NEW LIGHT ON THE SPREAD OF LEPROSY

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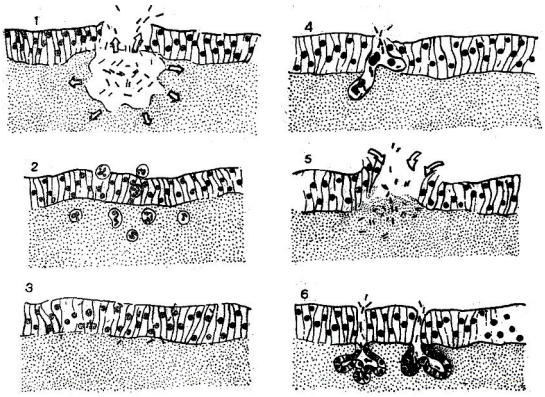
Research in the last few years indicates that, contrary to popular belief, leprosy is most readily transmitted through the nose, where it forms a seat of infection long before other symptoms have become noticeable. The correct explanation was postulated by 19th century doctors in clearly documented observations, which apparently no one followed up.

Leprosy is one of the major diseases in the world today, affecting well over 10 million patients, mainly in the developing countries. It is an infectious disease caused by a bacterium, *Mycobacterium leprae,* related to the tubercle bacillus. Leprosy, like tuberculosis and the other major infectious diseases of man, was recognised as having a bacteriological etiology in the latter part of the last century. But advances in our basic knowledge of infectious diseases which have led to successful methods for their control and treatment have, unfortunately, not helped with leprosy.

The reason it has lagged behind is that, unlike the other causative bacteria, *M. leprae* failed to grow in the test tube (*in vitro*). But while all attempts to cultivate *M. leprae in vitro* have failed, in 1960 Dr. Shepard showed that *M. leprae* recovered from tissues of patients with leprosy multiplied when inoculated into the foot-pads of mice. This mouse foot-pad technique provided for the first time a laboratory method for studying the bacteriology of *M. leprae* and in the last 14 years it has been extensively exploited as a substitute for *in vitro* cultivation of the other major infectious agents of man. In this relatively short period, the mouse foot-pad technique has enabled our knowledge of leprosy to catch up with that of the other infectious diseases.



In many of these studies the mouse foot-pad infection has been used simply as a substitute for *in vitro* cultivation, but it does have the added advantage providing a laboratory model for elucidating the disease process. It is on the basis of these combined features of the infection in mice that the Medical Research Council, at the National Institute for Medical Research, has attempted to elucidate the mode of transmission in leprosy.

Previous Clinical Concepts

There are broadly speaking two forms of leprosy, the tuberculoid and the lepromatous, and while in both there are skin manifestations and nerve damage resulting from invasion of the tissues by *M. leprae,* there are very many more bacteria in lepromatous than in tuberculoid leprosy. The most heavily infected sites in patients with lepromatous leprosy are the skin, nose and upper respiratory tract so it is from these sites that excretion of bacilli is to be expected. Indeed, in the late 19th century Sticker and Schaffer demonstrated large numbers of bacilli in nasal discharges from leprosy patients and postulated that leprosy was transmitted by bacilli from the nose.

In spite of these early and clearly documented observations, they seem to have been forgotten, since 'prolonged and intimate skin-to-skin contact' has for many years now been favoured as the most likely route of transmission. This probably derived largely from the obvious cutaneous clinical signs of the disease, despite the paucity of bacilli found on the skin surface.

However, from the clinical side interest in the nose and nasal secretions as sources of infection was reawakened in 1970 by Dr. J.C. Pedley working then in Nepal. He convincingly demonstrated many bacilli in stained smears of nasal discharges from patients with lepromatious leprosy, but insignificant numbers of bacilli on the skin surface.

Leprosy in the Mouse

At the time of Pedley's observations in man, our systematic studies at the National Institute for Medical Research on the evolution of infections with *M. leprae* in the mouse had pinpointed the nose as being a site of particular interest. Thus, the nose appeared to be a favoured site for the localisation and multiplication of *M. leprae* when the infection spread from a locally inoculated foot-pad. The nose was more frequently and more heavily infected than any other tissue site and bacilli were discharged in secretions from the nose, but not discharged from skin sites.

