CONTENTS

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Editorials

INDETERMINATE LEPROSY

"Indeterminate Leprosy" is a subject of some confusion. The term dates back to the Havana Congress (1948) at which indeterminate was designated as a rather indistinct clinical group, with macules or nerve involvement, of variable resistance and uncertain evolution. The histology showed simple inflammation and bacilli, if present, were few. The only other groups were tuberculoid and lepromatous. The Madrid Congress (1953) introduced the borderline group, but did not modify significantly the definition of indeterminate. No mention was made of its histology.

The usage of the term indeterminate has been somewhat confused in practice by the fact that the official classification of leprosy is primarily clinical and the wish of many Indian workers to designate maculo-anaesthetic as a separate group. Thus Fernandez (1953) thought that for reasons of practical convenience all macular patients should be classified as indeterminate, while Dharmendra in stressing the differentiation of indeterminate and maculo-anaesthetic admitted that the distinction could be difficult.

Despite some confusion there is no doubt that "indeterminate" has usually been applied to early lesions, early that is in terms of evolution if not in years, which are sometimes self healing, and that as the name implies they are called indeterminate because they have not yet reached the stage when they can be called anything else. Browne (1966) uses the term in this sense, of a case that cannot be "determined", and so do Ridley and Jopling (1966). One wonders if that is what was intended by the Congresses of Havana and Madrid. The primarily clinical definition and the presumed intention that the term was to be applied to immature and otherwise unclassifiable lesions are probably consistent with each other if classification is based exclusively on clinical evidence. But other sources of evidence are being utilized on an increasingly wide scale, and under these circumstances the two meanings of the term are not necessarily consistent, though usually they are. In this, as in other aspects of classification, there is a possible conflict of interest between workers in rural areas and others. If there are occasions when it is still useful to have a group to which macular patients can be assigned without resort to other considerations it is difficult to see why it could not be labelled macular anaesthetic or macular non-anaesthetic (with appropriate clinical definitions). To those who accept that the spectrum of leprosy is essentially a matter of immunology, surely almost everybody, and wish to classify it accordingly, there is need for a more flexible group to which to assign patients who, on all the evidence available, are still unclassifiable within the spectrum. It would seem a pity if this group, or more correctly non-group, could not be called by the time honoured "indeterminate" which so aptly describes it.

Used in this sense (as it will be throughout the remainder of this paper),

indeterminate is a relative term. On the Havana classification, with a two group spectrum, almost every patient with post-primary lesions would be readily identifiable as tuberculoid or lepromatous. If one uses a spectrum with five groups, or possibly even more, one might be unable to assign the patient exactly to any of the groups and to this extent he would be indeterminate, though one could still say that he was broadly tuberculoid or lepromatous. A patient might be classifiable as BT clinically though histologically indeterminate. In this case if the clinical findings were definite the classification would be BT. A case that was histologically indeterminate after the examination of two sections might become determinate after the examination of serial sections, or following a second biopsy.

The histology of indeterminate leprosy is that of a relatively simple non-specific inflammation and the criteria by which it is defined are those by which early leprosy is diagnosed. This involves mainly the demonstration of nerve involvement, or the detection of acid-fast bacilli in nerve or certain other situations such as the sub-epidermal zone or arrectores pilorum muscles. The histology has been described in greatest detail by Bungeler (1943). Recent papers which discuss the current problem of diagnosis are those of Binford (1971) and Nayer, Narayanan and Job (1972).

Histologically, leprosy ceases to be indeterminate and becomes classifiable with reasonable accuracy when a granuloma develops. This may be of the epithelioid cell type, usually first seen in nerves or sub-epidermal zone, or it may be a macrophage granuloma, loaded with bacilli, which usually makes its first appearance in a peri-neural or peri-vascular situation (Ridley, 1973). The problem of early classification, therefore, is to find a granuloma which, being very small, often requires the examination of serial sections. Unless a very careful search is made it is quite likely that early leprosy will become determinate to the clinician sooner than the histologist (Myrvang *et al.*, 1973). On the other hand once the granuloma has developed the histology will usually give a more accurate and up-to-date indication of classification than the clinical picture since the latter is slower to change when there is an immunological shift.

With regression following successful prolonged therapy the granulomata eventually resolve and the histology reverts to indeterminate. Clinically it is likely that the stigmata will remain until healing is complete and the indeterminate picture will not recur.

In short, indeterminate should be regarded as a necessary term of convenience. The characteristics of indeterminate patients are fairly homogenous and can be described, but as a group indeterminate can only be defined in negative terms.

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D.S. Ridley

THE NOSE IN LEPROSY: STEPS TO A BETTER UNDERSTANDING

The face we present to the world matters a great deal to most people. Its most prominent feature, the nose, is a focal point of emotional feelings, whether of family pride or of private resentment at one's genetic inheritance. Because personal attractiveness is at stake, diseases which may disfigure the nose are inevitably charged with high emotional content, and none more so than leprosy. The cosmetic problems which confront the sufferer from lepromatous leprosy are severe enough. Unfortunately the nasal deformity which he dreads is distinctive, a stigma which he cannot conceal, and which betrays to the world the disease from which he is suffering. To the patient, the involvement of his nose is a profound cause of anxiety, and one which merits far more attention than it has often received in the past.

The early leprologists were in no doubt as to the importance of the nose in leprosy, though their concern was not so much with the psychology of the patient as with the acid-fast bacilli they discovered in his nose. Here, their observations were of great relevance and importance. The universality of nasal involvement in what we now call lepromatous leprosy was widely recognised. Several leprologists observed that the nasal mucosa could be infected *very early in the disease.* Leloir (1886), Goldschmidt (1891), Glück (1897) and Jeanselme and Laurens (1897) all made this observation. Nasal involvement was associated with a nasal discharge in which acid-fast bacilli could be found, often in large numbers. Jeanselme (1934*a*) expresses this succinctly as follows. "Le muco-pus . . . contient souvent d'innombrables bacilles agglutinés en boules epineuses. Ce sign assure donc le diagnostic dès les premiere phases de l'évolution morbide".

The severity of nasal involvement as compared with skin and internal organs was also recognised. Cohn (1890), Glück, and Breda, are all quoted by Klingmuller (1930). Schäffer (1898) demonstrated that large numbers of acid-fast bacilli could be projected in coughing, sneezing, and in normal speech, in one patient 185,000 bacilli to a distance of 1.5 m in 10 min. There was of course no proof that the bacilli concerned were in fact *Myco. leprae,* neither was it possible to check their viability. Questions about this were nevertheless raised by Jeanselme (1934*b*).

When some workers, notably Goldschmidt (1891), Sticker (1897) and Schäffer (1898), proceeded to propose the nasal mucosa as the site of primary infection in leprosy, they ran into difficulties. Up till this point, the study of leprosy had largely been confined to western Europe, and among patients in whom the lepromatous form predominated. With the development of research in the Philippines, India, and Africa, the non-lepromatous forms of the disease came into

prominence, and tuberculoid, and later, indeterminate leprosy were recognised. Among these, the concept of a primary involvement of the nasal mucosa could not be sustantiated, and for this and other reasons interest in the nose declined, with serious detriment both to patients and to the progress of knowledge. Nevertheless, Rogers and Muir (1946) stated, "In some cases, where there are no external signs of disease visible, bacilli may be found in the nasal discharge. Such patients are a special danger to the community, as they may spread the disease without knowing that they are suffering from it." Prabhu (1946) also drew attention to the early involvement of the nasal mucosa in lepromatous leprosy.

In 1964, Cochrane stated, "The early changes in the nose have never been thoroughly investigated". It is instructive to consider some of the reasons for the neglect of the nose in leprology during the past 40 years.

First is undoubtedly the low priority given to the examination of the nose at many centres. The earlier leprologists, concerned mainly with relatively few patients in a sophisticated European setting, were able to undertake an exhaustive examination with the help of appropriate consultants. A generation later, the centre of concern in leprosy had shifted to the developing countries, where a comparatively small body of leprologists found themselves confronted with large numbers of patients, major administrative problems, and the need to organise leprosy control activities, all too often in conditions of professional isolation. Only in exceptional circumstances was a specialist ophthalmologist or otorhinologist likely to be within reach of the centres where the relevant leprosy patients could be found in significant numbers. In such circumstances, as the writer knows only too well, priority had to be given to the most pressing issues, and as, at any rate in the pre-sulphone days, little could be done to help the patient where his nose and eyes were concerned, these aspects of leprology suffered from neglect. At most centres in Africa and India, rhinoscopy was not undertaken as routine, reliance on the situation in the nose being placed chiefly on the results of nasal smears and the subjective statements of patients.

Unless undertaken as routine, anterior rhinoscopy can lend itself to misleading conclusions. In the normal nose, the inferior turbinate, protruding into the lumen, easily catches the eye, and in very early lepromatous leprosy pathological swelling, discolouration and a granular or nodular appearance of this structure rivets attention. As the disease progresses, though still may be at an early stage, the inferior turbinate shrinks, and may be eroded and almost disappear from view, but by this time the septum is certain to be involved, and may be ulcerated. This dramatic appearance instantly catches the eye of the examiner, and it is easy to conclude that it is the septum which is the focal point of the infection. The theory of a primary infection of the nasal septum, induced by trauma, is thus readily understood.

A second source or error is the fallacy, engendered by the results of nasal smears, that leprosy in the nose simply reflects the general situation elsewhere in the body, with the disease in the nose having no distinctive features, and advancing parallel with the advance of the disease in the body as a whole. Thus Cochrane (1947) reporting on patients at Chingleput, found positive nasal smears in 36.59% of L1 (early) cases, 85.88% of L2 (established) cases, and 100% of L3 (late) cases of lepromatous leprosy. Inevitably with such findings the belief gained credence that nasal smears are of only secondary importance, in that the information gained could have been gathered more easily, and with less discomfort to the patient, from routine skin smears.

Cochrane's findings were based on nasal smears. While Muir (1938) mentions the inferior turbinate as a suitable site for smearing, all other authorities advise the nasal septum, and the anterior segment of it, as is made clear, with one exception, by the choice of instruments advocated, *vide* Cochrane (1964), Wade (1935), Goodwin (1967) and Dharmendra (1967) who mentions a point ½ in from the orifice as suitable. The one exception is Browne (1965) whose suggestion of a sharpened piece of bicycle spoke, does provide access to deeper levels. Davey and Barton (1973) in a study of 100 patients, have shown that of all areas readily available to the examiner, the anterior segment of the septum is the one least likely to provide a reliable sample of the bacteriological situation in the nose, especially in early cases. Smears from this area in such cases frequently will not yield results significantly different from those found in the skin, whereas had the inferior turbinate been utilised, or the septum itself been examined at a deeper level, very different results would frequently have been obtained. Even with the use of routine anterior septal smears Davey (1959*a, b*) and Browne (1965) did observe that under chemotherapy the clearance of acid-fast material from the nose sometimes took longer than from the skin, and in relapse the nose could yield positive findings at an early stage. Some unusual features regarding leprosy in the nose could have been suspected from these findings.

The technique of nasal smearing yields material scraped from not more than 1 cm^2 of the nasal mucosa, out of a total area of 70 cm^2 and over liable to involvement in leprosy. The earlier procedure of wiping the interior of the nasal cavity with a pledget of cotton wool was a procedure better calculated to reveal *Myco. leprae* in their true numbers, but in general the far simpler procedure of examining the nasal discharge, which is drawn from this entire affected area, is greatly to be preferred. This procedure, utilised by the early leprologists, suffered decades of neglect, and Pedley deserves the gratitude of leprologists and patients alike, for resurrecting it. Davey and Rees, in this issue of the *Leprosy Review,* both demonstrate the frequency of highly bacilliferous nasal discharges in very early lepromatous leprosy, and give quantitative values for the numbers of bacilli involved. The only situations in which a nasal smear could have advantage over a specimen of nasal discharge are (a) in the very temporary phase when a very early nasal infection has not yet reached the stage of producing an inflammatory exudate, a situation only arising as the lepromatous type of the disease is just developing, (b) in a patient whose nasal discharge has dried up as a result of chemotherapy and (c) in the late stages when with gross secondary infection, especially in atrophic rhinitis, a satisfactory specimen of the discharge may be difficult to obtain.

A third reason for delegating the examination of the nose to a secondary position was the fear, applicable to all techniques, that preparations could be contaminated with saprophytic acid-fast organisms, and spurious positive findings result. A serious misconception arises here. The specific nasal discharge in leprosy is not a mucoid discharge in which *Myco. leprae* may be floating. It is an inflammatory exudate derived from an intensely lepromatous granuloma within the nasal mucosa, *the exudate from which is of high cell content,* consisting of macrophages, usually in very large numbers, easily identified under the microscope, and containing intra-cellular acid-fast bacilli, usually displaying globus formation in all its stages. This is a finding specific for leprosy, and doubt could only arise in the very earliest stages, when individual bacilli, escaping from the involved epithelium of mucous glands could be found in a specimen on their

own. In several hundreds of examinations the writer has never witnessed this appearance without at the same time encountering at least one focus of macrophages in the specimen where the ingestion of acid-fast bacilli was evident. In practice therefore, saprophytic acid-fast bacilli pose no significant problem. Bacteriological examination of the nose may be highly revealing, and is indicated in every case of suspected lepromatous leprosy.

A fourth problem arises from the frequent reticence of patients to tell the truth regarding their noses. In the writer's experience in India, at any rate, the psychological trauma resulting from nasal infection was so profound that at a first consultation patients with obvious nasal problems said nothing about them, and when questioned, would admit to symptoms, but be vague as to their date of onset. It was only later, when hope was beginning to replace despair, as a result of chemotherapy and care of the nose, that patients felt able to tell the full story of their sickness, and it was quite remarkable how frequently nasal symptoms figured among the earliest signs of it, with no leading questions being asked.

More recently, the widespread availability of dapsone has led to further confusion. Because they have come for treatment, patients attending at hospitals and clinics will rarely admit that they have already taken some dapsone tablets on their own. Many a patient, presenting with what looks like active lepromatous leprosy, with skin smears highly positive, and a M.I. of up to 5 or even 10, may be unable to offer a specimen of nasal discharge, or if he can, a discharge no more bacilliferous than skin, when in fact he has taken some dapsone tablets for a few weeks. Because the nasal infection responds so quickly to dapsone, this period may have been quite sufficient for bacteriological improvement in the nose to have masked its significance.

The nose in lepromatous leprosy thus presents many traps for the unwary.

A resurgence of interest in the nose in leprosy during the last three years owed its origin to the application by Shepard (1961) of quantitative and cultivation techniques to nasal qashings from patients with lepromatous leprosy. The studies of Goodwin (1967), Pedley (1970,1973*a, b*), Davey and Rees (1973,1974), Davey and Barton (1973), Barton *et al.,* (1973), Barton (1974), McDougall *et al.,* (1974) in the human subject, and of McDougall, Rees and Weddell (1973) and Rees, McDougall and Weddell (1974) in the mouse, and Kirchheimer (1973) in the armadillo, all point to a single conclusion. *In lepromatous leprosy, in man, in the immunologically suppressed mouse, and in the armadillo, the nasal mucosa is a site of election for* Myco. leprae *of particular interest and significance.*

Progress in this aspect of leprology has occurred solely because leprologist, bacteriologist, otorhinologist and pathologist have together brought their distinctive experience and skills to bear on a problem of common interest and concern. This issue of the Journal includes the studies of McDougall, Rees and Weddell on the mouse, the clinical and bacteriological study of Davey and Rees, and a clinical study by Barton, from the standpoint of an otorhinologist.

The predilection of *Myco. leprae* for the nasal mucosa has important consequences.

(a) It is inconceivable that the discharge of millions of viable *Myco. leprae* from the nose daily has no relation to the transmission of leprosy. The enormous numbers involved are now well documented. Rees (Davey and Rees, 1973) demonstrated the presence of viable *Myco. leprae* in 100% of 31 specimens examined by the mouse footpad technique. Holmes and Hilson (1973) offered convincing evidence that the morphological index is an underestimate rather than an overestimate of the proportion of viable *Myco. leprae* in a laboratory

preparation, and a figure of 3.1×10^7 viable bacilli for fourteen 24 h specimens and 1.9×10^7 viable bacilli for 17 single specimens of nasal discharge 30 h and more after production of the specimen, by Rees on the basis of the M.I. is valid. As Browne (1973) put it, "It is the abundant mucoid discharge from the hyperaemic nasal mucosa that is probably the vehicle for the exit of the vast majority of *Myco.leprae* leaving the body of the infected host."

(b) The persistence of viable bacilli in nasal discharge kept in the dark, and dessicated in the atmosphere, has also been demonstrated by Rees, in 3 specimens up to 2 days, and in 1 specimen up to 7 days (Rees and Davey, 1973). While sunlight may be expected rapidly to destroy bacilli discharged onto the open ground, dust and fomites in dark houses and insanitary conditions may obviously harbour living bacilli long enough for these to be a source of infection to others. A rational explanation can now be offered for the frequent infections in leprosy which arise outside the circle of close and intimate physical contact.

(c) The very early and serious involvement of the anterior part of the inferior turbinate must once again arouse suspicion as to whether in persons lacking resistance to *Myco. leprae,* inhalation is a possible means of infection. Projecting into the main stream of inhaled air, moist, and constantly cooled by the air passing over it, the anterior end of the inferior turbinate is the first structure in the nose likely to be encountered by inhaled microscopical material, and obviously provides conditions congenial to *Myco. leprae.* Now that we know that the bacillus can survive for some days in dust, what was thought to be a closed subject is once again wide open. Findings among children of patients at Culion long ago do not negate the possibility of infection by inhalation, *if the constant association between nasal involvement and the gross immunological defect found in lepromatous leprosy is appreciated.* While no child was found to show a primary nasal infection (i.e. a positive anterior septal smear), 13 out of 24 children with primary skin lesions did produce positive nasal smears. Nolasco and Lara (1949), reporting on the histological findings in "primary" lesions in 14 such children in Culion, found clear signs of an immunological response in 11, leaving 3 only as potential future lepromatous cases, a proportion far less than the proportion of children with positive nasal findings in the earlier series. If lack of the capacity for immunological response is the key to intranasal infection, the Culion findings certainly do not invalidate the possibility of a primary lesion on the inferior turbinate in such circumstances.

(d) Whether future study will negative or confirm the existence of infection in leprosy by inhalation, the very early appearance and special character of the infection in the nose could well have a sinister relationship to the development and spread of the disease. The frequent findings of a higher B.I. and M.I. in the nose as compared with skin must have meaning. The heavy involvement of the endothelium of blood vessels in the nose noted by Harman (Pedley, 1973*a*) and McDougall (Barton *et al.,* 1973), means that the nose is an important contributor to the continuous bacillaemia which is characteristic of untreated lepromatous leprosy, and described in detail by Drutz, Chen and Wen-Hsiang (1972). Could the nose play a significant role in the degeneration of the borderline to the lepromatous type of disease? Evidence exists that it could. Dharmendra and Sen (1946) report on a patient with borderline leprosy with negative skin smears who nevertheless had a gross lesion in the nose loaded with *Myco leprae.* The 6 patients mentioned by Davey and Rees in this number of the *Leprosy Review* may also be significant.

