Lepr Rev (1999) **70,** 384–400

News and Notes

Variations in the *NRAMP1* gene and susceptibility to tuberculosis in West Africans

This is the title of a paper published in the *New England Journal of Medicine* by Bellamy R *et al*., Volume 338, Number 10, March 5, 1998, pages 640–44. The *Abstract* reads as follows:

Background Genetic factors may affect the susceptibility to tuberculosis, but no specific genes governing susceptibility have been identified. In mice, natural resistance to infection with some mycobacteria is influenced by the gene for natural-resistance-associated macrophage protein 1 (*Nramp1*), but the role of the human homologue of this gene, *NRAMP1*, in tuberculosis is unknown. We typed polymorphisms in *NRAMP1* in a case–control study of tuberculosis in the Gambia, West Africa.

Methods Sequence-specific oligonucleotide hybridization and microsatellite analysis were used to type *NRAMP1* polymorphisms in 410 adults (mean age, 34·7 years) with smear-positive pulmonary tuberculosis and 417 ethnically matched, healthy controls. Patients with human immunodeficiency virus infection were excluded.

Results Four *NRAMP1* polymorphisms were each significantly associated with tuberculosis. Subjects who were heterozygous for two *NRAMP1* polymorphisms in intron 4 and the 3′ untranslated region of the gene were particularly overrepresented among those with tuberculosis, as compared with those with the most common *NRAMP1* genotype (odds ratio 4·07; 95 percent confidence interval, 1·86–9·12; chi-square = 14·58; $P < 0·001$).

Conclusions Genetic variation in *NRAMP1* affects susceptibility to tuberculosis in West Africans.

—and the final paragraph of the *Discussion:*

The association of *NRAMP1* variation with a major infectious disease provides support for the strategy of mapping and identifying genes for resistance to infectious disease in mice and then testing their homologues as candidate genes for susceptibility to related infections in humans. Further analysis of the mechanism of action of *NRAMP1* and its genetic variants may lead to new approaches to controlling tuberculosis, which kills more people than any other disease caused by an infectious pathogen.

Report of WHO/TDR Scientific Working Group on the Utilization of Genomic Information for Tropical Disease Drug and Vaccine Discovery, Geneva, 18–20 February 1998

This Report (TDR/GENOMICS/98.1) deals with the impact of genomics on the future of drug and vaccine discovery in tropical disease.

The *Introduction* reads as follows:

The availability of complete microbial genomic sequence data offers unique opportunities to improve our understanding of the basic biology of these organisms. Eighteen microbial genomes have been completed and approximately another 40 are in the process of being sequenced. For human pathogens

such as those of interest to TDR it also opens up the opportunity to identify weaknesses that leave them open to chemotherapeutic or immunological attack, i.e. it offers unique possibilities for the discovery of new drugs and vaccines. The major target diseases of TDR are:

- Malaria
- Leishmaniasis
- African trypanosomiasis
- Chagas' disease
- Onchocerciasis
- Lymphatic filariasis
- Schistosomiasis

It is expected that the complete genomic sequence of the most significant of the human malarial parasites, *P. falciparum*, will be available by 2002. In addition, sequencing of many other pathogens of interest to TDR is under way, in part sponsored by TDR.

Many pharmaceutical companies have utilized genomic information from human pathogens for the discovery of drug targets and potential vaccine antigens, but very few, if any, are engaged in drug or vaccine discovery research for the diseases of interest to TDR. It is therefore imperative that, where possible, public sector organizations and academic scientists interested in tropical diseases interact and learn from these industrial endeavours and try and apply them to tropical diseases.

In addition, post-genomic tools are being rapidly developed for organisms, such as yeast and *C. elegans*, which are of scientific interest. Here too, tropical disease scientists can learn and develop appropriate tools for their pathogens.

TDR has recently reorganized its structure to enable it to approach the funding of drug discovery and vaccine discovery in a more focused way. It is also further developing its capacity to develop and register products, preferably with private sector partners, and so realise the full potential of any scientific discoveries that are made. Key to the future efficient use of TDR funds will be an appropriate and efficient funding of functional genomic research, often in collaboration with other agencies.

It was with these thoughts in mind that this meeting was organized. Concurrent with these needs, and integral to the philosophy and process of TDR funding, emphasis was also laid on the need to ensure that adequate opportunity and assistance is provided to developing country scientists and institutions to participate in these new technological developments. Ultimately, the best way to ensure the sustainable discovery and development of tropical disease products is to develop the capacity and resources for their resolution in the populations that are afflicted by these diseases.

The *Conclusions* (page 21) were:

The following conclusions from the round table discussion require action and deserve highlighting:

i) There is a continuing need to promote genomic sequencing efforts.
   - It was proposed that a small task force, in consultation with relevant agencies, should decide on an optimum malaria species for further genome sequencing projects
   - TDR may consider the stimulation of *Anopheles* genomics/EST projects

ii) There is a need for TDR, together with other agencies, to promote the appropriate curatorship of genomic sequence information and its annotation.

iii) There is a need for TDR, together with other agencies, to create repositories of reagents to assist functional genomics research.

iv) There is a need for TDR to actively promote activities in functional genomics.
   - Genomic approaches that require large-scale concerted efforts involving many labs (e.g. large scale knockouts) should be pre-discussed extensively between appropriate scientists and agencies to ensure their optimal implementation. *P. falciparum* may be an important starting point for these discussions and full use should be made of the experiences of the yeast and *C. elegans* scientific communities in this regard

v) There is a need for TDR to fund the development of new and improved technologies that will facilitate functional genomics research in its target diseases.

vi) Within TDR there is a need for functional genomic research to be coordinated effectively between the genome and pathogenesis committees of Strategic Research (TDS) and the drug and vaccine discovery committees of Product R&D (TDP).

vii) There is a continuing need to engage with industry where possible and appropriate to maximise the translation of genomics research into appropriate product R&D.
- Further efforts will be made by TDR to improve funding and support to projects that show particular promise for the future development of products (drugs and/or vaccines) for its target diseases.

viii) There is a need for appropriate training and institutional strengthening in disease endemic countries in functional genomics, especially bioinformatics.
- TDR undertook to make a major commitment in the training of DEC scientists in post-genomic technologies, particularly bioinformatics. Training and institutional strengthening will form an integral part of all its post-genomic activities.

ix) TDR should investigate the potential role it has to play in promoting partnerships between scientists and institutions in the bioinformatics field.

