REVIEW

Leprosy: a problem solved by 2000?

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Our legions are brim-full, our cause is ripe:
The enemy increaseth everyday;
We, at the height, are ready to decline.
There is a tide in the affairs of men,
Which, taken at the flood, leads on to fortune;
Omitted, all the voyage of their life
Is bound in shallows and in miseries.
On such a full sea are we now afloat;
And we must take the current when it serves,
Or lose our ventures.

[Julius Caesar, IV. iii. 213–222]

Introduction

Leprosy is an ancient disease, with the first recognizable descriptions from the middle of the second century AD.1 In Western Europe, incidence appears to have peaked in around the twelfth century, where it was subject to strict exclusion laws derived from the Book of Leviticus. Sufferers were legally regarded as dead, and segregated from the ‘living’. By the end of the twentieth century however, leprosy was virtually confined to the ‘poverty belt’ of the developing world.

The advent of multidrug therapy for leprosy led to the World Health Assembly adopting a programme in 1991 ‘to eliminate leprosy as a public health problem by the year 2000’ (WHA 44.9), whereby ‘problem’ was defined as a prevalence of greater than 1 case per 10,000 population. Leprosy elimination campaigns (LEC) were started in endemic countries. The result of the programme was the ‘cure’ of more than 10 million patients by the end of 1999.2 The latest data show a global prevalence of around 1.25 per 10,000 population on 1st January 2000.2 Given an 85% decrease in cases over the past 15 years,2 the current prevalence might be considered insignificant. But if one accepts WHO’s definition of health as one of complete physical, spiritual and social well-being, can we tolerate the existence of leprosy at all?
It is important to consider the example of tuberculosis, a close relative of leprosy. With the advent of powerful antituberculous chemotherapy in the 1950s, eradication seemed a real possibility. By the early 1990s, however, tuberculosis was increasing and is once again a major public health problem. In the light of the re-emergence of so many infectious diseases, can leprosy be viewed as a problem solved until it has been eradicated? And might eradication even be possible?

**Leprosy: the disease**

**CLINICAL FEATURES**

Leprosy is a chronic disease featuring a broad spectrum of clinical manifestations that reflect the expression of host cell-mediated immunity. Paucibacillary tuberculosis disease is characterized by localized neurological and dermatological lesions with a low bacterial load. In contrast, multibacillary lepromatous disease displays generalized multisystemic features. Problems posed by the large differential diagnosis are compounded by the lack of a ‘gold standard’ diagnostic test. Currently, diagnosis is on clinical grounds supported by a slit-skin smear; but the absence of acid-fast bacilli on skin smears does not exclude disease. In endemic areas, the false-positive diagnostic rate is probably high: evaluation after a campaign in Myanmar found 18% of cases had been misdiagnosed.

Leprosy is also characterized by immune-mediated ‘reactions’, responsible for many of the manifestations of this disease. Type 1, or reversal reaction, is a delayed-type hypersensitivity response, resulting in neuritis and residual neurological damage. Type 2 reaction, erythema nodosum leprosum, is probably an immune-complex disorder, and causes damage to infected tissues along with systemic illness. Type 2 reactions afflict over 50% of multibacillary patients. These occur in association with a high load of dead bacilli, decreased T-suppressor cell function and increased levels of tumour necrosis factor-α.

**DRUG THERAPY**

In the 1940s, dapsone replaced chaulmoogra oil, which had been used since the sixteenth century in China. By the late 1960s, several potent drugs were available and, with problems of dapsone resistance, combination therapy was found to be highly successful. This led to the recommendation by WHO that multidrug therapy (MDT) be implemented for all cases of leprosy. WHO has aimed for universal access to MDT, with the leprosy elimination campaigns ensuring that ‘leprosy diagnosis and treatment is available, free of charge, at all health centres, particularly in endemic areas’ but acknowledged that prior to the LEC ‘the problem of accessibility was not only geographic but also social, in view of the stigma attached to leprosy, and lack of awareness as well as inadequate availability of services for diagnosis and treatment’. It is unclear whether these problems have been overcome.

Evidence suggests that MDT is highly effective, so WHO defined ‘cure’ as the successful completion of a course of MDT. Data published from campaigns, however, showed a range of cure rates for paucibacillary leprosy between 67 and 100% and for multibacillary disease between 38 and 100%. In the absence of drug resistance to MDT, the likely explanation for these poor results is ‘problems with accessibility’.