On the basis of these observations in the mouse and Pedley's observations in man a multi-disciplinary project was undertaken to reappraise the clinical, bacteriological and pathological aspects of the nose in leprosy patients, applying techniques which would be likely to determine the importance of nasal infection in the transmission of leprosy.

Average annual age and sex specific attack rates for tuberculosis leprosy in family contacts, South India

	Male		Female	
Age	Tuberculosis	Leprosy	Tuberculosis	Leprosy
0-4	4.0	4.4	3.8	5.6
5-14	1.8	7.3	1.6	2.1

*Survival of M. leprae in dried nasal secretions after discharge

Number of nasal secretions tested	Time after discharge (days)	Survival of M. laprae*
3	0	100
3	1.0	100
2	1.75	10
2	3.0	0
1	7.0	1**
1	10.0	0

Allowed to dry in the dark at a mean temperature of 20.6°C and mean humidity of 43.7per cent

*Assessed as infectivity in the foot-pads of mice

** Growth of *M. leprae* obtained in only 2 of 12 foot-pads

Thus the bacteriological studies were of prime importance and for these the mouse foot-pad infection was fully exploited.

Clinical and Experimental Reappraisal

The essential clinical link for this study was based on Dr. T.F. Davey at Victoria Hospital, Dichpalli, India, who in 1972 had just completed an extensive study on the clinical and bacteriological aspects of nasal discharges of 936 leprosy patients, which he had undertaken because of Pedley's observations. Davey's data fully confirmed Pedley's findings. In particular, his detailed and meticulous records showed that bacilli could be present in large numbers in nasal secretions when, because of the gross appearance of the patients, skin lesions were not obvious and could easily be missed by routine examination. And, on questioning, patients were found to be aware of unpleasant nasal symptoms, described generally 'sticky noses', and of the frequent presence of blood in their nasal discharges.

In collaboration with Davey, single or 24- hour collections of nasal discharges were taken from a representative sample of patients with active and early forms of lepromatous leprosy. Detailed quantitative studies and biological identification of bacilli from these samples were undertaken in London using the mouse foot-pad technique. These showed that such patients were discharging on average 10^7 viable bacilli daily and that the organisms had the characteristics of *M. leprae.*

Advantage was also taken of the opportunity to study the survival of *M. leprae* in these natural nasal secretions when allowed to dry in the exterior environment, for example, on stone surfaces or in handkerchiefs. Survival was assessed by inoculation of these dried specimens into mice. The studies showed that *M. leprae* was fully infectious for mice one day after drying, some 10 per cent were still infectious at approximately two days, while in one such specimen approximately one per cent of bacilli was still infectious at seven days.

These studies established for the first time that *M. leprae* is relatively robust and can survive drying, in the dark, for several days in natural nasal secretions.

Near the surface

In addition to the bacteriological studies, detailed clinical and histological observations of the nose were undertaken in collaboration with Davey and Mr. R.P.E. Barton, an ear, nose and throat specialist, on 36 patients with early lepromatous leprosy. From each of these patients 3-5 small pieces of tissue were taken from nose by Mr. Barton. Representative samples of these tissues were submitted for bacteriological examination and for histological examination by Professor A.G.M. Weddell and Dr. A.C. McDougall at the Department of Human Anatomy, Oxford.

Quantitative bacteriological studies on these tissues as compared with pieces of skin from the same patient showed that the nasal tissues were more heavily infected and contained a higher proportion of viable *M. leprae* than the skin. The histological studies confirmed this, but even more important were, the finding that the leprosy

infection in the nose was only just beneath the surface mucosa, which was often invaded or eroded. Bacilli were frequently present in the cells of mucus glands and ducts. Small blood vessels reached up to the denuded surface of the nasal mucosa and these vessels were dilated and frequently undergoing degeneration.

These histological observations clearly demonstrated the ease with which *M. leprae* could reach the surface of the nasal mucosa and be discharged into the exterior.

