*Lepr Rev* (2001) **72,** 116–134

# News and Notes

## New NGO to promote elimination of leprosy

A new NGO by the name Leprosy Elimination Alliance (LEA) had been launched in Chennai (India) recently. The main objectives of the organization, set up in August 2000, with a special focus on India, are (a) to promote and advocate the cause of leprosy and leprosy elimination, (b) to promote exchange of information and ideas on leprosy elimination among leprosy workers and others, (c) to monitor progress towards leprosy elimination and assist towards development of better strategies and methods to achieve the goal in collaboration with other interested parties and (d) to produce and distribute among leprosy workers and others publications on leprosy elimination.

As part of its objectives LEA expects to produce and distribute a quarterly publication by the name *Bulletin of Leprosy Elimination Alliance* by the beginning of the year 2001. The publication will be available free of cost to all those interested in leprosy elimination. The chairman of Leprosy Elimination Alliance is Dr S. K. Noordeen, formerly Director of the Action Programme for Elimination of Leprosy at the World Health Organization headquarters in Geneva.

Further details on the NGO and its publications can be obtained from:

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## Report on the First Meeting of the WHO Technical Advisory Group on Elimination of Leprosy. WHO/CDS/CPE/CEE/2000.4. Geneva 2 and 3 May 2000

The 36-page Report should be studied in the original by all concerned with the elimination of leprosy.

The *Introduction* reads as follows:

Today, leprosy is no longer the dreaded disease that it used to be, and leprosy patients face a far better future than ever before. Over the last 15 years, there have been significant advances in reducing leprosy prevalence, thereby reducing the grossly disfiguring consequences of the disease, its pain and suffering, and the social stigma it causes. However, this does not mean that all the problems in leprosy have been resolved, nor does it mean that we can afford to slacken our efforts towards the elimination of the disease as a public health problem. In spite of the fact that the profile of the disease is much milder, and that disability among new patients is quite low, the social image of leprosy has not greatly changed in many parts of the world; this is all too well reflected in the attitude of the community, particularly towards individuals disabled or disfigured due to the disease.

The tremendous progress made in conquering leprosy in recent years has been largely due to the widespread implementation of multidrug therapy (MDT), which cured leprosy patients of their disease, and significantly reduced its burden in leprosy-endemic countries. This progress is essentially the result of a World Health Assembly resolution in 1991, which committed all leprosy-endemic countries of WHO to a global target of reducing the prevalence of leprosy to less than one case per 10,000 population, and setting the end of the year 2000 as the target date to achieve this.

These targets were extremely useful in generating political commitment to push ahead and achieve the results, which would otherwise not have been possible. This is well demonstrated by the fact that, since 1985, the prevalence of leprosy has been reduced globally by nearly 85% and nearly 10 million leprosy patients had been cured. A large part of the credit for this should go to the determination and commitment of leprosy-endemic countries in their elimination efforts, the consistent efficacy of MDT in curing leprosy, and the all-round support provided by various partner agencies of WHO, including international donor non-governmental organizations (NGOs).

The epidemiological situation in leprosy was also very favourable in many countries, especially in Africa. The progress made so far is more than just in numbers and statistics alone. The contribution of the progress in relation to reduced physical, psychological and social suffering, as well as an improved health image for countries is truly immeasurable.

Despite the fact that several major national programmes will not reach elimination by the set target date of 2000, WHO is confident that with extra efforts, the goal will be within reach of all the remaining countries by the end of 2005. But there must be no complacency in the years ahead, as many of these countries still face formidable problems that will require new and innovative solutions based more on local realities than before. And there are even more areas within countries where, long after the country has attained elimination at the national level, continuing and sustained efforts will still be required to reach similar targets at both the provincial and district levels.

In a major effort to achieve elimination in all countries by 2005, the *Global Alliance for the Elimination of Leprosy (GAEL)* was launched in Abidjan, on 15 November 1999. In addition to WHO, the core members of the Alliance are the governments of the 10–12 most endemic countries, the Nippon Foundation, the International Federation of Anti-Leprosy Associations (ILEP), and Novartis. The Alliance will cooperate closely with the World Bank, the Danish International Development Agency (DANIDA) and other non-governmental organizations. The objective of the Alliance is to exchange information so that better services may be delivered to the underserved communities. WHO will provide secretariat services and technical leadership, and the Government of India has agreed to chair the first year of the Alliance.

In order to advise WHO on effective implementation of the intensified strategy and the monitoring of its progress, particularly in the areas of capacity building, MDT supply, communication and information, and monitoring and surveillance, the Director-General decided to establish a *Technical Advisory Group on Elimination of Leprosy (TAG)*. The Group consists of six independent experts selected for their expertise in leprosy and programme management with particular reference to public health, epidemiology, community mobilization and advocacy, operational research, and disability prevention. The group forms a strong team with balanced technical expertise and geographical representation.

The terms of reference of the Group are:

- to review and monitor implementation of the intensified strategy for elimination of leprosy;
- to advise WHO on new strategies and approaches if necessary;
- to review progress towards elimination;
- to give technical advice and guidance on efforts towards elimination of leprosy;
- to identify gaps and obstacles that may deter smooth operations and find solutions in order to facilitate implementation of planned activities in the field;
- to address research issues.

The first meeting of the *WHO Technical Advisory Group on Elimination of Leprosy* was held in Geneva on 2 and 3 May 2000.

And the *Executive Summary*:

Leprosy elimination stands at a critical and extremely difficult juncture. This is partly because the commitment to eliminate leprosy in many endemic countries is beginning to slacken (among decision-makers and in the field). Moreover, those areas that are easy to reach and to work in, have been

effectively covered. The residual problem is far more difficult – from all perspectives – and is further complicated by structural inadequacies in local health services. Even today, people in many areas do not have ready access to diagnosis and MDT (including those with long-standing disease). Therefore, achievements will no longer be sustainable if significant numbers of hidden cases remain undetected and accessibility to treatment services remains difficult.

There is a need to critically review existing strategies and to develop pragmatic approaches adapted to field realities in order to facilitate the delivery of essential activities leading to elimination of leprosy at the local level. Failure to do so could be misinterpreted as a failure of the current elimination strategy as well as the technology behind it. This working paper outlines the progress made towards the elimination of leprosy as a public health problem, the challenges to be faced and the opportunities we have to accelerate activities at the most peripheral level.

## Combinatorial chemistry; a revolution in drug discovery, but still in need of logic to drive it forward

A leading article in the *British Medical Journal*, volume 321, 9 September 2000, pages 581–582, reviews the present situation with regard to combinatorial chemistry, the process by which millions of molecular constructions can be created and tested simultaneously and which now underlies the speed of new drug development. Extracts of the text include the following:

A key component of any drug discovery programme is synthetic organic chemistry, which has analogies with Lego blocks. Chemical building blocks are assembled according to precise rules, creating molecules of increasing complexity. Some of these blocks hold others in position, while others are capable of interacting with a biochemical target (such as the active site of an enzyme or a receptor). Some blocks are there to modify the metabolism of molecules and others modify the overall structure to improve drug delivery. 'Combinatorial chemistry' is the process by which millions of molecular constructions can be created and tested simultaneously and which underlies the speed of new drug development.