Genetic basis for susceptibility to mycobacteria

The following appeared on page 1027 of the *British Medical Journal*, Volume 318, 17 April 1999:

New research has suggested that there is a genetic reason why some people are more susceptible to infections with non-tuberculous mycobacteria.

Researchers at INSERM, in Paris, investigated disseminated non-tuberculosis mycobacterial infection, in which otherwise healthy individuals develop overwhelming infections with mycobacteria that normally are not virulent (*Nature Genetics* 1999;21:370–8). *Mycobacterium tuberculosis* and *M. leprae*—the organisms that cause tuberculosis and leprosy—are the most pathogenic mycobacteria, but most bacteria in the class are relatively harmless. Rare individuals develop disseminated infections with normally non-virulent non-tuberculous mycobacteria. Some develop fatal infections after vaccination with Bacille-Calmette-Guérin (BCG).

The researchers studied 18 people from 12 unrelated families with idiopathic reactions to vaccination with BCG or disseminated non-tuberculous mycobacterial infection. Previous investigations had shown that the receptor for interferon gamma—a cytokine with a central role in combatting infections—was implicated. The researchers found homozygous mutations in the DNA regions encoding for the interferon receptor.

Wellcome Trust (UK) and drug giants fund gene marker database

The following is taken from page 1093 of the *British Medical Journal*, volume 318, 24 April 1999:

A 2-year, £28 m ($44·8 m) initiative to create a high quality map of genetic markers, which will be available to everyone without charge, has been launched by the Wellcome Trust together with a group of leading pharmaceutical companies and academic centres.

The collaborative effort, called the SNP Consortium, will seek to identify and analyse single nucleotide polymorphisms involved in disease processes so that safer and more effective drugs can be developed.

Single nucleotide polymorphisms, sometimes called 'snips', are common variations that occur in human DNA. Scientists believe that the 'snips' can help pinpoint the subtle genetic differences that predispose some people to disease and underlie the variability in individual responses to drugs.

'A large, high density and high quality single nucleotide polymorphism map will be of great utility

to the medical research community, as it will help answer questions about genetic factors that contribute to disease susceptibility and response to treatment, and [will] suggest directions for future investigation,' said Arthur Holden, chairman and chief executive officer of the consortium.

'The members of the consortium believe that free and unrestricted access to this powerful tool will benefit scientific inquiry in industry, government, academic, and independent laboratories,' he added.

The consortium intends to identify up to 300,000 'snips' and map at least 150,000 of them so that they can then be used in association studies. Single nucleotide polymorphism patterns from a target population—such as patients who have a particular disease or who respond poorly to a particular drug—would be compared with patterns from unaffected populations to find genetic variations shared only by the affected group.

From these association studies disease specific genes might be identified, and novel therapeutic avenues and even tailor made treatments might be expected to evolve.

Using DNA from a diversified, representative panel of anonymous volunteers, sequence information from the publicly funded Human Genome Project, and advanced sequencing and mapping technologies, scientists from the academic centres will identify and map the polymorphisms. The laboratories involved include: the Whitehead Institute in Cambridge, Massachusetts; the Washington University School of Medicine in St Louis, Missouri; the Stanford Human Genome Center, in Palo Alto, California; Cold Spring Harbor Laboratory, New York state and the Wellcome Trust's Sanger Centre, in Cambridge, United Kingdom.

Cold Spring Harbor Laboratory will use computerized methods to organize, analyse and manage the resulting single nucleotide polymorphism database, and will also distribute the information contained in the database.

N-Acetyl transferase (NAT) activity in *M. tuberculosis* and isoniazid resistance

A recent publication in the *Journal of Bacteriology*, Feb. 1999, volume **181**, Number 4, p. 1343–1347 by Mark Payton *et al.* carries the following summary:

Arylamine *N*-acetyltransferases (NATs) are found in many eukaryotic organisms, including humans, and have previously been identified in the prokaryote *Salmonella typhimurium.* NATs from many sources acetylate the antitubercular drug isoniazid and so inactivate it. *nat* genes were cloned from *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*, and expressed in *Escherichia coli* and *M. smegmatis.* The induced *M. smegmatis* NAT catalyzes the acetylation of isoniazid. A monospecific antiserum raised against pure NAT from *S. typhimurium* recognizes NAT from *M. smegmatis* and cross-reacts with recombinant NAT from *M. tuberculosis.* Overexpression of mycobacterial *nat* genes in *E. coli* results in predominantly insoluble recombinant protein; however, with *M. smegmatis* as the host using the vector pACE-1, NAT proteins from *M. tuberculosis* and *M. smegmatis* are soluble. *M. smegmatis* transformants induced to express the *M. tuberculosis nat* gene in culture demonstrated a threefold higher resistance to isoniazid. We propose that NAT in mycobacteria could have a role in acetylating, and hence inactivating, isoniazid.

Under the heading '*Tuberculosis Treatment Technology*', a less technical account of this potentially important discovery appeared in *ISIS Innovation News*, Edition 26, Winter 1998, page 10:

Research in Oxford University's Department of Pharmacology has resulted in the discovery that Mycobacterium tuberculosis has the enzyme **N***-acetyl transferase (NAT). Because of the interaction between NAT and isoniazid, a major tuberculosis therapeutic, novel insights into tuberculosis treatment have resulted.*

Background

The incidence of tuberculosis is increasing. Currently TB accounts for >2 million deaths worldwide

each year. The prevalence of drug-resistant strains of *M. tuberculosis* are the core of the problem, in particular strains resistant to the major anti-TB drugs: isoniazid, rifampin, pyrazinamide and ethambutol.