We conclude where we began, with the patient. Quite clearly the internal

examination of the nose needs to become a routine part of the clinical assessment of every patient with leprosy, certainly where the presenting type of the disease is of low resistance. Every worker in leprosy should be competent to undertake at any rate a simple anterior rhinoscopy, and carry it out as a habit. Simple procedures for the care of the nose such as indicated by Barton (1973) need to be as much a routine at leprosy hospitals and clinics as the dressing of ulcers, not only on medical grounds, but as a morale builder of great significance in a disease where psychological factors are of such importance. Finally, the rapid drying up of the nasal discharge after only a few weeks of chemotherapy, and the consequent obliteration of an important, and maybe the principal factor in the transmission of leprosy, gives a new urgency in leprosy control to the widest possible application of dapsone treatment.

One intriguing question remains to be asked. Can there be any relation between the ease and frequency with which patients are able to clear their nose in moist atmospheric conditions, and the well known higher prevalence of leprosy in damp as distinct from arid areas of the world?

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T.F. Davey

Lepr. Rev. (1974), **45**, 104-111

Self-healing Leprosy: Report on 2749 Patients*

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Self-healing forms of leprosy account for a considerable proportion of patients suffering from diagnosable forms of the disease among the deeply-pigmented people of Africa. These lesions are described clinically; they are bacteriologically negative to standard methods of examination, and the histopathology is non-specific or frankly tuberculoid. The frequency is unsuspected unless whole-population examinations are regularly undertaken.

The continuing debate on "indeterminate" leprosy prompts the publication of a study made in the former Belgian Congo of a series of patients in whom lesions diagnosed as indeterminate or tuberculoid leprosy spontaneously regressed. Before sulphones became available, treatment by intramuscular or intralesional injections of chaulmoogra oil, or by proprietary derivatives of hydnocarpus oil, was not given to these patients, since the risk of unsightly keloid scarring developing was not inconsiderable and the probability of disappearance of the lesions was thought to be high. During the last 2 years of the 8-year period of the study, most patients diagnosed as suffering from leprosy were placed on treatment, but some with self-healing lesions were left untreated in order to conserve the limited supplies of the sulphones for those suffering from forms of leprosy considered to be progressive.

Basic Data

The average population at risk over the 8 years numbered about 45,035 persons, all of Bantu origin and representing several tribes (mainly Lokele, Torumbu, Foma, Topoke, Bambole). They lived in the medical sector of the Baptist Missionary Society, Yakusu, in small villages scattered along the banks of the River Congo and its tributaries, and in the equatorial rain forest. They were served by 18 health centres (each manned by a national *infirmier* who had had 5 years of training) and 36 treatment centres situated in the larger market villages.

Self-reporting had previously provided little indication of the real prevalence of leprosy, since only those with advanced deformity or peripheral ulceration presented themselves at the dispensaries, but as the result of regular annual whole-population surveys (undertaken originally for trypanosomiasis) complete records (including sketches of the lesions) of all persons suffering from leprosy were obtained, and 6 skin smears were performed on every patient on diagnosis.

* Received for publication 8 November, 1973.

In addition to the patients detected during the annual surveys, the rapport between the *infirmier* and the villagers he served became so mutally helpful that all persons with some persistent non-irritating skin lesion presented themselves voluntarily at the dispensary within a few weeks of its appearance; they were seen by the visiting doctor within the next 6 weeks. The records therefore are reasonably complete and contain the great majority of all patients who, during the 8 years, had leprosy lesions, however transient.

The population was very leprosy-conscious. The skin lesions of active leprosy carried no stigma, but ulcerating extremities were feared because they were thought to be contagious. The older people were very skilled in differentiating leprosy from other conditions, especially fungal infections. They could also readily distinguish pre-tuberculoid skin lesions from the scarcely visible prelepromatous macules, which they called "the mother of the bad leprosy".

Criteria for Inclusion

The various terms that have been used over the years in the literature to denote the early skin lesions of leprosy indicate the clinical appearances, the age-groups predominantly affected, and the prognosis. These are: hazy patches, benign infantile leprosy, juvenile adolescent leprosy, non-malignant leprosy, impermanent hypopigmented patches, abortive leprosy, incipient lesions, *formes frustes,* etc.

History of Contact

Since the prevalence rate of leprosy was extremely high in all the villages within the area, every person was considered to have a history of constant nearness to contagious index cases in the household or compound. It was not necessary to rely on verbal recall either for history of contact or for the occurrence of a leprosy lesion of the skin. The diagnostic criteria adopted were essentially those that were later promulgated by the World Health Organization: they were consistently and uniformly applied during the 8 years of the study.

The problem of definition in subjects with minimal and transient forms of leprosy was resolved by close clinical observation, noting the earliest visible skin abnormality of indeterminate leprosy and the appearance of changes indicating the development of tuberculoid or lepromatous polarity.

Prodromal Symptoms

In the deeply pigmented Bantu skin, loss of pigment proved to be an early and delicate indication of leprosy infection, but some intelligent patients recalled preceding recurrent or persistent paraesthesiae in the area in which pigment loss would subsequently occur. Sometimes these subjective symptoms were noted in the skin surrounding the lesion or in the area of distribution of a local sensory nerve.

The earliest signs observed were slight differences in shininess or reflectability of oblique incident light, accompanied or not by slight impairment of sweating.

Pigment was lost without preceeding erythema. The colour changes were constant. There was no desquamation of superficial scales, and routine examination of surface scrapings in 25% caustic potash—at once and after 24 h—

revealed no fungal elements. Antifungal preparations had no effect: these were tried on many patients with characteristic lesions, despite knowledgeable protests from the villagers.

Slight tactile impairment, with some misreference, was the commonest evidence of local neurological damage found. Disturbance of temperature sense and of pain sensation came later, if and when the lesion took on tuberculoid characteristics.

The lesions were classified as indeterminate or tuberculoid on clinical grounds. Patients with suspected early macular lepromatous leprosy were excluded from this study on the grounds of the presence of numerous small ill-defined hypopigmented macules and the demonstration of abundant bacilli in some or all of the 6 smears taken (from the lesion or lesions, the earlobes, the apparently normal skin, and the nasal mucosa). Many patients presenting this early clinical picture in whom bacilli could not be found were examined at fortnightly or monthly intervals. After a variable period, many of the lesions suddenly became highly bacilliferous.

As a histopathological control of the clinical diagnostic criteria, specimens of skin were taken from selected patients with characteristic lesions, removed under local anaesthesia, fixed in Zenker's solution, and examined by Dr R. G. Cochrane of the Leprosy Research Unit, London. All gradations of pathology were seen, from a non-specific scanty round-cell infiltration of the dermis to the typical tuberculoid picture of infiltration both around and within the small dermal nerve fibrils. With Fite-Faraco staining, acid-fast organisms were sometimes found when an infiltrated nerve was traced through serial sections.

Criteria for "Self-healing"

The diagnosis of "indeterminate" or "tuberculoid" leprosy having been made on the grounds indicated above, the lesions were included in the category of self-healing or spontaneous regression if at successive examinations they showed progressive repigmentation and resolution, in the absence of any systemic anti-leprosy treatment (prescribed, or clandestine) or local physical treatment (burning, cutting, scarifying, etc.) at the hands of native "healers".

The distribution of these patients with self-healing lesions observed over the 8-year period is given in Table 1.

TABLE 1

Population at risk		Number of patents with self-healing lesions over the 8-year period	Incidence per 1000 over the 8-year period
Age in years	Numbers		
0 - 9	12,319	106	9
10 - 19	10,369	282	27
20 - 29	7,330	410	56
30 - 39	5,258	880	167
40 - 49	4,813	653	136
Over 50	4,946	418	85
	45,035	2749	61

Of the 2749 patients observed with self-healing lesions, 1630 were males and 1119 females. Since the above figures represent the totals observed during the 8-year period, they include patients discovered during the initial surveys who may have had leprosy lesions for several years. However, during the last 2 years of the period under review, the actual incidence of cases of leprosy newly arising in the area could be accurately determined. These, including those seen to be spontaneously regressive, are indicated in Table 2.

TABLE 2

Age in years	Total number of cases of leprosy diagnosed in the last 2 years of the 8-year period	Number of cases of self-healing leprosy	Percentage of leprosy patients with self-healing lesions
0 - 9	115	9	8
10 - 19	140	24	17
20 - 29	141	39	28
30 - 39	135	66	50
40 - 49	98	55	56
Over 50	44	27	61
	673	220	33

Thus, about a third of all patients diagnosed as having leprosy during this 2-year period were considered to have lesions that were spontaneously regressing. In addition, an unknown proportion of those suffering from abacillary or paucibacillary forms of leprosy, diagnosed clinically as "indeterminate" or "tuberculoid", and placed under treatment, had lesions that might have proved to regress spontaneously had they not been given treatment.

Leprosy Patients Placed on Treatment

During the last 2 years of the 8-year period, treatment became available through the network of rural dispensaries and treatment centres; the total numbers (classified on the World Health Organization notation) placed on treatment were as follows (Browne, 1959):

Form of leprosy	Number of patients	%
Indeterminate	187	3.5
Tuberculoid	3889	72.7
Borderline	169	3.2
Lepromatous	1104	20.6
	5349	100.0

(N.B. 'Lepromatous' in this table would include patients suffering from borderline-lepromatous leprosy.)

The total of all patients with indeterminate or tuberculoid leprosy among the population is made up as follows:

Untreated, and resolving spontaneously		2749
Under treatment:		
with "indeterminate" leprosy	187	
with "tuberculoid" leprosy	3889	
		4076
		6825

Since 1273 patients with Borderline-lepromatous leprosy were also under treatment, the total prevalence was 8098 in a population of 40,035, or 180/1000, with a multibacillary/paucibacillary ratio of about 1:6.

Clinical Findings

Adequate clinical records are available for the 6-year study group of 2529 persons to form the basis of the following information:

NUMBER OF LESIONS

A single skin lesion was present in 2276 (90.0%); 181 (7.2%) had 2 lesions, and 72 (2.8%) more than 2 lesions (282 in all). Of patients aged under 19 years, 13 out of 255 (3.7%) had more than one lesion, compared with 240 out of 2174 (11.0%) in those over 19.

SITES AFFECTED

Apart from the scalp, the axillae, the inguinal regions, and a band of skin straddling the lumbar region, any area of skin could be affected. The sites were analysed according to the age at onset in an attempt to discern the possible protective role of clothing against contact or inoculation lesions. Children went unclothed up to the age of 3 or 4, and were scantily clothed thereafter; practically all were unshod.

Nerve Damage

The main nerve trunks at the sites of predilection were normal on clinical examination unless the related skin lesion either showed a very vigorous tissue response, or was situated in close proximity to the nerve, for example, near the elbow or knee, in the neck or forehead. The size of the nerve returned to normal as the skin lesion regressed, but an enlarged nerve near a major tuberculoid lesion was observed to remain harder than normal and tender for years after resolution of the skin lesion. Sometimes, small nerve fibrils running from a skin lesion, or across it, were palpable with the finger-nail, and tender.

Lepromin Testing

Lepromin was not available when the series was collected. In 124 cases of spontaneous regression recorded subsequently among 1015 newly-diagnosed leprosy patients in the former Eastern Nigeria, the Mitsuda test readings (taken

TABLE 3

Sites affected	Percentage affected			
	All patients		Patients under 19 years	
Trunk				
lumbar region	20.2		18.4	
scapular region	17.3		12.1	
shoulders	10.6		5.9	
abdomen	7.8		9.6	
buttocks	6.3		16.0	
chest	5.0	67.2	2.7	64.7
Upper extremity				
arms, forearms	15.9		13.4	
hands	1.3	17.2	0.5	13.9
Lower extremity				
thighs	5.9		7.2	
legs and feet	5.9	11.8	7.8	15.0
Face		3.8		6.4
		100.0		100.0

weekly over a period of 2-6 weeks) revealed no significant differences between patients showing spontaneous regression and those with indeterminate or tuberculoid lesions that persisted. The younger the individual, the more likely was the Mitsuda test to be negative or doubtful, even in the presence of a spontaneously resolving minor tuberculoid skin lesion.

The Natural History of a Typical Self-healing Lesion

The earliest lesion encountered is a small, symptomless round area of skin, slightly and uniformly hypopigmented, with limits that may be either well- or ill-defined. The macule enlarges slowly by regular centrifugal extension, the hypopigmentation remaining minimal and uniform. If spontaneous arrest occurs at this stage, the macule ceases to enlarge, its borders become less well-defined, and repigmentation occurs, beginning centrally. In 3 to 12 months, the lesion disappears completely, leaving no detectable abnormality of pigmentation, hair growth, sweating or sensation.

In other cases, the macule continues to enlarge, but the centre repigments and the normal fine architecture of the skin becomes more or less restored. This kind of lesion may ultimately be represented by an indolent, broad, flat, hypopigmented band that very gradually extends centrifugally before it slowly repigments.

The commonest type of regression occurs when the edge becomes sharply defined, and the skin—particularly around the margins—in the macule becomes thicker ("infiltrated"). A regular ring of small papules, discrete or coalescent, slightly or considerably raised, makes its appearance around the margin, or just within the margin, of the lesion. While the lesion is actually extending, the ring of papules may enlarge centrifugally behind an irregularly amoeboid or digitate hypopigmented zone, completely flat. The papules are firm to the touch and the

whole lesion becomes dry and rough. With an increasing depth of dermis affected, tactile sensation becomes impaired, temperature sense is disturbed, sweating is partly or completely lost, and superficial pain sense is diminished. The hairs are shed.

Spontaneous resolution may occur at this stage. Repigmentation and cicatrization proceed from the centre, taking two years or more before the process is complete. Permanent destruction of adnexa has in part occurred, with demonstrable persistent disturbance of sensation, sweating, hair growth and pigmentation. Bizarre relics of this process may remain, such as a ringlike distribution of scattered groups of hypopigmented papules; a puckered hypopigmented scar; linear furrows across an area of thickened dry skin.

When the tissue response has been vigorous, resolution is by gradual cicatrization, which involves the whole thickness of the dermis, including the adnexa. Repigmentation—partial and patchy and often irregular, with areas of hyperpigmentation—begins centrally while the periphery is still extending. The margin is papulated, dry and hard; it may be 2 or 3 cm wide, and during an acute phase it may ulcerate or desquamate. The patient may then complain of itching, burning, and painful sensations around the margin, symptoms distinctly uncommon in leprosy. The vigorous tissue reaction subsides gradually and the healing process takes over.

If the related nerve trunk has been damaged, the increasing intraneural cicatrization may show itself by an extension of cutaneous hypoaesthesia and muscle atrophy.

Discussion

The occurrence of spontaneous regression of leprosy has been noted by numerous observers from Hansen onwards, but its commonness is largely unappreciated unless regular and frequent whole-population examinations are done. In the absence of a laboratory test of infection that is applicable in field conditions, the diagnosis of early leprosy lesions is still mainly clinical, confirmed in selected typical patients by histopathological examination: in field work, such confirmation is impossible for every patient. Skin smears carefully performed according to standard techniques will indicate early macular lepromatous leprosy, and the characteristic appearance of tuberculoid lesions with their signs of local nerve damage should suffice for the diagnosis of early tuberculoid leprosy. The third group of early lesions falls into the convenient clinical category of indeterminate. Prolonged examination of serial sections would reduce the size of this group by providing histopathological evidence of the development of characteristics of polar or "determined" leprosy.

While the figures here reported suggest that many more people may actually have leprosy than official statistics indicate, they also imply that the seriousness of the leprosy endemic in Africa is not greatly affected by the large numbers of patients with self-resolving leprosy. The situation may be more serious elsewhere, for although spontaneous regression does occur outside Africa, a higher proportion of early leprosy lesions in the lighter-skinned races may be manifestations of multibacillary leprosy, undeclared because of fear or shame or ignorance.

The apparent success of control measures in Africa reflects the high proportion

of patients with easily curable disease; the leprosy problem elsewhere may be more serious and more intractable, despite relatively lower prevalence rates.

The age distribution of patients with self-healing leprosy here reported suggests that the preponderance of the younger age-groups in other recorded series may be the result of factors (such as family segregation, observation of child household contacts, etc.) that were not operative in an area of very high prevalence where leprosy sufferers remained in their villages.

Whereas among the deeply pigmented the skin would seem to be a delicate indicator of clinically established leprosy, the peripheral nerves may subserve that role in India, where, according to Noordeen (1972), up to a sixth of cases of leprosy may have abnormalities in nerves, the skin remaining clear.

The site of the only or the first lesion observed provides no indication that this is the point of inoculation of the organism; the frequency of these lesions on hands and faces would not support such a suggestion. As reported elsewhere (Browne, 1966), the nasal mucosa only very rarely contains *Myco. leprae* before they are demonstrable in skin lesions.

Since recent investigations provide evidence that persons exposed to leprosy for over 12 months manifest changes in the lymphocytes (Godal and Negassi, 1973), and since many observers have found (by concentration methods) acid-fast organisms in the dermis and in lymphatic nodes, the very high prevalence rates of clinical leprosy reported in some hyperendemic foci cannot be ruled out *a priori.* In one group of villages included in the present investigation, we were assured that "everybody gets leprosy sooner or later"; but the lepromatous rate did not exceed 2%, and most of those with diagnosable leprosy at any one time had self-healing lesions.

The antecedent and subsequent history of the patients in this series would suggest that spontaneously regressing lesions very rarely recur.

Since anti-leprosy treatment accelerates repigmentation, forestalls extension of the lesion and the appearance of new lesions, and usually prevents peripheral nerve damage, and since, moreover, it is difficult or impossible to predict which lesions will spontaneously regress, it is recommended that treatment should be given to all patients diagnosed as having leprosy. Such advice is acceptable to most patients and helps the leprosy campaign. Although in perhaps half of those with indeterminate or tuberculoid leprosy, treatment may not strictly be necessary, the rapid visible repigmentation of lesions following treatment may encourage those with undisclosed leprosy to declare themselves.

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The Nose in Mice with Experimental Human Leprosy *

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Normal and immunologically deficient mice inoculated with *Myco. leprae* (1) locally in the footpad or ear, (2) intravenously, and (3) intraperitoneally, were killed 1-2.5 yr later and their tissues examined bacteriologically and histologically. Quantitative bacterial assessments showed that by 1.5 yr a high proportion of all animals had a countable number of bacilli ($>5 \times 10^4$) in uninoculated ears, footpads or nose. Of these sites the nose on average was most frequently infected and contained significantly higher yields of bacilli. Moreover, nasal smears from a proportion of the mice showed acid-fast bacilli. Histology of the nose showed a variable number of bacilli within macrophages deep to the nasal mucosal epithelium but also bacilli within the overlying ciliated columnar-epithelial cells. In contrast bacilli were very rarely seen in the overlying squamous epithelial cells of the skin in the nasal vestibule and elsewhere, however heavily infected was the underlying dermis. These findings in the mouse are discussed. Attention is drawn to the frequent involvement of the nasal tissues and the excretion of large numbers of bacilli in the nasal mucus.

Introduction

Since 1965, systematic studies have been undertaken to follow at intervals from 6 months to 2.5 years the bacteriological and histopathological evolution of infections in mice inoculated with *Mycobacterium leprae*. In this period data have been collected from several hundred immunologically normal, and immunologically deficient CBA mice inoculated with some 30 strains of *Myco. leprae* locally in the footpad (occasionally in the ear), intravenously and intraperitoneally. The immunologically deficient mice were prepared by thymectomy followed by total body irradiation (T/900R) prior to inoculation (Rees, 1966).