BMS-201038 is Bristol-Myers Squibb's first molecule to get through to the clinic whose origins were within a focused combinatorial library of chemicals synthesized by robotics. Other examples have come from Merck, which has described several combinatorial cases, such as a series of molecules that interact with somatostatin receptors.

Medicinal chemists traditionally synthesized a handful of different molecules, submitted them for test in appropriate biological assays, and then waited for the results. As the results came through, the chemists would modify the design of the molecules and a new generation would be created and retested. Although modern refinements, such as drug design aided by computer, became an integral part of the process, this archaic regimen consistently represented one of the rate limiting steps in getting drugs from discovery to market.

Recent advances, however, have significantly compressed the discovery component of the pharmaceutical timescale for research and development. The study of gene sequences (genomics) has improved the identification of useful points of therapeutic intervention; combinatorial chemistry has generated massive numbers of molecules for testing; and screening using high throughput techniques has automated the process of doing large numbers of biological assays. All have reduced the discovery-to-market time from the conventional 10–14 years to the 5–8 years claimed today.

Not surprisingly, in today's entrepreneurial world many new companies are capitalizing on combinatorial chemistry. The combination of performing organic synthesis on solid support, along with automation and robotics, allows a single chemist to synthesize thousands of different molecules in 1 week, which can then be evaluated for biological activity in a high throughput manner. Such collections of molecules are referred to as libraries. Most of the pharmaceutical and biotechnology industries are now carrying out some form of combinatorial chemistry in their laboratories. Those who recognized the merits of this science early on have now got molecules in the clinic that came from

combinatorial chemistry and high throughput screening. The promise of considerably shortened discovery-to-market time has become a reality.

As chemistry becomes capable of being able to synthesize the universe of possible organic structural permutations, and high throughput screening is approaching the capacity to screen everything against every biochemical target ever identified, we wonder if science is taking a backward step towards empiricism. We will have a huge barrage of information without having thought about how all the pieces fit together. Today's approach is in danger of becoming haphazard, with little logic driving it forward.

The costs associated with this 'big, dumb science' approach are not trivial. But as new information is analysed and a more focused rationale emerges, the costs should diminish. People who begin to understand the processes involved, rather than simply generating large quantities of data, are going to rediscover the pleasure of becoming scientists again.

## A clinical prediction rule for nerve function impairment in leprosy patients

The above is the title of an important paper by Richard P. Croft, formerly working in the The Danish-Bangladesh Leprosy Mission (DBLM), Nilphamari, Bangladesh, published in the *Lancet*, volume 355, May 6, 2000, pages 1603–1606. The Summary reads as follows:

*Background*: Nerve-function impairment (NFI) commonly occurs during or after chemotherapy in leprosy and is the key pathological process leading to disability and handicap. We describe the development of a simple prediction rule for estimating the risk of NFI occurrence.

*Methods*: New leprosy cases who presented to a centre in Bangladesh were recruited and followed up for 2 years in a field setting. We used multivariable regression analysis by Cox's proportional hazards model to identify predictive variables for NFI. Discriminative ability was measured by a concordance statistic. Internal validity was assessed with bootstrap resampling techniques.

*Findings*: 2510 patients were followed up for 2 years, 166 developed NFI. A simple model was developed with leprosy group (either paucibacillary leprosy [PB] or multibacillary leprosy [MB]) and the presence of any nerve-function loss at registration as predictive variables. Patients with PB leprosy and no nerve-function loss had a 1.3% (95% CI 0.8–1.8%) risk of developing NFI within 2 years of registration; patients with PB leprosy and nerve-function loss, or patients with MB leprosy and no nerve-function loss had a 16.0% (12–20%) risk; and patients with MB leprosy with nerve-function loss had a 65% (56–73%) risk.

*Interpretation*: Our prediction rule can be used to plan surveillance of new leprosy patients. Patients at low risk of NFI may need no follow-up beyond their course of chemotherapy (6 months); patients with intermediate risk need a minimum of 1 year of surveillance; and patients with high risk should have at least 2 years of surveillance for new NFI. Current recommendations for surveillance of patients with leprosy (for the duration of chemotherapy only) exclude an important group of patients who are at risk of developing NFI after completion of treatment.

The importance of these observations is referred to in another, recent publication in the *Lancet*: 'Strengths and weaknesses of leprosy elimination campaigns', Volume 355, June 17, 2000, page 2089, by Pieter Feenstra, Department of Health, Royal Tropical Institute, Amsterdam 1092, AD, Netherlands. He proposes that the incorporation of the measures described by Croft *et al.* would improve the efficiency of disability prevention in Leprosy Elimination Campaigns.

## Remote access: tracking TB, leprosy and HIV in northern Malawi

The Wellcome Trust 'Karonga Prevention Study', based in Chilumba in the Karonga District of Malawi, is the fortunate inheritor of vital data and facilities from a major study of leprosy begun by LEPRA (the British Leprosy Relief Association) more than 20 years ago. The legacy of the LEPRA work included an

equipped and staffed field centre, a unique set of interviews and medical examinations on more than 250 000 people, and almost 100 000 stored blood samples. 'Initially, LEPRA funded us to set up a population laboratory to study the natural history of leprosy, employing tools developed during the 1970s,' explains Professor Paul Fine of the London School of Hygiene and Tropical Medicine. 'But as time went on we got hooked on the broader issues of mycobacterial immunity and the relationships between leprosy, TB and HIV.'

Karonga District was originally chosen as a research site because of its high incidence of leprosy. Beginning in 1979, a team of 75 locally recruited field workers surveyed the entire district, painstakingly conducting house-to-house surveys, and interviewing and examining 112 000 people. By 1984, the programme had developed into the largest and most detailed study of leprosy every carried out, with descriptions of the pattern of leprosy according to age, sex, area, socioeconomic status, household contacts, family histories, immunological status, and whether participants had received a Bacille Calmette–Guérin (BCG) vaccine. This vaccine is a live bacterium related to *Mycobacterium tuberculosis*, the cause of TB, and (in theory) stimulates immunity against mycobacterial pathogens.

One of the surprise findings of the study was that BCG vaccination provided good protection against the leprosy-causing bacterium (*M. leprae*), but not against *M. tuberculosis*—in stark contrast to northern Europe, where BCG successfully induces immunity to *M. tuberculosis*. The team went on to undertake the biggest vaccine trial ever carried out in Africa. This study of 120 000 people showed that a BCG vaccine that protects 70% of UK children offered no protection against the lung form of TB. The work showed conclusively that the UK vaccine simply does not work in Malawi, and ruled out the suggestion that differences in efficacy could be due to the use of different vaccines in the two countries.

'What seems most likely,' says Professor Fine, 'is that the high frequency of other mycobacterial infections in tropical countries impairs the effect of BCG vaccines. A person's immune response to other mycobacteria—which are found in the soil and even tap water—may offer some 'natural' protection against *M. tuberculosis*, but it also blocks or masks the effect of the vaccine.'

By the 1990s leprosy was on the decline in Africa. 'When we first went out to Karonga there were ten times as many leprosy patients as TB patients, but by 1995 the situation had reversed,' says Professor Fine. In part this was due to the success of their leprosy control programme, but it also reflected the rapid spread of HIV-infected individuals more susceptible to TB infection.