Resistance to isoniazid has been partially (≈70%) explained by changes in metabolic oxidation or reduction processes in resistant strains. However, no effective therapy currently exists to combat these genetic variations. The discovery of NAT activity in the bacterium may account for some of the isoniazid resistant events as acetylation interferes with isoniazid action.

Using proteins or peptides related to *M. tuberculosis* NAT should enable novel enzyme inhibitors to be identified using a combinatorial chemistry approach.

Applications arising from the Oxford Tuberculosis work

The Oxford Technology, which includes; sequence data of the new NAT, polyclonal antibodies capable of identifying *M. tuberculosis* NAT at very low concentrations and systems for expressing Mycobacterial NATs in a number of hosts, will enable both drug screening and drug development programmes. An immediate application is the ability to screen for and test compounds that reinstate isoniazid sensitivity to otherwise resistant strains of *M. tuberculosis.*

The Oxford Invention

Discovery of *M. tuberculosis*' latent ability to produce functional NAT together with development of associated molecular biology tools creates a new drug discovery opportunity.

Commercialization

This fundamental discovery is the subject of a patent application. Companies interested in product developments arising from the tuberculosis research are invited to contact Isis Innovation to discuss how they could interact with Oxford to utilize this technology.

Combinations to combat resistance

The following article appeared in *TDR news*, February 1999:

In our last issue, reference was made to an initiative to combat antimalarial drug resistance (*TDRnews*, 1998, 57: 7). Since activities under the initiative began in July 1998, three studies have been conducted and completed: a pharmacokinetic interaction study, a pilot clinical study, and a double-blinded clinical study of a combination of sulphadoxine/pyrimethamine + artesunate. Studies with chloroquine or amodiaquine are about to start; and a meta-analysis is planned for late 1999—as soon as data on the over 4000 patients to be enrolled in the various studies become available.

Upon completion of this first 'proof-of-principle' phase, the intention is to select combinations of drugs to be tested in large, longitudinal population-based studies. Centres interested in carrying out community-based studies to test the hypothesis that antimalarial drug combinations can delay or contain the emergence of resistance should contact: Dr P. Olliaro, Manager, Working Group on Research on Drug Resistance and Policies, E-mail: olliarop@who.int; tel: (+41) 22 791 3734; fax: (+41) 22 791 4854.

Molecular targets for filariases drug discovery

The following article appeared in *TDR news*, February 1999:

Studies on the genome and biochemistry of *Onchocerca volvulus*, *Wuchereria bancrofti* and *Brugia*

malayi have led to the identification of a myriad of enzymes, receptors, and metabolic pathways as potential targets for chemotherapy. Modern drug discovery relies more on molecular targets such as these than it does on random screening.

Molecular targets in filarial diseases were the subject of a meeting of researchers from both public and private sectors (universities, institutes and biological laboratories) in Africa, America, Australia and Europe held in WHO/HQ in November 1998. The challenge was to identify potential chemotherapeutic targets and novel strategies from among all the candidates. There were 21 presentations that addressed, in this context, the stage of parasite life cycle, biological processes, and the specificity and uniqueness of possible targets as well as the availability of infrastructures (crystallography, genomics, proteomics, etc.) that could facilitate the drug discovery process.

TDR filarial drug discovery is now becoming more targeted. It is aimed at discovering new macrofilaricides, discovering anthelmintics which sterilize adult female worms, and identifying new microfilaricides to combat any emergence of ivermectin resistance. It includes work on existing drugs such as antibiotics, antifungals and anti-parasitic agents, whose spectra of activity seem likely to be extendable.

Calls for grant proposals for filarial drug discovery research have already been sent out and the first grants will be disbursed by mid-1999 through the Drug Discovery Research Steering Committee which meets in Geneva, April 26–30. The closing date is February 28. Anybody interested in this area should contact:

Janis Lazdins, Manager Filariasis R&D, E-mail: lazdinsj@who.int; tel: (+41) 22 791 3818/2111; fax: (+41) 22 791 4854; or Rob Ridley, Manager, Steering Committee on Drugs Discovery Research; E-mail: ridleyr@who.int; tel: (+41) 22 791 3884; fax: (+41) 22 791 4854.

SPIN online

This is a free abstract service for anyone with an interest in science policy. *SPIN* (*Science Policy Information News*) is published weekly by the Unit for Policy Research in Science and Medicine (PRISM) at the Wellcome Trust.

SPIN is a collection of article abstracts with relevance to biomedical science policy. Issues covered include UK research policy, funding, employment and research ethics.

The articles are abstracted from a large number of relevant medical and scientific journals as well as other publications concerned with higher education and research issues, ranging from *BMJ* (*British Medical Journal*) and the *Lancet* to the *THES* (*Times Higher Education Supplement*) and *The Guardian.*

SPIN is a popular publication with scientific researchers and policy makers in both the UK and abroad.

The online version will be free and updated every Friday—and even be distributed by e-mail on request. www.wellcome.ac.uk/spin

Source: *Wellcome News.* Research & Funding News from the Wellcome Trust, 183 Euston Road, London NW1 2BE, United Kingdom. Tel +44(0)20 7611 7236. Fax +44(0)20 7611 7288. E-mail tropical@Wellcome.ac.uk

WHO: the new structure

The following is taken from *TDR News* (UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases), No 58, February 1999, pages 1 and (conclusion) 12:

