SESSION VII: PROMOTION OF LEPROSY RESEARCH

CHAIRPERSON: PROFESSOR BAOHONG JI

Leprosy research—setting priorities and facilitating collaborations: a personal perspective

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Summary In recent years, as the prevalence of leprosy has declined and the tuberculosis epidemic has gained increasing attention, leprosy research has generally taken a 'back seat' to research in tuberculosis and other emerging and re-emerging infections. This has resulted as much from perceived differences of scientific opportunities in these fields as from differences of the disease burden. At the United States National Institutes of Health (NIH), research priority setting is typically based on a number of factors. In the case of leprosy research, the technical difficulties associated with this scientific area have clearly lessened enthusiasm for and progress in this field. Today, however, we are confronted by the reality of not having sufficient scientific understanding to explain a stable or increasing number of leprosy cases detected annually in the face of a dramatically decreasing total number of identified cases. We also lack adequate tools for diagnosis and prevention. At the same time, new molecular and cellular approaches and knowledge of the complete sequence of the genome of *Mycobacterium leprae* render leprosy research significantly more tractable than ever before. The combination of these factors has led a number of groups, including the National Institute of Allergy and Infectious Diseases of the NIH, to review the current state of knowledge in leprosy research and draft recommendations for future leprosy research priorities. It is clear that many of the necessary and exciting research activities can best be addressed through collaborations among investigators, with control programmes, and among countries of high and low endemicity.

Funding of leprosy research has suffered, relative to that in many other biomedical fields in recent years, at the United States National Institutes of Health (NIH) and the National Institute of Allergy and Infectious Diseases (NIAID), as well as at many other scientific and biomedical funding agencies throughout the world. Scientific funding agencies take many factors into account in setting research priorities. At the NIH/NIAID, these include an assessment of public health need, the scientific quality of a proposed project (assessed through rigorous peer review), the desire to maintain a large and diverse portfolio of research activities, scientific opportunity, and the potential contributions to human capital and material assets of science.[1] Figure 1A and B depicts the relative support at NIAID during the period 1986–1998 for leprosy and tuberculosis (TB) research, as reflected in the number of NIAID-supported leprosy and TB projects listed in the federal CRISP database for these years.[2]

These data demonstrate that NIAID's leprosy research programme has shrunk by two-thirds (from a high of 27 projects in 1988 to only nine projects in 1998), whereas its TB research programme has grown almost 15-fold during approximately the same period (from

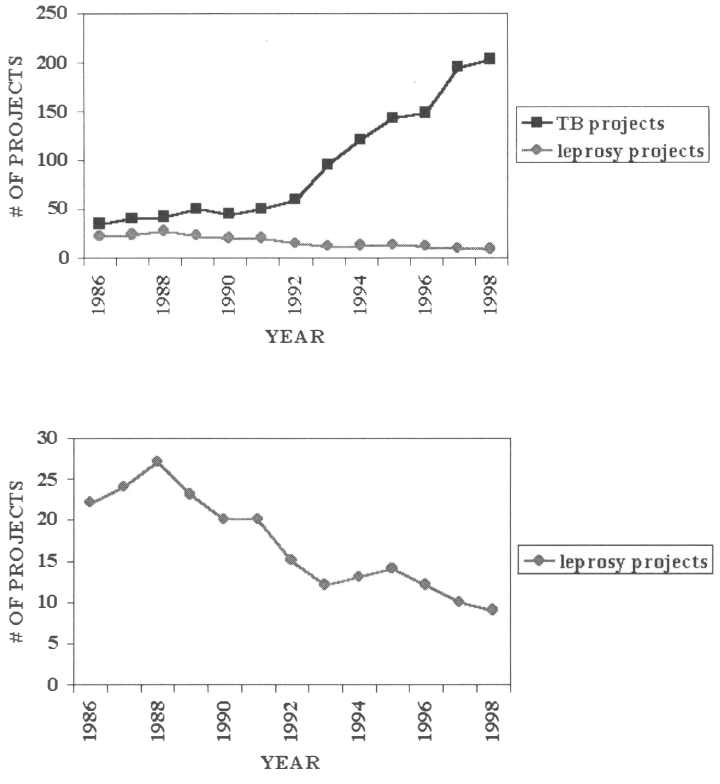

Figure 1. A The numbers of tuberculosis and leprosy research projects per year supported by NIAID from 1996–1998, as retrieved from the CRISP databases, using a simple keyword search based on the search terms 'tuberculosis' and 'leprosy', respectively. **B** the same data for leprosy research projects as presented in **A**, with a different scale on the X-axis, to demonstrate more clearly the changes in support for leprosy research over this time period.