Many of the general features of these infections have been published (Rees and

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Weddell, 1968, 1969; Rees *et al.*, 1969; Weddell, Palmer and Rees, 1970). In particular they have demonstrated that there is a close resemblance between the histopathology of the disease in the mouse model and in man. They have also shown that sooner or later immunologically deficient and normal mice, inoculated locally in the ear or footpad, intravenously and intraperitoneally, develop bacilliferous and pathological lesions in particular sites, which include the nose (a site never inoculated) and the non-inoculated ears or footpads. It is on the basis of these sites of predilection, and particularly the nose because of its long-established importance in patients with lepromatous leprosy, that we now present the nasal data from experimental infections in mice.

Observations

BACTERIOLOGICAL STUDIES

Earlier studies have shown that 12 months and more after the inoculation of *Myco. leprae* either into the footpad or intravenously, there is systemic spread and localization of bacilli within several preferred sites (Weddell, Palmer and Rees, 1970). Following local inoculation into the footpad the preferred sites were the ear and nose, and following intravenous inoculation, the same sites as well as the footpads. To compare the relative susceptibilities of these sites for the localization and multiplication of *Myco. leprae* the bacteriological data from our relevant experiments were analysed. The data was based on total yields of acid-fast bacilli from weighed footpad, ear and nasal tissues, the latter being included in a snippet taken from the whole nose and upper lip, and standardised to bacillary yields per unit weight (1 g) of tissue. The proportion of solidly staining bacilli (i.e. Morphological Index, M.I.) was also assessed.

A simple analysis of the data from immunologically normal or immunologically deficient (T/900R) mice in which bacilli had been inoculated into the footpad, is given in Table 1. The results show that there was systemic spread to the nose

TABLE 1

Spread and yield of acid-fast bacilli in mice after footpad inoculation of Myco. leprae

Comparison of nose and ears as sites of spread (56 mice)	
Spread to nose alone	16
Spread to nose and ear	36
Spread to ear alone	4
Analysis of relative yield of bacilli in nose and ear where both sites were infected (52 mice)	
Yield in nose > ear	38 mice
Yield in nose = ear	9 mice
Yield in ear > nose	5 mice
Average Morphological Index	
Nose	25.6
Ear	10.8

more frequently than to the ear; where spread to both sites occurred, the yield of acid-fast bacilli as well as the M.I. were higher in the nose than in the ear. All these results were statistically significant ($P = < 0.01$).

Similar data were analysed from 26 immunologically normal or immunologically deficient mice inoculated intravenously with *Myco. leprae,* who at the time of killing had a countable number of acid-fast bacilli in the ear, footpad and nose. The yields of bacilli at the various sites was very variable for they were related both to time of killing after an inoculation and to the immunological competence of the individual mice. Thus a particular statistical technique was applied in order to compare the levels of infection at the three sites (see Appendix). In summary the analysis showed a highly significant difference ($P = < 0.001$) between the mean infection levels observed at the three sites. They showed that the mean infection levels recorded at the nose of each animal were significantly higher than those of the ear or footpad which did not differ significantly from each other. A sample of the counts obtained from five of the animals is given in Table 2.

TABLE 2

Representative yields of acid-fast bacilli from the footpad, ear and nose of five mice inoculated intravenously with Myco. leprae

Yield/g tissue		
Footpad	Ear	Nose
7.1×10^5	1.3×10^6	4.7×10^6
2.5×10^4	1.3×10^4	2.4×10^6
5.7×10^7	9.5×10^7	1.9×10^8
2.0×10^7	3.3×10^7	1.8×10^8
4.0×10^5	1.2×10^6	7.0×10^5

While saline-wetted smears prepared from the surface of the footpad rarely showed acid-fast bacilli, many smears from the nose contained bacilli (Fig. 1).

HISTOLOGICAL STUDIES

These studies were routinely based on the nose-tip (snout) which included the anterior part of the vestibule. Such biopsies were obtained from 14 immunologically deficient or normal animals.

The most marked and widespread bacillation was seen in the thymectomised-irradiated group, and in most of these there was a high percentage of solid-staining organisms. Despite the differing routes of inoculation, and the range of inoculation-to-killing time (13-28 months), no significant histological differences were noted in relation to these two factors. Cellular reaction was never marked, and often minimal; when present it was mainly of histiocytes, with a few lymphocytes. Bacilli were widespread in the dermal macrophages but were also seen frequently in hair follicles, plain and striated muscle, and in blood vessel endothelium. In numerous animals solid-staining organisms were found in the endo- and perineurim of dermal nerve filaments. Bacilli were either single, in small groups, or in globi of moderate size. In a few animals where some anterior turbinate was included, the mucoperichondrium contained bacilli in isolated macrophages, in macrophages in lymphoid tissue, blood vessel endothelium, and

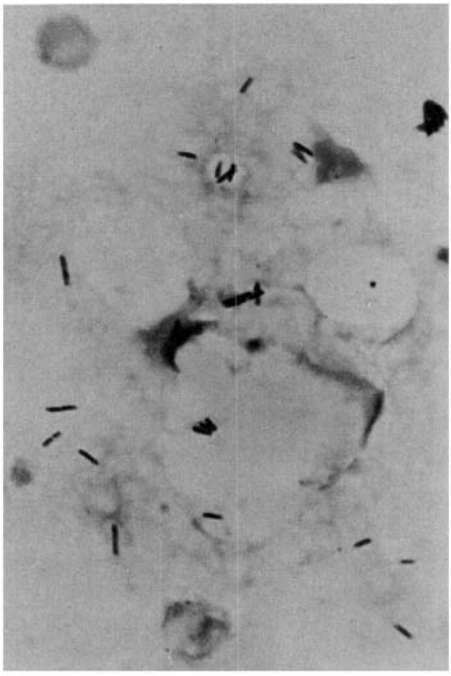

Fig. 1. Nasal smear immediately after killing. All fields contained large numbers of solid-staining bacilli. Ziehl-Neelsen, oil immersion.

nerves; bacilli were not found invading the cartilage directly. On reviewing a large number of sections from the vestibular region, no bacilli have been found in squamous epithelium or keratin, though on the hairy skin surface, one or two animals showed occasional bacilli emerging from hair follicles or vibrissae.

In the immunologically normal mice, only one, killed 24 months after inoculation, showed changes approaching in degree those just described. However, the localization of bacilli resembled those in the thymectomized-irradiated group. In these normal animals at this later stage histiocytes and lymphocytes were more frequent, and the number of bacilli in nerves often appeared relatively greater than in other tissue elements.

These findings suggested that much more significant histopathology might be revealed if tissues from the more posterior parts of the nose, including septum and turbinates, were taken. We therefore examined in detail the nasal tissues fixed *in situ* by perfusion with buffered formaldehyde from an immunologically deficient mouse 15 months after a footpad inoculation of *Myco. leprae*.

The findings were of considerable interest. Footpads were checked and found characteristically positive for an immunologically deficient animal on killing at 15 months, and a fairly high percentage of organisms were solid-staining. The nose tip (snout) was highly positive for bacilli, which permeated the dermis and invaded plain and striated muscle. Globi were abundant. Nerve filaments were bacillated, although not markedly so, but a very high percentage of organisms were solid-staining. The turbinates were highly positive for bacilli, but the highest

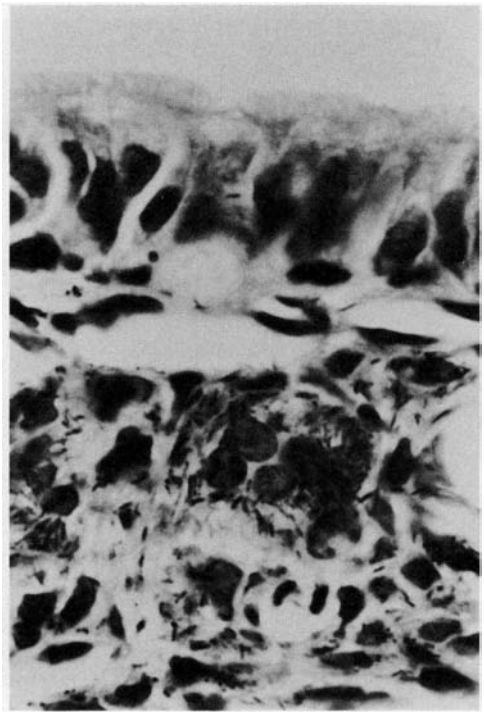

Fig. 2. Inferior turbinate; submucosal macrophages and perivascular histiocytes carry large numbers of bacilli. One (Upper centre) is seen between columnar epithelial cells, oil immersion.

concentration of organisms were in the septum, at about the level of the mid-cavity, and in an area of typical respiratory mucous membrane (Fig. 2). The mucoperichondrium here was full of bacilli and globi were profuse. Bacilli were seen in macrophages, fibroblasts, mucous glands, and in small filaments of the trigeminal nerves (Fig. 3). Of particular interest was the finding of bacilli in perivascular histiocytes and lining cells of blood and lymph vessels (Fig. 4). Bacilli were also seen in the basement membrane area of the epithelium, and both between and in epithelial cells apparently pursuing a course to the surface (Fig. 5). The sections did not show goblet cells too clearly, and bacilli were not in fact seen in this position. The olfactory mucous membrane revealed very few bacilli in the stroma, and they were not seen in any of the non-myelinated olfactory nerve filaments. Some bone from this area was included in these sections, and bacilli were numerous in the marrow. The Gasserian ganglion, the sensory root, and one or two other divisions were also processed, and found negative for bacilli. The nasopharynx and choanal region showed abundant bacilli, mainly in isolated histiocytes and histiocytes in lymphoid follicles.

Discussion

Since the early days of informed clinical observation in Norway and elsewhere, there have been frequent references to the importance of the nose in the spread of

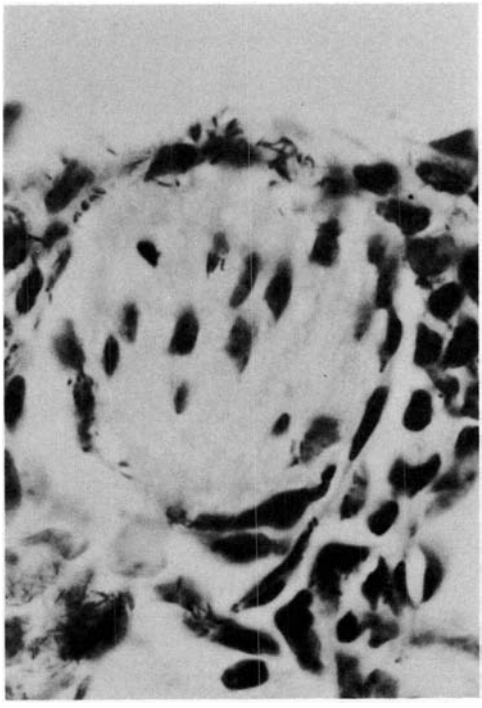

Fig. 3. Inferior turbinate; bacilli are seen in the peri- and endoneurium of a tiny branch of the trigeminal nerve, oil immersion.

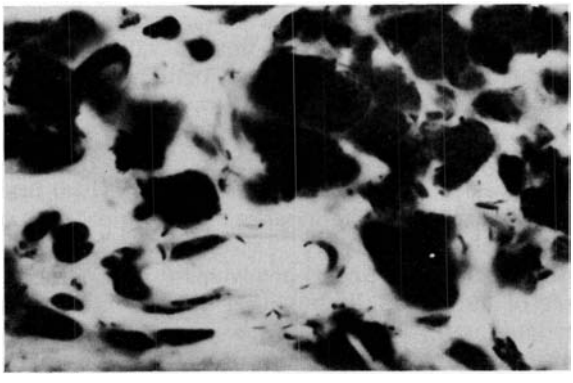

Fig. 4. Septum, mid-cavity. Above and to the right are large dense globi of bacilli. A small vessel (lower centre) has solid-staining bacilli in its endothelial lining, oil immersion.

leprosy. Most textbooks (Muir, 1921; Eggston and Wolff, 1947; Cochrane and Davey, 1964) have described changes in the interior of the nose, and emphasis has usually been given to septal perforation and cartilaginous involvement, rather than to the significance of bacilli in nasal discharges.

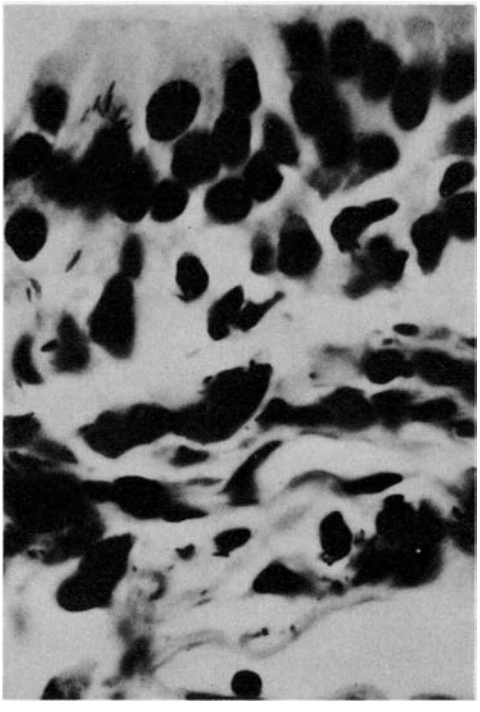

Fig. 5. Middle turbinate, mid-cavity. Bacilli (top left) are shown between, and in the cytoplasm of pseudo-stratified columnar epithelial cells, and in macrophages adjacent to a venous sinus (bottom right), oil immersion.

On the question of the value of nasal smears or scrapings, there have been suggestions that they may be either of limited value, or possibly misleading (Dungal, 1961; Padma, 1965; Arnold, 1966; Cochrane, 1971). By contrast, their value has been admirably summarised by Browne (1966), and numerous other authors have drawn attention to the clinical and public health importance of these examinations (Davey and Rees, 1973; Shepard, 1962; Bueno, 1968; Goodwin, 1967*a*, *b*). In recent years, Pedley (1970, 1973) has revived interest in the large numbers of solidly-staining bacilli in nasal smears from patients with lepromatous leprosy, as seen in Nepal.

Our studies of the evolution of nasal involvement in experimental mice infected with *Myco. leprae* of human origin show that the nose is a particularly favourable site for the seeding, multiplication and excretion of viable bacilli into the environment, thus resembling the situation in man. As compared with excretion from the skin (Pedley, 1970), or in breast milk (Pedley, 1967, 1968), the nasal route is now shown to be of the greatest significance. While bacillary excretion from open lepromatous ulcers has already been shown (McDougall and Rees, 1973) to be in excess of 20 millions daily, collections of nasal mucus over 24 h, also from lepromatous patients, have yielded counts in the region of $3.2\text{-}3.4 \times 10^8$ bacilli (Rees and McDougall, 1973).

Although bacilli can be seen in vascular endothelium in lepromatous leprosy in man and in the experimental animal, we were impressed with the finding of

solid-staining bacilli in perivascular histiocytes and in lining cells of small blood and lymph vessels. This situation resembles very closely our current findings in a large series of nasal biopsies from lepromatous patients.

The localization and multiplication of leprosy bacilli in the nose of mice in the present study adds weight to the possibility that the nose may play a more important part in the pathogenesis of leprosy than is at present believed. The model not only confirms the nose as a heavy—possibly almost continuous—exit route for bacilli, but also raises two obvious questions: (1) do *Myco. leprae* multiply more effectively in the nose than elsewhere and (2) is the suggestion of Sticker (1897) that the nose may be a portal of entry for *Myco. leprae* worthy of reconsideration?

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Appendix

ANALYSIS OF LEVELS OF INFECTION IN VARIOUS SITES FOLLOWING INTRAVENOUS INOCULATION

Twenty-six immunologically intact or T/900R mice had a countable number of acid-fast bacilli ($> 5.0 \times 10^4$) in their ears, footpads and nose following an intravenous inoculation of *Myco. leprae*. To compare the levels of infection at these sites the following statistical technique was applied:

(1) That each individual animal has an overall level of infection A (animal).
(2) The level of infection at each site is P (site) × A (animal) when P (site) is a constant specific for each site but similar for all animals.
(3) Thus the level of infection at the 3 sites for an animal is P (footpad). A (animal); P (ear). A (animal); P (nose). A (animal).

Inspection of the data indicated that the technique was valid and for mathematical convenience the data was converted to logarithms.

A two-way analysis of variance was carried out on the data as logarithms and indicated that there was a highly significant difference ($P < 0.001$) between the mean (log) infection levels observed at the three sites.

Further examination of these mean values indicated that the mean of the log infection levels recorded at the nose of each animal was significantly higher than the mean of the log infection levels observed at each of the other two sites (the mean values for which did not differ significantly from each other).

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The Nasal Discharge in Leprosy: Clinical and Bacteriological Aspects

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Nasal discharges containing acid-fast bacilli were studied broadly, in India, in relation to their clinical setting in 363 patients, and intensively, in London, in relation to their bacteriology.

The rarity of such a nasal discharge in borderline leprosy was in striking contrast to its frequency in untreated lepromatous leprosy. In this series the nasal discharge did not develop gradually with the advance of lepromatous leprosy. Highly bacilliferous discharges were encountered in early lepromatous leprosy, indicating nasal involvement far more severe than external appearances suggested. At a later stage the bacteriological importance of the discharge waned, but became once again of great significance with the onset of recrudescence.

The typical nasal discharge is an inflammatory exudate rich in both *Myco. leprae* and macrophages displaying every stage in globus development. The exceptionally high B.I. and high M.I. often encountered in untreated patients in this series frequently exceeded the highest values found in skin. The nasal discharge was encouraged by moist atmospheric conditions and diminished rapidly with even small doses of dapsone.

Fresh early morning specimens and 24 h collections of nasal discharges from 31 patients in this series were sent on wet ice to London, together with fresh biopsies of highly infected skin from 11 of these patients.

Bacillary isolates from the nasal discharges of all 31 patients produced growth curves in the mouse footpad characteristic for *Myco. leprae*, indisputable proof that this organism was present in every case. The mean total yield of acid-fast bacilli in 24 h collections was 2.4×10^8, with a morphological index of 12.8. Single nose-blow collections showed a mean discharge of 1.1×10^8 acid-fast bacilli with a mean morphological index of 16.9. Comparison between the content of acid-fast bacilli/g of skin and that of the specimen of nasal discharge from the same patient showed a significantly higher proportion of solidly staining bacilli in the nasal discharge.

In 3 patients, mouse inoculation tests for dapsone sensitivity of *Myco. leprae* isolated from nasal discharges and skin biopsies revealed dapsone resistant bacilli both in the skin and in the nasal discharge.

The capacity of *Myco. leprae* in nasal discharge to survive outside the body was tested in 3 cases, by allowing the discharge to dry in the dark, at room temperature, and sampling for mouse inoculation being undertaken at 1, 1.75, 3, 7, and 10 days. Full survival was found after 24 h, and 10% after 1.75 days, but none after 3, 7 and 10 days, except in 1 sample in which some growth occurred after 7 days.

Similarities with tuberculosis, and the significance of both clinical and bacteriological findings to the transmission of leprosy are discussed.