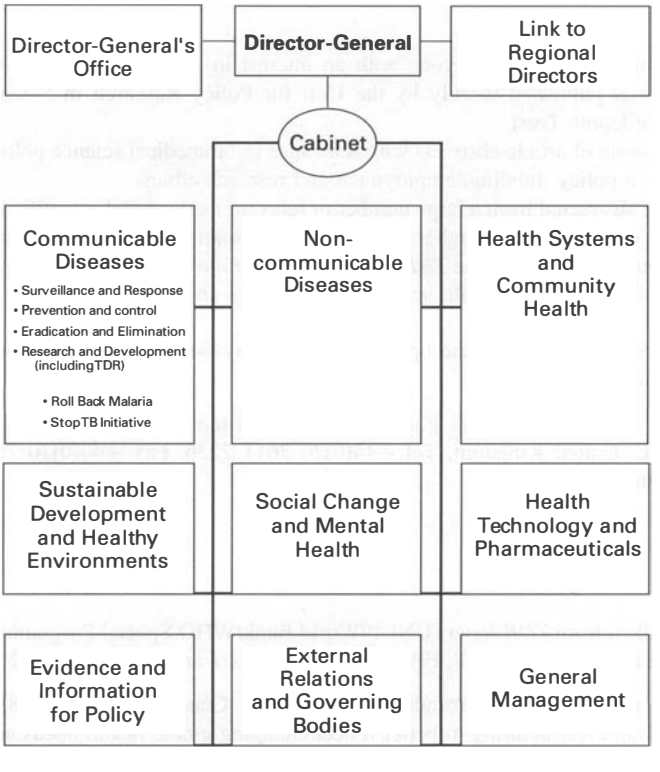
Since the advent of Gro Harlem Brundtland as Director General in July 1998, WHO has been undergoing a profound restructuring to better reflect changing global health needs and priorities.

Dr Brundtland has also been championing the role of the private sector as another vital player in the changing response to meet the world's health needs, especially in technology development and provision of health services. 'We need open and constructive relations with the private sector and industry, knowing where our roles differ and where they may complement each other' said Dr Brundtland.

Apart from the private sector, Dr Brundtland is also reaching out to NGOs, whose influence 'goes beyond that of any official body'. She is also intent on making a difference from grassroots level (combatting disease, premature death and disability) to policy-making level, and has established a separate function on Evidence for Health Policy— 'WHO will speak out for health, back its case with solid evidence and thereby be a better advocate for health towards a broader audience of decision-makers', she says.

Although still a 'Special Programme', and an entity independent of WHO, TDR is now managed administratively along with several other programmes in a 'cluster' concerned with Communicable Diseases (CDS), headed by David Heymann, former director of the Division of Emerging and other Communicable Diseases Surveillance and Control. The CDS cluster has four departments, of which one is 'Research and Development including TDR', and Carlos Morel is Director of this Department. This means that, for the first time, the WHO structure as a whole has a R&D section. Joining us in CDS are the erstwhile WHO programmes on Control of Tropical Diseases, the Action Programme for the Elimination of Leprosy, the Global Tuberculosis Programme, the Division of Emerging and other Communicable Diseases Surveillance and Control, and the WHO project known as Roll Back Malaria.

But what does this mean for TDR? How integrated will TDR become in the new WHO? Will TDR eventually lose its status as a Special Programme? Will TDR broaden its disease portfolio? Will TDR's established good contacts and working practices with industrial partners serve as a guide for improved



collaboration with the private sector? As yet, these questions and others remain unanswered. Answering them will involve TDR's governing bodies—the Standing Committee, the Scientific and Technical Advisory Committee, and the Joint Coordinating Board, as well as the scientific and donor communities.

As to Dr Brundtland's emphasis on the private sector, a number of initiatives in which TDR is involved are already taking off.

Periodicals and serials published by the World Health Organization

Bulletin of the World Health Organization

The International Journal of Public Health

Presents original research findings selected on the basis of their immediate or potential relevance to problems of human health. Although editorial scope includes all topics relevant to international public health, priority is given to research that advances understanding of health problems in the developing world.

Beginning in 1999, the journal's traditional editorial scope has been expanded to include papers of direct practical relevance to public health policy and practice. By placing scientific findings together with policy-relevant discussions, WHO aims to help ensure that decisions and practices affecting human health are based on the best scientific evidence available. The *Bulletin* now appears, in its expanded format, in monthly issues.

ISSN 0043-9686; monthly
1999 (Vol. 77): Sw.fr. 200·–/US $160·00

International Digest of Health Legislation

The only periodical that allows readers to follow worldwide developments in laws and regulations designed to protect public health and the human environment. Scope includes any new or amended legal text, whether national or international, that has a bearing on health protection or medical care. In recent years, the *Digest* has become a key reference to new AIDS legislation enacted throughout the world.

ISSN 0020-6563; quarterly
1999 (Vol. 50): Sw.fr. 230·–/US $184·00

Weekly Epidemiological Record

An essential instrument for the collation and dissemination of epidemiological data useful in disease surveillance and control on a global level. Priority is given to data on diseases known to threaten international health. The *WER* also serves as a medium for conveying technical and practical experiences relevant to WHO-sponsored programmes such as those for the control of tuberculosis, the elimination of leprosy, the expansion of immunization coverage, and the eradication of poliomyelitis and guinea-worm disease. Data on AIDS include updates on the global number of cases.

Weekly issues can now be accessed electronically at the following address: http://www.who.int/wer/

ISSN 0049-8114; weekly
1999 (74th year): Sw.fr. 230·–/US $184·00

WHO Drug Information

Communicates drug information that is either developed and issued by WHO or transmitted to WHO by

research and regulatory agencies throughout the world. News briefs, which may number more than 50 items per issue, serve to alert manufacturers and prescribers to:

— newly detected side effects
— dangerous drug combinations
— drugs considered contraindicated in certain patient groups
— amendments in product information
— changes in treatment of choice for specific disorders

The Journal also includes regular presentation of newly recommended International Nonproprietary Names (INN) for Pharmaceutical Substances.

ISSN 1010-9609; quarterly
1999 (Vol. 13): Sw.fr. 75·–/US $60·00

WHO Technical Report Series

Since the inception of the World Health Organization in 1948, the *WHO Technical Report Series* has served as a mechanism for collecting the views of international experts on technical issues crucial to the improvement of human health. Each volume in the series, which has released close to 900 titles, records the consensus reached by a group of experts commissioned to advise the world's scientific and medical communities on the best way to tackle a selected health or medical problem.