WHO declares that more than 10 million people have been ‘cured’ of leprosy by MDT. This statement is misleading and diverts attention from the most significant problems
associated with leprosy: reactions and disability, with the ensuing social rejection. Reactions may occur long after ‘cure’ by chemotherapy, and persist for years, especially in multibacillary patients. Management of these ‘cured’ patients is particularly problematic, as they have often been discharged from clinics. It is clear that until recently, the sociological impact of the disease, eminently open to intervention, has been underestimated. Leprosy will remain a health problem until the quality of life for such patients is significantly improved. The LEC have diverted attention from these aspects of healthcare, which are particularly vulnerable under the present definitions of cure and elimination.

**Mycobacterium leprae: the organism**

**MICROBIOLOGY**

*Mycobacterium leprae* has not yet been successfully cultured in artificial media. This deficiency, together with the lack of adequate diagnostic tests for infection, means that it has been extremely difficult to study the relationship between *M. leprae* and the human host.

*M. leprae* is an obligate intracellular organism, and its ability to survive within macrophages and Schwann cells is a key feature of its pathogenicity. In the absence of efficient cell mediated immunity, dead and disintegrating organisms provide a persistent reservoir of antigen that may trigger reactions.

**TRANSMISSION**

A better understanding of transmission of leprosy might help efforts to eliminate the disease. The most likely route of transmission is through the respiratory tract: many studies show large numbers of bacilli excreted from the nose in untreated lepromatous leprosy, whilst experimental transmission has been achieved in mice through this route. *M. leprae* is excreted in breast milk of lepromatous mothers and may infect infants. Parenteral routes have been proposed: direct entry of the organism through the skin seems unlikely to play a significant role; and while some arthropods may carry the bacillus, there is no evidence that they transmit the infection.

Humans provide the major reservoir of infection world-wide, and contact with *M. leprae* is frequent in endemic areas. There is strong support for the occurrence of direct spread, with increased rates among household contacts. DNA from *M. leprae* has been isolated from nasal secretions of 7.8% of healthy persons in endemic areas. Evidence of exposure to *M. leprae* as determined by lymphocyte transformation was found in 24% of non-immune immigrants into an endemic city, and in more than 50% of those with known contact. Further, *M. leprae* has been shown to exist free in the soil around houses of lepromatous patients, and may remain viable for some time extracorporally. There is little support for animal reservoirs playing a significant role in transmission, although wild armadillos in southern USA have been found infected since the 1980s and occasional cases have been reported among handlers.

**Epidemiology: what is happening to the incidence of leprosy?**

As the global leprosy burden approaches ‘elimination’ levels, so it becomes increasingly important to know incidence rates in the remaining endemic areas. Persistently high
incidence rates would call for the identification of additional interventions (such as socioeconomic changes or vaccination with BCG), which might have an impact on disease transmission locally. Without incidence data, there are only a few, indirect means to measure the efficacy of LEC. Much leprosy epidemiology is based upon prevalence data, defined as the number of patients registered for treatment at any one time point. Prevalence data are suitable for caseload management as they are particularly sensitive to change, easy to measure, and appropriate for a chronic disease. However, they are susceptible to various forms of bias, particularly duration of therapy. Most significantly, there is a large burden of unidentified ‘hidden’ cases, estimated at about 260,000 patients in 1997, approximately a quarter of the total prevalence. Hidden cases are due partly to the social implications of the disease, which discourage patients from registering, and partly to the relatively asymptomatic nature of paucibacillary disease.

Globally, the prevalence of leprosy has fallen by 85% in the last 15 years, and has started to stabilize at approximately 3 per 10,000 population in the most endemic countries (Figure 1). The annual case detection rate, however, has only declined by 4% in these countries. WHO claims that case detection is not ‘robust enough’ to extrapolate true incidence, and that the discrepancy between changes in prevalence and in case detection rates represents the hidden cases. WHO supports this by stating that their campaigns ‘were

![Figure 1. Leprosy prevalence and case detection rate in 32 endemic countries (Bangladesh, Benin, Brazil, Burkina Faso, Cambodia, Chad, Columbia, Congo, Côte d’Ivoire, Democratic Republic of Congo, Egypt, Ethiopia, Guinea, India, Indonesia, Madagascar, Mali, Mexico, Mozambique, Myanmar, Nepal, Niger, Nigeria, Pakistan, Philippines, Senegal, Sudan, Thailand, Venezuela, Viet Nam, Yemen, Zambia) from 1985 to 1999 (data as at year end). [Data taken from Weekly Epidemiology Record, 2000; 75: 225–232.]]
able to pick up most of the hidden cases in the community\textsuperscript{4}, although the justification for this statement remains unclear. There may be a simpler explanation, in that prevalence data 'mainly reflect changes in the intensity of programme activities, rather than variations in the transmission of the disease'.\textsuperscript{4}

It is instructive to compare figures from countries that have recently achieved elimination with those in which leprosy remains endemic. In six countries in which leprosy has recently fallen below the elimination level, the prevalence over the last decade has shown a steady decline (Figure 2). The case detection rate has remained below 0.4 cases per 10,000 population per year, and is falling. This contrasts dramatically with the situation in the more endemic regions. One explanation might be a difference in the underlying transmission mechanisms between regions.