Introduction

Very soon after the discovery of *Mycobacterium leprae,* it was recognized that what we now call lepromatous leprosy was associated with a nasal discharge containing acid-fast bacilli, sometimes in large numbers, and that this phenomenon can occur early in the disease. Gerber (1901), Jeanselme and Laurens (1897), Sticker (1897), and Klingmuller (1897) all drew attention to this. Schäffer (1898) went further, and demonstrated that large numbers of acid-fast bacilli could be projected in coughing, sneezing, and in normal speech, up to a distance of 1.5 m and beyond, in one case 185,000 bacilli in 10 min. The importance of the nasal discharge as a possible source of infection to others was emphasised by Schäffer (1897), Sticker (1897), Jeanselme (1897), Muir (1929), and Rogers and Muir (1946).

There was no proof that bacilli discharged from the nose were in fact viable *Myco. leprae,* and no way of assessing their viability. This and other factors combined to diminish interest in the nose in leprosy, and a generation of neglect followed. In 1961, Shepard examined nasal washings from 4 patients with lepromatous leprosy, and using new techniques, proved that the bacilli concerned were in fact *Myco. leprae,* that at least some were viable, and that total numbers involved were very great, 10^7 in 1 patient. The bacilli concerned had not been discharged by a natural process. Pedley, however (1970, 1973*a, b*), found large numbers of bacilli morphologically identical with *Myco. leprae* in natural discharge from the nose of patients with lepromatous leprosy in Nepal, in contrast with almost negative findings in contact smears from unbroken skin in the same patients.

These findings pose fundamental questions. Is this bacillary laden discharge a general attribute of lepromatous leprosy? If not, which patients are implicated, and who most seriously? Are the bacilli discharged in fact *Myco. leprae?* If so, what numbers of viable *Myco. leprae* are involved? At what stage does a bacteriologically positive nasal discharge develop, how persistent is it, and how is it affected by chemotherapy? What is its relation to the pathology of the nose in leprosy? Finally, what happens to the bacilli after they have been discharged?

Here we report the findings of an extensive clinical study of patients with bacilliferous nasal discharges, attending for the first time at the Victoria Hospital, Dichpalli, Central India, combined with a quantitative bacteriological investigation of the discharge from some of these patients, undertaken at the National Institute for Medical Research, London. Conditions were unusually favourable for such a study, both from the angle of the clinical material available, and the speed with which fresh discharges could be transmitted to London. This work was the first stage in a wider clinical, histopathological and bacteriological study which is still in progress, and initial findings of which were reported at the Tenth International Leprosy Congress, Bergen, 1973, by Davey and Rees (1973); and Barton *et al.* (1973).

Definition and Method

This study is limited to the nasal discharge itself. Nasal smears were a separate issue, not dealt with here.

During the 9 months September 1971 to March 1972 and July - August 1972, all patients with lepromatous (LL,L1) or borderline leprosy on the lepromatous

side (BL), attending for the first time, or after an absence of at least two years, were invited to blow their noses into new plastic bags on arrival, simultaneously with the routine bacteriological examination of multiple skin sites. Any discharge obtained was then smeared and examined for *Myco. leprae* in the usual way by a single observer (TFD), cell content also being observed. In dry weather, if patients complained of a discharge, but found it difficult to produce a specimen because of hard crusting in the nose, a gentle spray with distilled water, using an atomiser, assisted the process. Patients with indeterminate, tuberculoid, or borderline leprosy on the tuberculoid side were not included in this study.

Patients with highly bacilliferous discharges were admitted for more detailed observation and care, where agreeable, for periods up to 12 months. In selected individuals, records and smears of the discharge were made daily. Individual samples and 24 h specimens from selected patients were sent on ice to London, arriving within 30 – 54 h of production.

Clinical Studies

PREVALENCE OF NASAL DISCHARGES CONTAINING *MYCO. LEPRAE*

During the 9 months under review, 936 patients came to the hospital for the first time, or in a few cases after an absence of more than two years, presenting either with lepromatous or borderline leprosy on the lepromatous side, all with skin smears positive for *Myco. leprae.* Of these 936 patients, 407 were able to profer a nose-blow on arrival. The specimens produced included discharges from coryza and other catarrhal conditions, but 363 of them were found to contain acid-fast bacilli identical in all respects with *Myco. leprae,* an overall prevalence of 39%.

Four reasons may be given for believing this to be too low a figure for the actual prevalence of bacteriologically positive nasal discharges among these patients.

(1) It is the universal custom in India for people to clear their noses as part of their early morning ablutions. What we were observing in almost every case was in fact a *second specimen* produced later in the morning. The ability to produce this was clearly indicative of an active, established pathological condition, and in the early and late stages of their disease some patients could not always oblige.

(2) The exudate, especially in dry weather, and in the early and late stages, often solidifies into hard crusts which can be both large and adherent, and render the clearing of the nose very difficult. Patients were encountered, not infrequently, who were able to clear their nose only at irregular intervals, with the production of a considerable amount of hard material. The day of arrival may not have coincided with such an occasion.

(3) The discharge is speedily and grossly altered as a result of even a short period of chemotherapy. Some patients on arrival were loath to admit that they had already taken some dapsone. The suspicion of this, aroused when bacilli in the discharge were found to have a morphological index of zero or near zero, led to our instituting urine tests for sulphone as routine. This proved very useful, and revealed this important source of fallacy.

(4) Finally, the human factor cannot be ignored. Some patients who could have produced a specimen were in too psychologically disturbed a condition to cooperate immediately, and it was not always possible to devote the time and

attention necessary to encourage a patient to expose to other people what was to him the terrifying state of affairs in his nose.

Thus, 39% is an exceedingly conservative figure for the prevalence of nasal discharges containing *Myco. leprae* in this large series of patients.

TYPE AND STAGE OF LEPROSY IN RELATION TO NASAL DISCHARGE

An analysis of the findings in relation to type and stage of leprosy is given in Table 1.

In Table 2, the bacteriological findings in nose-blows are compared with those in routine skin smears taken simultaneously.

TABLE 1

Prevalence of nasal discharges containing Myco. leprae

Clinical group	Total patients	No. with nasal discharge ctn.AFB.		No. with nasal discharge B.I. 5 or 6	
		Total	(%)	Total	(%) of Col. 2
(1) Borderline	208	6	(3)	nil	nil
(2) Early lepromatous	295	158	(54)	103	65
(3) Established lepromatous (over 3 years history)	295	103	(35)	47	46
(4) Lepromatous in exacerbation, including histoid	114	90	(79)	79	88
(5) Lepromatous in ENL	24	6	(25)	nil	nil
Total	936	363	(39)	229	(23)

TABLE 2

Bacteriological comparison between nasal discharge and routine skin smears

Clinical group	Patients with Bact. +ve nose-blows	B.I. in nose-blow compared with skin			M.I. in nose-blow compared with skin		
		Higher (%)	Similar (%)	Lower (%)	Higher (%)	Similar (%)	Lower (%)
Borderline	6	numbers insignificant					
Early lepromatous	158	25	59	16	48	46	6
Established lepromatous (over 3 years history)	103	8	51	41	29	60	11
Lepromatous in exacerbation, including histoid	90	20	64	16	57	41	2
Lepromatous in ENL	6	numbers insignificant					

The following findings command attention.

(1) Among 208 patients classified as suffering from borderline leprosy, only 6 produced a specimen of nasal discharge containing *Myco. leprae,* none of them highly bacilliferous. All 6 patients were in an unstable exacerbating condition.

(2) The frequency and often highly bacilliferous nature of nasal discharges in patients with *early lepromatous leprosy* is a striking and significant finding. Thus 158 (54%) of 295 such patients, some of them in a very early stage of the disease, gave positive findings, and in 65% of these a bacterial index of 5 or 6 was encountered. The morphological index exceeded that found in skin in 48%.

(3) In well established lepromatous leprosy the bacteriological importance of the nasal discharge had waned. Thus 35% of 295 patients were able to produce a nasal discharge positive for *Myco. leprae,* a decline of 19% as compared with early cases, and the prevalence among them of a B.I. of 5 or 6 fell from 65% to 46%.

(4) On the other hand, phases of exacerbation and recrudecence were once again of great importance in relation to the nasal discharge, 90 (79%) out of 114 patients in this condition producing nose-blows positive for *Myco. leprae.* 79, i.e. 88% of these specimens had a B.I. of 5 or 6, the morphological index in nose-blows exceeding that in skin smears in 57%.

(5) In *erythema nodosum leprosum* the nasal discharge was of minor importance. While 6 out of 24 patients produced positive nose-blows, the baccilli were few and granular in all cases.

(6) The exceptionally large numbers of bacilli often present, and the high values for the morphological index frequently encountered, both deserve attention. The maximal reading of 6 on the international scale is inadequate to describe a smear coloured red by enormous numbers of globi and sometimes huge aggregates of bacilli. Such appearances were not rare.

PATHOLOGY

The findings of such highly bacilliferous nasal discharges in very early cases of lepromatous leprosy was unexpected, and led to the introduction of anterior rhinoscopy as routine. The very first patient so examined was a boy of 12 years, just approaching puberty, who had noticed vague reddish patches on his skin one month previously, combined with a sensation of blocking of his right nostril. Four days previously his nose had bled a little, and it was this which prompted his mother to bring him for examination. He presented signs of lepromatous leprosy in its very earliest stages. There was however a scanty but highly bacilliferous nasal discharge, and anterior rhinoscopy, using only a nasal speculum and hand torch for illumination, immediately revealed a soft nodule on the right inferior turbinate, a far more striking lesion than anything seen in the skin. This nodule, when smeared, yielded *Myco. leprae* in enormous numbers, with a M.I. of 50%. This patient was the first of many who presented similar appearances. A thorough investigation of the nasal mucosa in early lepromatous leprosy was clearly indicated, and as a result of the cooperation of the National Institute for Medical Research, London, the Department of Human Anatomy, Oxford University, and LEPRA, this was initiated and is still in progress, based on a subsequent series of patients to those with whom we are concerned here.

We have been unable to discover any detailed account of the nasal discharge in the literature, and as it has many points of interest, a brief description of it, as encountered among the patients in the first series, is appropriate. It may be described in three stages.

Stage 1. Development

In its beginnings, as observed in very early lepromatous leprosy, the nasal discharge is seen as a sticky yellowish exudate quite unlike the mucous secretion encountered in coryza, and the use of the word "mucus" in relation to it can be misleading. We are not simply encountering here an enhanced activity of the mucous glands in the nose, but an *exudate with high cell content,* and with a marked tendency to solidify and adhere to the underlying mucosa. Crust formation takes place early. Bleeding is easily provoked by attempts to blow the nose, and a specimen of exudate as discharged into a plastic bag at this stage is likely to be scanty, with traces of blood, and some crusts. Microscopically, concentrations of macrophages are typical, with very active phagocytosis of acid-fast bacilli, clearly seen inside the macrophages, and with early globus formation. Bacilli are frequently rather slender and elongated. The exudate thus has some distinctive features.

Stage 2. Efflorescence

As the disease in the nose extends, the exudate takes on its fully developed appearance. Macroscopically it may be voluminous, up to 5 ml or more daily. It is often not homogeneous, in parts thick and saneous, elsewhere with a muco-purulent appearance, often streaked with blood, and containing crusts of various sizes, often of a dark colour from changed blood. It varies considerably in amount from specimen to specimen. Some patients need to clear their noses several times a day. In others the sticky exudate is more easily retained, and clearing the nose once daily may suffice, though crusting is likely to be severe in such cases, so much so that the posterior nares can be completely blocked by a solid mass of dried exudate. The humidity of the weather and secondary infection both exert an important influence.

Microscopically, the discharge presents its own pattern. Because it is often not homogeneous, smears need to be taken from more than one area. Samples from areas adjacent to streaks of blood are often the most productive. Under the microscope, a wide range of foreign bodies such as pollens and fragments of dust may be evident. Shed epithelial cells are frequent, and in decay often take on a pale pink colour with Ziehl Neelsen staining. With secondary infection, and rarely in reactive conditions, polymorphonuclear leucocytes may be numerous, but *the basic cell component is the macrophage,* always present, and usually in large numbers.

A wide range of bacteria may be observed including the normal inhabitants of the nose, cocci, diplococci, and bacilli of various types, with occasional fungal elements. In advanced stages, bacterial flora may be enormous in both numbers and range. The essential constituent, *Myco. leprae,* is seen in all its characteristic features, and in untreated cases, often in exceedingly large numbers, with elongated and curved forms common. Every stage in their ingestion and development in macrophages may clearly be demonstrated. Because the discharge may be retained in the nose for varying periods before being expelled, the M.I. may vary widely between one part of the specimen and another, with actively developing globi in one field, decaying globi in another. Because of this we have made it our practice in the direct examination of slides from the discharge to record the upper and lower limits of the M.I. between one part of the specimen and another.

Stage 3. Decline

The discharge tends to be most copious, and contain the largest numbers of *Myco. leprae,* in very active established lepromatous leprosy, shortly before ulceration of the septum has led to its perforation. With perforation, the area from which bacilli are being discharged is reduced. By this time too, the inferior turbinates, as a source of discharge, are often past their peak through erosion and atrophy, and the diminishing area from which the discharge is drawn tends to result in a diminished volume. At the same time, secondary infection may become important and responsible for a change in the character of the discharge, which may be either more mucoid or frankly purulent, and in the later stages offensive with much crusting, but less evidence of bleeding. The discharge may be very persistent, but with reduced content of *Myco. leprae.*

Nowadays the natural course of events is usually interrupted by sulphone treatment, and the discharge then rapidly diminishes in volume as does the M.I. of the bacilli contained in it. Among 12 patients in this series whose nasal discharges were recorded and examined daily, and the nose given local care, a striking diminution in the volume of the nasal discharge was apparent within six weeks in all cases on an initial dapsone dosage of 5 mg on alternate days during the first month, rising to 10 mg during the second month on a rising scale. By this time the morphological index in the discharge had fallen to near zero in 10 cases, and the B.I. had fallen by more than 1 unit in the international scale in 7 cases. The same trend was generally apparent in 40 other patients under frequent observation. In 3 cases, with no improvement, dapsone resistance was later demonstrated.

Bacteriological Studies

METHODS

Detailed bacteriological studies were undertaken on the nasal discharges from 31 patients selected as representing a cross section of the various clinical groups of lepromatous patients at Victoria Hospital who had at the time of admission active disease and bacteriologically positive nasal discharges. All these studies were undertaken in London at the National Institute for Medical Research on nasal discharges collected at Dichpalli and then immediately despatched by air on wet ice to London, where they were processed within 36-54 h. From the 31 patients 11 nasal discharges were single specimens collected in plastic bags from the first early-morning nose-blow, and from 17 patients the nasal discharges were 24 h-specimens collected in plastic sputum pots. From 11 of these patients a biopsy of skin from a representative active lesion was taken at the same time and also despatched on wet ice to London. Samples of bacilli from all the nasal discharges and biopsies of skin were cultured on Loewenstein-Jensen medium and inoculated into footpads of mice using the standard methods previously described (Rees, 1964). The total content of acid-fast bacilli from each nasal-discharge specimen and skin biopsy was assessed (Hart and Rees, 1960), as was the morphological index from smears prepared from these suspensions. For the quantitative bacteriological assessments and mouse footpad inoculations of the nasal discharges the specimens were first dispersed by exposure for 15 min to sputolysin (*n*-acetyl-l-cysteine as a mucolytic agent) as used for the isolation of *Mycobacterium tuberculosis* from sputum (Kubica *et al.,* 1964). For culture and mouse inoculation these nasal

specimens were decontaminated by treatment with sodium hydroxide (2% for 20 min at room temperature).

These specimens of nasal discharge and biopsies of skin were used to assess the total yields of acid-fast bacilli, to identify the organism as *Myco. leprae* and from 3 patients to determine the dapsone sensitivity of the bacilli in mice using the standard techniques previously described (Rees, 1967).

Additional nasal discharges from 3 patients were used to determine the survival of *Myco. leprae* within the natural secretions. These assessments were made by comparing the infectivity of *Myco. leprae* following mouse footpad inoculation of bacilli isolated from freshly discharged specimens with bacilli retrieved from aliquots of the same nasal discharges allowed to dry under standardised external environmental conditions for varying periods of time.

IDENTIFICATION OF *MYCO. LEPRAE* FROM NASAL DISCHARGES

From all 31 nasal discharges the stained acid-fast bacilli had the morphological characteristics of *Myco. leprae,* none of the isolates produced cultures of mycobacteria on Loewenstein-Jensen medium cultured at 30, 34, or 37°C and all isolates following mouse footpad inoculation multiplied and gave growth curves identical to those obtained from isolates of *Myco. leprae* from skin lesions of patients with leprosy.

TOTAL YIELDS OF *MYCO. LEPRAE* FROM NASAL DISCHARGES

The data from these assessments are summarised in Table 3. Thus the 24-h collections showed a mean discharge of 2.4×10^8 acid-fast bacilli (range 4.1×10^5 - 1.5×10^9) with a mean morphological index of 12.8 (range 8 - 26) and the single nose-blow collections showed a mean discharge of 1.1×10^8 acid-fast bacilli (range 1.4×10^6 - 4.3×10^8) with a mean morphological index of 16.9 (range 4 - 29). Assuming that the morphological index is a reasonable assessment of the proportion of viable *Myco. leprae* these figures represent an average output/day from the nose of an active lepromatous patient of 31,000,000 live organisms and an average of 19,000,000 live *Myco. leprae* from a single early morning specimen of nasal discharge. This data stresses the relative importance of the early morning

TABLE 3

Number of Myco. leprae *(acid-fast bacilli) in nasal discharges from 31 patients with lepromatous leprosy*

	Single nose-blow (17 patients)	24-h nose-blow collection (14 patients)
	Number of acid-fast bacilli	
Range	1.4×10^6 - 4.3×10^8	4.1×10^5 - 1.5×10^9
Mean	1.1×10^8	2.4×10^8
	Morphological Index	
Range	4 - 29	8 - 16
Mean	16.9	12.8

nasal discharge in containing the bulk of bacilli discharged compared with the relatively meagre contribution during the rest of the day. In Table 4 is set out the total content of acid-fast bacilli in single or 24-h nasal discharges from lepromatous patients compared with the concentration of bacilli/g of tissue in their skin lesions. These data show clearly that there is a significantly higher proportion of solidly staining bacilli (morphological indices) in the nasal discharges compared with the bacilli in the skin lesions. Thus the mean morphological index of the bacilli from the nose was 16.3 (range 4 - 28) compared with the skin with a mean of 9.3 (range 2 - 19).

In 3 of the selected patients there was clear evidence from their clinical history that their current active disease had evolved as a relapse after many years of intermittent treatment with dapsone. As this history was suggestive of the emergence of dapsone resistance, bacilli from their nasal discharges and biopsies of skin were inoculated into the footpads of mice in groups of untreated and dapsone treated animals in order to determine the dapsone sensitivity of the *Myco. leprae* isolates. In all 3 patients the results showed that the bacilli were dapsone resistant in the skin lesions and that similarly dapsone resistant bacilli were being excreted from the nose.

