Current Research And Future Development In Leprosy And Tuberculosis Control

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Abstract: During recent years we have witnessed a burst of activity in leprosy research. By definition, leprosy is an infectious disease, the causative organism being cobacterium leprae. The leprosy bacillus is virtually non-toxic and may occur in large amounts in tissues with only moderate clinical symptoms. In fact, leprosy may to a great extent be regarded as an immunological disease since most symptoms arc due to immune reactions against antigens liberated from the leprosy bacilli. During recent years leprosy research has been centred, to a great extent, around studies of immunological phenomena since a better understanding of basic immunological mechanisms would provide a rational basis for improved treatment of patients with established disease, and for advancements in our understanding of the epidemiology of leprosy and its control.
[Esmaeilzadeh M, Kazemzadeh F, Borhani M. **Current Research And Future Development In Leprosy And Tuberculosis Control**. *Life Sci J* 2012;9(4):1061-1064] (ISSN:1097-8135). http://www.lifesciencesite.com. 161

Keywords: Leprosy, Tuberculosis, Research and Development

1-Introduction

1-1-The Course After Infection With Mycobacterium Leprae

Figure 1 provides a schematic outline of the course after infection with M. leprae. This course is highly variable, and the figure points out several distinctive features of major importance for our understanding of the epidemiology of leprosy, its control, and variation in clinical picture in patients with established, chronic disease. Only a minority of the individuals who have been infected with M. leprae go from infection

to disease. Many of them have probably gone through a subclinical stage limited multiplication of M. leprae terminating without development of any clinical symptoms at all. Other individuals develop " indeterminate leprosy" with one, or a few, vague lesios that heal sponstaneously. To the right in the figure, we see the individuals who develop determinate. Persisting disease which is classified as a spectrum between the two polar forms.

Lepromnatous (LL) leprosy is characterised by lack of resistance, exten8ive bacterial multiplication with large amounts of bacilli in the lesions which are multiple and tend to become nodular in appearance. The other polar group, tuberculoid (TT) leprosy, is characterised by one or a few well-defined flat lesions, being hypopigmented in dark skinned people, containing few or no detectable acid fast bacilli as evidence of marked resistance.

The factors which determine whether an infected individual will develop no clinical symptoms of the infection or experience bacillary multiplication and eventual development of persisting, chronic disease are not well known. There is a great need for additional Information and for identification of risk factors favouring development of clinical disease after infection.

The present epidemiology of leprosy is, to a great extent, the epidemiology of disease. There is a great need for development of new methods by which infection with M. leprae could be reliably diagnosed. This would make us able to study both the epidemiology of infection and the epidemiology of clinical disease, and to define risk! factors favouring progression from infection to disease, In tuberculosis, development of the tuberculin reaction has been of fundamental importance, providing an indicator of infection permitting determination of annual incidence rates of infection in various populations.

A similar test is not yet available with regard to leprosy, but important information in this area was initially obtained by the lymphocyte transformation test (LTT) at the Armauer Hansen Research Institute in Addis Ababa (1,2) and through studies of more refiner! lymphocyte stimulation tests (LST) measuring lymphocyte proliferation by recording the in corporation of labelled thymidin into newly synthesised DNA after stimulation of lymphocytes in vitro with various antigen preparations derived from M. leprae (3).

The Iymphocyte transformation t('Sts provided evidence of immunological conversion in individuals coming from leprosy non endemic countries to work at leprosy hospitals in Ethiopia (1). The frequency of conversion in this group is much higher than the probability of subsequent development of clinical signs of the infection.