ISSN 0512-3054; approximately 10 volumes in 1999
1999: Sw.fr. 132·–/US $106·00

Environmental Health Criteria Series

This series was launched in 1976 in response to concern over the risks to human health and the environment posed by the growing number of chemicals on the market and in the environment. In planning the series, the aim was to give national authorities all the information needed to understand the specific hazards posed by a chemical and then devise appropriate protective measures, whether for the health of workers, the safety of the general public, or the survival of the environment.

In keeping with this aim, volumes in the series issue authoritative conclusions about human and environmental risks based on a study of virtually everything ever written about a selected industrial chemical. To date, over 200 chemicals and other environmental contaminants have been critically assessed.

ISSN 0250-863X; approximately 12 volumes in 1999
1999: Sw.fr. 242·00/US $194·00

Further information: WHO, Marketing and Dissemination, CH-1211, Geneva 27, Switzerland. Tel +41 22791 2476. E-mail: publications@who.ch

Eliminating world poverty: new strategy from the Department for International Development, UK

The following is extracted from *International Health Matters* (details below) Issue 3, December 1998, page 3:

The Department for International Development (DFID) replaced the Overseas Development Administration (ODA) following Britain's general election in May 1997. Unlike ODA, DFID is a separate

government department, independent of the Foreign and Commonwealth Office. DFID is headed by a Cabinet minister, Clare Short, who is Secretary of State for International Development.

In November 1997, the Government published a major policy document (a White Paper) on international development, under the title *Eliminating World Poverty: a challenge for the 21st Century* (available from Her Majesty's Stationery Office, or from DFID's Web site at http://www.dfid.gov.uk). This White Paper commits DFID to the goal of eliminating poverty in poorer countries—that is, the developing countries of Africa, Asia, Latin America and the Caribbean, and the countries of Central and Eastern Europe and Central Asia that are now undergoing economic and political transition.

DFID is working with partners toward the internationally agreed development target of a 50% reduction in the proportion of people living in extreme poverty by 2015.

Improving health is a key component of poverty elimination, not only because poverty increases the risk of ill-health, but also because illness tends to impede poor people's escape from poverty. DFID is committed to meeting three international development targets for health and population by 2015:

- a two-thirds reduction in the mortality of infants and children under 5 years,
- a 75% reduction in maternal mortality,
- access to reproductive health services for all individuals of appropriate ages.

In order to use scarce resources in a way that gives the greatest benefits to poor people, DFID wants to discover and test new interventions; to find out which ones work best; to identify the most cost-effective measures for different settings; and to determine the most equitable ways to deliver them. Health policy makers, health care practitioners and the public all need reliable evidence concerning the feasibility, effectiveness and equity implications of different strategies for disease prevention and control, and of different approaches to the organisation, financing and management of health care systems. DFID helps make the necessary knowledge available and accessible by:

(i) promoting a pro-poor international health research agenda in its dialogue with other UK and international funders of health research,
(ii) supporting a range of knowledge-related activities.

In July 1998, DFID's Health and Population Knowledge Strategy was revised to reflect the policy changes set out in the White Paper. DFID's Health and Population knowledge priorities and channels for the support of knowledge activities are detailed in the Health and Population Knowledge Strategy Paper for 1998–2001, which is available on request from: Knowledge Section, Health and Population Division, DFID, Room V217, 94 Victoria St, London SW1E 5JL, UK. E-mail: T-Burdett@dfid.gtnet.gov.uk.

International Health Matters is a digest of information about 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, and also includes details of other projects funded by the Health and Population Division. *International Health Matters* is published twice a year.

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Rapid health assessment protocols for emergencies

1999, vi + 97 pages (available in English; French and Spanish in preparation) ISBN 92 4 154515 1. Sw.fr. 31·–/US $27·90. In developing countries: Sw.fr. 21·70, Order no. 1150463

This book provides a collection of 10 protocols for conducting rapid health assessments in the

immediate aftermath of different types of emergencies. Noting the vital importance of rapid and accurate information in the earliest stage of an emergency, the protocols respond to the urgent need for common standardized technical tools for assessing damage, gauging health risks, and gathering the information immediately needed by decision-makers at the national and international level.

The protocols were prepared by WHO in collaboration with a large number of international agencies and experts with broad experience in the field of emergency management. Although all protocols follow a common format, each is specific to the circumstances, potential hazards, and immediate information needs that characterize a distinct type of emergency. Emphasis is placed on the exact information needed, the best sources of data and methods for rapid collection, and the specific questions that need to be answered in order to draw initial conclusions and direct immediate actions. Although the advantages of using experienced assessments teams are stressed, the book also explains how the protocols can be used to train general health workers as part of emergency preparedness.

The book opens with an introductory protocol covering the aims and methods, responsibilities, complexities, and inherent difficulties of rapid health assessments. Addressed to health authorities as well as assessment teams, the chapter also includes abundant advice on preparedness for emergencies. Details range from the comparative need for speed in different types of emergencies, through a suggested format for presenting the results of assessments, to a list of common logistic, organizational, and technical errors. Advice on the best working practices, including ways to avoid being an 'emergency tourist', is also provided.

Against this background, the additional nine protocols are presented according to a common format which covers the purpose of the assessment, preparedness, the steps to follow during the assessment, assessing the impact on health, assessing local response capacity and immediate needs, and presenting results. A general protocol on epidemics of infectious origin is followed by protocols specific to meningitis outbreaks, outbreaks of viral haemorrhagic fever, including yellow fever, and outbreaks of acute diarrhoeal disease, with information specific to dysentery and cholera.