13 projects in 1986 to 194 in 1998). Comparable changes in the fortunes of leprosy and TB research have occurred in other venues around the world during these years. What factors contributed to these changes, should support for leprosy research now be increased, and if so, how might this be accomplished?

A number of factors contributed to the decline in leprosy research during the past 10–15 years. The technical difficulties involved in working with *Mycobacterium leprae* (e.g. inability to culture it *in vitro*, and the expense and unwieldiness of working with the armadillo), compared to the relative ease and availability of new tools for working on other mycobacteria, including *M. smegmatis*, *M. avium*, *M. marinum* and *M. tuberculosis*, have played a role in limiting the sense of scientific opportunity in leprosy research. Raised expectations by the World Health Organization's Leprosy Elimination Campaign that the public health burden of this disease was soon to be eliminated contributed to a sense that further research need not be a priority. Finally, increased funds for TB research, a result in large part of the public, political, and medical attention paid to the TB epidemic during the late 1980s and the 1990s, encouraged many leprosy investigators to turn their attentions to TB research instead.

However, several factors are now contributing to changing perspectives of the need for a

more intensive effort in leprosy research. The first is the recognition that, despite heroic efforts on the part of WHO and its partners throughout the world to eliminate leprosy, there remains a public health need. Approximately 800,000 new cases of leprosy were detected in 1998, and the number of new cases detected annually now approximates the number of prevalent leprosy cases globally. This is not unexpected for a disease for which the average duration of treatment is 1 year; however, it also indicates that, after almost a decade of an intensive elimination campaign, transmission of *M. leprae* still occurs at a significant rate. These data suggest the need for improved methods of early diagnosis of *M. leprae* infection, and emphasize the inadequacy of our knowledge about the transmission of *M. leprae* and the natural history of the disease.

A second major factor that creates a more favourable environment for leprosy research is a sense of increased scientific opportunities. The recent sequencing of the *M. leprae* genome[3] has opened new avenues to finding answers to long-perplexing questions about leprosy. Sequencing the entire genome of microbial pathogens has been a boon to many areas of research in microbiology and infectious disease in the course of the last few years,[4–8] but it holds the greatest promise for organisms that, like *M. leprae*, are difficult to approach by traditional techniques, because of a lack of good methods for culture *in vitro* and inexpensive, facile animal models of infection. Functional analysis of the entire genome holds out the promise of elucidating the presence or absence of key metabolic pathways, facilitating understanding of growth requirements. Such an analysis could lead to identification of gene products involved in the neurotropism or intracellular persistence of *M. leprae*. This information can, in turn, suggest potential, novel drug targets, protective antigens, and virulence factors to be capitalized upon in devising new strategies for prevention, and improved methods for early diagnosis of infection and detection of relapse.

Knowledge of the sequence of the entire genome opens the possibility of defining the proteome (the complete set of proteins synthesized by the organism) of *M. leprae* as well. Structural analyses of key proteins could then contribute to identification, for example, of potential drug targets. The sequence of the genome could also serve as a basis for devising strain-typing methods and means of detecting and diagnosing drug resistance.

Recent advances in immunology, neuro- and cellular biology, and the human genome project, also hold promise for helping to answer important questions related to leprosy, such as elucidation of the human immune response to *M. leprae* (which would contribute to identification of correlates of protection and novel vaccination strategies), and explication of the mechanism underlying neurotropism, nerve damage and reactional states.

The desire to maintain a diverse portfolio of research projects has helped to maintain even a small leprosy research programme at NIAID in recent years. This factor continues to play to leprosy's advantage in at least a minor way.

How can interested investigators contribute to a resurgence of leprosy research? One way is by thoughtful participation in priority-setting exercises, such as this and a similar exercise held by The Heiser Trust and the NIAID in Dulles, Virginia, USA, in November 1999. At the November 1999 workshop, which was entitled 'Leprosy Research in the Post-Genome Era', 25 leprosy researchers from around the world met with six outside experts (with expertise in epidemiology, immunology, cellular biology, molecular biology, genetics, dermatology and pharmacology) to discuss the current status of leprosy globally, the major research questions, and scientific opportunities for approaching them. At the end, the panel of outside experts identified and discussed potential research priorities. A separate report of this workshop, prepared by the Panel Chair, Dr Roy Curtiss, is currently being prepared for publication

(personal communication, Dr Roy Curtiss, Washington University, St Louis, MO, USA). The contributions of the leprosy scientists to that workshop, as well as the thoughtful deliberations of the Panel, were key to the credibility and potential impact of that workshop report.