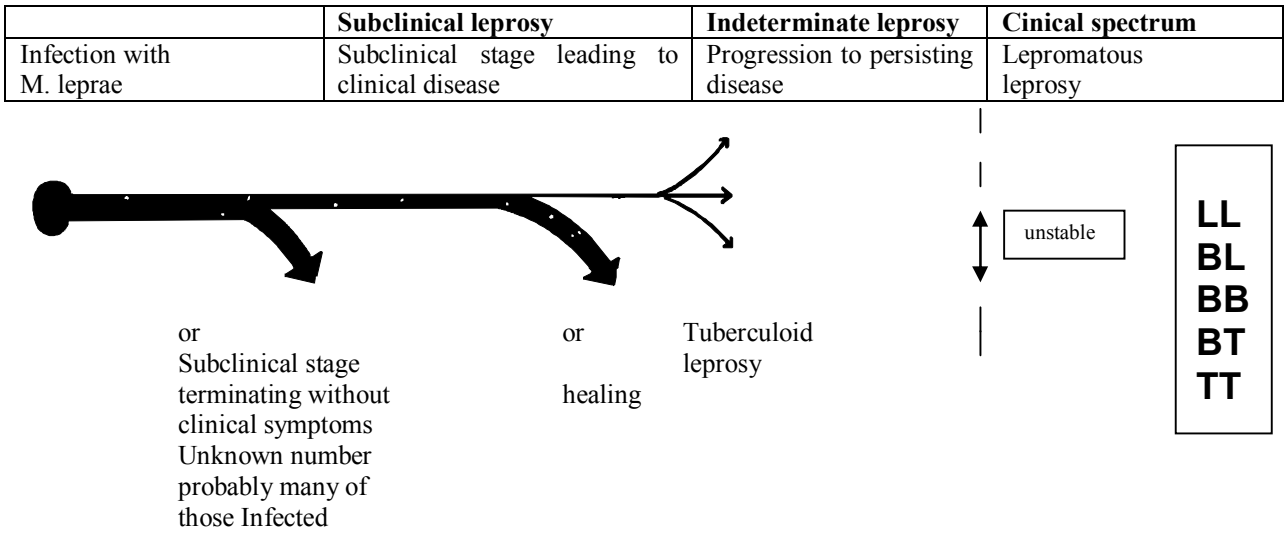

Figure I. The course after infection with *Mycobacterium leprae.* Reproduced from M. Harboe, The Immunology of Leprosy, Chapter 4 in *Textbook of Leprosy.* R.C. Hastings, Ed. Churchill, Livingstone, London, 1985.

So, further development of lymphocyte stimulation tests and corresponding delayed type hypersensitivity skin tests may result in methods for diagnosing infection with M. leprae, but at present it can not be foreseen how these tests might predict the probability of further development towards clinical disease. It is particularly important in this connection that patients with multibacillary leprosy usually have entirely negative tests both in vivo and in vitro for cell mediated immune responses towards M. leprae.

Extensive experiments have been carried out on various sensitive antibody assays, both with "global tests" demonstrating antibodies directed against a variety of different constituents of M. leprae (e.g. radioimmunoassay and ELISA tests for antibodies against total M. leprae sonicates), tests for antibodies against M. Leprae antigen 7 which cross reacts widely with other mycobacteria (4), and assays for antibodies against M. leprae specific antigenic determinants (5).

There are still problems with regard to development of sufficiently sensitive but nevertheless specific assays, and with false negative results since, even in patients with multibacillary disease, there is a wide variation in antibody content in individual patients and some of them have only low antibody activity (4,.5,6).

In experimental models, it has been demonstrated that there is a striking relationship between development of systemic infection after inoculation with M. leprae and, formation of an ti-M. lepra 7 antibodies (4). So it is e'xpected that antibody assays will turn out to be fairly reliable indicators of the total antigenic load in a given individual, and thus for thus extent of bacillary multiplication and probability of development of disease.

The combined use of a test for cell mediated immune reactions and antibody response against M. leprae antigens is expected to provide the best information on the occurrence of infection with M. leprae and the tendency to further development of clinical disease.

In patients with determinate, established clinical disease there is a wide variation in clinical appearance. The area between the polar groups denoted "B" for "Borderline" could also be seen as being denoted "B" for "Beware of reactions". In this area of the clinical spectrum, there is the greatest tendency for development of particular forms of reactions, denoted reversal reactions, due to delayed type hypersensitivity reactions against antigens 1iberated from M. leprae in the tissues.

The symptomatology depends greatly on the location of liberated antigen, the most severe results being extensive nerve damage due to local DTH reactions in nerves after release of antigen from M. leprae residing inside Schwann cells. Immunological studies of leprosy have, during recent years, been centred around the study of these reversal reactions providing improved understanding of their pathogenesis (3,7,8) and thus a more rational background for treatment.

Patients with lepromatous (LL) leprosy are characterised by a profound, specific cel-lular immuno-deficiency, detectable both by in vivo and in vitro tests (9). This lack of cell mediated immune reactions against M. leprae is probably directly responsible for the lack of resistance, extensive

multiplication of M. leprae, and the great risk of relapse after treatment since this specific immuno-deficiency persists after prolonged chemotherapy. Recent findings at the Armauer Hansen Research Institute in Addis Ababa have provided new insight into the mechanisms of this deficiency (10).

The development of cellular immune responses after antigenic stimulation depends upon activation and proliferation of reactive cell clones. This proliferation in turn depends upon production and release of cell growth factors being produced in some cells (particularly T helper cells) and affecting cells in the immediate neighbourhood. Interleukin-2 (IL-2) is of main importance in this regard.