Sudden-impact natural disasters are covered in the next protocol, which includes a day-by-day list of information priorities for different stages of the disaster. A protocol dealing with sudden population displacements offers guidelines for conducting rapid health assessments in all emergencies caused by sudden displacement of refugees or population groups within a country. Included are a sample checklist for rapid assessments and a sample form for weekly reports on morbidity and mortality. Subsequent protocols deal with the special situations of nutritional emergencies and chemical emergencies, including those caused by food contaminated with chemicals or toxins. The final protocol addresses the difficult task of conducting assessments in complex emergencies in which the cause of the emergency, as well as the assistance to the afflicted, is complicated by intense levels of political considerations. The protocol includes a form which has recently been used for rapid health assessment at local level in Bosnia and Herzegovnia.

The book concludes with a brief summary of survey techniques, followed by a tabular presentation of reference values for assessing needs, hazards, and logistic requirements in developing countries.

Two LECS in Bangladesh and Nepal

Bangladesh and Nepal are two Asian countries which are embarking on National Leprosy Elimination Campaigns in order to further the drive towards elimination within the target year of 2000.

Bangladesh has already reduced the estimated prevalence from about 13 cases per 10,000 population in 1991 to the current level of 3·3 per 10,000, and the caseload has fallen from 136,000 in 1991 to an estimated 40,000. There is every hope that the country will achieve the elimination goal. Nepal had a registered prevalence of 6·2 per 10,000 in 1996 and had brought this down to 5·3 per 10,000 2 years later, but the new case detection rate has remained at a high level of 3 to 4 cases per 10,000 for the last 3 years.

Bangladesh has planned a large-scale LEC between 7 and 12 February this year, drawing on the

resources of all available general health staff, NGO workers, local leaders, schoolteachers and volunteers from the communities affected. These were expected to total around 47,500. Imams and priests were being recruited or at least asked to mention the salient facts about leprosy during their weekly discourses in the 50,000 mosques of the country.

As many as possible of these 'human resources' were being given some degree of training or orientation. Extensive use was to be made of the meda, both electronic and print. Television 'spots' were being broadcast at prime time, twice a day over a period of 30 days, while radio jingles conveyed appropriate messages and special press conferences were arranged. A total of half a million flyers were being printed, underlining that leprosy *is* curable, thanks to MDT.

Nepal's Nationwide LEC (NLEC) was planned for 31 January to 5 February in 27 hyper-endemic districts with the main objective of detecting all existing cases, including the backlog of 'cases of consequence.' Besides generating community awareness and widespread support for leprosy elimination activities, there was to be a high degree of capacity building among health workers to undertake assigned tasks during and beyond the NLEC. A deliberate effort will be made to bring MDT services—including initiating appropriate WHO-MDT regimens for MB and PB cases and single-dose ROM for single-lesion PB cases—as near to the patients as possible.

Around 1300 general health service personnel were to have a 1-day training course, and 14,000 voluntary health workers would also receive training. Orientation was offered to members of Village Development Committees.

Many thousands of posters, pamphlets and stickers were being prepared as well as announcements in newspapers. BBC-MPM (the London-based Marshall Plan of the Mind sponsored by the BBC) was helping the Nepalese government to arrange television advertisements, radio spots, drama productions for both TV and radio, and radio question-and-answer sessions. Street dramas and anti-leprosy rallies all formed part of the campaign. Every household in all villages and municipalities in the districts were to be visited by around 6600 two-member teams to look for suspected signs and symptoms of leprosy cases, and every case detected was being assured of a cure through MDT. Altogether 10·7 million population were being covered by this NLEC.

Reproduced from *LEP NEWS*, March 1999

Research Awards in Tropical Medicine for Young Investigators, 1999–2000: The Wellcome Trust, UK

The Trust encourages young science, medical and veterinary graduates from the UK/Republic of Ireland and abroad to pursue research in tropical medicine by providing opportunities for training and for undertaking research projects in the tropical countries of the world. Studies on all aspects of health and disease in the tropics including both infectious and non-infectious human diseases in developing countries are encouraged, together with research relating to veterinary problems in these regions. Cancer and AIDS/HIV-related studies relevant to tropical regions are acceptable.

Fellowships in Tropical Medicine

Research fellowships provide for research into diseases of developing countries. Fellows will normally carry out the majority of their research project abroad.

Advanced training fellowships provide an opportunity for individuals to train in scientific skills that will enhance their ability to carry out research in the field of tropical medicine. Fellows will be expected to undertake research training in a discipline that differs from their previous experience. A period of training may be spent in an appropriate overseas laboratory.

These awards are open to postdoctoral basic scientists and to veterinary graduates with a minimum of 2 years' research experience. Candidates should be graduates of a UK/Republic of Ireland university,

or be overseas graduates who have worked for at least 3 years in a UK/Republic of Ireland university, hospital or research institute. Awards are usually for 3 years and are tenable in a UK/Republic of Ireland university.

The closing date for submission of full applications to the Trust for the coming year is **4 October 1999**. Interviews will be held in February 2000.

Research Development Awards

These awards are to enable young clinical (medical or veterinary) and non-clinical researchers from developing countries to establish a programme of research within their home institution with the continued collaboration and support of a UK/Republic of Ireland sponsor. The candidate must have recently completed PhD training or held a research fellowship in the UK or Republic of Ireland. Research proposals should address issues of health and disease that are of regional significance in the country concerned.

All applicants must hold a full-time established post in an appropriate university or research institute in a developing country. Awards are tenable for a maximum period of 3 years. The Trust will provide funds for research and equipment within the applicant's home institution, some assistance towards research costs in the UK/Republic of Ireland and funds for exchange visits.

Applications are considered three times a year and the closing dates for submission of full applications for the next year will be **16 November 1998, 14 February 2000 and 31 July 200**.

