***significant improvement on current practice*** but fall short of the "best care." This approach is illustrated by the bold trial of ambulatory care of tuberculosis when the "best standard of care" was institutional treatment in sanatoria, and by the use of oral rehydration solutions in place of intravenous therapy. Both studies – ambulatory care of tuberculosis patients and oral rehydration – helped to develop new effective methods that were of particular interest to developing countries; but these approaches have also been adopted in developed countries. It would be unrealistic to insist that countries with Gross National Products (GNP) below

US$500 should offer their people the "best standard of care" that more affluent countries with GNP's over US$5,000 have adopted. It is ***necessary, logical, compassionate and ethical*** to evaluate ***alternative, affordable and sustainable options***. It should be possible to define a middle ground in which research can explore the possibility of ***ethical progressive improvement*** in health care without insisting on a quantum leap to the "best standard of care" (Figure 1).

Conclusions and recommendations

As long as the private pharmaceutical drug companies remain the main source of new innovative drugs, it is essential for reputable medical institutions to collaborate with them in evaluating the potential new products for efficacy and safety. Such trials are carefully regulated in developed countries. Because regulatory mechanisms are less well established in developing countries, it is important for studies to be closely scrutinised to ensure that the highest ethical standards are observed. In cases involving less developed institutions, it might be in the interest of both parties to use a neutral third party as an arbiter. For example, the national ethical committee and the pharmaceutical company may request the World Health Organisation to review the proposal and give guidance on ethical matters. In particularly sensitive cases, it may be useful to appoint an independent clinical trial monitor who is not employed by the pharmaceutical company nor by the host institution. The Nigerian case cited in Box 2 would have benefited from these two mechanisms.

1.2 Bilateral Collaboration – institution to institution

This model involves a long-term linkage between two institutions, often characterised by multidisciplinary involvement and providing opportunities for the development of a variety of projects. This model is often used in situations where the primary interest is the strengthening of the less developed institution that is linked to a more advanced institution. The linkage also provides international experience and training for the junior staff of the developed country institution.

The sponsoring agency usually provides support over a long period, usually for 5 years or more. The joint research projects provide the means of training and capacity strengthening and at the same time engage the interest of the scientists from the more advanced institution. The elements of the partnership include:

- Joint research projects;
- Training of junior staff from both institutions;
- Two-way exchange of staff; and

- Transfer of technology

Some of these relationships have been very highly successful as shown by the productivity of the joint research projects and by the more confident, more competent and more self-reliant institution that develop after several years of the linkage. The UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR) has used this mechanism extensively for strengthening the research capacity of institutions in developing countries. For example, the Department of Clinical Pharmacology of the University of Ibadan, Nigeria was linked to a department at the Karolinska Institute in Stockholm Sweden; the main area of research was on the chemotherapy of malaria.

Other sponsors have used variants of this model. In the 1980's, the European Economic Union (EEC -- now European Union) within its Science and Technology for Development Programme offered grants to scientists for studies on tropical diseases. The EEC specified that each proposal should include joint work between scientists in two EEC member countries in association with an institution in a developing country. In some cases, the collaboration was highly successful both with regard to scientific output and the strengthening of research capacity. Others were less successful and, in extreme cases, the developing country institution was exploited.

The Rockefeller Foundation in collaboration with TDR also sponsored a highly successful twinning programme involving linkage of developing country institutions to more advanced institutions. It involved 34 groups in 12 partnerships. Rockefeller Foundation funded the northern groups and TDR funded the southern groups.

The main lesson learnt from these cases is that the outcome is very much influenced by the leadership in both institutions. Much depends on their commitment to the goal of using the linkage for the combined objective of doing good science and at the same time strengthening the capacity of the developing country institution. The process of building and strengthening capacity is time-consuming and so the sponsoring agencies must ensure secure funding over time. At the same time, the contract should include agreement by which the developing country progressively takes over the funded activities on a sliding scale.

Another important determinant of long-term success is secure funding of sufficient duration to ensure durable changes in the less developed institutions.

In order to protect the weaker partner, it may be a good idea to make the grant to the developing country institution. TDR uses this approach. This strengthens the developing country institutions in negotiating with their northern partners. It enables the developing

country institution to select the most compatible partner who shares the common goal of advancing science and strengthening capacity.

Conclusion

Institution to institution linkage has proved a useful model for promoting research and strengthening capacity. In designing such programmes, the sponsors should sensitive to the need to protect the weaker partner. For linkage programmes, it might be better to make the grant to the developing country institution; this would empower the institution and give it flexibility in its dealings with its foreign partners. Public-private partnerships also raise sensitive issues about ethics and intellectual property rights.

2. International networks

The term "networking" is used to represent many different types of relationships and activities:

- *Information* exchange
- *Interaction* among participants – involving reaction and response to ideas and results; and
- *Integrated action* in which the participants in a network link defined activities as an integral part of an agreed programme.

This paper examine three models of international networking for health research:

2.1 Interactive networks
2.2 Multicentric studies
2.3 Integrated networks

2.1 Interactive Networks

Interactive networks link groups of scientists who have a common interest in a specific research area; others have been designed to promote general access to scientific information. The network provides mutual support and often links the participants to sources of technical assistance.

Information exchange networks

The expansion of electronic communications has facilitated interactive networks that support research scientists by providing access to relevant scientific information. Some of these networks relate to specific health issues but others promote links to sources of information on a broad base. For example, the African Networks for Health Research & Development (AFRO-NETS) has set up an electronic conference whose main purpose is exchange of information between the different networks active in Health Research for Development in the Eastern and Southern African Region.

List of networks linked through AFRO-NETS – a network of networks

Essential National Health Research	AfroImplement: Evidence to Action
Health Systems Trust - South Africa	Blair Research Institute - Zimbabwe
Biomedical Research & Training Institute	International Health Policy Programme
African Malaria Vaccine Testing Network	Medical Research Council of Zimbabwe
International Clinical Epidemiology Network	Medical Research Council of South Africa
Social Science and Medicine Africa Network	Support for Analysis and Research in Africa
Council on Health Research for Development	Joint Programme on Health Systems Research
Commonwealth Regional Health Community Secretariat	International Development Research Centre - Canada
Independent Group for Health in Africa	
Regional Network on Equity in Health (EQUINET)http://users.harare.iafrica.com/~gtz-hsr/marf.htm	
Medical and Actuarial Research Foundation - Zimbabwe	
Partners in Population and Development - A South-South Initiative	
Scientists For Health And Research For Development (SHARED)	
Health Systems Research for Reproductive Health & Health Care Reforms in the Eastern & Southern Africa Region	

There are many examples of highly successful interactive networks such as the International Clinical Epidemiology (INCLEN) and the Applied Diarrheal Disease Research (ADDR) Project and its successor, the Applied Research for Child Health (ARCH) Project. A brief review of two examples illustrate the operations of interactive international research networks:

2.1.1 International Health Policy Program (IHPP)

The International Health Policy Program was initiated as a means of strengthening the capacity of developing countries to undertake relevant policy analysis in collaboration with policy makers. With the encouragement of WHO and the World Bank, and the financial support of two private foundations, IHPP operated 14 centres in Asia and Africa. These centres have undertaken policy relevant research that has influenced decisions in some of their countries. (Box 3)

2.1.2 The Prevention of Maternal Mortality Network (PMM)

> "Every minute of every day, somewhere in the world, a woman dies as a result of complications arising during pregnancy and childbirth. The majority of these deaths are avoidable."

More than half a million or more women die each year from complications of pregnancy and childbirth; most of these deaths occur in developing countries. In Africa, the lifetime risk of dying from pregnancy and childbirth is 1 in 16 as against 1 in 3,700 in North America. The clinical causes of the deaths are well known and are amenable to treatment: severe bleeding, infection, eclampsia, complications from abortion, and obstructed labour.

In response to a global call for action to promote SAFE MOTHERHOOD, a team of researchers at the Columbia School of Public Health, New York, USA developed and managed a network of centres in West Africa dedicated to operational research aimed at reducing maternal mortality. (Box 4). Eleven centres in Nigeria, Ghana and Sierra Leone participated in the network which focused on access to and quality of emergency obstetric care as vital elements for the prevention of maternal mortality.

