Evolution of *Mycobacterium leprae* towards reduced virulence

Leprosy has been a dreaded disease for at least a few thousand years[1]. After the Dapsone treatment became available in the 1940s (ref. 2) and further, the MDT regime came into practice in the early 1980s (refs 2–4), there has been a substantial reduction in the prevalence of leprosy almost throughout the world[2,3,5,6]. This is not too surprising given the effectiveness of MDT. But it is not only the incidence that is seen changing. A curious anecdote generally noted by all leprosy clinicians is that the 'face of leprosy' is changing. Not only is the proportion of patients with deformities going down, the textbook leonine faces are much less infrequently seen now. While an obvious factor can be early detection of cases and treatment, more subtle processes can lead to reduction in virulence of *Mycobacterium leprae*. Evolutionary changes in the virulence of the pathogen can take place over just a few decades and can significantly affect the clinical as well as epide-

miological picture[7]. Here we suggest an evolutionary explanation for the change in the clinical picture of leprosy. We further discuss the hypothesis in the light of available epidemiological data and suggest more testable predictions of the hypothesis.

The different forms of leprosy are at least partially due to differences in the immune state and genetic background of individuals. However, it is also likely that there are variants of *M. leprae* with different virulence. The hypothesis assumes that variants with high virulence are more likely to cause even more severe and infectious forms of leprosy. Due to social stigma and ignorance, the milder cases are less likely to come forward for treatment. The severe cases, on the other hand, will almost certainly undergo treatment. As a result, MDT will select against the more virulent variants. The milder strains would then enjoy a competitive advantage over the virulent ones, and therefore evolution under the influence of MDT would drive *M. leprae* towards reduced virulence.

The time trends available in published literature show that although there is considerable variation in the time trend in different areas, the proportion of lepromatous (LL) or multibacillary (MB) cases is generally going down[2,4,8–12]. Figure 1 shows that out of the ten differential time trends in lepromatous or MB leprosy, seven have a significant negative trend, two do not have any significant trend and only one has a significant upward trend. The clinical picture is therefore compatible with the hypothesis. The downward trends have been interpreted as being clinical and epidemiological effects of the treatment but not as evolutionary effects of the treatment. The reduction in deformities can be the sole effect of early detection and treatment. Increasing awareness can result in greater proportion of milder cases volunteering for treatment and therefore the proportion of Paucibacillary (PB) cases in clinical records can go up. The initial decrease in the percentage of lepromatous cases can be attributed to 'backlog clearance'[12]. These explanations, however, cannot account for the consistent trend seen among the newly detected cases in population surveys over a prolonged time span[2,11]. Specifically, trends in the young-age class also have been consistently negative[2], suggesting that an evolutionary cause is likely in addition to a clinical one.

The evolutionary hypothesis makes a number of subtle assumptions that need justification and empirical or epidemiological testing. If different variants are partially responsible for the different clinical pictures, it could be shown that the contacts of lepromatous patients are more likely to develop lepromatous type[13] and so on. This question has not been seriously addressed, but an apparent tendency for the clinical picture to mimic the source is seen in some published data[14–16]. The pattern needs to be tested rigorously. The earlier belief that only LL or MB patients are infectious no longer exists, and BB or PB leprosy is also shown to be infectious[17–19]. The clinical course of leprosy is self-curing at times[20,21]. The milder forms are more likely to be self-healing, although lepromatous cases have also shown this phenomenon[21]. The benign self-curing cases are important because they can go undetected and spread the milder variant effectively.

The assumption that milder cases more often go undetected and therefore untreated, has substantial evidence. A comparison of clinical record and intensive population surveys in southern India reveals this. The proportion of MB cases recorded before the survey was substantially greater than that recorded after the survey[5], indicating that a large proportion of PB cases did not volunteer for treatment and only intensive surveys could detect them.