SURVIVAL OF *MYCO. LEPRAE* IN NASAL DISCHARGES

This study was undertaken to determine the survival, and duration of survival, of *Myco. leprae* in nasal secretions *after* their discharge from the nose. Nasal discharges from 3 patients with active lepromatous leprosy and positive nasal smears were selected. A portion of each freshly obtained nasal discharge was set aside for immediate mouse footpad inoculation and the remaining nasal discharge was allowed to fall on a stone surface to replicate the every-day fate of such discharges ejected direct from the nose or indirectly in the sputum. The nasal specimens as they fell on the stone surface were freely exposed to the air in the dark and allowed to dry under the environmental temperatures and humidities defined in Table 5. Aliquots from each specimen were taken from the surface of the stone at various intervals of time from 1 to 10 days. All 3 specimens were sampled at 1 day, 2 of the specimens were sampled at 1.75 days and 3 days and 1 of the specimens sampled at day 1 was also sampled at days 7 and 10. All samples from the stone surface were dry from day 1 onwards. All the fresh samples of nasal discharges and those taken after drying from the stone surface were homogenised and inoculated at 3 acid-fast bacillary concentrations into the footpads of mice. On the basis of these data it was possible to determine the proportion of *Myco. leprae* surviving in dried nasal discharges compared with the viability of the bacilli in their respective fresh nasal secretions. The results of these studies are summarised in Table 5 from which it can be concluded that there is full survival of *Myco. leprae* in nasal discharges allowed to dry for 24 h, and that 10% of *Myco. leprae* survive for 1.75 days in dried nasal discharges. With 1 exception no viable bacilli were detected in nasal discharges allowed to dry for 3, 7 or 10 days. The 1 exception was from a nasal discharge dried for 7 days, where 2/12 mice inoculated with the highest dose of bacilli showed bacillary multiplication in the footpads. On the basis of this small proportion of isolates after 7 days of drying and the fact that the same dried specimen gave no multiplication after 3 days of drying it must be concluded that there were few survivors and certainly less than 1%.

TABLE 4

Data comparing Myco. leprae *(acid-fast bacilli: AFB) in the nasal discharge and skin from 11 pairs of patients with lepromatous leprosy*

	Nasal discharge		Skin biopsy	
	Total yield of AFB	Morphological Index	Yield of AFB/g skin	Morphological Index
	1.6×10^8	14[a]	3.5×10^7	7[a]
	7.5×10^7	26	3.2×10^7	16
	1.9×10^7	11	1.8×10^7	9
	4.1×10^5	18[a]	5.5×10^8	9[a]
	4.3×10^8	19	3.9×10^8	5
	8.3×10^6	18	3.2×10^9	19
	3.4×10^8	28[a]	3.1×10^8	5[a]
	5.9×10^7	19	2.1×10^9	2
	3.0×10^6	15	1.5×10^8	10
	1.8×10^7	4	7.0×10^8	9
	3.2×10^8	8	2.0×10^9	12
Mean	1.3×10^8	16.3	8.6×10^8	9.3

[a] *Myco. leprae* from these sites proved to be dapsone resistant in the mouse footpad test.

TABLE 5

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

Number of nasal secretions tested	Time after discharge (days)	Survival of *Myco. leprae*[a] (%)
3	0	100
3	1.0	100
2	1.75	10
2	3.0	0
1	7.0	<1[b]
1	10.0	0

Nasal secretions allowed to dry in the dark at a mean temperature of 20.6°C (19.8 × 21.8°C) and mean humidity of 43.7% (35 - 47).

[a] Assessed as infectivity in the footpads of mice.

[b] Growth of *Myco. leprae* obtained in only 2 of 12 footpads.

Discussion

The application of quantitative bacteriological assessments of acid-fast bacilli to nasal discharges from patients with active lepromatous leprosy and the further assessment of the identity and viability of these bacilli based on the mouse

footpad infection, have reestablished the importance of nasal infections in the aetiology and epidemiology of leprosy.

Thus the quantitative assessments of acid-fast bacilli in nasal discharges from the present studies and similar studies recently published (Rees and Ridley, 1973; Rees and Meade, 1974) have established beyond doubt that millions of bacilli are discharged daily in nasal secretions from lepromatous patients with active and, importantly, early disease. When these millions of bacilli are being discharged from the nose the patients may well be unaware that they have leprosy and clinically they have insignificant skin lesions. Moreover, biopsies of skin from these very patients, or from patients with more advanced skin infections, frequently harbour bacilli with a lower morphological index than in their nasal discharges. From this data and the elegant studies of Pedley (1970) who has shown that relatively few, if any, bacilli are discharged from closed lesions in the skin, it is clear that the main source of *Myco. leprae* discharged into the environment must be from the nose and upper respiratory tract. From our current systematic studies on the bacteria in nasal discharges from 31 patients, it has been established beyond doubt that the acid-fast bacilli in the nasal discharges are not contaminating culturable mycobacteria, but from their behaviour in the mouse are indisputably identified as *Myco. leprae.*

Having established from these series of patients in India the very large numbers of *Myco. leprae* discharged within single or daily accumulations of nasal secretions, and bearing in mind the biological similarities of nasal secretions and sputum and similarities in their every-day ejection and disposal by patients with leprosy or patients with pulmonary tuberculosis, it seemed essential to know the number of *Myco. tuberculosis* discharged in the sputum of patients with pulmonary tuberculosis. Comparable data provided by Rees and Ridley (1973) and Rees and Meade (1974) have shown that patients with advanced pulmonary tuberculosis discharge in their sputum a similar order of *Myco. tuberculoses* as is discharged in nasal secretions from patients with similar order of *Myco. tuberculosis* as is discharged in nasal secretions from patients with active lepromatous leprosy. While these similarities in the nature of the discharges from leprosy and tuberculosis patients and their comparability in bacillary content do not justify the conclusion that the transmission of the two infections are similar, it is of interest that Rees and Meade (1974) have shown that the attack rates of leprosy and tuberculosis are very similar where figures are available for both diseases in comparable areas.

Having established beyond doubt that the large number of acid-fast bacilli in nasal secretions are *Myco. leprae,* that the number of *Myco. leprae* discharged daily from the nose is comparable to *Myco. tuberculosis* discharged in sputum from cases with pulmonary tuberculosis, and the physiological similarity of these discharges, it was of the utmost importance to determine whether *Myco. leprae* survived in nasal secretions *after* their discharge. This information was of the greatest importance because it has long been established that the transmission and epidemiology of the spread of tuberculosis is dependent upon the significant, and unusual survival of *Myco. tuberculosis* in desiccated specimens of sputum (see Caldwell, 1925). Hitherto, no studies have been undertaken to determine the survival of *Myco. leprae* outside the body, and particularly within natural secretions. Our data show that significant numbers of viable *Myco. leprae* can survive in dried nasal discharges for 1 to nearly 2 days and probably very reduced numbers of viable *Myco. leprae* may persist in these natural excretions for even 7

days. Such information could have only been obtained with the establishment of an animal model and has been dependent upon the mouse footpad infection, since *Myco. leprae* has still not been cultured *in vitro*. However, these findings are of paramount importance, since they establish for the first time that *Myco. leprae* can survive for a significant time outside the body and within natural secretions. These findings in conjunction with the insignificant numbers of *Myco. leprae* discharged from the skin of leprosy patients provide overwhelming evidence against the current hypothesis that the transmission of leprosy is predominantly dependant upon prolonged and close skin-to-skin contact. Our data is consistent with the uniform epidemiological findings in leprosy that less than 50% of patients with leprosy can be traced to a known contact. Our findings are also consistent with the likely possibility that patients who contract leprosy may well be infected with persisting viable bacilli shed into the environment several days previously by an index case. These findings still leave the route of infection undetermined. While the similarities between tuberculosis and leprosy as outlined may well favour the nose or lung as the site of entry, they do not exclude the possibility of entry via the alimentary tract or via the skin surface. It is likely that further studies using the mouse model will play an important part in elucidating these various possibilities. Current and preliminary studies suggest that aerosols of *Myco. leprae* can give rise to systematic infections in mice.

The patients from whose nasal discharges these detailed bacteriological studies were made, were by no means exceptional. A tight time schedule, both for air transport, and immediate processing on arrival in London, meant that specimens could be obtained and despatched to London on only one day in the week. Specimens were selected on the basis of a bacterial index of 5 or 6 and high morphological index in the nasal discharge from patients who happened to arrive early on that day, or overnight, or at most 48 h previously, the point being that patients could not be admitted to hospital without the promise of immediate chemotherapy and nasal care. Many suitable patients arriving on other days, thus could not be used. Clearly we are not dealing with the exceptional few. Excluding patients with borderline leprosy and those in ENL, whose nasal condition had already been transformed by chemotherapy, there were in the series as a whole 333 patients with nasal discharges positive for *Myco. leprae*. Among these a bacterial index of 5 or 6 in the discharge was encountered in 208, or 60% on first arrival, and in most of them, this was the second specimen of the day. As proved in the material sent to London, the early morning specimen, as in tuberculosis, was the greatest in importance. There can be no reasonable doubt that the discharge of large numbers of viable *Myco. leprae* from the nose is a general attribute of untreated lepromatous leprosy.

The relation of the nasal discharge to clinical type and stage of the disease has several points of interest. Contrary to traditional beliefs, the heavy involvement of the nose reflected in the nasal discharge is not something which develops gradually as lepromatous leprosy progresses. Its relationship is not with the length of history of the lepromatous condition, but with its degree of *activity*.

The presence of a highly bacilliferous nasal discharge in *early* lepromatous leprosy is of particular interest and importance. In this series, patients in whom lepromatous leprosy arose as a degeneration from an earlier borderline condition were distinguished from those in whom the lepromatous type appeared from the start, but in both groups the onset of clinical lepromatous leprosy was associated very quickly with, and in some cases preceded by, symptoms of nasal involvement

with discharge. Very often the external appearance of the nose and face gave no clue to the severity of the condition in the nasal mucosa.

In fully developed lepromatous leprosy, gross pathological changes in the nose, secondary infection, and the effects of even intermittent chemotherapy, combine to reduce the importance of the nasal discharge, which tends to be reduced both in amount and in bacillary content, both where bacterial and morphological indices are concerned. Nevertheless, the discharge is persistent, and it once again assumes great importance as soon as there are signs of exacerbation or recrudescence, when a voluminous discharge of exceedingly high bacillary content may be encountered, notably in patients with the histoid type of the disease.

The extraordinary sensitivity of *Myco. leprae* in the nose to even small doses of dapsone was well brought out in this study. The nasal discharge can diminish very greatly in volume and bacillary content within a few weeks, well before clinical improvement in the skin condition is apparent. The nasal discharge is thus a quite sensitive guide as to whether dapsone is being taken or not. The absence of a bacilliferous nasal discharge in a patient with active lepromatous leprosy as a rule admits of only two interpretations. Either chemotherapy has been taken in the recent past, whatever the patient may say, or the nose is blocked with hard encrusted exudate. A copious bacilli laden discharge in a patient with active lepromatous leprosy likewise has two interpretations. In general, it is strong evidence that dapsone has not been taken. In rare circumstances, in a patient with a long history of chemotherapy, it may be indicative of exacerbation with sulphone resistant organisms.

The striking difference between the findings in early lepromatous leprosy and those in borderline leprosy is another matter of great interest. The rarity of a bacilliferous nasal discharge in borderline leprosy in our series is entirely in line with the findings of Pedley (1973*a*), and is in marked contrast with the frequency and severity of the infection in the nose in very early lepromatous leprosy. Clearly, the nasal mucosa reflects in a very sensitive way, the immunological competence of the body as a whole. Where this is congenitally lacking, or is depressed for any reason, the nasal mucosa becomes a highly significant site of predilection for *Myco. leprae*, where the bacillus is able to establish itself and multiply more intensively than in the skin.

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A Clinical Study of the Nose in Lepromatous Leprosy

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A detailed study of the nose in cases of lepromatous leprosy was undertaken at Victoria Hospital, Dichpalli, India and the results correlated with the general clinical findings. The histological details of the study will be presented elsewhere. The signs and symptoms of nasal involvement are described and it is stressed that this involvement occurs early in the disease process. The importance of all leprosy workers being aware of nasal involvement is pointed out and it is recommended that facilities for local care of the nose in leprosy should be established wherever the disease is treated. Possible mechanisms whereby leprosy may be transmitted are discussed.

Introduction

The late results of nasal involvement in lepromatous leprosy are well recognized and have been widely documented in the past. The absorption of the bony nasal skeleton and destruction of the cartilaginous nasal septum give rise to the typical external deformity of the nose which differs from that seen in lupus vulgaris, syphilis and other granulomatous diseases affecting the nose. In contrast, the nature of the intranasal lesions occurring early in lepromatous illness have never been fully or systematically investigated (Jaffe, 1971). Stanton (1964) reported a case of leprosy presenting primarily with nasal obstruction, but, considering the great importance of the nose in lepromatous leprosy, the paucity of detailed study is somewhat surprising. Davey (1972) while working at Victoria Hospital, Dichpalli, India noticed abnormalities of the nasal mucosa and felt that his observations merited detailed and specialist study. As a result of this initiative the author, at that time a registrar in E.N.T. surgery at a London teaching hospital, was invited to spend 3 months at Victoria Hospital in the winter of 1972-1973, and a further period of 1 month in 1974.

The patients that were studied fall into two separate groups:

Group A: 34 patients with early lepromatous leprosy were studied in detail. Clinical, including full nasal examination, skin and nasal smears, collection of nasal secretions ("Nose-blows"), lepromin testing and skin and nasal biopsies were carried out on all patients, although in a few cases, one or more investigations were not done for unavoidable reasons. In most cases clinical and intranasal photographs were taken.

Group B: Approximately 150 other patients were assessed clinically and rhinologically while selecting patients for Group A. Although these patients did not undergo the same intensive investigation, they were all carefully examined,

many on repeated occasions, and all underwent routine skin smearing. Nasal smears and "nose-blows" were obtained from about one half of this group, and many had lepromin tests and nasal or skin biopsies performed.

This group therefore consists of patients with all stages of lepromatous leprosy, from early to advanced, including some with borderline elements and also patients with borderline leprosy which was in the process of downgrading to lepromatous.

The Clinical Manifestations in the Nose

(A) SYMPTOMS

In India attention to hygiene of the upper respiratory tract and thorough cleansing of the nose and throat is an important part of the normal daily routine for many people. Thus patients were always ready to discuss the state of their nose and, while the initial reason for attending the hospital was often the observation of a cutaneous patch, sensory disturbance, ulceration or deformity of the extremities, etc., nasal symptoms were extremely common and readily admitted on direct questioning if not previously volunteered.

The symptoms of lepromatous involvement of the nose are:

(i) *Nasal obstruction* which is due to narrowing of the nasal airways by granulomatous infiltration of the mucous membrane lining the nasal cavities. Patients suffering advanced intra-nasal changes (*vide infra*) may complain of a sensation of obstruction despite apparently patent nasal passages: This has been described as a common symptom of atrophic rhinitis of non-leprous origin (Simpson *et al.*, 1967) and is probably associated with the accompanying loss of common sensation causing lack of perception of the normal inspiratory and expiratory air currents. It should be noted that obstruction may initially be unilateral, although, especially in more advanced disease, bilateral obstruction is more common.

(ii) *Crust formation* is caused by drying of the nasal secretions which are often increased in infections of the nose, including leprosy. As the crusts harden they become adherent to the mucous membrane and the patient may complain of difficulty in clearing them from his nose. Crusts frequently become secondarily infected and may to others be foul smelling, even though the patient himself does not notice or complain of the smell.

(iii) *Bleeding and discharge.* This does not often take the form of frank epistaxis. More frequently the muco-purulent discharge or sticky exudate that is produced is stained with fresh or stale blood.

(iv) *Pain and headache* are not commonly a feature of nasal involvement in leprosy. Should a history of these symptoms be obtained, additional or alternative pathology should be suspected. In the present series only one patient complained of true nasal pain which could not be ascribed to a cause other than leprous infection of the nose.

(v) *Miscellaneous.* Two patients complained of a burning sensation and one of "stickiness" in the nose.

The incidence of common symptoms in 77 unselected patients with lepromatous leprosy is summarized in Table 1.

(B) INTRANASAL CHANGES

Patients were examined by routine anterior and posterior rhinoscopy and details of these techniques may be found in the standard textbooks of

TABLE 1

Incidence of nasal symptoms in 77 patients with lepromatous leprosy

Symptom	No. of patients	%
Obstruction	51	66
Crust formation	57	74
Bleeding	40	52
Total with symptoms	72	94
Total with *no* symptoms	5	6

Otorhinolaryngology. For those unfamiliar with the normal appearance on anterior rhinoscopy it may be helpful to mention this briefly. The nasal vestibule, normally hairy, is lined by ordinary skin which merges posteriorly with the nasal mucosa. This is normally pink or reddish-pink in colour, smooth, shiny and moist from the thin layer of mucus that coats it. In vasomotor or allergic disorders the mucosa is paler than normal and may be tinged with mauve, while in inflammatory conditions the redness of the mucosa becomes increased. Medially the septum, which may be deviated from the midline, is seen and laterally on either the most obvious landmark is the bulky inferior turbinate. This juts out into the nasal cavity almost meeting the septum and may be mistaken for a polyp or a tumour by the inexperienced. Higher in the nasal cavity above the level of the inferior turbinate is seen the smaller middle turbinate, but it is unusual, in a normal nose, to see the superior turbinate. It should be remembered that, in the sitting position, the floor of the nasal cavity passes horizontally backwards.

It seems logical considering the findings, and also taking into account the progression of intra-nasal changes in untreated lepromatous leprosy, to classify these changes as early, intermediate and late, while remembering that each sub-group merges with its neighbour.

(i) *Early changes.* The earliest intra-nasal change specifically recognizable as leprosy is a pale, often yellowish, thickening of the mucous membrane. This presented most frequently as a generalized nodular infiltrate, but discrete raised nodules or plaques, 2 - 5 mm across, were observed arising in areas of apparently normal mucous membrane. Abnormal dryness of the nasal mucosa was often seen and may be due to damage to parasympathetic nerves which are secreto-motor to the mucus glands. Mild inflammatory changes were occasionally observed, but they are not a prominent feature of early disease. However areas of the nose showing certain minor irregularities of the mucosa which could not be accepted on clinical examination as specifically representing leprous changes, turned out to be involved histologically. Similarly when biopsies were taken it was not uncommon to find a marked submucosal thickening when the visible surface of the mucosa was unremarkable. In areas that were, clinically, heavily involved the considerable infiltration and thickening of the submucosa was striking and often had a characteristic "gritty" feeling when incised with a scalpel. This submucosal infiltration frequently caused a considerable increase in the width of the nasal spetum. Its thickness, both anteriorly and posteriorly, could be increased by a factor of up to three times. The size of the inferior turbinates shows less apparent

increase as the erectile tissue, which they contain and which gives bulk to them, is merely replaced by the lepromatous infiltration. Nasal biopsies were all taken with the use of cocaine as a surface local anaesthetic agent. This is a strong vaso-constrictor and results in rapid shrinking and blanching when applied to normal nasal mucous membrane. It is interesting to note that this does not occur when there is much lepromatous infiltration of the mucosa.

(ii) *Intermediate changes.* Lepromatous infiltration of the nasal mucosa increases progressively, causing obstruction to the nasal airways. When this occurs, patients attempt to clear the nose by various manoeuvres such as picking and strenuous blowing, which result in ulceration and increased inflammation. Amongst the present patients any marked ulceration was confined almost entirely to the most anterior part of the nasal septum and appeared to be clearly related to direct trauma. Certainly in patients who attended for regular nasal treatment and who were instructed not to pick or traumatize their nose, any ulceration or inflammatory changes that were initially present were noted to undergo rapid healing. It is in these patients with intermediate nasal pathology that the secretions of the nose are most interesting. It has been noted that in early intra-nasal involvement the mucous membrane may be more dry than normal, but at this stage it was often more moist. The discharge ranged from a thin, clear secretion to a thick, opaque, grey or yellowish material. This discharge was most frequently, muco-purulent or exudative and was at times bloodstained. Often it was strung across the nasal cavities giving the appearance of adhesions or atresia. Above all, in untreated cases, it invariably contained large numbers of viable *Myco leprae* (Davey and Rees, 1973). In dry atmospheric conditions, the secretions thicken and give rise to crust formation. In this group, as the nose became blocked, crust formation was apparent even in those few patients who did not actually complain of nasal symptoms.