With LEPRA shifting its focus to India, where most of the world's leprosy cases are now found, Professor Fine and his team were loth to close a site they had invested so much effort in setting up, particularly with so much valuable data on the population collected and so many intriguing puzzles yet to be solved. Why did the BCG vaccine protect against leprosy but not TB in that population? Why was HIV having a greater effect on TB than leprosy? What factors predisposed individuals to infection and to disease? The desire to answer such questions led Professor Fine to apply for Wellcome Trust funding.

From the LEPRA work, records and pedigrees exist for more than 250 000 people, with details on whether they have suffered from leprosy or TB. One aim of the Trust-funded study is to use these data to identify genes that predispose to leprosy or TB. Key to this aim is the coding system used in the LEPRA projects, which uniquely identifies each participant and enables complex family trees to be constructed. Making use of these data, field workers are now going back to selected individuals to collect blood samples. This material is being sent to the Wellcome Trust Centre for Human Genetics in Oxford, where Professor Adrian Hill's group is looking at the frequency of candidate genes—previously identified genes that might potentially affect susceptibility to leprosy or TB—in patients and uninfected individuals living in similar conditions.

In the second part of the genetics project, family trees are allowing field workers to identify affected sibling pairs and to undertake a 'fishing' exercise for susceptibility genes. If a particular genetic marker turns up in affected sib pairs more often than would be expected by chance, then that marker is probably associated with the disease—generally, it will be close to a susceptibility gene.

These studies could have significant medical benefits: 'If we could identify the genetic factors which control the immune response this would have major implications for diagnosis, vaccination and treatment of TB,' says Professor Fine.

In the immunology arm of the study, researchers are exploring how the BCG vaccine affects the way people respond to different mycobacteria. Blood was collected from 635 Malawian teenagers who had never been exposed to BCG. The blood samples were exposed to 35 different mycobacterial antigens. Then two-thirds of the individuals were vaccinated, and the same tests were repeated 1 year later. 'We will be able to see how people respond to a large panel of different mycobacterial antigens, and interpret patterns as reflecting differences in background exposure and genetics,' says Professor Fine, who in this area is collaborating with Professor Jenefer Blackwell of the Wellcome Trust Centre for Molecular Medicine in Cambridge. Results will be compared with those from an identical study being carried out by Professor Fine and his colleague Hazel Dockrell, among school children in Essex (funded by the World Health Organization and LEPRA), a comparison that will help to explain why the vaccine protects against TB in the UK but not in rural Africa.

The group is also looking at patterns of TB, and at the evolution and interaction of the dual epidemics of TB and HIV. With the permission of the Malawian Government, 60 000 blood samples collected since 1980 have been tested for HIV. 'We have been able to identify a few hundred HIV-positive patients from the early phase of the epidemic there, and are comparing their families with controls to see the effect of the epidemic on morbidity, mortality, demography and social structure over the course of 20 years,' says Professor Fine. 'Ultimately, such information could contribute towards control of the disease.'

The project is one of many remote projects the Trust has funded. Based seven hours' hard drive from the capital, there have been particular challenges in transporting scientific equipment, such as freezers, over dirt tracks to their specially built labs. Another challenge has been recruitment of scientific staff from the West. 'To live in a place like Chilumba you need staff with a pioneering spirit who find self-sufficiency rewarding. This means that you narrow the field in terms of applicants.' Last year, for example, it was all hands to the deck to construct a ford when the bridge to the headquarters was washed away in floods.

The success of the project depends on teams of locally recruited field workers, who travel to remote areas in the Karonga district to collect samples and interview the population. Part of the Trust grant has been used to provide them with 30 Yamaha 125 motorcycles, as well as modern lightweight camping equipment. Although the teams are serviced by support Land Rovers and a camp attendant, they need to be able to carry everything on the back of a motor bike when they go off into the hills.

One aspect of the work that Professor Fine has found particularly rewarding is that the research has made a valuable contribution to the district's health services. 'The population know that in the course of our research we diagnose and care for the tuberculosis, leprosy and skin disease patients in the district. In the early days, the need to examine people for leprosy led to our setting up a general dermatology service. Our staff travel and are known throughout Karonga District, and because of the benefits of the research the people have responded well to us over the years, accepting our intrusive efforts to understand the diseases of this population.'

(Taken from *Wellcome News*, issue 22Q1, 2000)

## RELEASE: Leprosy Control Programme in western and mid-western regions of Nepal

We are grateful to the Programme Manager for sending a copy of the report on activities throughout 1999. Four elements are included - leprosy control and prevention of impairment and disability; rehabilitation services to people with disability from causes other than leprosy; addictive drug rehabilitation and support for victims of AIDS. The report includes detailed information on the epidemiological situation and continuing progress, in collaboration with His Majesty's Government in Nepal, towards the goal of elimination. The closing paragraph of the *Preface*, however, adds a word of warning about the additional work and effort still needed to achieve this goal, hopefully by the year 2005:

In the first week of February 1999 the whole of RELEASE worked together to support the National Leprosy Elimination Campaign (NLEC). Starting on World Leprosy Day, the campaign worked in 27 districts of the country, moving from house to house to find backlog cases of leprosy. In just 1 week, we detected 11,961 new cases of leprosy in the country, out of which 1284 were in the Western Region. This doubled the number of registered cases. The cases found included large numbers with extensive disease (MB), pre-existing deformity and children. In view of this, we are reluctant to say that we can achieve leprosy elimination by the end of 2000 AD. The World Health Organisation have already announced an extension to the elimination target, up to 2005 AD, in 12 highly prevalent countries of the world, including Nepal. We believe, however, that with the co-operation of the Government of Nepal, the NGO sector and the active participation of the people of Nepal we can achieve the elimination target before that date.

## The THELEP controlled clinical trials in lepromatous leprosy. TDR/IDE/THELEP/99.1

This document, A4 format, 158 pages, edited by Professor Louis Levy, gives a detailed description of a remarkable series of trials from 1977 onwards set up to address two major concerns at that time, namely microbial persistence and drug-resistance in the chemotherapy of leprosy.

The preface by Dr S. K. Noordeen, Director (1994–1998), Action Programme for the Elimination of Leprosy, reads as follows:

During the last quarter century, leprosy work throughout the world has greatly benefited from the fruits of research in several areas including chemotherapy. In this regard, major contributions to research into the chemotherapy of leprosy have come from the Scientific Working Group on Chemotherapy of Leprosy (THELEP), now replaced by a Steering Committee on Chemotherapy of Mycobacterial Diseases (THEMYC), under the UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases, which has worked in close collaboration with the Leprosy Programme of the World Health Organization (WHO). THELEP made important contributions to the development of modern multidrug therapy (MDT) in leprosy, which is currently central to WHO's goal of elimination of leprosy as a public health problem. THELEP/THEMYC's contributions include mapping the problem of dapsone resistance, better understanding of the effectiveness of currently available drugs and their contributions, and development of newer regimens to treat leprosy, including the recently recommended treatment of single-lesion paucibacillary leprosy by administration of a single dose of the combination of rifampicin, ofloxacin and minocycline. Apart from these contributions, the THELEP/THEMYC clinical and field trials have engendered a whole new outlook in the chemotherapy of leprosy and built research capacities in many leprosy endemic countries.

This compilation of studies carried out under THELEP brings out the tremendous collaborative efforts made by scientists all over the world to improve the treatment of leprosy as well as to understand better some of the basic issues in the chemotherapy of leprosy.

I am confident that the compilation of this work will be of considerable use to researchers and leprosy workers alike.