Comment

These and similar interactive networks have stimulated and supported health research in developing countries. The two cases cited illustrate some of the important features of this type of networking:

- A central co-ordinating mechanism that serves as the hub of the network, mobilises funds, provides technical assistance and generally manages the programme;
- The central secretariat organises technical assistance from is own institution, from one of the participating centres or from outside the network;
- The secretariat organises workshops for developing research protocols, for reviewing on-going work and preliminary findings, for data analysis, or for teaching new techniques;
- A capacity-strengthening component is often built into interactive networks. It may include formal training of young scientists at the masters and doctoral degree level;
- Such networks promote technical collaboration among developing countries. Because there are still relatively few qualified experts in some developing countries, their scientists often work in isolation. Interactive networks provide the opportunity for them to obtain a critical appraisal of their plans and progress, and it provides a sounding board for their innovative ideas;

Such networks require secure sources of funding to maintain the secretariat and to support technical assistance and interactive workshops. An obvious danger is that a high proportion

of the resources may be expended in the administrative services of the secretariat or that too high a proportion of the resources may be locked up in the developed country institutions. An independent review of the International Clinical Epidemiology Network (INCLEN), an interactive network, initiated by the Rockefeller Foundation, drew attention to such problems. The management of the programme has since been revised and a new co-ordinating mechanism was established in a developing country.

Difficulties and constraints

Political difficulties, poor communications, travel restrictions and other extraneous issues often make it difficult for developing country scientists to interact effectively.

Conclusion

Interactive international research networks, when well designed and efficiently managed can make significant contributions to knowledge. Furthermore, the network facilitates co-operation among scientists in developing countries. This type of networking helps to overcome the isolation of scientists in developing countries, who lack the opportunity of discussing their work with scientists with similar interests.

2.2 Multicentric studies

Multicentric studies have been used extensively in clinical research especially for trials of new drugs. In such projects, the collaborating centres carry out studies based on a standard protocol. The usual reason for setting up such networks is to generate a large number of eligible candidates for the study. By pooling the results from the network, the sponsors of the study can arrive at conclusive findings much earlier than if they relied solely on the small number of cases that occur in any one of the centres.

This approach has also been adopted for epidemiological studies. In such cases, there is particular interest in international comparisons, looking for differences and similarities from which to generate and test general hypotheses. International collaboration in health research sometimes involves comparative studies in two or more nations and in subjects from different cultures and ethnic groups.

Successful examples include the national epidemiological surveys of Chagas' disease in Latin America that TDR and the Pan American Health Organisation co-ordinated. Based on standard protocols and laboratory methods, the situation analyses derived from these studies, facilitated progress towards the elimination of the disease.

2.2.1 Global epidemiology of diabetes

One recent example was the global study of diabetes that WHO co-ordinated (Box 5). Using a standard protocol and diagnostic criteria, WHO co-ordinated an international survey which

generated information about the global distribution of diabetes and impaired glucose tolerance.

2.2.2 Comparative studies on atherosclerosis

Some investigators have noted and probed the striking differences in the pattern of ischaemic heart disease and stroke between West Africans and people in many developed countries. In order to elucidate the risk factors associated with these differing patterns of cardiovascular diseases, some researchers have compared clinical and pathological findings in populations at various sites. (Box 6) These studies showed a higher frequency and earlier age of onset of atherosclerosis in Americans compared with Africans.

2.2.3 Cross-national studies on senile dementia

Another collaborative programme focussed on the prevalence and pattern of senile dementias. The cross-national study, funded by the National Institutes of Health, Bethesda, USA, linked Professor Osuntokun and his colleagues in Ibadan, Nigeria to partners in Indianapolis, USA. The investigators using standardised protocols, compared the occurrence of Alzheimer's disease in communities in Indianapolis and in Nigeria. (Box 7). The preliminary findings showed a lower prevalence of Alzheimer's disease in Ibadan as compared with its relatively high occurrence among black Americans in Indianapolis, USA. They also noted a lack of correlation between APOE-epsilon 4 allele frequency and Alzheimer type of dementia. Their findings, published in over 20 papers in peer reviewed journals, have made major contributions to the understanding of senile dementias.

2.2.4 Monitoring Trends in Cardiovasular diseases

WHO designed and managed an elaborate multicentric study for monitoring trends in cardio-vascular diseases involving the prospective follow up of 10 million persons in 21 countries. (Box 8)

Comment

Cross-national and cross-cultural comparative studies have made useful contributions to scientific knowledge and disease control including:

- Identifying risk factors;
- Testing hypotheses generated in one locality at other sites; and
- Developing and testing appropriate, cost-effective technologies.

a) Identifying risk factors

Cross-cultural and cross-national studies provide useful clues for unravelling the complex web of risk factors and determinants of health and disease. International comparisons provide opportunities for examining key variables in high prevalence and in low prevalence groups; and also in situations where the disease is newly emerging or rapidly declining.

b) Testing hypotheses

Cross-cultural and cross-national studies enable scientists to examine hypotheses that seem valid in one country or geographical area, by testing them at other sites and in other settings.

c) Developing appropriate cost-effective technologies

International comparative studies can be used to develop and test new or modified technologies for prevention, diagnosis and the management of diseases. Studies in developing countries have helped to adapt some expensive, complicated technologies into affordable cost-effective interventions. Not only do such modified techniques benefit developing countries but they have in turn, been adopted by developed countries. Classical examples include ambulatory care of tuberculosis and outpatient surgery.

Developing and managing international comparative studies

The promotion of international comparative studies requires the commitment of sponsors and investigators who have vision and effective management skills. The process of developing such initiatives may involve several steps:

- **Convening function** Bringing together potential collaborators from different parts of the world to identify research projects of common interest;

- **Defining procedures and designing protocols** International collaborative studies that use standard protocols and quality controls provide a more powerful tool than independent studies designed by individual scientists, each one using different methods and different diagnostic criteria.

  A recent example of the problem created by scientists working in isolation is the question about the impact of the treatment of common sexually transmitted diseases on the risk of acquiring HIV infection. Two major studies that were recently concluded gave opposite findings but the design of the studies were so different that the results were not comparable. (Grosskurth et al., 2000). In order to obtain conclusive findings, WHO and/or UNAIDS should set up a multicentric study, using a common protocol to carry out

this investigation.

- **Shared Resources** e.g. a central laboratory to carry out special tests.
- **Regulatory function** Sponsoring agencies, national or international agencies, must ensure that the rights of all the participants, especially the weaker partners, are adequately protected and that all parties adhere strictly to ethical standards.
- **Dissemination of findings** The sponsors should ensure that the results of the studies are widely disseminated so that the findings can be used in making policies and developing strategies for disease control.

Missed opportunities

One interesting idea that is worth exploring is the promotion of international research collaboration based on comparative epidemiological studies on people whose ancestors have migrated and settled in foreign lands. For example, people of African origin are now settled in the Americas and in Europe. Some of the clinical epidemiological findings point to the continuing role of genetic factors; others indicate the effects of their new environments and altered lifestyles. For example, in West Africa, glaucoma, the commonest cause of irreversible blindness in some parts of Africa, shows many unusual clinical and epidemiological features. (Olurin, 1973) People of African origin in Europe and the Americas also show some of the atypical clinical features and response to therapeutic interventions. A formal mechanism for research collaboration among ophthalmologists in Africa, USA, the Caribbean, and in Latin America could facilitate advances in our knowledge of this problem. Other conditions that could be treated in like fashion include sickle cell disease, cancer of the prostate, and hypertension.

Conclusion

Multicentric studies have been a powerful tool especially for making international comparisons on the epidemiology and risk factors associated with particular diseases and conditions. Private foundations and other sponsors have supported small-scale studies involving a few centres. The World Health Organisation is particularly well placed to promote and co-ordinate large, global studies. This powerful tool deserves more support.

Recommendation

It would be useful to establish a global fund that would enable WHO to sponsor, design and manage international multicentric studies on priority problems.

2.2.3 Integrated networks

An integrated network is designed to co-ordinate the activities of the collaborating centres to achieve specifically defined goals. The component elements of the network acting jointly provide the critical mass for achieving the specific goals of the programme. A central secretariat co-ordinates the network, allocating tasks and ensuring that the sequential stages of the programme occur smoothly. WHO has managed two major integrated networks; the first was its special programme on human reproduction (HRP) followed by the tropical diseases research programme that was based on the same model.

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) provides examples of integrated networks. TDR has two interrelated objectives:

> **Research & Development**: to develop safe, acceptable and affordable methods of prevention diagnosis, treatment and control of TDR's target diseases. (Malaria, Schistosomiasis, African trypanosomiasis, Leishmaniases, Dengue, Lymphatic filariasis, Onchocerciasis, Chagas disease, Leprosy, Tuberculosis) including drugs, vaccines, diagnostic tools and innovative methods of vector control
>
> **Training & Strengthening**: to strengthen the capability of developing disease-endemic countries to undertake the research required to develop new technologies.