In regions with high leprosy prevalence, the great majority of new cases are paucibacillary. However, as prevalence decreases, the proportion of multibacillary cases increases (Figure 3). Could this be evidence of inefficient case-finding in the 'eliminated' countries? An indirect indicator of failure of case detection is an increase in the rate of cases presenting with grade 2 disabilities. In endemic countries, the rate of such cases has been steadily declining, whilst in 'eliminated' countries, it is slowly increasing, again suggestive of inefficient case-finding (Figure 4). The mean proportion of cases presenting with new grade 2 disabilities is 81% higher in non-endemic as compared to endemic areas. WHO

\begin{figure}
\centering
\includegraphics[width=\textwidth]{leprosy-figure2.png}
\caption{Leprosy prevalence and case detection rate in six countries (Benin, Burkina Faso, Mexico, Pakistan, Thailand, Venezuela) that have fallen below the elimination threshold from 1985–1997 (data as at year end). \cite{weekly epidemiology record, 1998; 73: 169–176.}}
\end{figure}
accepts that an increased disability rate is evidence of ‘weak leprosy services’. These figures seem to provide some support for the accusation levelled by Fine and Warndorpf, ‘as anyone knows, an efficient way to make a disease disappear is to stop looking for it…’.

Leprosy: the future?

RE-EMERGENCE

In 1931, Henry Sigerist wrote ‘Most of the infectious diseases… have now yielded up their secrets… Many illnesses… had been completely exterminated; others had been brought largely under control…’ whilst in 1969 United States Congress heard that it was time to ‘close the book on infectious diseases’. At the beginning of the twenty-first century, this optimism has been shaken by a series of outbreaks of new, re-emerging and antimicrobial resistant infections. By the early 1980s in the United States, the decline of tuberculosis had been consistent, with eradication predicted by the year 2010. Consequently, treatment programmes, set up to ensure compliance and prevention of drug resistance, were stopped. But the impact of HIV...
and immigration on tuberculosis was not appreciated, and the result was resurgence, with many strains resistant to multiple drugs. Leprosy shares many traits with tuberculosis; could a tendency to re-emerge be one of them?

The Institute of Medicine (IOM) examined the trend of infectious disease re-emergence in 1992, and identified six influential factors.\textsuperscript{29} These are:

- Microbial adaptation
- Demographic changes
- Changes in industry and technology
- International travel
- Environmental changes
- Breakdown of public health measures

Not all of the factors identified by the IOM appear directly relevant in the case of leprosy. Probably the single greatest threat that infectious diseases pose to the Western world is microbial change and adaptation, particularly antibiotic resistance. To date, leprosy has not developed the multidrug resistance frequently displayed by \textit{M. tuberculosis}, partly due to the use of multidrug regimens within supervised programs. Such a change in \textit{M. leprae} seems

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\textbf{Figure 4.} Scatter plot of the proportion of cases presenting with Grade 2 disabilities between 1985 and 1997 (data as at year end) in endemic countries (Bangladesh, Benin, Brazil, Burkina Faso, Cambodia, Chad, Congo, Côte d’Ivoire, Democratic Republic of Congo, Egypt, Ethiopia, Guinea, India, Indonesia, Madagascar, Mali, Mexico, Mozambique, Myanmar, Nepal, Niger, Nigeria, Pakistan, Philippines, Senegal, Sudan, Thailand, Venezuela, Viet Nam, Yemen, Zambia) and in countries declared eliminated of leprosy (Benin, Burkina Faso, Mexico, Pakistan, Thailand, Venezuela). \cite{WeeklyEpidemiologyRecord}
unlikely, especially given the remarkable genetic similarity among *M. leprae* bacilli isolated across the globe.\textsuperscript{30}

Demographic change encompasses change within populations, society and behaviour. Such change might facilitate transmission and increase susceptibility to disease. To be infectious, leprosy requires a deficient T-cell response to *M. leprae*. Thus, it might be expected that factors depressing cellular immunity would predispose to an increase in incidence. Threats include HIV, malnutrition, ageing of the population and the use of immunosuppressive drugs. HIV infection results in suppression of cellular immunity, and would be expected to influence incidence and disease type in leprosy as it does in tuberculosis and leishmaniasis.\textsuperscript{\textit{31}} Studies with leprosy have been inconclusive, although there are some reports of a shift towards multibacillary disease in HIV-seropositive patients.\textsuperscript{\textit{32}}

Despite the distribution of leprosy across the ‘poverty belt’, a study in India could find no relationship between nutritional status and leprosy prevalence.\textsuperscript{\textit{33}} Factors such as increase in age of population, prevalence of diabetes, use of childcare, promiscuity and intravenous drug use, whilst instrumental in the transmission of other diseases, are probably less relevant with regards to leprosy. It seems reasonable to suggest therefore, that if socio-economic conditions that underlie demographic change improve, leprosy will become less likely to re-emerge.