(iii) *Late involvement.* The classical triad of external "saddle" deformity, septal perforation and atrophic rhinitis is well documented both in the standard leprosy textbooks and in many original articles. Amongst others, Job, Karat and Karat (1966) have described the histopathological changes that accompany the clinical signs and suggest the mechanism whereby deformity occurs.

Inside the nose massive crusting, often foul smelling due to colonization with saprophytic bacteria or fungi, large perforations frequently amounting to total loss of the cartilaginous septum, and atrophy of the normally bulky inferior turbinates were all commonly observed. It is interesting to note that in a group of 19 patients with severe atrophic changes in whom the whole nasal cavity was visible, in 9 the mucous membrane at the level of the middle turbinate and above appeared normal.

Adhesions of scar tissue between the lateral and medial walls of the nose were observed in a relatively small number of patients and ranged from, at the least, a tenuous band of fibrous tissue between the septum and the inferior turbinate to total atresia of the nostril, this latter finding being noted in one patient. These adhesions were seen only in treated patients when resolution and healing of previously active intra-nasal infiltration had taken place.

Sites of Involvement and Progression of Infection

Table 2 summarizes the sites involved clinically in the 34 patients of Group A with early lepromatous leprosy. In the anterior part of the nose no area that was

TABLE 2

Clinical involvement of different intranasal sites in 34 patients

Site	Total patients	Definite involvement	Possible involvement	No involvement
Inferior turbinate anterior	34	33 (97%)	—	1
Septum anterior	34	28 (85%)	3	3
Septum posterior[a]	24	6 (25%)	4	14
Inferior turbinate posterior[a]	24	3 (13%)	1	20
Middle turbinate[b]	27	4 (?Higher)[b]	3	20

[a] In 10 patients posterior rhinoscopy did not give adequate diagnostic information.
[b] In 7 patients the middle turbinates were obscured by gross involvement anteriorly. The probability is that they were involved in these cases, and the true figure therefore is in the region of 40%.

thought to be clinically involved was histologically negative. Examination of the posterior part of the nose was less reliable and several sites that were accepted as being clinically normal showed histological infiltration when biopsied. It should be pointed out that the very technique of examining the posterior part of the nasal cavities (per-orally with a small mirror) means that detailed close-up inspection is not possible. However of 19 patients in Group B with advanced lepromatous leprosy in whom the post nasal space was visualized, 12 (63%) had definite involvement of the septum or inferior turbinates posteriorly.

Therefore it is concluded that lepromatous infiltration of the nasal mucosa commences anteriorly, and particularly in the inferior turbinate, spreading more widely in the nasal cavity as the disease progresses. This is supported by the observation of smears of the nasal mucosa taken from multiple sites which confirmed that the most heavily bacillated site was the anterior end of the inferior turbinate, and that this site was less likely to be negative for *Myco. leprae* than any other (Davey and Barton, 1973). The importance of the anterior end of the inferior turbinate will be discussed *(vide infra).* The steady progression of intra-nasal pathology in untreated lepromatous leprosy is frequently in advance of the systemic changes. Indeed the Morphological Index (M.I.) of bacilli in the nasal biopsies of patients in Group A was greater than 30% in 75% of biopsies, 5 - 30% in 15%, and less than 5% in only 10% of biopsies. In every instance these figures were markedly higher than those recorded in the corresponding skin smears.

Fig. 1 illustrates a patient typical of Group A who showed little in the way of external sigmata. However, his nose was extensiely involved internally with perforation of the septum and atrophic changes. Fig. 2 shows a wooltipped probe passing through the septal perforation. These two photographs also illustrate that gross intra-nasal changes may occur in the absence of any external nasal deformity.

Prevalence of Nasal Involvement

The high prevalence of nasal involvement in lepromatous leprosy has, of course, been accepted for many years. Typical findings are those of Dharmendra and Sen (1948) who found *Myco. leprae* present in over 90% of nasal scrapings in a large series of lepromatous cases.

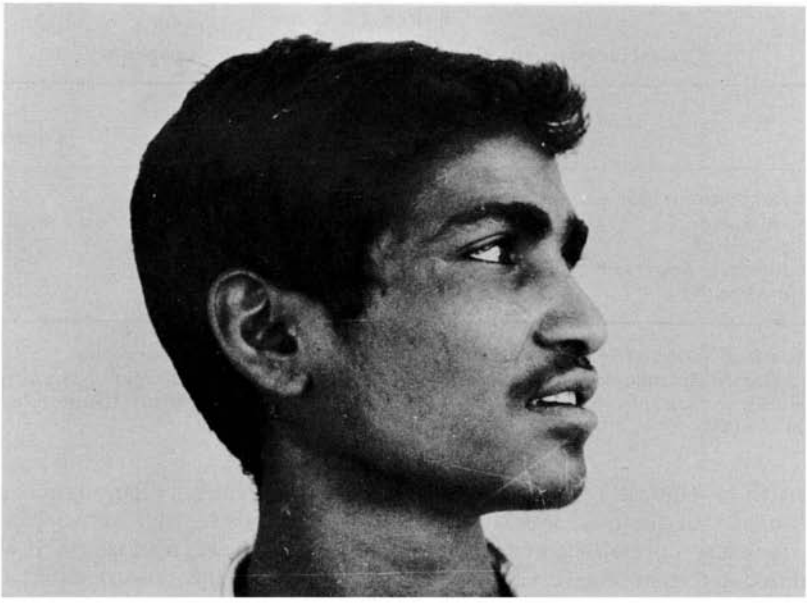

Fig. 1. A typical patient from Group A.

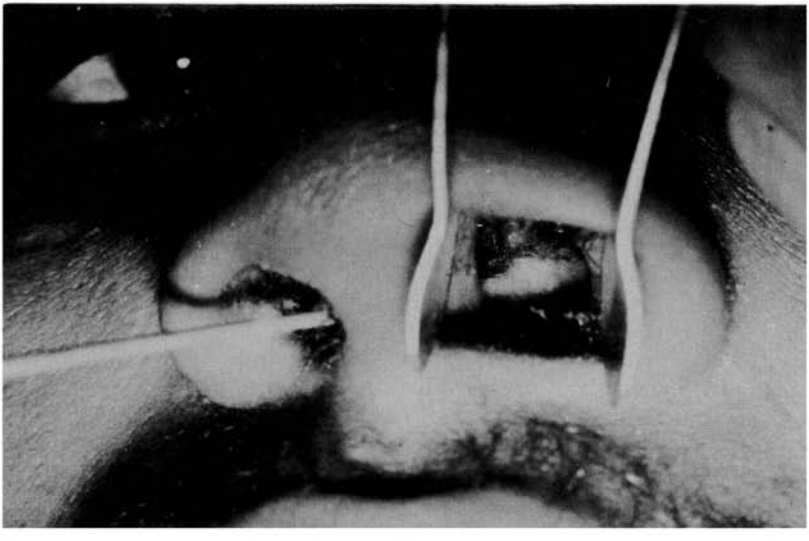

Fig. 2.

Thirty three out of 34 (97%) of our Group A patients had clinical changes in the nasal cavities recognizable as leprosy, and in only 7 (6%) of 118 cases with lepromatous leprosy in whom sensation and olfaction were tested (see below) did the nose appear free from lepromatous involvement. However all these patients were receiving regular chemotherapy and it is clear now that, provided the patient

receives adequate treatment early in the course of the disease, that even heavily involved noses may revert to a state of clinical normality. Allowing that apparently normal mucous membrane may be histologically positive, it can be firmly reiterated that at least 95% of all patients with lepromatous leprosy will have nasal involvement and, that this involvement occurs early in the disease process.

Loss of Olfaction and Common Sensation in the Nose

Olfaction and sensory loss were measured in 150 unselected leprosy patients, and for fuller details of olfactory loss the reader is referred elsewhere (Barton, 1974 *a*). Summarizing the findings, the sense of smell was found to be impaired in 38% of patients, but in patients with lepromatous leprosy, this figure becomes 44%. The incidence and severity of olfactory loss were closely related to the severity of the clinical changes in the nose. Sensation was measured by gently probing the nasal mucosa with cotton wool tipped sticks. It was possible, by considering both the voluntary and involuntary responses of the patient, to establish three categories:

(i) No apparent sensory loss

(ii) Impaired sensation

(iii) Severe sensory loss.

Cochrane (1964) points out that lepromatous nasal involvement does not necessarily imply anaesthesia, but 65% of 118 lepromatous patients tested had some degree of sensory loss. The present findings, including the relation of sensory loss to the clinical state of the nose, are summarized in Table 3. It has already been pointed out that ulceration of the nose is normally confined to the anterior part of the septum and generally undergoes rapid healing when the patient is persuaded to stop "picking" or violently blowing or otherwise attempting to clear the nose. Reduced sensation of the nasal mucosa is clearly a most significant factor in the aetiology of nasal ulceration and it is therefore of great importance that patients should receive instruction in the care of the nose, just as they do, in many places, for their hands and feet. The rate of healing in the

TABLE 3

Loss of common sensation in the nose according to severity of intranasal changes

Intranasal change	Number	No sensory loss	Some impairment of sensation	Severe sensory loss
Normal	7	7	—	—
Early	34	26	8	—
Intermediate	41	6	35	—
Late	36	2	16	18
Total	118	41 (35%)	59 (50%)	18 (15%)

Note: (1) Lepromatous patients only. (2) Overall 65% (77/118) had some degree of sensory loss.

nose compares favourably with that of normal nasal mucous membrane: indeed, over 250 separate dissected and "punch" biopsies were taken from the nose in the course of these studies and the sites of biopsy were noted to be well healed within 48 - 72 h.

Treatment of the Nose

Institution of treatment with dapsone or other effective systemic drugs in early lepromatous leprosy results in rapid clinical and histological improvement of the nose. Seven of the Group A patients were re-assessed 6 - 8 weeks after commencing dapsone. Although the period was short and the numbers small, all 7 of these patients noticed improvement in their nasal symptoms and rhinoscopy confirmed that some regression of the intra-nasal changes had taken place.

Five of the 7 had nasal smears repeated and in each of these a dramatic fall in both the Bacteriological and Morphological Indices was noted. All 7 patients had repeat nasal biopsies performed and in 4 of these a definite change towards granularity of the bacilli was seen. 16 of the group A patients were reviewed one year after their first attendance. The results, including histological studies are at present being processed, but the clinical improvement, both systemically and nasally, of these patients was remarkable.

These findings confirm those of Browne (1966) and Pedley (1973) who, among others, have shown a rapid decrease in the numbers of viable bacilli present in nasal smears and in the mucus itself, respectively, when anti-lepromatous chemotherapy is started.

However in later involvement, atrophic rhinitis and crusting frequently persists despite adequate chemotherapy. The symptoms caused by these late changes are often extremely distressing to the patient who is grateful for any help that can be offered.

It is strongly recommended that in all institutions and situations where leprosy is treated facilities should be established for the local care of the nose. Details of suggested methods of local treatment are presented elsewhere (Barton, 1973, 1974*b*) and the reader is referred accordingly. Reconstructive surgery may be of benefit to many patients with nasal deformity where facilities are available, but the details are beyond the scope of this present article.

Discussion

It is clear that the nasal mucosa is involved extremely early in the course of lepromatous leprosy and this involvement is often out of all proportion to that which might be expected from the routine clinical examination of the patient. In many of the patients who were studied heavy infiltration of the nasal mucosa was noted when the changes in the skin were barely perceptible. It is just these patients, whose nasal discharge has high Bacteriological and Morphological Indices, and who are therefore liable to spread the disease, that will fail to be spotted by inexperienced workers in control programmes. It therefore follows that all who are involved in the diagnosis of leprosy, whether in hospitals, village clinics or in peripatetic control programmes, should realize the full importance of examining the inside of the nose and of recognizing the various abnormalities that may be seen. If suspicious intranasal changes are seen, then a specimen of the nasal discharge or, alternatively, multiple nasal smears (Davey and Barton, 1973) should be taken and examined in the usual way for acid fast bacilli.

In the classification of leprosy the presence of nasal involvement indicates LL or BL disease or borderline disease in the process of "downgrading" with the nasal changes in advance of the systemic signs. During the course of this study no patients with stable purely borderline, BT or TT leprosy showed intranasal involvement even in those few cases where a patch on the face and nose extended to the skin of the nasal vestibule.

The transmission of leprosy is too large a subject to discuss fully in this paper, but certain facts have emerged during the course of this and related studies which should be considered briefly.

In untreated lepromatous disease (i.e. infectious leprosy) the daily discharge of viable bacilli from the nose runs into millions and greatly exceeds the rate of discharge from the skin. The different ways in which the bacilli are transported across the mucous membrane of the nose to the nasal cavities are described elsewhere (Barton *et al.*, 1973) and they are then discharged to the exterior by patients while talking, sneezing, blowing the nose and even simply while breathing. While a person is in close proximity to such a patient it is therefore certain that many thousands of bacilli will land on his skin, possibly being transferred to the mouth, eyes or nose, or be directly inhaled.

It has been shown that the site in the nose involved earliest and most consistently is the anterior part of the inferior turbinate, although later in the disease process there is little histological difference between this and other sites. However when examining a normal nose it is immediately obvious how the anterior end of the inferior turbinate juts out into the nasal cavity and therefore takes the initial force of the inspired airstream. Although the cooling effect of the inspired air reduces the temperature of the nasal cavities anteriorly by a greater degree than it does posteriorly, compared with central body temperature, this alone fails to explain the significantly greater involvement of the anterior end of the inferior turbinate compared with the anterior part of the nasal septum, opposite to it and at the same level in the nasal cavity.

Taken together these facts lead to the conclusion that viable leprosy bacilli are spread *from* the nose in patients with untreated lepromatous leprosy and that these bacilli are then inhaled by those with whom they come into contact. The possibility then arises that bacilli, trapped by the nasal mucus, may penetrate the mucous membrane, conceivably of the inferior turbinate, and thus enter the body at a favourable place or so-called "site of predeliction". Bacilli remaining in the mucus film would be swept backwards by the ciliated mechanism of the mucous membrane and eventually swallowed, while those bacilli not entrapped and remaining free in the airstream itself would be inhaled to the lungs and there come in contact with the mucus and mucous membrane of the bronchial tree.

Acknowledgements

My grateful thanks are due to Dr L. M. Hogerzeil, Director, Victoria Hospital, Dichpalli for allowing the study of patients under his care, to Dr T. F. Davey and Dr R. J. W. Rees for much help and encouragement, to Professor A. G. M. Weddell and Dr A. C. MacDougall who have been responsible for the histological studies in this and related projects, to Mr I. G. Robin and Mr G. P. Walsh-Waring and the Board of Governors of St Mary's Hospital, London for granting leave for study purposes and finally to The British Leprosy Relief Association (LEPRA) who supported me most generously during this time.

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Lepr. Rev. (1974), **45**, 145-152

The Value of Scrotal Biopsy in Leprosy

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Forty-five scrotal skin and underlying dartos biopsies from leprosy patients of varying types, duration and treatment status were examined for quantitative bacteriology and qualitative histology. 33% on homogenization and 34% on histology were positive for acid fast bacilli. The average bacillary load/g of positive tissue was 1.5×10^7. 45% of scrotal biopsies were positive against 42% of the skin patch when examined for qualitative changes diagnostic of leprosy. These changes were more marked in the scrotal biopsies in the borderline and lepromatous types. They were chiefly restricted to the neurovascular bundles with unaffected smooth muscle. A stained smear obtained from scrotal skin homogenate is recommended for bacteriological diagnosis as a superior method than routine multiple skin smears or nasal scraping. Repeated use of scrotal biopsies is emphasized when frequent observations of neurological changes are necessary.

Introduction

Both unstriated and striated muscle have been described as favoured sites for *Myco. leprae* in man. Nishihura, Sirset and Khanolkar (1960) reported the finding of *Myco. leprae* in smooth muscle cells of blood vessels in an electron-microscopic study of leprosy lesions. Hashizume and Shionuma (1965) reported finding *Myco. leprae* in and between smooth muscle cells of the iris in a similar study. The erector pili and dartos have been described by Harman (1968) and Esiri (1969) to contain *Myco. leprae.* Rees and Weddell (1968) described the striated muscle as a privileged site of *Myco. leprae* in the mouse and Pearson, Rees and Weddell (1970) have demonstrated the presence of *Myco. leprae* in human muscle. Convit, Arvelo and Mendoza (1960), Ishihara (1959), and Job (1969) have also described leprous myositis.

All these reports emphasize the presence of *Myco. leprae* in the actual muscle fibres and not in the interstitial tissue between the fibres.

Materials and Methods

Scrotal skin and underlying dartos muscle was biopsied from 45 male patients who were undergoing multiple biopsies of other tissues as a part of a larger study.

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Their age varied from 11 to 51 years. The duration of the disease since the appearance of the first symptoms varied from 3 months to 30 years. Five patients were untreated when first seen while 40 patients had received treatment with DDS for a period varying from one month to 30 years. These patients were studied clinically in great detail including bacteriology and were classified according to the Ridley-Jopling Scale using both clinical and histological features. (Table 1). Of the total 45 patients, 12 were tuberculoid, 22 borderline, and 11 lepromatous in type.

TABLE 1

Percent positivity, by histology, and bacillary load/g of tissue, of Myco. leprae *on homogenization in the various tissues examined*

Tissue	Positive by histology (%)	Homogenization bacillary load/g
Nerve	60	8.6×10^7
Lymphnode	25	4.4×10^7
Nasal Mucosa	22	2.0×10^7
Scrotal Skin	34	1.5×10^7
Skin	24	2.85×10^5
Muscle	8	2.6×10^5

An ellipse of scrotal skin with underlying dartos muscle, approximately 2 cm × 1 cm was obtained as a biopsy and divided into two equal halves, one half for homogenization and other half for histology. A manual glass homogenizer was used and bacillary count was done according to the method of Rees (1964). TRIFF (a combination of Trichrome and Fite Faraco) stain, which presents a consolidated picture showing acid fast bacilli in the tissue, was used. Similar studies were undertaken on biopsies of the skin from the most evident and active skin site, nasal mucosa, voluntary muscle, lymph node and nerve. Multiple skin and nasal smears and the sternal marrow biopsy was also obtained.

All homogenates positive for acid fast bacilli were plated on Jensen Lowenstein medium. No growth was seen in any case.

Results

Of the total of 45 scrotal biopsies, 40 were homogenized and 13 (33%) showed presence of acid fast bacilli. Of all the 45 studied by histology, 15 (34%) showed the presence of acid fast bacilli. The average bacillary load g of positive tissue was 1.5×10^7. Histologically, scrotal skin was next only to the nerves in positivity but in terms of bacterial load it was preceded by the nerves, lymph node and nasal mucosa. Nevertheless as compared to the skin, the bacillary load was almost a hundred fold greater. (Table 2).

Table 2 shows a comparative study between the skin patch and scrotal skin according to the classification when compared in the same patients.

