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EDITORIAL

Collaborative Programmes of Research in Leprosy: the INFIR Programme

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Recent trends in medical research are, for a smaller number of large research programmes, developed to address the big questions rather than for large numbers of small projects. This is a trend encouraged by research funding bodies and the research community. This trend requires more collaboration between research groups and international cooperation, as well as increased inter-disciplinary working. This has also promoted greater standardisation of methods to produce comparable results as well as encouraging the use of common technical terms to facilitate working across disciplines. Recent examples of this trend in leprosy research are the TRIPOD trials,[1] the Participation Scale programme,[2] the SALSA programme,[3] IDEAL[4] and the INFIR programme. This paper presents an overview of the INFIR programme to illustrate a collaborative programme of research in leprosy describing the background, funding, implementation and output.

INFIR is the ILEP Co-ordinated Programme of Research on Nerve Function Impairment and Reactions in Leprosy. ILEP (International Federation of Anti-Leprosy Associations) identified the need for more research to address the challenges of nerve function impairment and reactions in leprosy at a working session in December 1997. An expert workshop was convened in June 1998 with representatives from a range of related disciplines as well as field representatives from the leprosy world. This workshop identified a number of priorities and opportunities which were developed into a single proposal for a programme of coordinated research. This proposal was presented to the ILEP meeting in December 1998 and funding was approved from the Follereau Foundation of Luxembourg with support from LEPRA Health in

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Action and The Leprosy Mission International. The proposal involved a range of field centres, field laboratories and Universities in several countries in Africa, Asia and South America.

There were four specific strands to the programme and an INFIR steering group was established in February 1999 and Dr. Jo Colston was appointed as chair of the overall steering group. The strands reflected the priorities that emerged from the workshop and one important aspect of the overall steering function was to ensure standardisation of methods and terminology across all four strands. The four strands of research were: a Cohort study to investigate prediction, detection, and pathogenesis of NFI in new patients, trials of new treatments for reactions, study of recurrent and late reactions, and studies of delay in detection and start of treatment of leprosy.

Cohort Study to Investigate Prediction, Detection and Pathogenesis of NFI in New Patients

The cohort study was primarily based in India and involved centres in Naini, Faizabad and Delhi working with laboratories in Miraj and Hyderabad. The study recruited a cohort of 303 new MB leprosy patients and conducted a detailed baseline assessment which included clinical (sensory and motor), neurological (sensory and motor nerve conduction, dynamometry, vibration and thermal tests), biopsies (skin and nerve), and blood samples. The cohort was followed up 4-weekly for one year, and 8-weekly for the 2nd year. This study was an immense undertaking employing novel methods of neurological assessment that had not been used together with clinical and serological assays in a coordinated way.[5] The findings produced included the setting of standards and describing of reference values for many neurological functions previously unreported in leprosy.[6] The programme has already produced a series of important publications,[7,8] with a number about to be published.[9] It also has created a bank of serological data, neurological data and tissues that are still being used to address specific questions. The study has set a standard for cohort investigations of neurological function and reactions in leprosy, created new standard methods and informed new research.[10] Important findings to date include validation that monofilaments and voluntary muscle testing reflect neurophysiology, the fact that neurophysiological tests show nerve damage to be much more widespread than is clinically apparent, and that nerve conduction and temperature testing can detect nerve damage in a sub-clinical stage, often weeks or months before such damage becomes detectable with current clinical methods. The findings show that neurological function impairment and certain changes in serology improve prediction of new events and help understand the pathogenesis, and that nerve function improves during MDT. An important question to be addressed in a future prospective study is whether sub-clinical neuropathy treated at diagnosis would reduce the risk of permanent nerve damage at the end of treatment.