Since its inception in 1975, TDR has funded over 8000 projects involving 6500 scientists: 5300 research and development projects in 127 countries totalling US$300 million. TDR in partnership with industry and others has been involved in the development of 67 disease control tools of which 38 are in use for disease control. TDR funded 2700 Research Capability Strengthening projects in 80 countries totalling US$117 million. 260 institution strengthening grants were awarded. 1100 scientists from developing countries completed research training and over 90% of trainees returned to home countries; 200 scientists are currently in training. Using the new technologies and strategies generated with TDR support, there is now the prospect that four of the diseases can be eliminated -- leprosy, onchocerciasis, lymphatic filariasis, and Chagas' disease. Box 9 and Box 10 give illustrative examples of the strategies that TDR adopted in its integrated networks.

Comment

Several features of TDR's operations contributed to its success, principles that can be applied in other programmes:

- Clear, goal-oriented objectives for the programme as a whole and for its constituent parts;
- Global networks of scientists for planning, implementing, monitoring and evaluation;
- Multidisciplinary inputs both biomedical and social sciences;

- Flexible and innovative strategies;
- Objective decision making buffered against political pressures;
- Partnerships including extensive links with the pharmaceutical industry; and
- Strong sustained support from co-sponsors, donors and scientist.

The integrated networking that TDR developed has been a highly successful cost-effective programme. By linking scientists and institutions around the world, TDR created virtual institutes.

Conclusion

Integrated networks can be rather complex operations calling for creativity in their design but they have proved highly cost-effective if well managed.

Recommendation

Any new integrated networks should utilise lessons learnt from the TDR experience. TDR has matured into a reliable productive programme that deserves continuing support. In view of its outstanding success, international agencies should ensure stable funding for HRP and TDR at a level of about $50 million dollars annually for each programme.

3. Research Institutes

International collaboration based on research institutes takes many forms:

3.1 Bilateral collaboration

3.2 Multilateral collaboration; and

3.3 National centres fulfilling international/regional functions

3.1 Bilateral Collaboration

Most of the research institutes that were established during colonial era were handed over to national authorities or regional bodies at independence. In a few cases, the former colonial power continues to run the institute in collaboration with the national authorities.

Such institutes have the advantage of receiving stable financial support from the foreign government. They also attract scientists from the developed country who want to have research experience in developing countries. They also train local scientists but not all the foreign directors of such institutes commit themselves unequivocally to build a strong cadre of local scientists. In the past, they mainly used local staff in junior capacities – as bottle washers in the laboratories and as "fly boys" in the field.

The British Medical Research Council Institute in the Gambia is an example of a bilateral institute. The United Kingdom government heavily funds it and it has attracted outstanding British scientists who have done excellent research on malaria and other tropical diseases. It has also been an important training site for West African scientists.

The Pasteur Institute in Paris is the "hub of a wheel whose spokes are the 24 associated institutes in Asia, Latin America, Africa and Oceania, and Europe itself. Some of these have gained considerable prestige since decolonisation: the World Health Organization recently made the Pasteur Institute in Abidjan, in the Ivory Coast, its main centre for research on the HIV 2 virus in Western Africa."

Comment

Few examples of this model remain and it is unlikely that any one would propose setting up a new one. The examples of the MRC laboratories in the Gambia and the Pasteur Institutes show how the post-colonial transition can be used to good effect in remodelling and modernising institutions that were founded in colonial days.

3.2 Multilateral collaboration

There has been much debate and discussion about the international institutes for health research. Strong advocates have strongly urged the international health community to copy the CGIAR model of research institutes. When TDR was establishes, the World Bank hesitated for several years to co-sponsor the programme because senior management of the Bank felt that the proposed networking approach would be much less efficient than the international research institutes. In the first few years of the programme, it was the UNDP/WHO Special Programme for Research and Training in Tropical Diseases. Later, the Bank was persuaded to join WHO and UNDP in sponsoring the programme.

An objective analysis of the CGIAR research centres raises important questions about the performance of some of the centres. Although the centres in Asia and Latin America seem to have made significant impact on agriculture in their respective regions, the achievements in Africa have been much less significant.

3.2.1a The International Institute for Tropical Agriculture (IITA)

Established in 1967, the IITA became a member of the CGIAR group in 1970 when research started. The objectives were clear and unambiguous – to tackle food production through research. IITA documents over the past 30 years show evidence of high quality research and significant outputs in terms of new varieties of crops and of pest control technologies. There has been no significant impact on the steadily deteriorating situation with regard to food production in sub-Saharan Africa. The most recent statements suggest that the goals may not be realisable – at least not on the basis of IITA's input:

Mission Impossible?

"In fact, given the poor resource base in the African situation, it is unlikely that crop productivity under small scale farming conditions, relying mainly on

biological inputs, can ever jump to very high levels." *Report of the Fourth External Programme and Management Review of the IITA, 1996 Page 5*

Goals and achievements of IITA

Promise	Performance
"… the real objective of the Invstitute, which is to contribute to the improvement of the quantity and quality of food crops in the tropics by testing, and encouraging the application of, research results at the farm level." *Report of the TAC Quinqennial Review Mission to the IITA (1978) Page 12 paragraph 20.*	"Sub-Saharan Africa is the only region in the world where per capita food production has declined in the past two decades" Report *of the third external programme review of the IITA" 1990, page 74 section 7.1.*
"IITA aims to improve the nutritional status and well-being of low income people in the humid and sub-humid ones of sub-Saharan Africa by carrying out research and related activities for increasing agricultural production in a sustainable manner." *CGIAR mission statement in 1990 quoted in Report of the Fourth External Programme and management Review of the IITA, 1996 Page 5*	"…..food production per caput in sub-Saharan Africa continues to show a declining trend while food self-sufficiency ratios are low" *Report of the Fourth External Programme and management Review of the IITA, 1996 Page 1*

3.2.1 b The International Laboratory for Research on Animal Diseases, (ILRAD)

Established in 1974, ILRAD's objectives were defined as: *"controlling the disease of trypanosomiasis and East Coast Fever by immunological and related means."* (Report of the TAC Quinqennial Review of ILRAD, 1980, page 1) ILRAD embarked initially on basic research in both diseases that would hopefully lead to control by immunological means.

The scientific output from ILRAD has been very impressive with significant contributions to the understanding of the basic biology of the parasites and their hosts. More recently, ILRAD broadened out to include a socio-economic programme as a means of diffusing scientific advances to the clients. In spite of its enormous output of research results on basic biology, the goal of generating technologies for the control of animal diseases still eludes this Centre.

Comment on CGIAR in Africa.

Even the most fervent supporter of CGIAR must admit that the lofty promises that were made when the institutes were established in Africa have not been realised. ILRAD is still to make a breakthrough that would have an impact on its two target diseases: Theileriosis and trypanosomiasis. Although IITA was established with the objective of improving food production, there has been a steady decline in *per caput* food production since the institute was established. This comment is not made in a carping spirit nor must one underestimate the daunting challenge posed by the problems that the two institutes are addressing. The

important point is that neither institute has produced *prima facie* evidence that its approach was more productive or more cost-effective than other models. With relatively modest investments, TDR generated tools that have had demonstrable impact on some of the target diseases. There may still be a place for international research institutes for health research but the experience from IITA and ILRAD should induce caution.

3.2.2 International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B)

> "Achievements of the Centre over the years
>
> Since 1960, the Cholera Research Laboratory (CRL) and its successor ICDDR,B has been recognised as the leading international health research centre located in a developing country. CRL conducted research that now forms the core of the world's knowledge of diarrhoeal diseases, and led to the development of Oral Rehydration Solution (ORS). CRL was internationalised and renamed ICDDR,B in 1978 to become one of the most important and influential health research institutions in the world. The work of CRL/ICDDR,B is often cited as the authority for important health and population-related decisions taken by multilateral, governments, and development agencies throughout the world. Indeed, many of the Centre's alumni have become influential policy makers in these agencies.

Independent observers will agree to this self-assessment by ICCDR,B of its own achievements. It is a unique resource that has been consistently productive over the years.

Comment on Multilateral International Research Centres

International research centres have achieved outstanding scientific results by recruiting good scientists from the global market and providing well furnished laboratories and infrastructure. In this way, it has been possible to organise world class research using the most advanced research technologies in the basic sciences in tackling problems in developing countries.

But the course of events at these international research centres is not always smooth. Some of the difficulties encountered include:

- Leadership of an international research institute is critical in providing the vision and establishing appropriate management for achieving the goals. Leadership crises within international research institutes have from time to time undermined the effectiveness of some institutes;
- Not all scientists adapt well to working in a multicultural setting, within teams consisting of colleagues from widely diverse backgrounds. Some scientists who have achieved good

results in their home institutions do not necessarily perform well in the environment of the international research institute.