### THE ORGANIZATION OF THE THELEP TRIALS

The THELEP controlled clinical trials of combined chemotherapy of lepromatous leprosy were designed as a multi-centre trial, the first two[1] participating centres being the Institut Marchoux,

[1]Initially, no decison was taken to limit the participation to two centres. However, it soon became clear that the laboratory at the NIMR, at that time the only laboratory capable of work with *M. leprae*-infected TR mice, could cope only with the specimens to be supplied by the first two centres, and that no additional trials could be undertaken among patients with lepromatous leprosy until additional laboratory facilities had been developed. In fact, the THELEP SC considered the development of such additional facilities a matter of high priority.

Bamako, Mali, and the Central Leprosy Training and Research Institute, Chingleput, South India. Among the requirements of such a trial were; i) a Standard Protocol; ii) standard forms for reporting the clinical and laboratory data; iii) a central facility for data-storage and retrieval; and iv) a coordinator, responsible for overseeing the work of the treatment centres and collaborating laboratories. Finally, it was agreed that the data resulting from the trials were to be the joint property of those participating in the trials – the collaborating laboratories and treatment centres, together with the THELEP Steering Committee (SC), and a 'Subcommittee on Clinical Trials of the Chemotherapy of Leprosy (THELEP) Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases', composed of the participants, was informally established. The scientific papers resulting from the trials were to be published under the rubric of the Subcommittee.

As was noted in the preceding chapter, preparation of the *Standard Protocol for Chemotherapy Trials in Lepromatous Leprosy* was commissioned by the Planning Committee, and the Standard Protocol was reviewed and adopted by the SWG at its first meeting, and subsequently published in both English and French. Standard data forms were then prepared with the assistance of the WHO Health Statistical Methodology Unit (HSM), as it was then known, and also published in both English and French.

Consequent to decisions taken by the SC, the clinical laboratory studies incident to the trials were carried out at the two centres, histopathologic examinations were performed by Dr A. C. McDougall at the Slade Hospital, Oxford, normal mice were inoculated in Professor G. R. F. Hilson's laboratory at St George's Hospital Medical School, for the purpose of measuring susceptibility of the patient-strains of *M. leprae* to dapsone, and TR mice were inoculated in the Laboratory for Leprosy and Mycobacterial Research, National Institute for Medical Research (NIMR), for the purpose of detecting persisting *M. leprae*. Dr M. F. R. Waters was appointed Clinical Trials Coordinator, assisted in Bamako by Professor S. R. Pattyn. Dr Waters also organised and conducted a Standardisation Workshop, to ensure that uniform criteria and procedures were employed at the two treatment centres. Finally, Mr J. L. Duppenthaler, HSM, was responsible for data-storage, retrieval and analysis.

## DISCUSSION AND CONCLUSIONS

At the time that the THELEP programme began, the two major concerns of the scientists working in the area of chemotherapy were the phenomena of microbial persistence and drug-resistance. It appeared certain that relapse caused by the emergence of drug-resistant *Mycobacterium leprae* could be prevented by employing combined (multidrug) therapy, particularly combinations including rifampicin, which was known to exert a powerfully bacterial action against the organism. It was also clear that control of leprosy by chemotherapy would be possible only if chemotherapy of finite duration were curative; long experience with dapsone as monotherapy had demonstrated that neither patients nor the treatment services could be expected to comply with treatment of indefinitely long duration. However, rifampicin as monotherapy had recently been shown to be incapable of eradicating *M. leprae*. And it was feared that persistence of viable organisms in the lepromatous patient, whose immune response to the organism was known to be deficient, would lead inevitably to relapse after cessation of the chemotherapy. Workers hoped that a multidrug regimen could be discovered that was curative, i.e. capable of eradicating persisting *M. leprae*, thereby preventing relapse.

As its first priority therefore, the THELEP Scientific Working Group undertook to conduct comparative trials of multidrug regiments, employing measurements of the proportion of persisting *M. leprae* as the index of efficacy. Trials of regimens of varying intensity, all including rifampicin, were mounted in Bamako, Mali, and in Chingleput, South India, involving finally a total of 215 patients with multibacillary leprosy, who were believed to have had no previous treatment. Persisting *M. leprae* were detected in 43 (7.8%) skin-biopsy specimens among a total of 554 specimens obtained at intervals of 3, 12 and 24 months from 38 of a total of 203 patients during treatment with five combined drug regimens. The proportion of specimens in which persisting organisms were discovered could not be shown to vary with regimen or duration of treatment. The regimen consisting of a single large initial dose of rifampicin plus daily dapsone was not shown to be less effective, in terms of the proportion of specimens in which

persisters were detected, than regimens consisting of rifampicin, dapsone and clofazimine or protionamide, each drug administered daily. The average patient's burden of persisting *M. leprae* was calculated to lie in the range 50,000–250,000 at each of the intervals, numbers of organisms much smaller than those that had been anticipated. These data were consistent with information regarding the relatively small risk of relapse after cessation of chemotherapy among patients with multibacillary leprosy, information that was not available when the clinical trials were mounted. In addition, the small numbers of persisting *M. leprae*, which appear to reflect the role of rifampicin as a component of the drug-combination, provided strong support to the multidrug regimen recommended for treatment of multibacillary leprosy by the World Health Organization Study Group on Chemotherapy of Leprosy for Control Programmes.

An important by-product of these trials were the data on primary resistance to dapsone. Approximately 37% of the 131 patients with lepromatous leprosy admitted into the THELEP controlled clinical trials in Bamako and Chingleput, whose *M. leprae* obtained from pretreatment biopsy-specimens could be tested in mice, were found to harbour dapsone-resistant organisms, and were presumed to represent instances of primary resistance to dapsone. Although the majority of these patients harboured strains of a low degree of resistance, 20% harboured organisms of an intermediate degree of resistance. These data represented an important addition to the published evidence, obtained from surveys among similar numbers of patients, of the increasing frequency with which primary resistance to dapsone was being encountered, and served to emphasize the need to employ multidrug therapy in the treatment of patients with multibacillary leprosy.

Fourteen cases of jaundice were observed among 212 patients – 9 among the 51 patients who had been treated by the maximal regimens, that included daily administration of rifampicin for the entire 2 years of the trials, and 5 among the remaining 161 patients. The probability that jaundice could have occurred with such different frequencies among two samples drawn from the same population of patients is only 0·001, i.e. jaundice was significantly more frequent among those patients treated by rifampicin administered daily for 2 years. These results suggest that daily administration of rifampicin as a component of multidrug therapy, as has been advocated in the USA and in other countries, in which the added cost of daily, compared to monthly, administration of the drug is not important, carries an increased risk of hepatotoxicity.

In summary, the THELEP controlled clinical trials of combined chemotherapy of previously untreated lepromatous leprosy at Bamako and Chingleput demonstrated that, after treatment by one of several combined-drug regimens, all of which included rifampicin, persisting *M. leprae* comprised only a tiny proportion of the total population of organisms harboured by the average patient. In addition, these trials confirmed the alarmingly large proportion of such patients who present with their *M. leprae* already resistant to dapsone. And, finally, daily administration of rifampicin, as opposed to its monthly administration, could not be shown to be more efficacious therapeutically, whereas daily administration appeared to carry a greater hazard of hepatotoxicity.