45% of scrotal biopsies were positive against 42% of skin biopsies when examined for qualitative changes diagnostic of leprosy even though the skin site which was selected was a clinically involved patch while the scrotal biopsy was obtained from a clinically uninvolved area.

The histological changes were noticed more in the scrotal biopsies in the

TABLE 2

Comparative histological study for AFB between skin patch and scrotal skin according to classification in the same patients

Type	Total	Skin patch (%) positive for *Myco. leprae*	Scrotal skin (%) positive for *Myco. leprae*
Tuberculoid	12	5 (40)	3 (25)
Borderline	22	10 (45)	8 (37)
Lepromatous	11	4 (37)	9 (82)
Total	45	19	20

lepromatous type (88%) while skin changes were better observed in the tuberculoid type (40%).

The advantage of scrotal skin over other skin sites for the histological detection of bacilli is confined to the lepromatous side.

Of the 11 patients showing changes both in the skin patch as well as scrotal skin, 7 showed greater changes in the scrotal biopsies, 2 in skin patch, and 2 similar changes in both tissues.

Of the 3 lepromatous patients in this group one scrotal biopsy showed greater changes than the skin patch while the other two showed changes of equal intensity. In the borderline type, all the six scrotal biopsies showed greater changes than the skin patch. In the two patients of tuberculoid type, the skin patch changes were more marked than the scrotal skin.

Discussion

Our results demonstrate the much higher rate of bacterial positivity in scrotal biopsy as compared to the routine skin and nasal smear technique or even multiple skin smear or skin biopsy (Table 3).

TABLE 3

Percentage of samples yielding positive findings for Myco. leprae *by different procedures*

Procedure	% positive for *Myco. leprae*
Routine skin patch and/or ear lobule	12
Multiple smears	14
Nasal scraping	14
Scrotal skin on homogenization	33

Another equally and probably more significant finding on histology was that in almost all cases the involvement was chiefly restricted to the neurovascular bundles. The nerves showed Schwannian proliferation and infiltrate of macrophages and lymphocytes, the nature of the infiltrate corresponding to the

classification of the case and was the same type as seen in the skin or nerve of the same individual. The extent of the infiltrate was often more marked than seen in the most prominent skin patch. The presence of bacilli was also generally restricted to the site of the neurovascular bundles, being in the schwann cells and macrophages.

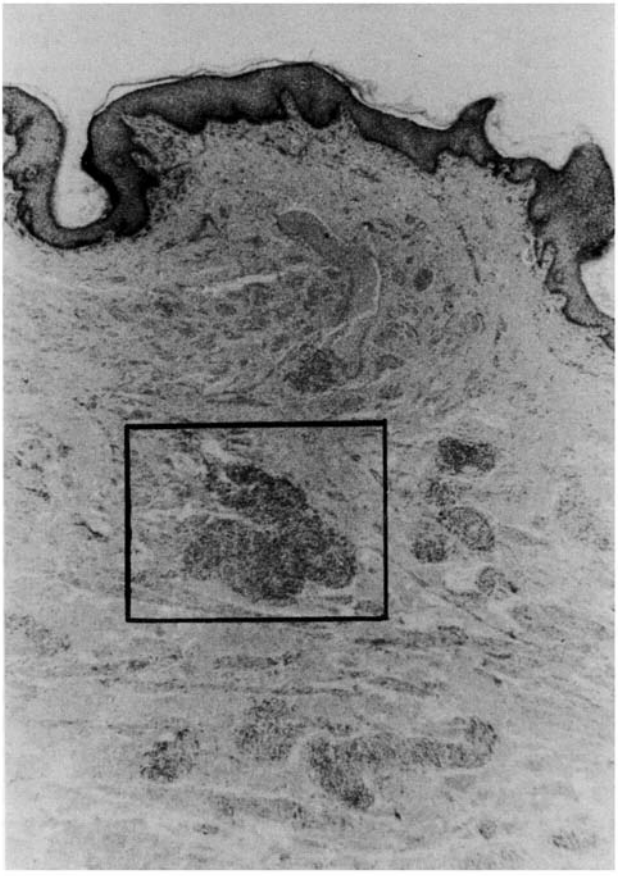

Fig. 1. Scrotal skin to show heavy cellular infiltration of the neurovascular bundles throughout the field.

Another remarkable feature was the absence of infiltrate and bacilli in relation to the smooth muscle fibre and bundles of the dartos. Infiltration of the dartos (true myositis) was seen only in 4 cases and even here it was of minimal nature as compared to the involvement of the neurovascular bundles. *Myco. leprae* were observed in the smooth muscles in 3 biopsies. These were solid and well preserved, the muscle architecture being normal in spite of their presence.

These histological and bacteriological results were observed even though none of these cases showed any evidence of clinical involvement of the scrotal skin.

In fact the presence of bacilli in lepromatous cases probably emphasises that

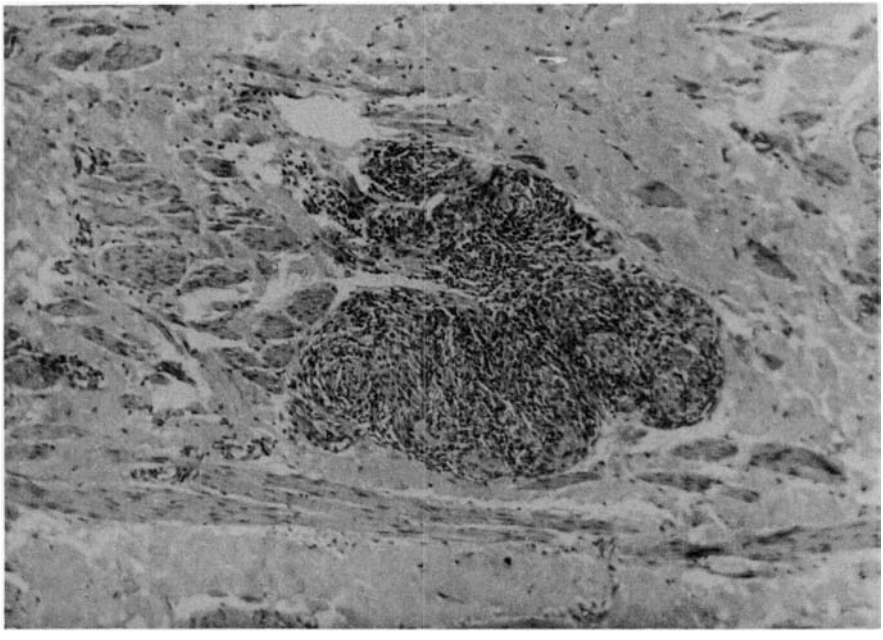

Fig. 2. Magnified view of the nerve in Fig. 1 to show the heavy cellular infiltrate. Note the normal muscle architecture.

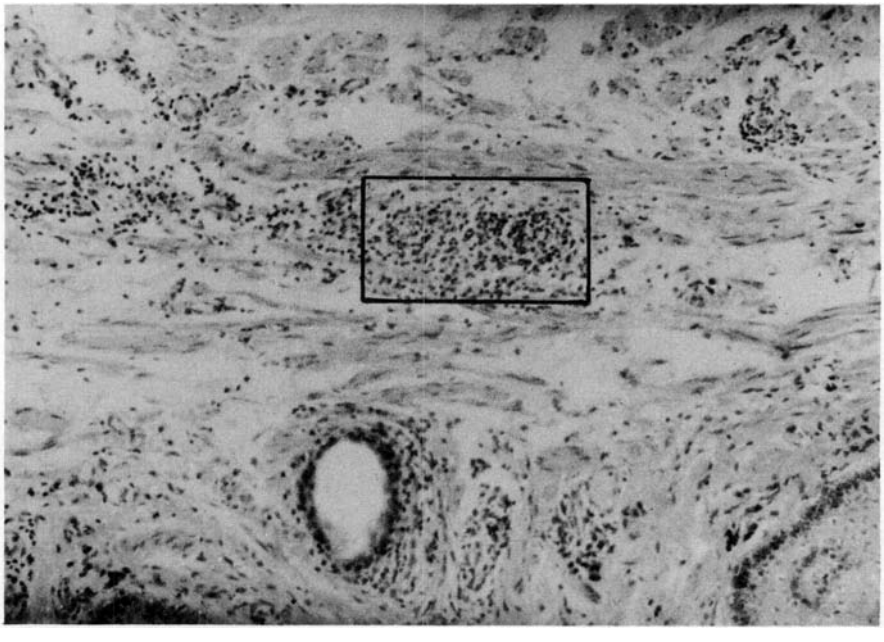

Fig. 3. Intermuscular cellular infiltration.

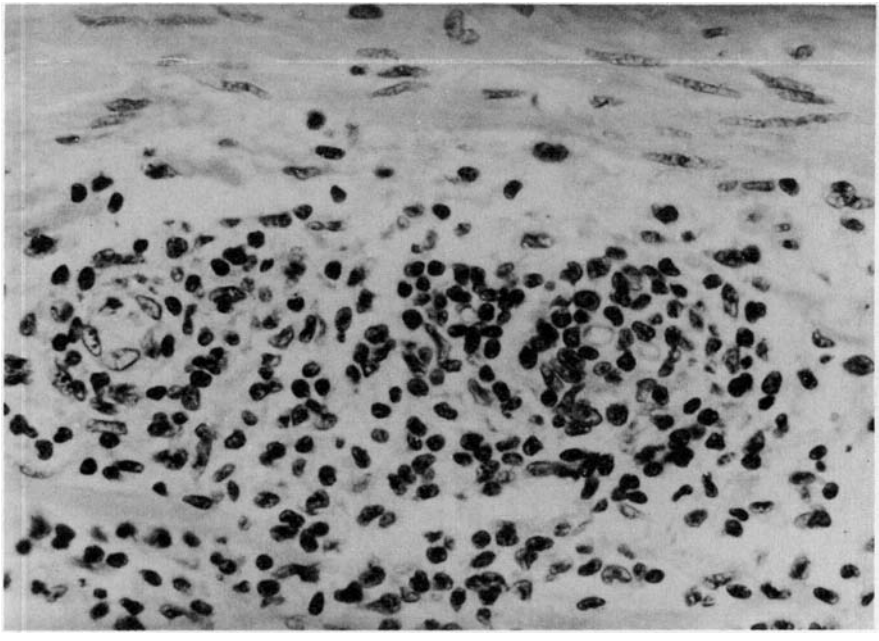

Fig. 4. Magnified view of the area seen in Fig. 3. Note the normal muscle fibres.

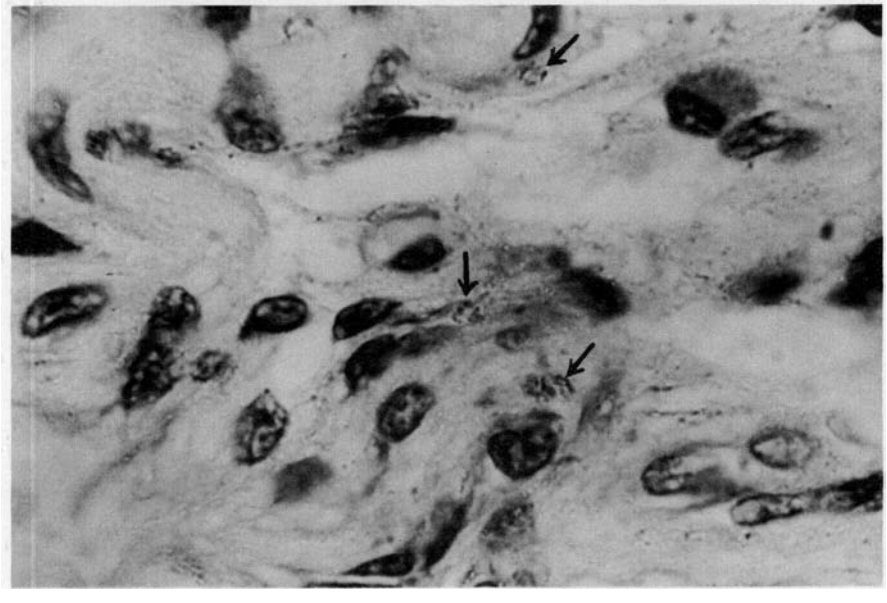

Fig. 5. *Mycobacterium leprae* in the Schwann cells of the nerves in the scrotal skin.

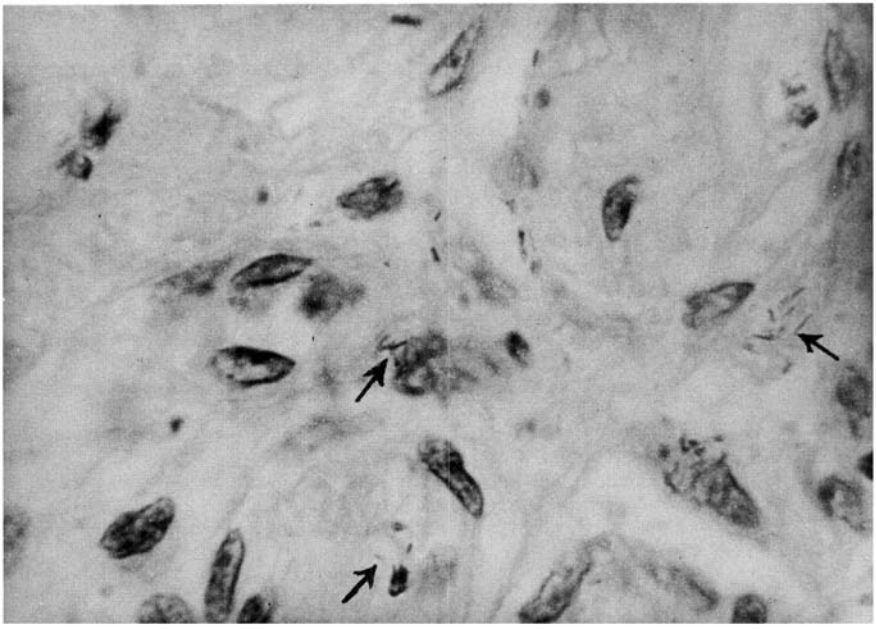

Fig. 6. *Mycobacterium leprae* in the scrotal muscle fibres in the same patient. Note the relatively better preserved bacilli.

scrotal biopsy will provide evidence of bacillation in long standing leprosy even where the skin may be negative bacteriologically. This may be because scrotal biopsy gives a better sampling of nerves than skin biopsy.

Since the larger nerves are in the deeper part of the dartos muscle, the depth of biopsy is considered important. After incising the skin, the pink muscle should be grasped by a toothed forceps, pulled out of the wound and excised with sharp scissors. One or two deep sutures help to close the wound and produce hemostasis. The resulting scar is unnoticeable.

The scrotal skin is more liberally supplied with nerves and these are larger than other cutaneous nerves. Presence of these nerves and a virtually unnoticeable scar, makes this site a suitable source for repeated observations of neurological changes, as in cases where the response to treatment may need to be studied at intervals.

Quantitative bacteriology by homogenization and qualitative histology gave similar findings for the presence of acid fast bacilli. Wherever histology facilities are not available, the presence of acid fast bacilli can be ascertained by the examination of a stained smear obtained from the homogenate. This would prove to be a superior method of bacteriological diagnosis than multiple skin smears or nasal scraping and could be particularly useful in field studies in the developing countries.

The nerves in scrotal skin showed definite changes in those patients especially with primary neuritis. This would indicate that the involvement of these nerves is a part of a generalized diffuse peripheral neuropathy.

Acknowledgement

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The Role of Punch Grafting in Eyebrow Replacement

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Many techniques of eyebrow replacement are now available, each with its own advantages and disadvantages. For complete replacement of eyebrows punch grafting has no particular advantage. However it can be recommended for restoring hair to the important medial end of an otherwise successful vascular island transfer in anyone distressed by hair loss in this area. Important technical details are described.

Many methods of eyebrow reconstruction have been advocated. Droogenbroeck (1971) has listed these as:

(1) Transplantation of small islets from the scalp.
(2) Transposition of scalp flap without artery pedicle (Antia, 1964).
(3) Temporal artery island scalp flap described by Brand (Antia, 1964).
(4) Free graft of scalp described by Gillies (Fritschi, 1971).
(5) Single hair transplant method of Arakaw (1967) otherwise known as the rice-planting technique.

He then goes on to describe the latter method in detail as practised by Kanazashi (Droogenbroeck, 1971). No one would deny that the technique of single hair transplantation can give cosmetically excellent results. But the transplantation of 280 individual hair follicles in two 2½ h sessions must be very tedious indeed. One can have nothing but admiration for the patience and skill of those who would devote so much effort to so worthy a cause.

At the other extreme free grafting is the easiest and least time consuming method of replacing lost eyebrows. It can give a good growth of hair, a little less luxuriant perhaps than the vascular island transfer but in societies where eyebrows are not normally bushy a quite adequate result. Great care must be taken to defat the graft but it must not be excessively defatted or the germinative cells which lie at the very bottom of each hair follicle will be lost. The chief advantage of the technique is that the transplant used can be so aligned as to allow the hairs to be directed in a natural direction.

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The Value of the Island Transfer

At the Schieffelin Leprosy Research Sanatorium we have preferred the vascular island transfer based on the temporal artery. When correctly performed it usually gives a luxuriant growth of hair. This bushy growth is preferred in India as eyebrows are normally bushy here and also because those who have feared ostracisation or contempt due to loss of eyebrows now have no doubt of their acceptance by society. There is a second and equally valid reason for continuing the use of the vascular island transfer. By teaching the technique the surgical trainees here learn the importance of gentle handling of tissues. Then when sufficient skill has been developed with this technique the surgeon can turn his hand to the valuable but somewhat more hazardous task of restoring sensation in partially anaesthetic hands by means of a neuro-vascular island transfer (Lennox and Ranney, 1973).

Problems With the Island Transfer

The island transfer may rarely fail completely. During dissection, unless sufficient care is taken, the temporal artery may be inadvertently severed. If so, the island should be defatted and transferred as a free graft. This is particularly unfortunate if a successful vascular island transfer has already been done on the other side because there may be diminished hair growth on the free grafted side.

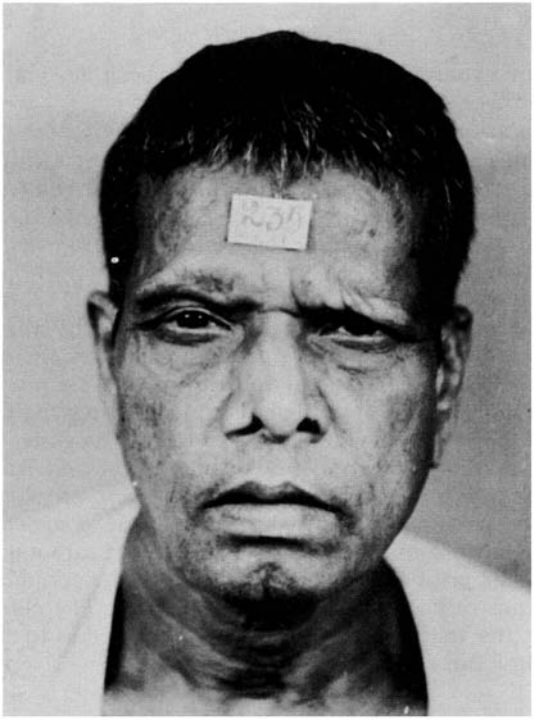

Fig. 1. The appearance of bilateral failure of eyebrow after failed temporal artery island scalp flap.