- Financial insecurity is a constant worry for many international institutes. Being mainly or exclusively dependent on soft money from donors, research institutes often face the problem of "donor fatigue" i.e. the shifting interests of donors from one scheme to the next. Some institutes have had secure funding over a long period but many have had to contend with fluctuating fortunes;
- International research institutes are expensive to establish and to maintain even though some of their costs are hidden in the form of contributions in kind from the host country. It is difficult to analyse the cost-effectiveness of international research institutes as compared with other options. One can however, ask the question as to what might have happened if instead of funding two CGIAR centres in Africa at a combined cost of about $40 million per annum, the same resources had been used strategically to support agricultural research in African universities and national research institutes. Would the network type of approach by TDR have produced the same quality of scientific results as achieved by ILRAD and IITA at much lower cost? Would the network approach have strengthened national institutions to the point where they can play a role in translating research findings into usable technologies? Both institutions in their later development moved somewhat outside their exclusively intramural work to develop networking operations with national institutions but these were clearly add-ons and not part of the original strategy. The initial approach that was based on doing upstream basic research, was perhaps more suited to Asia and Latin America where national capacity existed to do the downstream work of applying the products of basic biomedical research. The revision of the mandates of the two African Institutes suggests that CGIAR eventually did recognise this difference and the need for an alternative approach in Africa.

3.3 National centres fulfilling significant international functions

Most research institutes have varying degrees of international contacts. In some cases, the international programme is formally designed as an integral element of the institute's mandate and it forms a significant part of its programmes. In other cases, the international programmes grew through the accumulation of discrete projects and activities. In either case, a number of national research institutes in developing countries have developed significant international programmes.

SEAMEO/TROPMED is a 'Regional Tropical Medicine and Public Health Network is composed of four regional Centres in Indonesia, Malaysia, the Philippines and Thailand.' The Central Office is located in Thailand. SEAMEO/TROPMED was founded on the premise that each of the four countries cannot readily develop meaningful programmes on all priority health topics. Each centre selected areas of specialisation:

Indonesia: Community Nutrition

Malaysia: Medical Microbiology, Parasitology and Entomology

Philippines: Public Health and Hospital Administration, Occupational and Environmental Health

Thailand: General and Clinical Tropical Medicine and Tropical Paediatrics

Each centre provides training of scientists and practitioners as a service to all the members of the network and for other countries as well. The network is sustained from financial support from national sources as well as grants made directly to the institute or through the SEAMEO/ TROPMED network.

British colonial governments in East and West Africa used a similar strategy in establishing research institutes in various colonies for research on specific subjects: Malaria in the Gambia, helminthiasis in Cameroon and viral infections in Lagos. These collaborative networks collapsed after independence; the assets of West African Council for Medical Research and the East African Medical Research Council were transferred to their host countries.

Centres of Excellence

A number of outstanding institutes in developing countries have achieved international stature on the basis of their research and training capacity. This is particularly true of some of the institutions in the more advanced developing countries. For example, Thailand provides services to neighbouring countries through the WHO office:

- Individual Training Out of about one thousand applications, WHO places over 500 trainees in Thai institutions;
- Group training Seminars and workshops to enable other countries in the region to share some of Thailand's experience, e.g. management of hospital wastes;
- Technical Laboratory Services Quality control of drugs, diagnostic virology, etc.;
- Joint research and action programmes e.g. field research on malaria; and
- Consultants and advisers.

Clearly, Thai institutions are recognised as centres of excellence in the health field and they are playing significant regional and international roles. Institutions in Brazil, Mexico and other more advanced developing countries have similarly achieved international recognition. Centres of excellence are also found in less developed countries. In Africa, the Kenya Medical Research Institute, with its international links to institutions in Japan and the USA is providing leadership in the sub-region. In Mali, the Malaria Research Institute has achieved outstanding scientific results on the basis of its core of national scientists in collaboration with their international partners. A recent scientific breakthrough illustrates the power of this combination. Malian scientists in collaboration with their partners in Baltimore have identified a molecular marker for chloroquine resistance in falciparum malaria. This new tool will no doubt find useful application in disease control as well as for further research. (Djimde et al, 2001)

Comment

Useful lessons can be learnt from the examples of national centres of excellence that are fulfilling regional and international functions. Such centres have been highly productive at relatively low cost. The winning formula seems to be the combination of a stable national institution under effective visionary leadership and committed international partners. The institute in Mali evolved out of a small unit under the leadership of Professor Yeya Toure, a medical entomologist. Institutional strengthening support from TDR and linkage to foreign partners in USA and Italy through a Rockefeller Foundation grant, set the unit on the path of great achievements.

C. **HOW can the lessons learnt be applied to expand and optimise international collaboration?**

International collaboration in health research is a valuable mechanism for expanding the contributions that science can make to human health and welfare. This paper has reviewed some of the models of collaboration from regional and global perspectives.

Type of Collaboration	Benefits	Risks and Problems
North to South	• Complementary skills and assets • Sharing of resources, • Capacity strengthening and transfer of technology	• Diversion of local resources to issues that are of low priority; • Exploitation of the weaker partner; • Unethical experimentation on local populations;

South to south (TCDC)	• Mutual reinforcement in tackling issues of regional importance; • Complementary skills and resources.	• Limited resources to support research and sustain network; • Poor communications; • Travel restrictions limiting travel between developing countries

This paper summarises the strong case in support of international collaboration for health research and some valuable lessons learnt from current and previous programmes. It also indicates the need to expand and strengthen such collaborative ventures. With the diversity of needs and opportunities, no single initiative can usefully meet the requirements. The following recommendations, based on the preceding analysis, propose a multivalent approach to the issue:

I. Strengthen national capacity for health research in developing countries
II. Developed countries should increase the support for their scientists thereby enabling them to tackle national priorities and benefit from international collaboration
III. Identify and strengthen national centres of excellence to support their regional and global functions
IV. Support WHO programmes and increase its ability to launch and manage initiatives
V. Multilateral and bilateral agencies should review and intensify their contributions to health research
VI. Public institutions and organizations should expand their collaboration with the private sector using mechanisms that protect public interest.
VII. International research institutes

i. Strengthen national capacity for international health research

The recommendations of the Commission for Health Research for Development as published in their 1990 report remain valid. Developing countries should review their national health research policy adopting the concept of Essential National Health Research as a mechanism for managing health research (Commission for Health Research for Development, 1990; Task Force on Health Research for Development, 1991). So far, few developing countries have committed themselves to the target of earmarking at least 2% of their national health budget for research. Countries should monitor resource flows for health research and ensure that priority projects receive adequate funding. (Global Forum for Health Research, 2001)

Experience has shown over and over again, that without a solid foundation of well managed national research programmes, external aid can do little to strengthen research

capacity. In the chaotic situation where some governments in developing countries rely exclusively on foreign donations to support health research, external inputs cannot be properly aligned to national goals and priorities. Underpaid and under funded, scientists have to rely on lucrative contracts from outside agencies for their survival. Without complementary national commitment to health research, externally funded programmes have failed and will continue to fail to strengthen research capacity. **Capacity for what?** It is important to persuade governments that they need to acquire the capacity to achieve ***science-based, knowledge-based decision making at all levels of the health services***..

ii. Developed countries' support for their scientists and their international activities

Medical research councils in developed countries should provide increased support for their national scientists to enable them to undertake research on international health problems. Each medical research council should earmark a proportion of its budget, say 5%, for international research. These resources should be used to support researchwork in home institutions and also partnerships with scientists and institutions in developing countries. The policy should include long-term commitment to sustain bilateral linkages.

iii. Strengthen national centres of excellence to expand regional and international activities

National centres of excellence that can expand their international role should be selected on a competitive basis and funded to expand their international activities. The aim should be to promote regional collaboration so as to cover the major health issues in the area whilst avoiding unnecessary duplication of effort. The SEAMEO/TROPMED model could be used a s a reference. National institutions should be encouraged to compete for resources that would enable them to extend their activities to involve international collaboration. This is particularly pertinent in the more advanced developing countries that already have significant level of research capacity that can be used to strengthen neighbouring countries in the region.

iv. Support WHO programmes and increase its ability to launch and manage initiatives

WHO should intensify its leadership role in promoting and supporting health research. This is not an exclusive role but WHO should work collaboratively with other relevant agencies – multilateral, bilateral, regional and national bodies as well as the private sector.