Enquiries should be directed to: **The Grants Section (Tropical), The Wellcome Trust, 183 Euston Road, London, NW1 2BE, UK. Tel: +44(0)20 7611 8409/8641. Fax: +44(0)20 7611 7288. E-mail: tropical@welcome.ac.uk**

Further details of this and other schemes that may be relevant to individuals, especially medical and veterinary graduates, with an interest in tropical medicine are available upon request from the Trust and can be found at **www.wellcome.ac.uk.**

NB: *Applicants may not apply for more than one Trust fellowship scheme at any one time.*

Publications from Healthlink Worldwide (formerly AHRTAG)

Healthlink Worldwide (formerly AHRTAG) publishes newsletters, resource lists, manuals and briefing papers containing practical information for health and development workers.

Healthlink Worldwide's four newsletters—*AIDS Action, CBR News, Child Health Dialogue* and *Health Action*—are published in over 20 regional editions, reaching an estimated two million readers worldwide.

Single copies of most of Healthlink Worldwide's publications are FREE to individuals and indigenous organizations in developing countries.

NEW PUBLICATIONS

Caring with Confidence

Practical information about preventing and treating HIV infection in young children.

We Can Play and Move

Ideas for play activities that help disabled children to move and balance.

For details of these and other publications, please contact: Publications Administrator (TC), Healthlink

Worldwide, 29–35 Farringdon Road, London EC1M 3JB, UK. Tel: +44 171 242 0606. Fax: +44 171 242 0041. E-mail: publications@healthlink.org.uk. Or visit the Healthlink Worldwide website: http://www.healthlink.org.uk

Health Promotion in Developing Countries: University of London

- Do you want to develop your career in community health education and health promotion?
- Do you have experience working in a developing country?
- Do you have a professional qualification but not a first degree?
- Do you want to study by distance learning?

IF THE ANSWER IS 'YES'—then we have a new module which has been especially prepared for you. This module is called 'Concepts and Determinants of Health and Models of Health Promotion'.

What is the module about?

- This course provides a comprehensive introduction to the theory of health promotion in the context of international development. It is essentially educational and is planned for practitioners concerned with health promotion in developing countries.
- It aims to equip participants with the understanding needed to plan health promotion programmes and services.
- The distance learning package includes participatory learning materials, a reader and a text book. It comprises 8 Units:

1. **Concepts and models of health**
2. **Determinants of health**
3. **Inequalities in health**
4. **Understanding human behaviour**
5. **Concepts and models of health promotion**
6. **How adults learn**
7. **The ethics of health promotion**
8. **Communication for health**

- The course is assessed by a 4000 word essay.

How much does the course cost?

Overseas students—£750 (20 credits). Home/EU students—£495 (20 credits).

When can I start?

You can start whenever you want to but you must complete the assessment for the module within a maximum of 12 months from the time you start the module.

How can I use this course to gain a qualification?

- You can use it as part of the access route to the internal MA degree in Education and International Development: Health Promotion. (MA EID/HP)
- You can use it as part of an internal Certificate in Primary Health Care, Education and Development.
- You can also use it as part of the MA EID/HP degree if you already have a first degree.

Contact The Student Programmes Office, Institute of Education, University of London, 20 Bedford

Way, London, WC1H OAL, UK. Tel: +44 171 612 6102 or 6104. Fax: +44 171 612 6097. e-mail: Liaison@ioe.ac.uk

The St Francis Leprosy Guild, UK

The St Francis Leprosy Guild held its Annual General Meeting in May 1998. Accumulated funds totalling £283,900 were allocated to leprosy workers in Angola, Bangladesh, Bolivia, Brasil, Cameroon, Egypt, Ethiopia, Ghana, India, Indonesia, Jamaica, Kenya, Korea, Madagascar, Mozambique, Myanmar, Nigeria, Pakistan, Papua New Guinea, Philippines, Sri Lanka, Sudan, Tanzania, Thailand, Uganda, Vietnam, Zaire, Zambia and Zimbabwe.

The Guild aims to help *cure* people who suffer from leprosy (Hansen's Disease), to *rehabilitate* into the community those who have been cured wherever possible and when necessary to give residential *support* to those whose disabilities require it.

Further information: St Francis Leprosy Guild, 26 Inglis Road, Ealing, London W5 3RL. Tel: 0181-992 0799. Fax: 0181 752 0119

Dr S. K. Noordeen meets with Pune dermatologists

Dr Noordeen, former Director, Action Programme for Elimination of Leprosy, WHO, Geneva met a group of senior teaching and practising dermatologists of Pune on 9th June 1999 in an advocacy meeting organized by the Indian Association of Leprologists, Maharashtra State Branch, Bombay Leprosy Project, Hind Kusht Nivaran Sangh, and RRE Society. The main objective of this advocacy meeting was to clarify controversies and doubts about current treatment regimens for leprosy raised by the practising dermatologists. Dr Noordeen while interacting with the participants clarified the following issues.

1. The current strategy for leprosy elimination of WHO is to reach MDT to all leprosy patients to achieve leprosy elimination by the end of this century. To achieve this target, WHO simplified treatment and diagnostic technologies to suit the health workers even in the most difficult situations. The treatment strategy has been designed for a public health programme.
2. So far, more than 10 million patients have been cured in 121 endemic countries with a very low relapse rate of 0·1% annually which is much lower than for other diseases and acceptable in a public health programme. This has built up confidence in the current treatment strategy.
3. Public health treatment strategy is to eliminate all viable *M. leprae*, including drug resistant mutants with powerful drugs and allow the body to heal residual skin lesions. Any addition of drugs by the physicians after the minimum course of treatment will not be of any use either to hasten the clearance of bacterial debris or healing of skin lesions.
4. The current treatment regimens have been recommended based on WHO prospective multicentre double blind trials and retrospective data analysis of drop out patients from MDT. Both these studies have shown that 12 months MDT in MB leprosy is quite adequate as compared to 24 months MDT. The concern about high relapse rate among high BI cases reported by certain studies is limited to those studies only. Even with reduction in duration of MDT in MB leprosy one cannot expect a high relapse rate. Similarly, ROM single dose treatment in single skin lesion-PB (SSL-PB) leprosy has been evaluated in a WHO double blind controlled study and found to be as effective as 6 months MDT. As SSL-PB leprosy patients have lesser number of bacilli as compared to PB leprosy with two to five lesions, the risk of relapse rate is also likely to be very low. In a country like India, where SSL-PB leprosy is very high, this regimen would be quite suitable to save manpower and resources. As such self-healing rate is also very high in such cases.
5. There is a concern about high risk of relapse in MB leprosy patients, as their nerves are likely to

harbour higher proportion of bacilli. However we have no knowledge about viable proportions in the nerves. The risk of relapse rate is acceptably on the lower side in MB leprosy.