Trials of New Treatments for Reactions

The need for improved drug therapy of leprosy reactions had been identified as a research need at the preliminary workshop. Azathioprine and cyclosporine A were then identified as potential drugs that could be used to improve immunosupression or as alternative therapies for patients who are non-responsive to steroid therapy. Azathioprine and cyclosporine are

well established immunosuppressant with many years of clinical experience in their use, so their side effect profiles are well established. They are also both out of patent and so are potentially affordable second-line drugs. Studies were developed with local clinicians in Nepal and Ethiopia. These were designed as phase two studies to examine tolerability and feasibility. The study in which azathioprine was added to prednisolone showed that patients who received an azathioprine and prednisolone combination had similar outcomes to patients who received prednisolone alone.[11] The study in which cyclosporine A replaced prednisolone for part of the treatment showed that patients receiving the combination some evidence of improved nerve function outcome.[12] A clinical severity score was also developed during this study.

The studies were important because they demonstrated the potential for these drugs in the treatment of leprosy reactions. They also enabled the development of study protocols and they gave clinicians experience in using these agents. A formal pharmacokinetic comparison of generic Cn against the Sandoz preparation showed that the generic and drug company preparations were equivalent. The data from these small studies has been crucial in providing the platform on which to develop the larger, better powered studies of azathioprine and cyclosporine treatments in leprosy reactions which are being conducted in India and Ethiopia.

Study of Recurrent and Late Reactions

The research questions on late and recurrent reactions were posed by field staff who recognised these as specific challenges in the management of people with leprosy. The issue of late reactions is an increasing challenge as the duration of MDT is reduced making the ability to predict which patient will develop late reactions and methods for promptly detecting such late reactions important. The question of recurrent and repeated reactions stimulated discussions that were finalised at a workshop associated with an ILA congress and the conclusions were published which proposed standard definitions to facilitate research and make findings between studies comparable.[13]

Studies of Delay in Detection and Start of Treatment of Leprosy

The final part of the programme focused on delay in diagnosis as it was recognised that a high proportion of all patients with nerve function impairment had developed the nerve damage prior to diagnosis. This generated a number of studies using both quantitative and qualitative methods to address the problem in a range of countries including Bangladesh, Nepal, India, Malawi, Brazil, and Paraguay.[14–17] The findings demonstrated that there was no single reason for delay and that the factors associated with delay varied between local settings. The work resulted in the production of a guideline for field use in identifying the factors associated with delay in diagnosis in the local context. This guideline has now been widely disseminated (more than 2000 copies) and is available in a number of languages such as Spanish and Portuguese, it is available from the ILEP website.[18] This work is now very relevant to the validation of new case detection and delay in detection in studying the rapid declines in new case detection being observed in several countries.

Conclusions

INFIR has been a highly successful and a very productive research initiative which has contributed to prevention of nerve function impairment and better treatment of reactions. This approach to research is an important model of inter-disciplinary, collaborative research that has focused on recognised priority areas for leprosy research. The approach has important added value to research in exchange of expertise, research capacity strengthening, and the development of standardised research methods ensuring comparability of results between countries and research centres. It led to the formation of a collaborative network for research on reactions and nerve damage in leprosy called 'Synapse'. The approach has also helped secure significant research funding for the key research priorities of nerve function impairment and reactions. The INFIR findings have been used as the basis for generating new research ideas and stimulating new programmes at a workshop in the Netherlands. This workshop was co-organised by Synapse members and the Netherlands Leprosy Relief, bringing together scientists, clinicians and other experts to discuss the current state-of-the-art and outline proposals for further research. The resulting consensus report was published in 2007.[19] At least one proposal (called TENLEP) has already been submitted for joint funding to several ILEP partners. A similar model of a large multi-disciplinary, collaborative research programme managed by a steering committee has been adopted by the IDEAL project to develop new tests for early diagnosis and understand transmission. It is vital that such endeavours are funded. The global leprosy strategy is based on the same methods that have been used for over 25 years and it is important that new research findings and evidence is generated to inform future strategies. A commitment to new research is vital in leprosy to improve the quality of treatment for patients, to reduce the disability and impairment associated with leprosy and to work towards the control and eventual eradication of the disease.

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