WHO's major functions in health research

FUNCTION	COMMENT
ADVOCACY	Promoting health research in all its activities with member states and in its relationships with other agencies.
ANALYSIS	Through its Global and Regional Advisory Committees on Health Research,

	defining global and regional needs for health research, identifying gaps and monitoring progress on important issues.
EXPERT REVIEW	Using expert panels and other mechanisms, critically reviewing important problems and determines the "STATE OF ART" on specific issues. This role is particularly important in dealing with controversial issues, especially where political, economic and other extraneous considerations may tend to interfere with objective scientific analysis. E.g. BSE in Europe.
PROJECT SUPPORT	Designing and managing research projects where it has comparative advantage e.g. cross-national comparative studies and integrated networks.
CAPACITY STRENGTHENING	Through global and regional programmes, contributing to the strengthening of health research capacity.
INFORMATION DISSEMINATION	Through its own publications and by facilitating access to other sources, enhancing the access of scientists, policy makers and health practitioners to relevant information.

The international community should provide guaranteed resources to support WHO's successful major research programmes. For example, on the basis of the significant achievements of HRP and TDR, donors should guarantee resources at a level (say $50 million a year for each one) that would enable the programmes to continue its unbroken record of achievements.

WHO is well positioned to design and manage international comparative studies that can generate knowledge that will inform national health policies. A special fund should be established to enable WHO, under the guidance of the Advisory Committees on Health Research, both Global and Regional, to identify promising projects.

v. Contributions of other multilateral and bilateral agencies to health research

All international agencies should consistently support health research as a tool for development. (COUNCIL FOR HEALTH RESEARCH AND DEVELOPMENT (COHRED) (2001)). It is often stated that in World Bank projects, countries usually fail to use the budget line assigned for health research. The Bank should work with national authorities to ensure that such resources are appropriately utilised as an important indicator of the performance of the project.

Other international agencies should also ensure that their programmes are adequately supported by relevant research and that every available opportunity is used to strengthen research capacity of developing countries.

vi Collaboration with the private sector

Public-private collaboration is essential for accelerating the discovery and development of new and improved technologies for controlling diseases affecting people in developing

countries. There is much interest in promoting such collaboration whilst at the same time protecting public interest.

Two specific recommendations are made with regard to the specific issue of clinical trials of new drugs in developing countries. In studies involving poor communities and other vulnerable groups in countries where regulatory mechanisms are not well developed:

- The sponsors should submit the clinical protocol for ethical review by an independent panel, e.g. by WHO. If necessary, experts should pay a visit to the proposed site of the study;
- WHO or some other independent agency should appoint a clinical monitor to supervise the trials.

vii International research institutes

Great caution should be exercised in contemplating the establishment of international health research institutes. They are expensive to build and maintain, and their effectiveness is unpredictable. They lack the flexibility of network programmes; poorly performing institutes tend to be maintained through long periods of crisis.

CONCLUSION

International collaboration for health research has been a most valuable strategy for tackling diverse problems especially in dealing the needs of poor people in developing countries. Various successful models have shown how strategically placed resources can achieve outstanding results. No single central programme can meet all the identified needs or exploit the variety of opportunities. New initiatives for strengthening health research should therefore include flexible mechanisms that can be adapted to individual situations. The over-riding need is to recognise the valuable contributions that research has contributed to health development and to ensure that all health and development programmes include appropriate research components.

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Table 1

Bilateral Programmes					
Model	**Strengths**	**Capacity Strengthening**	**Problems and Risks**	**Overall Assessment**	**Recommendations**
1.1.1 Bilateral – scientists in public sector	• Personal relationships & mutual respect; • Complementary skills and resources; • Facilitates international comparative studies	May provide good opportunities for training scientists from both institutions	• Exploitation of weaker partner • Distortion of research priorities; • Fragmentation of effort	A useful model that can be mutually satisfactory and beneficial to both parties	• Careful planning of partnerships spelling out responsibilities & rewards • Provide stable funding from national resources • Research Councils in developed countries should increase support for international research
1.1.2 Bilateral – scientists public private	Can generate useful knowledge	Strengthen infrastructure & intellectual activities	• Ethical concerns • Diversion of national scientists to studies on low priority	• Public-private partnerships can accelerate the transfer of scientific knowledge to useful products • Clinical trials are absolutely essential for generating knowledge for improved practice	▪ Expand public-private partnerships ▪ Promote good clinical research ▪ Protect vulnerable groups
1.2 Bilateral – institutions	Long term relationships aid can make significant impact on developing country institution	Valuable training for scientists from both institutions	▪ Lack of commitment of the leadership of wither party ▪ Mismatched parties	A useful mechanism for generating new knowledge & strengthening institutions	▪ Promote such linkages in suitable cases ▪ Give the weaker partner control of the budget.

Table 2

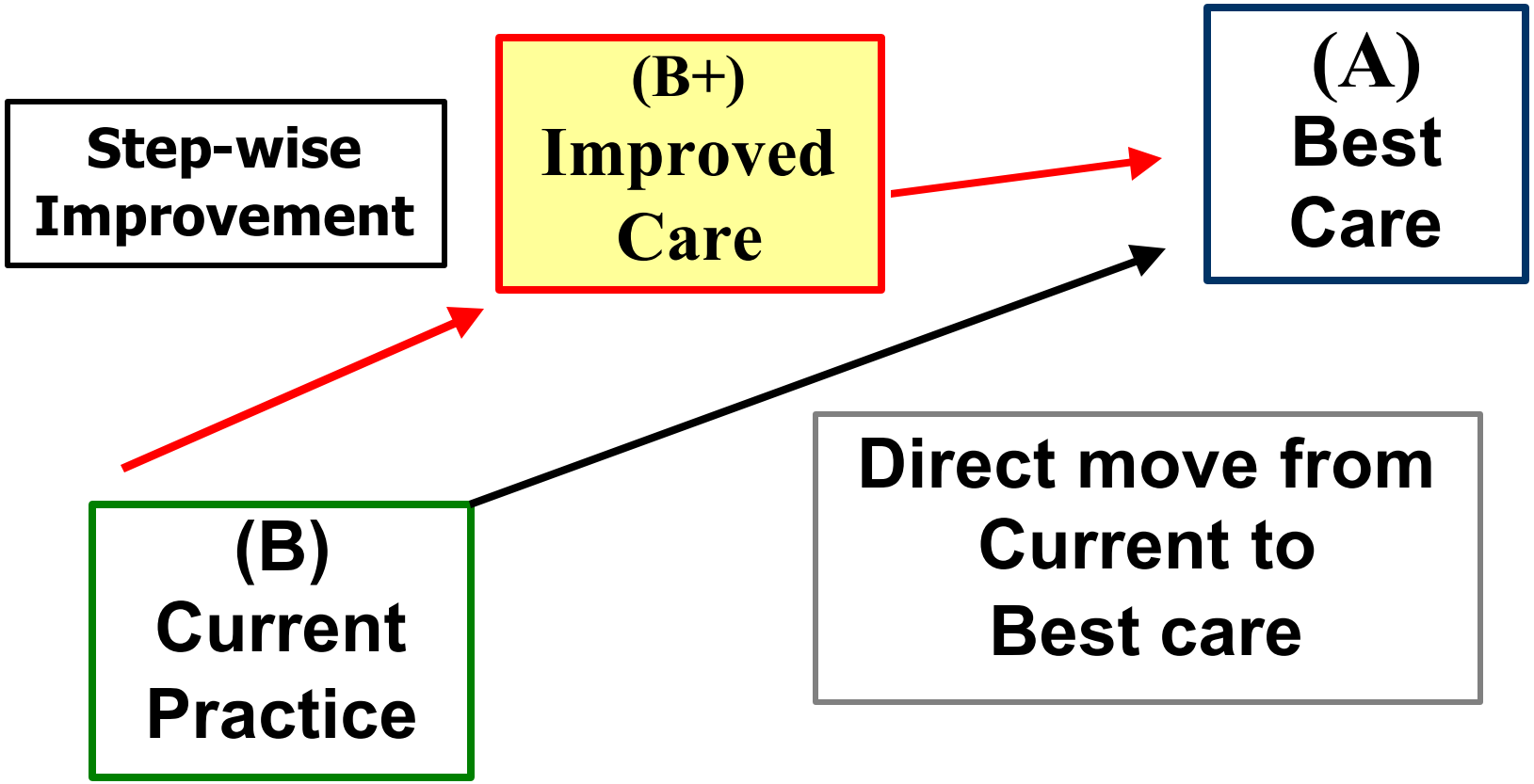
International Networks					
Model	**Strengths**	**Capacity Strengthening**	**Problems and Risks**	**Overall Assessment**	**Recommendations**
2.1 Interactive networks	▪ Facilitates access to information ▪ Overcomes isolation of developing country scientists & promote TCDC ▪ Facilitates technical assistance & funding ▪ Generates good research	▪ Informal & formal training ▪ Facilitates technology transfer	High costs of: ▪ Administration; ▪ Technical assistance ▪ Training in developed country institutions	Can be highly successful and cost-effective	• Enhance capacity of scientists to access information through electronic communications • Promote support for interactive networks
2.2 Multicentric studies	Standard protocols and procedures facilitate comparability of results	• The discipline & experience are beneficial • Training opportunities	Limitation of local resources may exclude some potential participants	A powerful tool	• Promote wider use of this model • Create fund to enable WHO sponsor studies on priority issues
2.3 Integrated network	Creates virtual institute from network	Good opportunities	Complex operation	Can be highly productive and cost-effective	Stable support for successful programmes