6. A large majority of reported new cases are backlog-hidden prevalence and not incidence cases. It is difficult to assess the incidence rate at this stage. Currently India contributes more than 60% of the global caseload. In all probability India may not be able to reach the target of leprosy elimination by the turn of this century.

Dr Noorden expressed his satisfaction over increasing interest shown by the dermatologists over a period of time in different countries. However he pointed out that only about 10–15% of leprosy patients are handled by dermatologists as compared to about 80–90% of TB patients by the private physicians. Of course, dermatologists will be dominating the field of leprosy in years to come.

Dr C. R. Revanker
Honorary Secretary, IAL-MB

Immunotherapy with *Mycobacterium vaccae*

The following summary is taken from a paper submitted to the *Lancet*, July 10, 1999 by the Durban Immunotherapy Trial Group. The commentary is by Dr Lee B. Reichman, and is taken from the same issue.

Summary

Mycobacterium vaccae, an environmental saprophyte, has immunogenic properties that enhance the host immune response. Immunotherapy with *M. vaccae* has been suggested to shorten short-course antituberculosis chemotherapy. We tested the hypothesis that the addition of *M.* vaccae to standard short-course antituberculosis chemotherapy would decrease the time to achieve a negative sputum culture. Patients with newly diagnosed tuberculosis were randomly assigned an injection of saline (placebo) or *M vaccae* on day 8. All patients received antituberculosis chemotherapy with rifampicin, isoniazid, pyrazinamide, and ethambutol. Sputum samples were checked by microscopy and culture every week for the first 8 weeks and monthly until the end of chemotherapy at 6 months. The primary outcome was the time to a negative sputum culture in the first 8 weeks. Intention-to-treat analysis was used and time to sputum clearance was assessed by log-rank test and Cox's proportional-hazards regression. A total of 172 patients received *M. vaccae* and 175 patients received placebo. At 8 weeks, 70 patients in the *M. vaccae* group and 65 patients in the placebo group had a negative culture; there was no difference between groups in the time to a negative culture ($P = 0.83$). There was no interaction between HIV status and treatment. *M. vaccae* immunotherapy was concluded to have no benefit when added to standard antituberculosis chemotherapy.

Commentary

Whither *Mycobacterium vaccae?*

Tuberculosis used to be feared and respected, but more recently it has also been taken for granted and even ignored. The paradox that this preventable, curable disease remains, of any single infection, the greatest killer is difficult to understand and impossible to accept.

Few diseases have been as extensively studied. The most reliable information on treatment became available after the introduction of randomized controlled trials (RCTs), the first of which on tuberculosis was published 50 years ago and related to the use of streptomycin.

The history of tuberculosis is one of disappointment – of therapeutic measures that, in many instances, were fads. Many were sincere, some were misguided – for example, horseback riding, sea voyages, blood letting, blistering, purging, starving, vomiting, cupping, leeches, counter-irritants, strict bed rest, lung-collapse therapy, phrenic crush, thoracoplasty, pneumoperitoneum, and plombage with paraffin, oil, bone fragments, or Lucite spheres.

The introduction of antibiotics with specific effects on tubercle bacilli led to great celebration (patients dancing in the aisles at New York's Seaview Hospital) but RCTs from the UK Medical Research Council, US Armed Forces, Veterans Administration Hospitals, US Public Health Service, and now the US Centers for Disease Control's Tuberculosis Trials Consortium have shown the strengths and weaknesses of new drugs and rhythms of administration.

Why RCTs are so critical for tuberculosis was stated in a leading article with the first RCT in 1948: 'In few infections is it so difficult to assess the results of treatment as in pulmonary tuberculosis, with its varied clinical picture and unpredictable course. Remarkable recoveries can take place with no treatment except rest in bed'.

It is against this background that the *Mycobacterium vaccae* story has lamentably come to a close. Lamentably, because *M. vaccae* immunotherapy was far more plausible and intellectually promising than some of the bizarre interventions mentioned above. *M. vaccae* was expected to be successful because the hosts' own immune response had long been suspected to be an effective 'cure' for tuberculosis, and several studies have yielded positive results and been widely publicized.

However, for ultimate proof, *M. vaccae* immunotherapy still had to be tested in an RCT. The conclusion, from the RCT of the Durban Immunotherapy Trial Group published in today's *Lancet*, is inescapable – *M. vaccae* has virtually no effect, positive or negative, on tuberculosis.

Two questions remain. First, why is there the discrepancy between past reports and this definitive one? The most likely explanation is that the earlier studies may well have had design problems resulting in biased observations that were obviated by an RCT.

The more important question is what the next step is. A few years ago in an unprecedented pronouncement, the WHO declared tuberculosis to be a 'global health emergency', the only disease ever so designated. Since then there has been an increase in the prevalence of multiple-drug-resistant tuberculosis (MDRFB) and its transmission worldwide, and MDRTB propagation, especially in Russian prisons with failure of the WHO retreatment regimen, has been reported.

The Durban study shows that a plausible therapy for tuberculosis has been lost. But the finding is an urgent reminder to health-care workers and policymakers of the seriousness of the global tuberculosis situation. The findings should once again underscore the necessity of addressing the crisis immediately, not only by expanding WHO's DOTS strategy, but also with a major research effort to find an effective vaccine and new, better, less toxic drugs and routes of administration, and most importantly the political will and commitment to bring all this about.