Such a multitude of escape mechanism of bacilli from the nose fully explained the large numbers of *M. leprae* present in nasal secretions. The histological situations in the nose, therefore, were in complete contrast with that in the skin, where the leprosy infection was deeply situated and not in juxtaposition with the skin surface. In fact the skin infection was clearly separated from the surface by a bacillary free zone-referred to as the 'clear zone'.

A particular feature of the histology of the nasal tissues was the invasion of bacilli into the lining cells of the blood vessels and the presence of very large numbers of bacilli free within the lumina of the vessels. Because it was impossible to obtain samples of blood from these vessels, an attempt was made to estimate the number of *M. leprae* present by measuring the area of these tissue-sections and their thickness. On the basis of these assessments it was shown that approximately 10^9 bacilli/ml blood were present.

Implications

These specially designed multi-disciplinary studies not only add considerably to our knowledge of nasal infections in patients with leprosy but provide very strong evidence in support of the nose as the primary site by which leprosy bacilli are discharged to the exterior, and therefore the importance of the nose in the transmission of the disease.

Thus, for the first time bacilli discharged from the nose have been established *M. leprae* by their behaviour when inoculated into mice. Moreover, the number of *M. leprae* discharged daily from the nose of lepromatous patients in comparable to the number of tubercle bacilli discharged in the sputum of patients with open and active tuberculosis. Of still greater significance is the evidence that *M. leprae* are relatively robust and can remain viable in dried nasal secretions for several days. Detailed histological studies of nasal tissues clearly show how readily bacilli can reach the surface and be discharged from the nose as compared with infections in the skin.

Together, these findings begin to build up a composite picture for the possible mode of spread of leprosy that has not hitherto been available, at least on the basis of scientific evidence. For not only do they suggest a source of infection, they also offer a possible explanation for the apparent failure of the chemotherapy used for overt disease to help with primary prevention of leprosy in endemic areas. The early lepromatous patient, shedding millions of *M. leprae* from nasal lesions, may infect many people in his family or in his environment before he is diagnosed; and his subsequent treatment may be largely irrelevant in terms of his ability to spread the disease further.

This is a pessimistic picture, but it is important to recall that patients at an early stage have symptoms of nasal blockage and bloodstained

nasal discharges. Therefore it may be possible to identify cases earlier by stressing the importance of these symptoms.

Spread involves not only a source of infection but also a portal of entry. Here analogies with tuberculosis may be helpful. Clearly, *M. leprae* could be spread by sneezing, coughing, spitting and unhygienic nose-cleaning methods—so in many respects by way of droplets, as in tuberculosis. In this context, the similarities in bacterial loads from nasal secretions and sputum of patients with lepromatous leprosy and open tuberculosis are of considerable interest.

Clearly, the portal of entry could still be the skin; but, equally, *M. leprae*-laden particles could also be inhaled or swallowed. It is therefore of interest that the attack rates for the two diseases in household contacts are of the same general order, especially in the young. These comparisons prove nothing, but they do suggest—and really for the first time—scientific ways of studying leprosy transmission.

Back to the Bloodstream

An unexpected but very significant finding from the histology of nasal tissues from leprosy patients was the very high concentration of bacilli free within the lumina of nasal blood vessels. As I have said, calculations from these tissues indicated an order of 10^2 bacilli/ml of blood.

This tremendous difference between the concentrations of bacilli within vessels of the nose compared with the general circulation is again of particular importance. It could be that the special vasculature of the nose is acting as a 'backwater' in which bacilli from the general circulation gravitate. However, bearing in mind the particularly high concentration of *M. leprae* in nasal tissues, plus the evidence from the mouse that the nasal tissues are a favourable site for the multiplication of leprosy bacilli, it seems more likely that the nose is also a site from which bacilli are readily shed into the bloodstream.

If this is true then nasal infections in leprosy are of the greatest importance since they represent not only a site from which bacilli reach the exterior and lead to the transmission of leprosy but also a particularly favourable site from which bacilli are fed back into the rest of the body.

So the application of sophisticated biomedical techniques now implicates the nose in elucidating many of the mysteries surrounding the pathogenesis and transmission of leprosy. But those who have diligently applied these techniques must admit that this is what our forefathers hypothesized in the late nineteenth century.

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