Tab le 3

International Research Institutes					
Model	**Strengths**	**Capacity Strengthening**	**Problems and Risks**	**Overall Assessment**	**Recommendations**
3.1 Bilateral	• Stable funding • Steady supply of scientists	Training from: • Developed country • Host country and region	• Training nationals may be accorded low priority • Research priorities may be set by developed country	• Being phased out ion most settings • Remodelling in post-colonial period has produced	No new cases based on this model
3.2 Multilateral	Top class research : • Mpdern laboratories • International scientists	• Good traning opportunities • Regional resource for other institutions in the region	• Expensive to establish and maintain • Variable performance	Can be valuable but efficiency & cost-effectiveness cannot be taken for granted.	Caution in planning a new institute. Other options may be more cost-effective
3.3 National centres-regional/ international functions	Core sustainable support from national sources	National and regional training and institution strengthening is possible	International functions may dilute main agenda & national priorities	An excellent model	Support & strengthen national centres to expand international role.

Figure 1

Ethical Progressive Improvement



Box 1

Cyanide metabolism and neuropathies

In Britain, Dr. John Wilson and his colleagues were investigating aspects of cyanide metabolism in patients with Leber's disease, a hereditary condition, characterised by optic atrophy and various other neurological lesions. (Wilson J. *Leber's hereditary optic atrophy: a possible defect of cyanide metabolism.* Clinical Science. 29(3):505-15, 1965 Dec., Adams JH. Blackwood W. & Wilson J. *Further clinical and pathological observations on Leber's optic atrophy.* Brain. 89(1):15-26, 1966 Mar.)

In Nigeria, Professor L. Monekosso, B. O. Osuntokun and their colleagues were studying tropical ataxic neuropathy, a disease characterised by optic neuropathy and a variety of other neurological lesions, affecting people in parts of Western Nigeria. Their studies pointed to disruption of cyanide metabolism in a population that subsisted on a monotonous diet of cassava.

Collaborative work between these two teams was highly productive. The British team contributed their more sophisticated laboratory services in carrying out investigations that initially could not be done in Nigeria. The comparative study of the tropical ataxic neuropathy in Nigeria side by side with the metabolic disorders in Leber's disease cases provided a clearer understanding of the pathways of cyanide metabolism in different circumstances. The findings from these studies facilitated the elimination of the neuropathy from the endemic area of Nigeria.

Later Dr. Wilson studied a similar tropical neuropathy in Tanzania. (Makene WJ. & Wilson J. *Biochemical studies in Tanzanian patients with ataxic tropical neuropathy.* Journal of Neurology, Neurosurgery & Psychiatry. 35(1):31-3, 1972 Feb.)

Several joint publications resulted from this linkage

1. Monekosso GL & Wilson J. *Plasma thiocyanate and vitamin B12 in Nigerian patients with degenerative neurological disease*. Lancet. 1(7446):1062-4, 1966

2. Osuntokun BO, Durowoju JE, McFarlane H & Wilson J**.** *Plasma amino-acids in the Nigerian nutritional ataxic neuropathy*. British Medical Journal. 3(619):647-9, 1968 Sep 14.

3. Osuntokun BO, Monekosso GL & Wilson J. *Relationship of a degenerative tropical neuropathy to diet: report of a field survey.* British Medical Journal. 1(643):547-50, 1969 Mar 1.

4. Osuntokun BO, Langman MJ, Wilson J, Adeuja AO, & Aladetoyinbo, A. *Controlled trial of combinations of hydroxocobalamin-cystine and riboflavine-cystine, in Nigerian ataxic neuropathy. Journal of Neurology,* Neurosurgery & Psychiatry. 37(1):102-4, 1974

Box 2
Ethical questions about a clinical trial

The Washington Post has recently published a number of reports of research projects that American institutions conducted in developing countries. The paper drew attention to significant ethical questions that the cases raised. One case concerned the trial of a new oral antibiotic, Trovan conducted by scientists from Pfizer company during a meningitis epidemic in Nigeria. The report included allegations of several ethical violations and concerns:

- Oral Trovan had not been approved for use in children;
- Relatives of the sick patients did not know that they were included in an experimental study;
- The investigators had not obtained informed consent;
- The clinical care of the patients was poor and it took place in an insanitary environment; and
- Dying children were not switched to more effective regime

In response to these charges, Pfizer responded that:

- Oral Trovan was a promising tool for tackling epidemics in developing countries;
- Nigerian government and a national ethical committee approved the study; and
- Informed consent was obtained using a form available in the local language.
- The outcome in the patients treated with Troxan was comparable to the group that received the standard antibiotic treatment.

This case which is currently under investigation illustrates the type of problem that arises when foreign drug companies sponsor drug trials in developing countries.

Box 3

The International Health Policy Program

Founded in 1986, the International Health Policy Program (IHPP) was sponsored by two private Foundations (Pew Charitable Trusts, Carnegie Corporation of New York) in collaboration with the World Bank, and the World Health Organisation. IHPP's objective is to strengthen national capacities for health policy analysis and reform. Its particular emphasis is on policies and reforms that permit the more effective use of resources to improve the health of the poor. The IHPP network comprises of fourteen groups of analysts and policymakers in Africa and Asia. A small secretariat, locarted in the World Bank, Washington, DC, managed the network.

The Health Policy Analysis and Development Groups (HPADGs), usually based in development research institutes, typically consist of four to six people. One or two are policymakers, usually but not necessarily from the Ministry of Health, whose active participation is designed to facilitate the use of the group's findings and recommendations. The other members, primarily economists and other social or management scientists, are from research and academic institutions in the countries concerned. Most groups are based in development research institutes, university economics departments, schools of public health, or ministry policy and planning units. The IHPP teams focus on resource issues of immediate relevance for effective, equity-oriented health policies. The teams have tackled such research topics as the:

- Allocation and use of health programme resources
- Financing of health programmes
- Contribution of non-governmental and private health services
- Health implications of policies outside the health sector
- Health consequences of individual behavior
- Adoption and implementation of effective health policies

The IHPP programme also included training and capacity strengthening inputs. Technical assistance was provided to solve specific problems; and longer-term investments included a fellowship programme for young scholars and the establishment of training programmes at the master's degree level.

Policy relevant research from these centres has produced findings that influenced policy making in their countries. IHPP centres have published their findings in peer reviewed journals and as special reports, some of which were disseminated by the IHPP secretariat.

Box 4

The Prevention of Maternal Mortality

Professor Allan Rosenfield, Deborah Maine and their colleagues at the Columbia School of Public Health, New York, USA co-ordinated and supported a research network in West Africa to examine the operational factors relating to maternal mortality. The Prevention of Maternal Mortality (PMM) network consisted of a group of 11 centres in Ghana (Accra, Kumasi), Nigeria (Benin, Calabar, Enugu, Ilorin, Lagos, Sokoto, & Zaria), and Sierra Leone (Bo, Freetown). The research questions focused on the particular circumstances in which the deaths occur. Each of the eleven teams included at least one person with expertise in these four disciplines:

- **Obstetrics** -- to deal with the clinical aspects of pregnancy and childbirth;
- **Midwifery** -- to analyse the delivery services;
- **Public Health Science** -- to examine the organisation of health care and the delivery of services; and
- **Social Science** -- to study the role of social and behavioural factors.

The PMM approach was based on the examination of practical interventions that can directly reduce maternal mortality. The investigations worked on the assumption that the provision and the timely utilisation of emergency obstetric care (**EmOC**) was the key to reducing mortality rate in developing countries. The network used the THREE DELAYS model in reviewing **EmOC:**

1. **Delay** at home in deciding to seek emergency treatment;
2. **Delay** in reaching an institution that can provide EmOC; and
3. **Delay** in providing effective EmOC at the referral institution.