In most instances, the addition of IL-2 to cultures of lymphoid cells from peripheral blood of patients with lepromatous leprosy exposed to M. leprae in vitro results in marked proliferation of lymphoid cells. This reconstitution of proliferation in response to M.leprae demonstrates clearly that patients with lepromatous leprosy do possess circulations M . leprae reactive T cells and that the lack of proliferation is due to deficient production of IL-2 (10). This demonstration of reversal of that specific immuno deficiency in vitro provided fundamental, new knowledge with regard to the mechanism of this immuno-deficiency.

Experiments with local injection of IL-2 into leprous lesions are expected to he performed soon and will he an important new feature in attempts at immunologic intervention to correct this basic immuno-deficiency which is of major importance for development of multi bacillary disease in the individual patient and for the total infectious load in the population.

2-Influence Of Treatment On Leprosy Control

The interaction between treatment and control is an essential issue in leprosy. At present, the major principle of leprosy control is to break the chain of infection by treating as many patients with multibacillary disease as effectively as possible and at an early stage. In the years to come, it will be essential to carefully follow up the effect of the new multiple drug therapy (MDT) regimens recommended by WHO and to assess their impact on the leprosy endemic in the population.

To assess the effect will be more difficult in leprosy than in tuberculosis since we have no practical means, at present, for direct determination of the annual incidence of infection in a population but would depend on observation of patients with established disease. The establishment of suitable epidemiological indicators is a matter of urgency.

Based on observation during the disappearance of the: leprosy endemic in Norway (11), it app4'ars that age specific incidence rates would provide important information, but it is a complicated project to obtain such data. Determination of the frequency and severity of deformity at the time of diagnosis is another obvious parameter which provides essential information for our evaluation of the extent of infection at the population level, and is concerned with matters of immediate relevance to the patients themselves.

The development of new technology is an obvious need has become a major problem during the era of dapsone monotherapy (12) and it is not clear how the new MDT regimens will cope with this problem under realistic field conditions. Dugs with bacteriocidal or acteriostatic effect on M. leprae are very few indeed. There is thus a great need for the development of new drugs and for the introduction of new techniques for primary intervention.

The development of a leprosy vaccine has been given top priority in the WHO Immunology of Leprosy (IMMLEP) Programme. Based on the use of M. leprae grown in vivo in armadillos, marked progress has been made in this area. However, it is not yet clear to what extent killed M. leprae will be able to induce protective immunity , that is, increased ability to limit bacterial multiplication. In humans, BCG must be given alive to induce protectivc immunity against tuberculosis.

At present, there are several candidate vaccines, killed armadillo-grown M. leprae given alone, killed M. leprae given together with live BCG, and the use of another carefully selected cross-reacting mycobacterium. Work on vaccine development occurs step-wise and will ultimately lead to field trials to determine the efficacy of the selected vaccination procedures. The essential field trials will be expensive and difficult to carry out in a disease like leprosy with a long incubation period and low incidence rates. The matter is further complicated considering prior experience in tests for efficacy of BCG vaccination against tuberculosis and leprosy .In both instances, the protective effect of BCG varies considerably in different populations, and we would therefore also expect the effect of new leprosy vaccines to differ markedly in different populations.

3-Trends In Tuberculosis Research

With regard to tuberculosis, much of the current interest is directed towards the development of new technology for prophylaxis. The effect of BCG vaccination against tuberculosis has been extensively discussed for many decades. In my opinion, one major point appears:

In some populations there is an indisputable, marked protective effect of BCG vaccination against subsequent development of infectious disease. fu other populations, the effect is less, or apparently nil.

The sad fact is that the smallest effect is obtained where an efficient vaccine is most nceded. In developing countries tuberculosis represents a major health problem, and there is an immediate need for improvements in strategies and techniques for tuberculosis control work (13).

Research is active and greatly needed for better characterisation of the antigenic structure of mycobacteria and to learn more about mechanisms for induction of effective protective immunity. In the WHO Immunology of Tuberculosis (IMMTUB) Programme, priority has been given to exploring the new biological technology, including DNA technology, to develop new principles for vaccine production.

These technologies have already proven to be very effective in the development of new vaccines against diseases in which humoral immunity is essential for resistance. It is hoped that this technology will also result in the development of new vaccines capable of inducting protective cellular immunity which is what is needed in the two most important mycrobacterial diseases, tuberculosis and leprosy.

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9/29/2012