The second and most important role interested scientists can play in the NIAID research funding process is to submit exciting research applications of high quality. Peer-review panels play a fundamental role in NIAID's research planning process, and applications that score in the 'outstanding' range in a review panel's deliberations, irrespective of the research topic, stand a very high chance of ultimately being funded. Conversely, no matter how high a priority NIAID might place on a given research area or public health problem, it must receive for review relevant applications of high quality, in order to build a research programme. In addition, in an area such as leprosy, in which the greatest impact on health is outside the United States, collaborations and coordination of research activities with scientists, health workers and control programs in leprosy endemic countries are key to having a sustainable, productive scientific programme. Individual scientists and their efforts and initiative play a vital role in establishing and maintaining important collaborations. NIAID Programme staff can also help to initiate, facilitate and maintain these contacts, and coordinate activities with other funding and research institutions.

A third role committed scientists can and will continue to play is to serve as contractors to NIAID for activities such as the maintenance of an armadillo colony (currently at the G. W. Long Hansen's Disease Center, Baton Rouge, Louisiana, USA). This contract supplies *M. leprae*-infected tissues to qualified investigators, and to another NIAID contractor (currently at the Colorado State University, Fort Collins, Colorado, USA), who, in turn, prepares and supplies standardized, *M. leprae*-derived research reagents of high quality to qualified investigators worldwide. Through these contracts, NIAID and the involved investigators hope to facilitate leprosy research and help maintain a strong leprosy research community globally.[9]

In summary, exciting scientific opportunities and public health need are driving renewed interest in leprosy related research at NIAID and elsewhere. Interested scientists and control programme personnel can play important roles in identifying key questions and recommending research priorities to funding agencies. Scientific collaboration and coordination with partners in leprosy endemic countries, other funding agencies and research institutions worldwide will be crucial to rebuilding a vibrant leprosy research community. Creative investigators taking advantage of new scientific opportunities will continue to be its foundation and core.

References

[1] NIH Working Group on Priority Setting, September 1997, 'Setting Research Priorities at the National Institutes of Health'. Report available at URL: http://www.nih.gov/news/ResPriority/priority.htm

[2] *C*omputer *R*etrieval of *I*nformation on *S*cientific *P*rojects; URL: http://www.commons.cit.nih.gov/crisp/ (CRISP is a pair of large searchable databases of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.)

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[4] Field D, Hood D, Moxon R. Contribution of genomics to bacterial pathogenesis. *Curr Opin Genet Dev*, 1999; **9**: 700–703.

[5] Jungblut PR, Zimny-Arndt U, Zeindl-Eberhart E *et al*. Proteomics in human disease: cancer, heart and infectious diseases. *Electrophoresis*, 1999; **20**: 2100–2110.

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[7] Strauss EJ, Falkow S. Microbial pathogenesis: genomics and beyond. *Science*, 1997; **276**: 707–712.
[8] NIAID 'Leprosy Research Support' contract website: http://www.cvmbs.colostate.edu/microbiology/leprosy/index.html

DISCUSSION

Dr van Brakel: Do you have a Web site from which one may download application forms?

Dr Ginsberg: www.nih.gov will bring you to the NIH home pages. Click on 'funding-opportunities'. Finally, you come to a 'grants' page, and the form is no. 398. This page will also provide information with respect to dates for submission and answers to frequently asked questions.

Professor Ji: Keeping in mind the record for the past 10 years, how do you assess the likelihood that the NIH will fund a field-research project in leprosy?

Dr Ginsberg: My response depends upon what you mean by a field-research project. A number of our projects involve collaboration with scientists in endemic countries. In the framework of Professor Brennan's project, we are trying to implement a skin test project with Dr Roche in Nepal. Phase I and phase II projects are easily incorporated into our research programme. Trials to test efficacy are more difficult, because of the amounts of time and resources involved, but we can often co-fund studies with other agencies.

Professor Brennan: Would you describe the role of the NIH in regulatory issues?

Dr Ginsberg: The NIH is not a regulatory agency. In the USA, it is the Food and Drug Administration (FDA) that oversees drugs, vaccines and diagnostics. However, staff members of the NIAID, who work with the FDA on a regular basis, can assist investigators with the necessary 'investigational and new drug' (IND) applications for use of a new or experimental product in phase I and phase II studies. If the NIAID is supporting the project, we may actually hold the IND; we hold more than 100 INDs at the moment.

Dr Lockwood: What is the proportion of your grants that are made to foreign investigators?

Dr Ginsberg: The proportion is small; I estimate that, in about 5% of our projects, the foreign investigator is the principal investigator. There is no reason that a foreign investigator cannot apply. However, his application must undergo one additional hurdle: the Study Section and I, if the application falls into my programme, must be able to certify that the research cannot or will not be done by an American investigator. Because the review process is so different from those you may have been exposed to, and because it is so difficult to win funding, we often encourage foreign investigators to begin by collaborating with an American investigator who has been successful in the past.