- McCarthy, J "*The Conceptual framework of the PMM network"* Int. Journ. Gynecology & Obstetrics, 59: (SUPPL No.2), S15-S22, 1997
- McCarthy, J & Maine, D, "*A framework for analyzing the determinants of maternal mortality"* Stud. Fam. Plan. 23: 23-33, 1992

The interventions tested included:

- Quality of EmOC in Hospitals and in Health Centres: Operating theatres, training of personnel, and essential drugs;
- Related Services: Blood transfusion, laboratory, drug revolving fund; and record keeping;
- Access to services: Transport and communications, community transport, maternity waiting homes;
- Utilisation of Services: Community information and education, community motivators and contact persons, community financing/Loan funds;
- Collaboration with the private sector: Private medical practitioners and NGO's

Publications

a) PMM Network *"Barriers to Treatment of Obstetric Emergencies in Rural Communities of West Africa".* Studies in Family Planning 23(5): 279-291. 1992

b) The PMM Network *"Situation Analysis at Emergency Obstetric Care Facilities. Examples from eleven sites in West Africa"* Soc. Sci. Med. 40: 657-667, 1995.

c) PMM Network (1997) *Prevention of maternal Mortality Network* International Journal of Gynecology and Obstetrics Vol. 59 (Suppl. 2) **(**This special supplement contains three dozen publications from the PMM network.)

Box 5

The Global Epidemic of Diabetes

During the past 12 years, the World Health Organisation has been collecting information on the prevalence of diabetes mellitus and impaired glucose tolerance (IGT) in adult communities world-wide. Within the age range 30-64 years, diabetes and IGT were found to be absent or rare in some traditional communities in Melanesia, East Africa and South America. In communities of European origin, the prevalences of diabetes and IGT were in the range of 3-10% and 3-15% respectively, but migrant Indian, Chinese and Hispanic American groups were at higher risk (15-20%). The highest risk was found in the Pima Indians of Arizona and in the urbanised Micronesians of Nauru, where up to one-half of the population in the age range 30-64 years had diabetes.

WHO drew three important conclusions from these findings:

- An apparent epidemic of diabetes has occurred--or is occurring--in adult people throughout the world.
- This trend appears to be strongly related to life-style and socio-economic change.
- It is the populations in developing countries, and the minority or disadvantaged communities in the industrialised countries who now face the greatest risk.

WHO is following up these findings by promoting further monitoring of trends in various countries and encouraging governments to develop national programmes for the control of this disease.

Based in part on the publication:
King, H & **Rewers, M**. *Diabetes in adults is now a Third World problem. The WHO Ad Hoc Diabetes Reporting Group.* Bulletin of the World Health Organization. 69(6):643-8, 1991.

Box 6

International Comparison of Atherosclerosis

The pattern of cardiovascular diseases varies considerably from region to region, from country to country and within countries, from community to community. One of the striking observations has been the rarity of ischaemic heart disease in some parts of Africa, a situation that is evolving as people in the region adopt foreign lifestyles.

Pathologists have probed this problem by conducting international comparative studies on the pattern of atherosclerosis. In a series of such investigations, a collaborative link was established between a team in Nigeria, led by Professor A. Olufemi Williams and their partners in the United States of America. First, they devised and validated a grading system that they used to classify the degree of atherosclerosis in autopsy material. The coding system was designed such that ***"the different grades are well defined, simple and quick to effect, takes cognisance of luminal and mural involvement of the vessels, and enough areas are examined to give an adequate assessment of the overall involvement."*** **(Loewenson RB, Bearman JE & Resch JA**. *Reliability of measurements for studies of cerebrovascular atherosclerosis.* Biometrics. 28(2):557-69, 1972 Jun.)

These studies showed striking differences in the degree of atherosclerotic damage to blood vessels between the African (Nigeria, Senegal) and American (Minnesota, Alabama) subjects. The amount of atherosclerosis in Africans aged 70 to 80 years was similar to the amount of pathology in American 40 to 50 years' old!

Joint publications

Williams AO, Resch JA, & Loewenson RB. *Comparative study on cerebral atherosclerosis between an African (Nigerian) and American population groups (caucasian and negroes).* East African Medical Journal. 48(4):152-62, 1971 Apr.

Resch JA, Williams AO, Lemercier G & Loewenson RB. *Comparative autopsy studies on cerebral atherosclerosis in Nigerian and Senegal Negroes,* American Negroes and Caucasians. Atherosclerosis. 12(3):401-7, 1970 Nov-Dec.

Williams AO, Resch JA & Loewenson RB. *Cerebral atherosclerosis--a comparative autopsy study between Nigerian Negroes and American Negroes and Caucasians* Neurology. 19(3):205-10, 1969 Mar.

Williams AO & Resch JA. *Cerebral atherosclerosis: a comparative study between an African and a Minnesota autopsy population*. Neurology. 18(3):287, 1968 Mar.

Box 7

International Comparative Study of Senile Dementias

Working in Ibadan, Nigeria, Professor Osuntokun and his colleagues had noted that the classical form of Alzheimer's disease was rare among their patients and they confirmed their clinical impression in community based studies:

- **Ogunniyi, AO & Osuntokun, BO.** *Relatively low prevalence of Alzheimer's disease in developing countries and the racial factors in dementia research.* Ethnicity and Disease **1:** *394-5,* 1991
- **Ogunniyi, A, Osuntokun, BO, Lekwauwa, UG & Falope, ZF.** *Rarity of dementia (by DSM-III-R) in an urban community in Nigeria*. E. Afr. Med. J. **69:** *10-14.* 1992

In Indianapolis, Professor Hendrie and his colleagues were working in communities in which Alzheimer's disease was a prominent problem as in many developed countries.

Funded by the National Institutes of Health the Indianapolis and Ibadan teams worked jointly on cross-national comparative studies of senile dementia including the following elements:

Development of survey tools and translation into local languages

- Hall, KS, Hendrie, HC, Rodgers, DD, Prince, CS, Pillay, N, Blue, AW, Brittain, HM, Norton, JA, Kaufert, JN, Nath, A, Shelton, P, & Osuntokun, BO. *The development of a dementia screening interview in two distinct languages.* Int. J. Methods Psychiatr. Res. **3:** *1-28.,* 1993
- Baldereschi, M, Amato, MP, Nencini, P, Pracucci, G, Lippi, A, Amaducci, L, Gauthier, S, Beatty, L. Quiroga, P, Klassen, G, Galea, A, Muscat, P, Osuntokun, B, Ogunniyi, A, Portera-Sanchez, A, Bermejo, F, Hendrie, H, Burdine, V, Brashear, A, Farlow, M, Maggi, S, & Kartzman, R. *Cross-national inter-rater agreement on the clinical diagnostic criteria for dementia: WHO-PRA Age-Associated Dementia Working Group, WHO Program for Research on Aging,* Health of Elderly Program. Neurology **44:** *239-242,* 1994

Pre-testing and evaluation of protocols including a trial in a Canadian community.

- Hendrie, H.C, Hall, K.S, Pillay, N, Rodgers, D, Prince, C, Norton, J, Brittain, H, Nath, A, Blue, A, Kaufert, J, Shelton, P, Postle, B. and Osuntokun, B.O**.** *Alzheimer's rare in Cree? A preliminary report.* International Psychogeriatrics **5:** *5-14,* 1993.

Comparative studies in Ibadan and Indianapolis

- Hendrie, HC, Osuntokun, BO, Hall, KS, Ogunniyi, AO, Hui, SL, Unverzagt, FW, Gureje, O, Rodenberg, CA, Baiyewu, O, Musick, BS, Adeyinka, A, Farlow, MR, Oluwole, SO, Class, CA, Komolafe, O, Brashear, A, & Burdine, V. *Prevalence of Alzheimers Disease and Dementia In Two Communities: Nigerian Africans and African Americans.* Am. J. Psychiat. **152:** *1485-1492,* 1995

- Ogunniyi, A, Gureje, O, Baiyewu, O, Unverzagt, F, Hall, KS, Oluwole S, **Osuntokun,** BO & Hendrie, HC. *Profile of dementia in a Nigerian community--types, pattern of impairment, and severity rating.* Journal of the National Medical Association. 89(6):392-6, 1997 Jun.