After the THELEP controlled clinical trials had been mounted, but well before their completion, it became apparent that persisting *M. leprae* do not pose as great a threat of relapse to the patient with multibacillary leprosy, once chemotherapy has been completed, as was earlier believed. As a consequence, the importance of these trials was diminished even before the results had been assembled. Nevertheless, the results of the THELEP trials have great relevance to the current efforts to control leprosy, and lend strong support to the intermittent, rifampicin-containing regimen recommended by the WHO Study Group for the treatment of multibacillary leprosy.

## Twenty countries pledge to wipe out TB

Ministers from the 20 countries most burdened by tuberculosis marked world tuberculosis day last week by agreeing a framework for action aimed at 'consigning to the history books' a disease that currently claims 2 million lives a year.

The Amsterdam Declaration was signed at a conference convened by the World Health Organization (WHO) and the World Bank, partners in the new Stop Tuberculosis initiative. The initiative aims to increase coverage of the highly effective directly observed treatment, short course (DOTS) programmes from 25% of patients with tuberculosis to 70% in 5 years.

The countries, representing 80% of the 8 million new cases of tuberculosis each year, committed themselves to supporting a global partnership agreement. This will help to finance and support national tuberculosis programmes, especially in countries worst hit but least able to afford to take action. The WHO and the World Bank are to work with governments to implement the agreement, which should begin in the autumn.

The initiative also plans a global fund for tuberculosis and a global drug facility to seek extra financing and ensure the supply, distribution, and monitoring of tuberculosis drugs. The conference heard that 'substantial and sustained funding' was needed. The health minister for Thailand, Korn Dabbaransi, hoped that other countries 'would be convinced of our true need for financial and manpower resources.'

The economic and development importance of investment was emphasized with figures showing that 95% of the 20 million people with tuberculosis lived in the developing world. Three quarters of cases in those areas, moreover, were in the most economically productive age group of 15 to 54 year olds.

Dr Arata Kochi, director of the initiative, said that more funding was being sought.

Source: *British Medical Journal*, volume 320, 1 April 2000

## Persistence of *Mycobacterium tuberculosis* in macrophages requires enzyme essential for metabolism of fatty acids

Writing from the Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, New York and other centres in the USA, J. D. McKinney and colleagues have recently submitted a letter to *Nature*, volume 406, 17 August, 2000, pages 735–738 entitled 'Persistence of *Mycobacterium tuberculosis* in macrophages and mice requires the glycoxalate shunt enzyme isocitrate lysase'. The first paragraph (summary) reads as follows:

*Mycobacterium tuberculosis* claims more human lives each year than any other bacterial pathogen. Infection is maintained in spite of acquired immunity and resists eradication by antimicrobials. Despite an urgent need for new therapies targeting persistent bacteria, our knowledge of bacterial metabolism throughout the course of infection remains rudimentary. Here we report that persistence of *M. tuberculosis* in mice is facilitated by isocitrate lyase (ICL), an enzyme essential for the metabolism of fatty acids. Disruption of the *icl* gene attenuated bacterial persistence and virulence in immune-competent mice without affecting bacterial growth during the acute phase of infection. A link between the requirement for ICL and the immune status of the host was established by the restored virulence of $\Delta icl$ bacteria in interferon-$\gamma$ knockout mice. This link was apparent at the level of the infected macrophage: activation of infected macrophages increased expression of ICL, and the $\Delta icl$ mutant was markedly attenuated for survival in activated but not resting macrophages. These data suggest that the metabolism of *M. tuberculosis in vivo* is profoundly influenced by the host response to infection, an observation with important implications for the treatment of chronic tuberculosis.

and the last paragraph of the letter:

Persistence of bacteria and chronicity of infection are hallmarks of tuberculosis. Patients with chronic tuberculosis are thought to harbour bacteria in various metabolic states, ranging from active cell growth and division to stationary phase. Conventional drugs target processes required for bacterial cell growth and division, such as cell-wall biogenesis and chromosome replication. Poor activity against slow- or non-growing bacteria is thought to be an important reason why conventional drugs take so long

to eradicate infection. Therefore, our demonstration that ICL promotes persistence of infection by enhancing bacterial survival within inflammatory macrophages makes it an attractive new target for chemotherapy. The development of ICL inhibitors will be facilitated by the recent solution of the three-dimensional structure of *M. tuberculosis* ICL in association with the prototypic inhibitors 3-bromopyruvate and 3-nitropropionate. Future efforts will focus on the development of ICL inhibitors as new drug candidates with preferential activity against persistent bacteria.

## TB transplant to TDR: rapid intake, minimal rejection

A recent issue of *TDR News* (UNDP/World Bank/WHO special Programme for Research & Training in Tropical Diseases) No 62, June 2000, carries the following news about TB:

Tuberculosis is slotting rapidly into the TDR portfolio and 'culture'. In February 2000, a scientific working group on TB met to make recommendations for research and capability strengthening activities in TDR. It clarified TDR's role and niche among the ongoing alliances and initiatives in TB. Later in the month, the recommendations were presented to the TDR Scientific and Technical Advisory Committee (STAC). Altogether, TDR input to TB research is now looking quite distinct, with significant funds already identified to support some of the proposed work. Further interest in TB will definitely have been stimulated by the Ministerial Conference on TB and Sustainable Development held in Amsterdam, 22–24 March 2000, from where the final declaration called for acceleration of both basic and operational research.

The scientific working group (SWG) recommended that TDR adopt a two-pronged policy on TB research:

- health systems and services research (HSSR) – being the most neglected area in TB research.
- research and development (R&D) of new diagnostics, drugs and vaccines – being an area where TDR has considerable comparative advantage.

The HSSR agenda should be driven by the needs arising from TB control programmes, and the SWG recommended that TDR develop a conceptual framework for the necessary research/control link. TB-HSSR also needs to be established in high burden countries (especially the 22 countries that account for 80% of the world's TB burden) e.g. through building up national TB research institutions, expanding assistance for protocol development, and linking with other TDR diseases.

In R&D of new tools for TB, the first priority is diagnostics. Particularly needed are a replacement for the sputum smear test, a rapid test for rifampicin sensitivity, and evaluations of marketed products, as well as expansion of the specimen bank established by the TB diagnostics initiative and already transferred to TDR. Second, equal priority is to both drugs and vaccines. In drugs, the particular need is to evaluate available antibiotics and 'off the shelf' drugs, and to encourage production by small pharmaceutical companies in the South. TDR will work with other actors in this area – the IFPMA/WHO Roundtable, Stop TB, and the Global Alliance for TB Drug Development. As a partner in the Global Alliance, TDR is delighted to announce the award (on March 24) of US$25 million to the Alliance by the Bill and Melinda Gates Foundation. With respect to vaccines, product profiles, animal models and correlates of protection are specifically needed, and the SWG encouraged TDR to look for ways to speed up vaccine development.

Research capability strengthening activities should be aimed at supporting research throughout these two main areas (HSSR and R&D of new tools). In particular, there is a need to build capacity for conducting field trials of new diagnostics, drugs and vaccines, and for carrying out post-regulatory assessments and functional genomics research.

TB was welcomed into the TDR disease portfolio by the Joint Coordinate Board (TDR's top governing body) in 1999, which requested STAC to prepare plans of action and a focus for TB research, assuming that a budget of US$5.5 million for 2000–2001 could be raised. Already some of these funds

are available, from, amongst others, the Rockefeller Foundation, Sweden (SIDA/SAREC), the Swiss Development Agency, Stop TB and WHO.