The final factor that the IOM identifies as leading to emergence of infectious disease is the breakdown of public health measures. Again, it is worth remembering the example of tuberculosis.\textsuperscript{\textit{34}} It is easy to imagine that after the year 2000 leprosy treatment programs will start to be curtailed. If programmes are allowed to slacken prematurely, there may well be a resurgence of leprosy, which could be compounded by demographic change.

**ERADICATION**

Regardless of whether WHO has reached its global elimination targets, there is no pretence that the year 2000 marks the total eradication of leprosy. Even if and when the prevalence of leprosy has truly fallen below 1 per 10,000 in every region, there will still be the threat of re-emergence should leprosy control programs be downsized too far. Until *M. leprae* is eradicated, leprosy will continue to pose a threat in the core endemic areas. However, can eradication even be contemplated?

There is a very real risk that after its ‘elimination’ leprosy will be viewed as a rare disease rather than a continuing public health problem, with loss of public interest and funding. As leprosy declines in incidence, the proportion of cases in less accessible regions will increase, resulting in higher unit costs. This discordance between cost and progress may result in further pressure to withdraw funding. Furthermore, there have been significant changes in the way health services are delivered, due in part to the World Bank 1993 Development Report, which encouraged decentralization of the health sector to secure greater efficiency, and discouraged vertical programmes.\textsuperscript{\textit{35}} These changes in finance and infrastructure will seriously affect the implementation, co-ordination and funding of future campaigns.

An effective vaccine would provide a boost to the idea of an eradication programme. Discovery and implementation of a vaccine solely targeted at leprosy seems a long way off,\textsuperscript{\textit{36}} but great benefit might be obtained from a tuberculosis vaccine that imparted partial protection against leprosy. The Karonga Prevention trial in Malawi demonstrated that BCG vaccination induced 50% protection against leprosy.\textsuperscript{\textit{37}} New vaccines against tuberculosis are likely to be developed; these might confer good protection against leprosy.
At the moment there are too many unanswered questions regarding incidence, transmission, pathogenesis and diagnosis of leprosy to design an eradication campaign, and a lack of tools with which to carry it out. When these questions have been answered, we might be in a better position to consider a realistic eradication programme.

Summary

It is now the year 2001, and in many endemic regions leprosy remains a public health problem by any definition. It is clear that defining leprosy purely by prevalence side-steps some of the real issues. There is still much to do to solve the problem of leprosy. Control programmes require better tests for early diagnosis if leprosy is to be reduced much further. Treatment of the infection and of reactions is still far from ideal, whilst an effective vaccine would be valuable in high-risk regions. Research into the true incidence in each endemic area is essential, and control programs of the future will need a more detailed understanding of the transmission of *M. leprae* to permit new logical interventions.

Leprosy remains a devastating disease. Much of the damage that it inflicts is irreversible, and leads to disability and stigmatization. This is perhaps the greatest problem posed. It is easy to dwell on the successes of the elimination campaign, so diverting attention from those populations of ‘cured’ patients who still suffer from the consequences of infection. Leprosy should be regarded as a problem unsolved so long as patients continue to present with disabilities. WHO has carried out a highly successful campaign in reducing the prevalence of leprosy, and this needs to be acknowledged, but what is happening to the incidence in core endemic areas? Maintaining this success, however, may be an even greater struggle if funding is withdrawn and vertical programmes are absorbed into national health structures.

We must take heed of the historian George Santayana, ‘those who cannot remember the past are condemned to repeat it’.

We should take the example of tuberculosis as a warning of the dangers of ignoring a disease before it has been fully controlled, and strive to continue the leprosy elimination programmes until there are no new cases presenting with disability. The World Health Organisation has shown that leprosy is an eminently treatable disease, and has prepared the ground. The leprosy elimination campaigns truly are ‘at a height... ready to decline’. Can it be that this is the chance to take leprosy ‘at the flood’? If so, perhaps an extension of the elimination programs beyond the year 2001 would indeed ‘lead to fortune’.

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References


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