Box 8

MONItoring Trends in **CA**rdiovascular Diseases

The WHO MONICA Project

In the early 1980s, the World Health Organisation established the MONICA Project now involving 32 Collaborating Centres in 21 countries to **MONI**tor trends in **CA**rdiovascular diseases and to relate these to changes in risk factor in the population over a ten year period. The project was designed to measure the trends in cardiovascular mortality and coronary heart disease, and cerebro-vascular disease morbidity. It would assess the extent to which these trends are related to changes in known risk factors, daily living habits, health care, and major socio-economic features measured at the same time in defined communities in different countries.

The studies have been designed to test hypotheses about the relationships:

- between 10-year trends in the major cardio-vascular disease (CVD) risk factors of serum cholesterol, blood pressure and cigarette consumption and 10-year trends in incidence rate of coronary heart disease and of stroke;
- between 10-year trends in case fatality rate and 10-year trends in acute coronary care; and
- between 10-year trends in event rates or mortality rates between stroke and coronary events.

The project is monitoring a total population of ten million men and women, aged 25-64 years. It has now completed 10-year data collection and the investigators are now publishing final results.

The official MONICA website contains detailed information about the design of the project and the results obtained so far:

http://www.ktl.fi/monica/index.html

Box 9

Developing Multiple Drug Therapy of Leprosy

Mycobacterium leprae, the causative organism of leprosy has not been cultured *in vitro* nor does it grow well in commonly used experimental animals. The detection of low level residual infection constitutes a difficult challenge in evaluating new treatments for leprosy. TDR tackled this problem by establishing a network linking researchers who were testing multiple drug regimes in India and in Mali to laboratories in Europe and America. The latter used sophisticated techniques e.g. immunologically nude mice, to detect residual infection in specimens collected from the clinical centres in Asia and Africa. TDR used this network to optimise the combination of drugs which became known as "Multiple Drug Therapy" (MDT).

In 1985, WHO recommended that member states should adopt the use of MDT as the strategy for controlling leprosy. Since the Organisation launched its programme for the Global Elimination of Leprosy, the prevalence of active disease has declined by 90%

Box 10

New drugs for Onchocerciasis

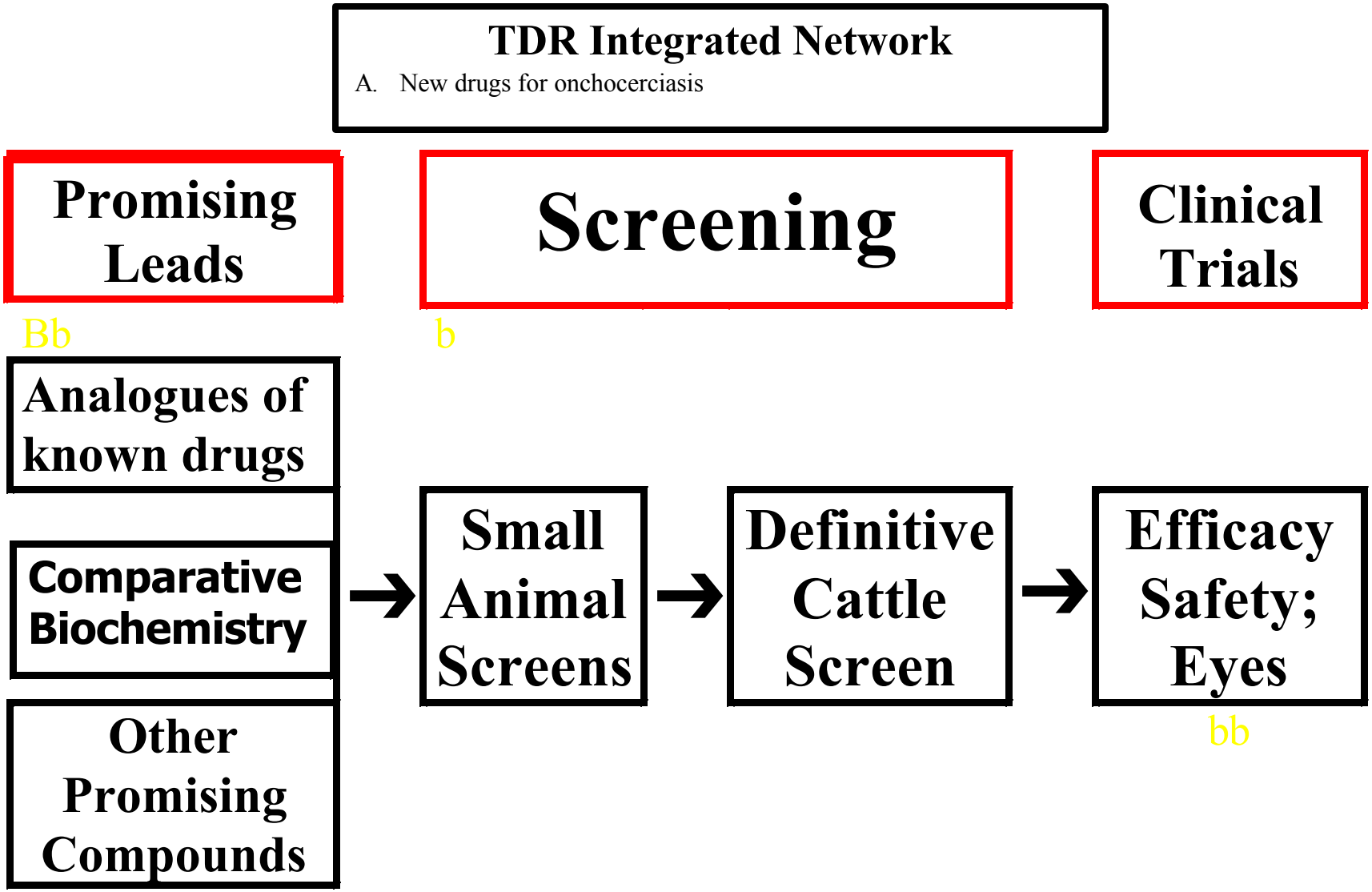
Until recently, there was no satisfactory drug treatment for onchocerciasis the cause of river blindness. Di-ethyl carbamazine, (DEC) that was widely used until about two decades ago required treatment over several weeks and treatment has to be repeated because the drug does not kill the adult worms. More importantly, serious side effects including severe eye damage accompanied treatment with DEC. Antrypol, (Suramin) which kills the adult worms, was given intravenously once a week for six weeks but the course was often stopped because of severe adverse events including renal damage. Neither drug was usable for mass treatment of this infection.

TDR developed a strategy that included a number of integrated components (Figure 2):

- **Comparative biochemistry** to identify metabolic quirks in the parasite that could be exploited as targets for therapeutic attacks;
- **Synthesis of analogues of existing drugs** in the hope of enhancing efficacy and tolerance;
- **Development and validation of biological screens** that would predict efficacy in human infections.
- **Screening of other promising leads** – compounds identified by biological activities in other tests;
- **Clinical evaluation of existing and new drugs** including assessment of impact on the eyes (Awadzi, K. *Research notes from the Onchocerciasis Chemotherapy Research Centre, Ghana.* Annals of Tropical Medicine & Parasitology. 91(7):703-11, 1997 Oct. Abiose, A. *Onchocercal eye disease and the impact of Mectizan treatment.* Annals of Tropical Medicine and Parasitology 1998; 92, Supl. 1, S11-S22).

Within two years of its establishment, the network validated a biological screen -- naturally infected cattle with *Onchocerca guttorosa* and *Onchocerca gibsoni* in Australia as giving the most accurate prediction of the effect of any compound on human onchocerciasis. Promising compounds that showed activity in the small animal models were evaluated in this definitive, but rather expensive screen. Over 10,000 compounds including substances submitted by drug companies, passed through this network of biological screens for testing candidate drugs for the treatment of onchocerciasis. One of the compounds tested was ivermectin (later registered as Mectizan), that eventually proved to be an outstanding product. Merck and Co., the company that had marketed the active principle extensively for agricultural and veterinary uses, decided to develop the drug for human use. This highly potent but generally well-tolerated drug, is normally given orally at a dose of 12 mg once a year. Following a detailed clinical evaluation of the drug in Ghana, Merck and Co. offered to all endemic countries, "….***to make needed quantities of the drug available to these***

governments and patients at no cost to them for the treatment of onchocerciasis..." Currently, 30 to 40 million doses of the drug are being provided through the Mectizan Donation Programme.


TDR Integrated Network
A. New drugs for onchocerciasis
Promising Leads
Screening
Clinical Trials
Bb
b
Analogues of known drugs
Comparative Biochemistry
Other Promising Compounds
Small Animal Screens
Definitive Cattle Screen
Efficacy Safety; Eyes
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