(*TDR News* is published three times a year Fax (+41) 22 791 4854.
E-mail: tdrnews@who.int, Web site: http://www.who.int/tdr)

## Reforms to the health sector must retain vertical programmes like those for tuberculosis

The following letter recently appeared in the *British Medical Journal*, volume 320, 24 June 2000, from Sir John Crofton, emeritus professor of respiratory diseases, University of Edinburgh, United Kingdom:

EDITOR—Health sector reform has become the policy urged on poor countries in the developing world. Basically it entails transferring responsibility for health services and health budgets to local communities. I am sympathetic to this approach. But its uncritical application by governments has a dangerous obverse.

Vertical programmes—for instance, central coordination and monitoring of the World Health Organization's DOTS (directly observed treatment short course) programme for control of tuberculosis—may be discouraged. The programme may be suddenly abolished. The economy of scale resulting from national bulk buying of antituberculous drugs disappears. The tuberculosis experts in the Ministry of Health, who provide leadership and coordination and who monitor the programme, are dispersed to other jobs. Suddenly there are no drugs for tuberculosis, either centrally or at the periphery, and no control programme.

I am told that this has already occurred in Zambia and Ethiopia. It almost occurred in Bangladesh. It is threatening to occur in many other countries.

With HIV infection and multidrug resistance, the World Health Organization has declared tuberculosis to be a global emergency. It is a desperate race against time to establish good national tuberculosis control programmes, especially in the 22 countries that contain four fifths of the world's cases. National control programmes would prevent the development of multidrug resistance—always the result of bad doctoring—before the alliance of multidrug resistance with HIV infection creates an almost untreatable pandemic (tuberculosis is no respecter of frontiers).

It is essential to retain the economies of scale offered by the central purchase of drugs and basic diagnostic equipment. It is essential to retain control of central monitoring and coordination and gradually to hand over the major responsibility of the service to local communities as their skill develops. Just as in community development projects in the United Kingdom, professionals continue to be needed in the background to pick up the bits when a local administration fails.

When I raised this problem at a recent symposium on global health the representative of Save the Children supported me. He said that the child immunization programme in Uganda had almost collapsed for the same reasons. I have just visited the School of Tropical Medicine in Liverpool and had discussions with people working on tropical disease problems in poor countries. Although sympathetic with the concept of health service reform, many are disturbed by the possibility of the sudden abolition of vertical programmes with no real provision for their effective replacement.

## Prospects for global tuberculosis control under the DOTS strategy. WHO/TB 98.251

This document of 34 pages, A4 format, is by Christopher Dye and colleagues, Global Tuberculosis Programme, World Health Organisation, 1211 Geneva 27, Switzerland November 1998. It describes the development of an age-structured mathematical model to explore the principles of tuberculosis control

under DOTS (Directly-Observed Therapy, using a Short-course regimen), and to forecast the impact of improved case finding and cure on TB epidemics in different regions of the world.

The closing page of the *Discussion* (pages 15 and 16) reads as follows:

There are numerous uncertainties in making projections with mathematical models, and their effects are only partly reflected in the bounds on our estimates. Most of what we know about the natural history of tuberculosis – which determines model structure and parameter values – comes from studies in industrialized countries, and yet we are most interested here in the prospects for TB control in the developing world. Apart from the ranges attached to model parameter values, there are critical but unpredictable external variables. We do not know precisely how many TB cases arise each year, and how many are currently found and cured. Nor can we be sure of the course of HIV epidemics, which particularly affect projections for Africa and Asia. However, the principles of TB control revealed by our analysis do not-depend on the exact results of model calculations. And, whilst predictions of the *numbers* of cases and deaths between now and 2020 are subject to great uncertainty, we can be more confident (roughly to the extent indicated by lower and upper bounds) about comparisons of the preventable *fraction* of the TB burden when control targets are met by different dates.

Even if WHO targets are met by year 2010, three-quarters of the global TB burden would *not* be averted over the next 23 years. Better diagnostics, drugs and vaccines, plus targeted preventive therapy, would undoubtedly help. But new control measures with the potential to have a major impact may not be available for years. Meanwhile, the most pressing tasks are to find ways of achieving higher cure rates, and reaching more cases, in the principal endemic countries of the world.

## HIV: Durban (South Africa) conference warns HIV levels on the rise again

With the subheading 'No reprieve on AIDS, experts warns west', the *Guardian* newspaper (UK) carried the following in its issue of July 12, 2000:

Western complacency over AIDS is ill judged because globalization means we cannot escape the consequences of major epidemics in Africa or Asia, a British expert warned in Durban yesterday.

Roy Anderson of the UNAids collaborating centre for epidemiological research, based at Oxford University, said the numbers of people infected with HIV were rising again.

'We have not by any means seen the worst of this problem' he said. 'It will get progressively worse over the next 10 to 15 years. People often cite the 1918 influenza pandemic, which caused over 30m deaths. This is going to be many factors bigger than that.'

There is an assumption among some in the west that the problem of Aids has gone away, he said. Drugs are suppressing the virus levels in infected people so that they can live normal lives.

But researchers in the field are finding that, as people live longer, so the pool of people infected with HIV who could potentially pass it to others increases, and there is no way of eradicating the virus.

In the US now, mortality is beginning to rise again very slowly said Professor Anderson. 'The virus becomes resistant to the drugs if people do not take their medication exactly as stipulated by doctors. There has also been an increase in risk-taking behaviour by people who assume the drugs will protect them from AIDS and an early death.'

In the UK, there has been a very slow but progressive spread among heterosexuals.

'It is creeping along. We're at the beginning of an epidemic for heterosexuals,' said Prof Anderson, warning that the full enormity of the global disaster is difficult to estimate. 'People don't fully understand that the timescale is 40 to 50 years for this epidemic.'

The crisis in sub-Saharan Africa, where 25m people are infected with HIV, is a tragedy for the world, he said.

'This is the biggest infectious disease problem that has faced humanity in the course of human history. We can't isolate ourselves... What happens in Africa does matter to us. There are also economic

factors too. If labour markets are not there because of the enormous burden of disease, that will have a knock-on effect.'

Anthony Fauci of the National Institute of Allergy and Infectious Diseases in the US yesterday told the AIDS 2000 conference in Durban that even when virus levels had been undetectable in infected people for considerable periods, they soared again within a month of stopping drug treatment.

The drugs appear to have little effect on a reservoir of virus in body tissues, even when they suppress it in the blood, he said.

But vaccines and cheaper drugs are, nevertheless, the hope for the future. Dr Fauci said he was running trials on interrupted drug regimes - where people whose HIV is under control are taken off medication every other week. His preliminary results show that the viral levels did not go up during the week off.

He warned that nobody should experiment alone with stopping their medication, because of the dangers of the virus developing resistance to the drugs.

'The numbers are still small and we need to look at the critical effect after a year or two. But it is encouraging,' he said.