What is so peculiar about leprosy? Antimicrobial treatments are available for a number of infectious agents. But there is hardly any evidence of reduced virulence in response to antimicrobial treatment. The social perception of leprosy makes it different from the evolutionary point of view. The difference between the true epidemiological picture and the clinical picture, as apparent in southern India[5], is due to the social factors that prevent a patient from coming forward for treatment voluntarily, unless the severity of symptoms compel. In most of the places, leprosy patients are not treated in general wards. There are separate leprosy-care units. For a patient,

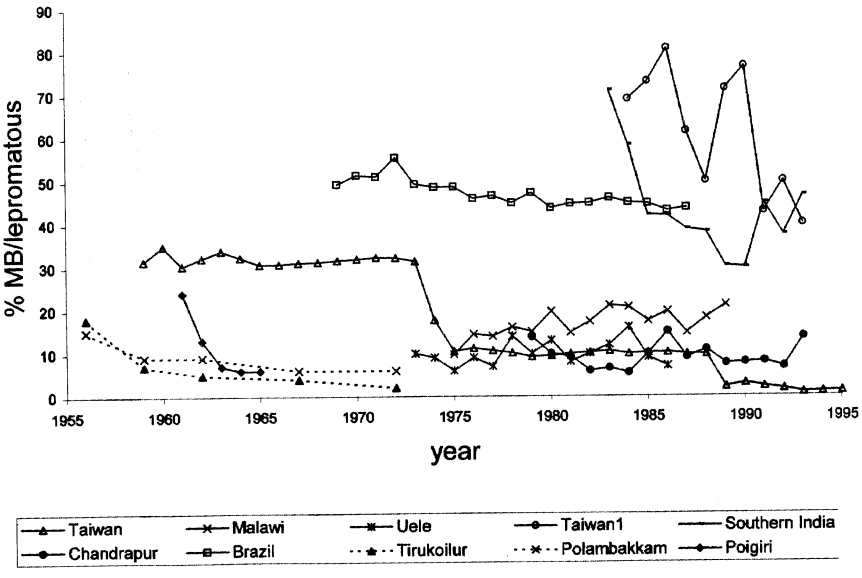

Figure 1. Time trends in the proportion of lepromatous or MB in newly detected cases. Data sets where a consistent survey methodology was used are chosen. Significance of the trend is tested using non-parametric correlation. In the Pune and Chandrapur data, the working definition of MB was changed in the mid-1990s. Therefore the data are terminated at 1993. Interestingly, most of the survey data show significant negative trend, whereas clinical data tend to have non-significant or positive trend.

MB in Taiwan. Survey data (cumulative and new all age and pediatric age patients with leprosy)[2], $r = -0.609$, $P < 0.05$; MB in Malawi. Clinical data[4], $r = 0.686$, $P < 0.01$; MB in Uele. Clinical data[8], $r = 0.212$, NS; MB in Taiwan. Survey data[2], $r = -0.902$, $P < 0.01$; MB in Pune. Clinical data Jogaikar *et al.* (pers. commun), $r = -0.399$, NS; MB in Chandrapur. Survey data (pers. commun), $r = 0.141$, NS; Lepromatous cases in Tirukoilur[9], $r = -0.99$, $P < 0.01$; Lepromatous cases in Polambakkam. Survey data[10], $r = -1$, $P < 0.05$; Lepromatous cases in Brazil[11], $r = -0.881$, $P < 0.01$; Lepromatous cases in Poigiri[12], $r = -0.974$, $P < 0.05$.

going to a leprosy centre amounts to advertizing the disease. This leads to reluctance that combined with effective drug treatment can result into differential chemotherapy against different strains of the pathogen. The differential treatment would result in a rapid evolution towards loss of virulence. If, on the other hand, the milder and the virulent variants have the same probability of facing drug treatment, the more virulent forms would gain a selective advantage owing to their rapid proliferation in a host body.

It is important to test this hypothesis rigorously in the context of leprosy. The relevance of the hypothesis, however, is much wider. If we accept that the strategies employed in the treatment of patients influence the evolution of virulence of the pathogen in some way, we can think of 'virulence management' of an infectious agent evolving in a host population[7], that would allow us better long-term health planning.

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ANAGHA U. KALE
SOMEDATTA CHANDA
MILIND G. WATVE*

Department of Microbiology,
Abasaheb Garware College,
Karve Road,
Pune 411 004, India
**For correspondence*
e-mail: watve@vsnl.com