## Links

**www.unicef.org.uk/breakthesilence**
Campaign focusing on AIDS orphans
**www.unaids.org**
Joint UN programme on HIV/AIDS

## News from the Damien Institute

*Damien News*, Summer/Monsoon 2000, carries the news that Father William F. Petrie will be leaving India in the near future, after 25 years of work on behalf of leprosy patients, mainly in Orissa. He is handing over the Directorship of the Damien Institute to Brother James Rukavina who will be based at N/5-525 Nayapalli, Bhubaneswar 751 015, Orissa, India. *Damien News* draws attention to the remarkable support given by Father Bill and his group over a long period of years, including surgical operations for disabled patients, free medical check-ups, training of para-medical workers, provision of tricycles, wheel-chairs and other aids, planting of fruit trees and the building of over a thousand houses for leprosy patients families. Father Bill will now spend some time on the island of Molokai, where Father Damien lived, worked and died. We wish Brother James and the Damien Institute every success in their future work in this high-endemic part of India.

## Th1 and Th2 cytokine responses

The *British Medical Journal*, volume 321, 12 August 2000 has an interesting commentary on these responses. The first three paragraphs read as follows:

Cytokines are the hormonal messengers responsible for most of the biological effects in the immune system, such as cell mediated immunity and allergic type responses. Although they are numerous, cytokines can be functionally divided into two groups; those that are proinflammatory and those that are essentially anti-inflammatory but that promote allergic responses.

T lymphocytes are a major source of cytokines. These cells bear antigen specific receptors on their cell surface to allow recognition of foreign pathogens. They can also recognize normal tissue during episodes of autoimmune diseases. There are two main subsets of T lymphocytes, distinguished by the presence of cell surface molecules known as CD4 and CD8. T lymphocytes expressing CD4 are also

known as helper T cells, and these are regarded as being the most prolific cytokine producers. This subset can be further sub-divided into Th1 and Th2, and the cytokines they produce are known as Th1-type cytokines and Th2-type cytokines.

Th1-type cytokines tend to produce the proinflammatory responses responsible for killing intracellular parasites and for perpetuating autoimmune responses. Interferon gamma is the main Th1 cytokine. Excessive proinflammatory responses can lead to uncontrolled tissue damage, so there needs to be a mechanism to counteract this. The Th2-type cytokines include interleukins 4, 5, and 13, which are associated with the promotion of IgE, and eosinophilic responses in atopy, and also interleukin-10, which has more of an anti-inflammatory response. In excess, Th2 responses will counteract the Th1 mediated microbicidal action. The optimal scenario would therefore seem to be that humans should produce a well balanced Th1 and Th2 response, suited to the immune challenge.

## International charity offers health and loans

The following is extracted from the *British Medical Journal*, volume 321, 9 September, 2000, page 592:

An international charity that provides small loans for women in impoverished communities had taken the unusual step of providing a health education service alongside its credit facilities. And from an early evaluation, it seems that financial and physical health messages mix well together.

The effectiveness of the village health bank scheme, run by Project Hope, whose international headquarters is in Millwood, Virginia, has been evaluated by researchers from the George Washington University Center for International Health, in Washington, DC.

The evaluation found that the health status of members of the village status of members of the village health banks (as measured by six critical health indicators including contraceptive use, annual cancer screening, postnatal care, immunization, child growth, and prevalence of diarrhoea) was 14% higher than that of participants receiving credit-only services and not health education.

Now Project Hope wants to expand its village health banking scheme, from the countries where it operates at present (Honduras, Ecuador, Malawi, Guatemala, and Peru), to several other developing countries, including Thailand and the Dominican Republic.

The idea of village health banking is simple. Women in the most impoverished areas of the world are given the opportunity to start their own businesses by being offered small loans of about $80 (£53). The businesses usually centre on buying and selling food and local textiles to rural areas.

Groups of about 25 women form one bank. They elect a committee to manage the bank and take responsibility for recouping the loans. Women are charged commercial rates of interest on their loans as experience shows that these repayments can be and are achieved.

Interleaved into regular health bank meetings is the health promotion part of Project Hope's scheme.

One member of each bank is elected as the health officer and provided with health education materials that are geared to the problems of the local population. 'The two elements of the scheme–credit and health education–are introduced in an integrated fashion. We appreciate that the best way to deliver health education is by an integral process so we have made provision for that by allowing a local health officer to facilitate a learning opportunity with the bank members,' explained John Bronson, director of the income generation programmes at Project Hope.

Typical discussions centre on the environment, nutrition, child health, and women's health. Activities that have been successful include cleaning up rubbish, operating health fairs, transporting a nurse to weigh and examine small children, and identifying locally available nutritious food.

With training from Project Hope, the banks quickly become self sufficient. General rules are laid out, and compliance has been excellent. Loans need to be repaid every 4 months, and if they are repaid successfully the member qualifies for a larger loan next time.

Altogether there are 400 banks that have benefited over 20 000 women and their families. Over $7m has been loaned out in five years with less than $20 000 not repaid–a default rate of less than 2%.

Although the project boasts a repayment rate that would make most banks envious, the real rewards of the scheme are the effects on people's lives. In Honduras, for example, women participating in village health banks showed an average improvement of 38% across important health indicators and were rated 37% better than women who did not belong to such banks. With increased wealth these women were able to spend 41% more on basic necessities such as food and medicine.

But is has not all been plain sailing. When some women are excluded from membership of a bank by other women, they can feel resentful. 'We are always advocating having a good mixture of people as members. We constantly argue for a diversity of membership. But the decisions are made by the participants themselves,' said Bronson.

There is a strong wish for the group to succeed, and the group as a whole guarantees the loans, so if a particular woman cannot pay back her part of the loan, the other women have to pay it for her. The result has been that some people with less education or who are less able have found themselves excluded.

'There are also conflicts with spouses and traditional leaders, something that you find with any scheme that empowers women,' Bronson added. 'We have heard of women who have been pulled out of the banks by their husbands.'

On top of these problems, which have occurred everywhere, there have been particular difficulties in operating in Malawi, owing to the exceptional poverty in that country. 'The average income of people in the Latin American countries where we operate is between $30 and $60 a month, but in Malawi, it is $10.

'We have a lot of repayment problems. The challenges are greater there than elsewhere because the people are much worse off. There is a 33% illiteracy rate. On the other hand, we are helping people who really need help, which makes it worthwhile,' Bronson explained.

One of the greatest benefits of running village health banks, is the boost it gives to a woman's self-esteem.

'Village banks can become very powerful groups in their own communities and extend their experience to other community problems,' said Bronson. He cited the example of a bank in Honduras that was wiped out by Hurricane Mitch in late 1998. 'Rather than wait for government or foreign assistance to arrive the people of the bank were proactive. They took charge and were trying to find solutions to their problems so that they could rebuild their lives.'

*Further information*
www.projhope.org

## *Liaison* Newsletter of the WHO Library and Information Networks for Knowledge

Volume 10, No 3, 1999 of this publication has an Introduction by Irene Bertrand, WHO HQ Library and a series of articles on BIREME, Sao Paulo Brazil, with emphasis on its creation in 1982 of a bibliographical database called LILACS and, more recently of a Virtual Health Library for Latin America and the Caribbean. The Introduction reads as follows:

In our first number of *Liaison* in 1999 we summarized our plans for forthcoming issues, amongst which was to continue our annual geographic theme by featuring Latin America. We are therefore devoting this number to the Latin American and Caribbean Center on Health Sciences Information (BIREME). BIREME was established in 1967 in Sao Paulo, Brazil, as the Regional Medical Library in an agreement between the Pan American Health Organization (PAHO) and the Government of Brazil. It was intended to perform a similar role for Latin America as that taken by the US National Library of Medicine for the USA.

The Regional Medical Library (BIREME) was later named the Centro Latinoamericano y del Caribe de Informacion en Ciencias de la Salud which better reflected its present objectives and functions. In its unique role, BIREME supports the regional network of health science information for the whole Latin

American continent which includes over 600 national and PAHO documentation centres and other specialized networks. It develops and promotes the use of tools for technical databases, e.g. DeCS (Descriptors in Health Sciences) and supports training and research activities in countries for the development of the decentralized LILACS CD-ROM bibliographical database.

BIREME has led the way in health information activities throughout the developing world and its first great achievement was the creation in 1982 of the bibliographical database of regional health literature entitled LILACS (the Latin American and Caribbean Health Sciences Literature database) which indexes some 600 journals as well as books, technical reports, etc. from the region. It aimed to complement the MEDLINE database whose coverage is primarily American and European health journals. Originally in the form of a printed bibliography, LILACS became another 'first' by being issued on CD-ROM in 1989, at approximately the same time as commercial firms were bringing out MEDLINE int he same format. Since then, the original database has been supplemented by others in more specific subject areas such as food legislation, toxicology, etc. LILACS uses the Medical Subject Headings (MeSH) of the US National Library of Medicine to index the local health literature but quickly saw the necessity to complement and expand this thesaurus with its own controlled vocabulary in the area of public health (DeCS – descriptors in health sciences).

The latest major BIREME initiative is the implementation of the Virtual Health Library for Latin America and the Caribbean which integrates its various information sources into a network of products and services on the Internet. It also includes the project SciELO – Scientific Electronic Library – a common model for electronic publishing by the Virtual Health Library.

BIREME is on the leading edge of health information dissemination and must be congratulated on its wide range of innovative activities and the example it sets for all regions to emulate; we thank them for providing the following articles describing their projects, which make up this issue of *Liaison.* In view of its topical importance, the description and development of the Virtual Health Library and its various components takes pride of place. Background information on the LILACS database and the DeCS thesaurus complete the overview of BIREME's remarkable activities.

*Further information*:

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Liaison is published three times a year in English, French and Russian by the World Health Organization, Library and Information Networks for Knowledge, 1211 Geneva 27, Switzerland

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## UK Department for International Development

One of DFID's publications, *International Health Matters*, includes the following information:

*International Health Matters* is a digest of knowledge gained from research funded by the Health and Population Division of the UK Government's Department for International Development (DFID). Each issue reports both completed and ongoing research on a particular subject, indicating implications for policy and practice. *International Health Matters* is published twice a year. A full-text Web version is available at: http : //www.liv.ac.uk/lstm/ihm – cov.html or http : //www.dfid.gov.uk.



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Design and desktop publishing: Paula Waugh, Robert Cole.

If you have any enquiries or comments please contact the editor at the above address.

*International Health Matters* is printed on chlorine-free, environment-friendly paper.

There are a number of ways to access information about DFID's policies and activities:

### *DFID Internet*

As a channel for communicating with external audiences, the Internet is increasingly important to DFID. Through the Internet, 130 million users worldwide can find out about UK development policy and DFID's structure and activities. Information resources available via the Internet include: DFID's Target and Institutional Strategy Papers, *Who We Are* (general information), Advisory Group information (e.g. Health, Education, etc.), Project Evaluations, Publications, Pipeline Projects, Recruitment pages, Research, Press Releases, Speeches.

DFID's Internet address is: http : //www.dfid.gov.uk/.

### *DFID Public Enquiry Service*

DFID operates a public enquiry service which provides information to external callers on the work of the Department. Typical enquiries include requests for information on DFID policies and expenditure, DFID publications, contact details, country programmes and project information. Customers include members of the public, NGOs, businesses, academic, other government departments, other bilateral and multilateral donors.

Tel: 0845 300 4100, (outside UK: +44 1355 84 3132). Fax: +44 (0) 1355 84 3632. E-mail: enquiry@dfid.gov.uk.

DFID's *Centre for Health Information* (CHI) is a useful contact for details about the Department's Health and Population activities. The CHI manages a database providing project-level information from DFID;s *Health Portfolio*, and can provide details of DFID's health activities by country and subject.

Contact: The Centre for Health Information, Health & Population Department, DFID, 94 Victoria Street, London SW1E 5JL. Tel: +44 (0) 207 917 0333. Fax: +44 (0) 207 917 0428. E-mail: CHI@dfid.gov.uk.

## New programme explores technologies to challenge disability and improve health care delivery to the poor

Identifying and making better use of appropriate technologies that will improve the lives of poor people

worldwide is the focus of a new £1.2 million Knowledge and Research (KaR) Programme that commenced in December 2000. This innovative programme will encourage the development and use of appropriate disability and healthcare technologies. It is managed by a unique partnership between a management consulting firm, GIC Ltd, and a UK-based health, development and disability communications charity, Healthlink Worldwide. Funding for the programme is being provided by the Department for International Development (DFID).

Three DFID departments are co-operating in the programme, in recognition of the overlapping areas of interest the programme will be covering. The three units are Infrastructure and Urban Development, Social Development and Health and Population. 'This is an exciting opportunity to pool resources and collaborate together to contribute to the global knowledge pool about how to improve the introduction of and use of technologies affecting the lives of poor people', said Director of the KaR Programme, Roger Drew, of Healthlink Worldwide.

The KaR Programme on Disability and Healthcare Technologies will make a total of £1.2 million available over the next 2 years to support a range of projects under the themes of: improving healthcare technologies and infrastructure for poor people and minimizing the detrimental effects of disability on the lives of the poor. The Programme sees technologies as including processes and management practices, organizational and supportive systems and dissemination practices that make them more accessible.

The Programme will support projects that fall within one of three broad indicative categories: development of a new technology, adoption of a newly developed technology and contribution to the wider use of a successful technology. An annual competition will be used to select the projects that will be awarded funding. Full details of the application process are available on the Programme's website (http://www.kar-dht.org). The second round of the competition will begin in September 2001. Projects can be awarded funding for up to 100% of their costs. In selecting projects, the Programme will seek to provide a good balance between small and large projects, between disability and healthcare technologies, among the three categories identified, and ensure broad geographic coverage. 'We're looking for projects that will show how technology can address the priority health problems of the poor and encourage effective health systems', said Programme Manager, Aron Cronin, of GIC Ltd. 'We're also looking for approaches that improve the access of disabled people to their basic rights, and that seek to prevent some of the poverty-based causes of disability'. Communicating the lessons learned and promoting the use of knowledge already generated will be a key part of individual project activity, as well as being a major activity of the Programme itself.

For further information about the Knowledge and Research Programme on Disability and Healthcare Technology, please contact: Roger Drew, KaR Programme Director, Healthlink Worldwide, Tel: +44 20 7539 1577; Fax: +44 20 7539 1580; e-mail: drew.r@healthlink.org.uk, Aron Cronin, KaR Programme Manager, GIC Ltd. Tel: +44 20 7253 7000; Fax: +44 20 7251 3100; e-mail: kar@giclimited.com, Website: http://www.kar-dht.org.

For information on application procedures, please contact Anne-Laure Ropars at GIC by e-mail or fax.