Post-operative hematoma or infection may also diminish or completely abolish hair growth. Hypertension and arterial vascular disease may reduce the chance of a successful transfer and are relative contraindications. Sometimes the cause of a poor result is unknown. Tortuosity of the temporal artery may be so great as to make it necessary to transfer a wide island which can later be reduced in width. Otherwise the most important more medial end of the transfer may be hairless. This complication is therefore preventable by carefully marking out the course of the artery with gentian violet pre-operatively. This may require exercises and therefore should be done before premedication is given. Then the island transferred is made wide enough to include the artery, and trimmed 3 months later. All these complications are usually preventable by good surgery and proper selection of cases.

The most distressing problem for which there has seemed no solution arises when the branch of the temporal artery chosen breaks up into a mass of little branches before reaching the medial end of the proposed eyebrow transfer. The possibility of punch grafting this end, using the same method as is used for scalp replacement, was considered (Orentreich, 1971). But before this could be tried a patient presented who had had a total failure of the island transfer on the right side and therefore refused a similar procedure on the left (Fig. 1). We could not guarantee the free graft would produce the generous amount of hair that we expected from a successful vascular island transfer on the other side, therefore

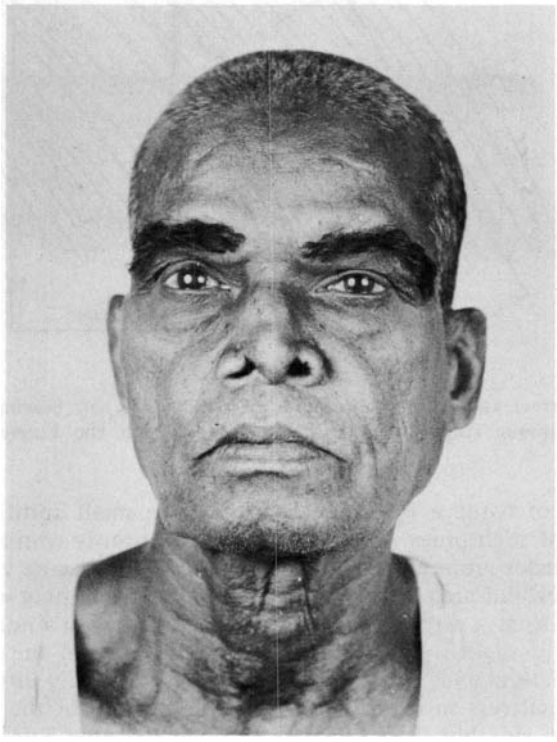

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Fig. 2. The same patient 4 months after eyebrow replacement by the punch grafting method.

punch grafting was performed on the right at the same time as the contralateral vascular island transfer. The island in this case also failed to produce any hair at all for no apparent reason although the technique was flawlessly performed and no other cause of failure could be found. The punch grafting also failed because the punch was not inserted at the correct angle (see below). Subsequent punch grafting was correctly done bilaterally with a good result (Fig. 2). Since then this technique has been used for other cases to enhance the growth at the medial end of a vascular island transfer.

The Technique of Punch Grafting

The technique of punch grafting is not very difficult but certain principles must be carefully observed. The donor area must be one which promises continued hair production if baldness later should occur since the transferred hairs will survive in their new site just as long as in their original site, but no longer. Usually the occipital area is best. The hair is clipped short, about 1/4 in. The direction of the hairs is noted and a 5 mm diameter skin biopsy punch is inserted into the scalp parallel to the shafts of the hairs (Fig. 3). By rotating while applying gentle

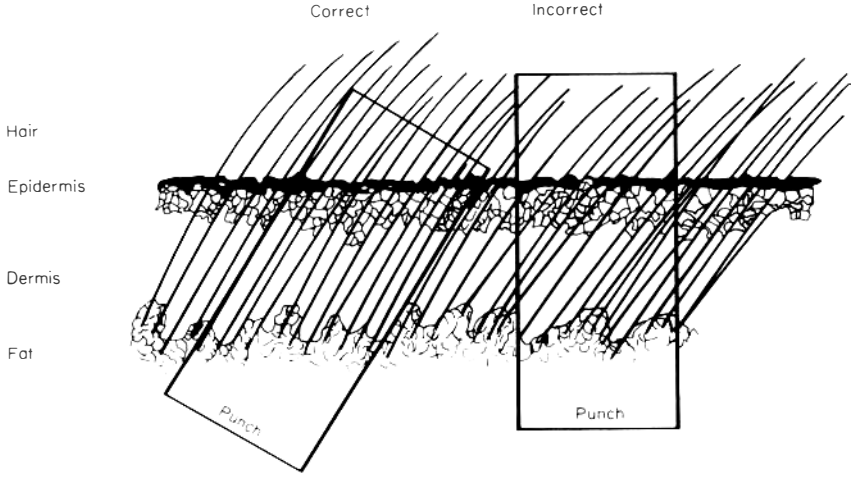

Fig. 3. The correct and incorrect methods of removal of hair bearing scalp tissue by the punch graft technique (reproduced with permission from the *Surgical Clinics of North America*).

pressure a plug of tissue is isolated. Occasionally a small knife is needed to sever the fatty base of such plugs. The excess fat is cautiously trimmed until the bases of the hair follicles are seen but not damaged. A 4 mm core of skin is removed from the supraorbital area at the same angle as the 5 mm plug which has been cut and directed in such a way as to allow the hairs to grow in a normal direction, i.e. upward and only slightly laterally if at the medial end of the eyebrow area and laterally at the lateral end. Usually a 5 mm plug fits securely into a 4 mm hole but occasionally a mattress suture is necessary over the top of the plug which enters the skin on each side but does not pass through the plug. Similarly smaller plugs may be used between the larger plugs to give a more even appearance and 4 mm

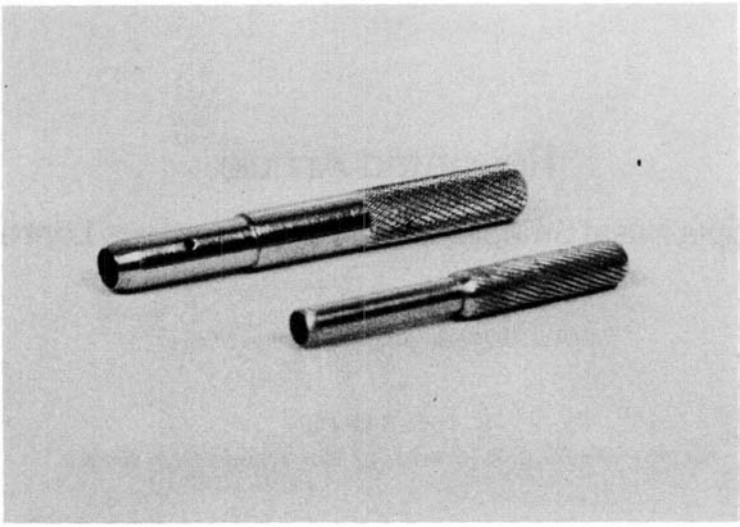

Fig. 4. Two different sizes of skin punch.

diameter plugs are inserted into 3 mm diameter holes. A moist saline dressing is applied and removed on the 5th day by which time the area is healed. The donor area is dressed with vaseline gauze. The healing here takes a little longer but time can be shortened by suturing the holes shut. The initial hair often falls out and the final appearance is best seen at 3 months.

A Suggested Role of Punch Grafting in Eyebrow Replacement

Eyebrows can be completely replaced by the technique of punch grafting as is usually practised in scalp hair replacement.* However the operation is tedious and for total eyebrow replacement a vascular island transfer or free graft is preferable. However punch grafting can be useful in "touching up" the medial end of an otherwise successful vascular island transfer.

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Reprinted Article

Multiple Nasal Smears in Early Lepromatous Leprosy

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Multiple smears for *Myco. leprae* were taken at various sites in the noses of 100 patients suffering from lepromatous leprosy in its earlier stages, with the object of investigating (a) the parts of the nasal cavity most intensely involved in early lepromatous leprosy, and (b) the concentration of *Myco. leprae* at sites in the nose as compared with sites in the skin. From 4 to 10 sites were tested in each patient.

The results were profoundly influenced by previous chemotherapy. Among 58 untreated cases of early lepromatous leprosy, nasal infection was very important, but was concentrated on the inferior and middle turbinates and the septum at a depth of 6 cm rather than in the anterior septal area, which in this series was an unreliable guide to the bacteriological situation in the nose.

At the same time, the Bacterial Index at sites in the nose exceeded the Bacterial Index at the most heavily infected skin site tested in 50% out of 100 patients. In this series the nose was an important site of election for *Myco. leprae*. Nasal infection was not something which developed as the lepromatous condition advanced. It was both present and severe in the early stages.

Introduction

In earlier years, the bacteriological examination of the nasal mucosa was regarded as a necessary part of the routine assessment of patients with leprosy. A method commonly adopted was to wipe the nasal cavity with a pledget of sterile cotton wool on a probe or thin stick, and smear the result on a slide. In the 1930's this method fell into disrepute on the grounds that smears could be contaminated with saprophytic acid-fast organisms. The method was replaced by the scraping of a small area of the mucosa under direct vision, usually on the nasal septum, with the object of transferring a fragment of mucosa onto the test slide, and so observe acid-fast bacilli *in* the mucosa rather than *on* the mucosa. This method of examination also fell out of fashion at many centres, on the grounds that while positive findings were usual in lepromatous leprosy, the information revealed could more easily have been obtained by routine examination of the skin by the scraped incision technique. As a result, interest in the nose in leprosy declined, the manifestations of leprosy in the nose often being regarded as secondary to its manifestations elsewhere.

When advising the scraping, as distinct from the wiping, of the nose, Muir (1938) suggested that either the nasal septum or the inferior turbinates could be employed. Subsequently, leprologists concentrated on the nasal septum, and for the past 30 years this has been the site usually selected. The method of examining the nasal septum has been described in detail by Wade (1935), Cochrane (1964), Browne (1965), Goodwin (1967), and Dharmendra (1967), who alone mentions the inferior turbinate as an alternative site when the septum is not convenient.

In the average adult, the surface area of the nasal cavity is approximately 100 cm^2 on each side. The technique of scraping with a small fairly sharp instrument means that one small area of approximately 1 cm^2 is examined. How valid is this method of sampling? We may indeed localize the area usually chosen still further. The choice of a scalpel (Wade), a straightened paper clip (Wade), a tenotomy knife (Cochrane) and similar instruments, limits the area available for examination to a site well in the anterior segment of the nasal septum, in practice around 3 cm from the nasal orifice. Dharmendra mentions ½ in from the orifice. The selection of this site is valid only if either (a) the nasal mucosa is invaded diffusely in leprosy, and therefore any readily available site will suffice, or (b) the anterior part of the septum is the site of election of the bacillus in the nose.

Two matters here are worthy of study, (a) the intensity of bacteriological involvement of the nasal mucosa as between one area and another, and (b) the intensity of bacteriological involvement of the nasal mucosa as compared with routine skin smears undertaken on the same occasion. Both subjects lend themselves to investigation by the simple procedure of taking multiple smears of the nasal mucosa at various sites, and comparing the results both directly, and with routine skin smears taken concurrently. The results of doing this on 100 patients are reported here.

Method

Patients were selected from among those attending for the first time at the Victoria Hospital, Dichpalli, Andhra Pradesh, between July 1972 and January 1973. Advanced, and long treated cases of lepromatous leprosy were excluded, the choice being confined to patients with lepromatous leprosy in its early stages, and patients with indeterminate, dimorphous or borderline leprosy now showing signs of degeneration to the lepromatous condition. Children with small noses were not included. Patients were chosen consecutively and no other basis of selection was employed. The 100 patients included thus represented a fair picture of these types of leprosy as encountered in central India.

Routine skin smears were carried out at at least six sites. In addition, smears were made of the nasal mucosa as follows:

(1) 4 sites.	Septum at a depth of 3 cm from the nasal orifice, right and left sides. Inferior turbinates, anterior end, right and left.	45 patients.
(2) 8 sites.	As (1), with the addition of septum and inferior turbinates at a depth of 6 cm on each side.	41 patients.
(3) 10 sites.	As (2), but with the addition of the middle turbinate on each side.	14 patients.
		100

It was usually possible to smear the septum and inferior turbinate in the anterior positions without difficulty. In 3 cases, septal perforations impinged on this area, and then the inferior margin of the perforation was used. In 6 cases gross swelling of the inferior turbinate obliterated the cavity at that level, and made access impossible to the posterior positions. In some cases atrophy of the anterior part of the inferior turbinate made this structure difficult to see, but did not prevent the examination. The middle turbinate was often also difficult of access.

In practice, Browne's suggestion of a piece of bicycle spoke as the essential instrument proved valuable. Beaten flat for 1 cm at one end to make a blade 2-3 mm wide and sharpened on one side only, its edge parallel with the stem, this instrument in a length of 15-20 cm could be employed with balance and delicacy. Marks on the stem at 3 cm and 6 cm from the blade end gave precision to the area being examined. No patient suffered any after-effects whatever from the use of this instrument. Further reference to technique is made later.

All nasal smears were examined by one of us (TFD), who also counter-checked many skin-smears. A very experienced technician read skin smears as routine and counter-checked many nasal smears. The margin for error is small. All smears were recorded on the logarithmic international scale (Maximum B.I. = 6.0). During the second half of the trial period, sulphone estimations were done as routine on the urine of patients. Clinical classification was confirmed histologically in 27 cases, and lepromin tests undertaken on the same number were negative in all.

Results

DIAGNOSTIC RELEVANCE

In this series, saprophytic acid-fast bacilli presented no problems. Two features in nasal smears enable *Myco. leprae* to be identified with confidence. The presence of globi characteristic of the multiplication of bacilli in macrophage cells is a certain indication of *Myco. leprae.* The only other acid-fast bacillus likely to cause confusion is *Myco. ulcerans,* and this has never been reported from the nose. The second feature is positive evidence of the ingestion of the bacilli concerned by macrophage cells, so that they are seen intracellularly, and beginning there to multiply in a characteristic way, so that the bacilli lie parallel with one another. In exceptional circumstances *Myco. tuberculosis* could be encountered in this situation but its intracellular appearances are different.

Across this series, the whole process of globus formation was witnessed with great clarity. Globi were encountered in nasal smears in 94 out of 100 patients. In a further 3 patients the early stages of ingestion by macrophages were clearly demonstrated. These three were borderline cases in an early stage of degeneration. In no case were acid-fast bacilli encountered, morphologically resembling *Myco. leprae,* and seen only extra-cellularly.

Heavy involvement in the nose was thus a characteristic feature of patients in this series, even though the lepromatous condition was clinically mild, and in 71 patients still in its early stages.

BACTERIAL INDEX: COMPARISON BETWEEN NOSE AND SKIN

From the standpoint of the relative level of Bacterial Index as between the nasal mucosa and the most heavily infected skin site, patients could be divided into two groups.

Group A: In whom the highest B.I. found in the nose was not higher than the highest B.I. found in the skin. Forty-seven patients came into this category. In 30 of them the nose and skin were at the same level of B.I., in 10 cases the B.I. in the nose was 1 point lower than in skin, and in 7 cases it was lower by more than 1 point in the scale.

Group B: In whom the highest B.I. found in the nose was higher by 1 or more point in the scale than the highest B.I. simultaneously recorded in the skin. Fifty patients came into this category. A further 3 were added, because although B.I. in their noses came within the same range as the most heavily infected skin site, the Morphological Index in the nose was much higher than in skin. Throughout this group the Morphological Index in the nose tended to be higher than in skin, but in these three the difference was striking (Skin M.I. 0-5, nose M.I. 20-50).

The distribution of patients between Groups A and B in relation to leprosy classification and stage and also to chemotherapy with dapsone, was as follows:

TABLE 1

Leprosy classification and treatment

Leprosy type	Total patients	Group A (Nose not more bacilli ferous than skin)	Dapsone taken	Group B (Nose more bacilli ferous than skin)	Dapsone taken
Borderline	7	5	(3)	2	
Early lepromatous (LL)	20	8	(2)	12	(1)
Early lepromatous (L1, LB)	51	18	(10)	33	
Established lepromatous (LL, L1, LB)	22	16	(8)	6	(1)
	100	47		53	

Although the same pattern can be discerned in both Groups, interest centres on Group B because here the situation is not confused by sulphone treatment to an appreciable extent, and the proportion of early cases is higher. The following points arise:

(i) Group A includes 23 out of 25 patients who either admitted to having taken dapsone treatment or whose urine gave a positive reaction to sulphones. It is well-known that dapsone acts speedily on leprosy in the nose, and this was therefore a predictable finding.

(ii) Group A also includes a much higher proportion of the more advanced established lepromatous cases than Group B. This is also not surprising.

(iii) In 11 out of 53 patients in Group B (21%) the Bacterial Index at one or more sites in the nose was at least 2 points higher in the international scale than the highest findings in skin smears, i.e. at those sites the nasal infection was around 100 times as intense as encountered in the skin. This figure is in fact a conservative one. In a further 11 patients in whom the highest B.I. recorded in the skin was 5.0, there was at least one site in the nose, where the smear revealed

huge numbers of globi, far more than were needed to give a B.I. of 6.0. The international scale has no place for such gross infections.

(iv) In two patients with negative skin smears, a bacilliferous focus with B.I. of 6.0 was found at one site in the nose, in both cases on the left inferior turbinate. Both were dimorphous cases in the earliest stages of degeneration, and thus in a very unstable condition. It is thus not true that bacteriologically positive findings cannot be obtained in the nose in the absence of positive findings in the skin. Dharmendra and Sen (1946) reported such a case with globi in the nose but negative skin smears. What matters is where one looks for the bacilli.

(v) The overall picture is given in Table 2, which relates to Group B only (53 patients).

TABLE 2

Bacterial Index in nasal and skin smears

Site	Total tests	6.0	5.0	4.0	3.0	2.0	1.0	Negative
Septum anterior	104	32	31	12	3	8	4	14
Septum posterior	42	14	12	6	2	1	2	5
Inf. turbinate ant.	104	46	32	11	4	2	5	4
Inf. turbinate post.	41	12	5	3	1	1	2	6
Middle turbinate	20	6	7	3	0	1	0	3
Ear lobes	106	19	58	9	10	0	4	6
Arm/back	106	9	61	12	6	7	6	15
Thigh/buttock	86	8	58	3	0	5	1	11
Face	23	6	13	4	0	0	0	0

It is obvious from these figures that the intensity of bacilli in the nose was frequently greater than in the most heavily involved skin sites (ear lobes and face), and much higher than at other sites in the skin.

SITES OF HEAVIEST INVOLVEMENT IN THE NOSE

(i) *Comparison between the two sides of the nose*

Although in individual patients there was a decided difference in involvement between one side of the nose and the other, over the group as a whole these differences largely cancelled each other out, and it was impossible to detect any general tendency for one side of the nose to be involved more than the other. The left inferior turbinate was in fact involved most frequently and intensely, but this was largely compensated by the heavier involvement of the right side of the septum as compared with the left.

(ii) *Comparison between inferior turbinates and nasal septum*

In this series the inferior turbinates were more frequently and seriously involved than the nasal septum, and this feature is particularly noticeable in the anterior positions at a depth of about 3 cm from the nasal orifice. This finding does not accord with generally accepted ideas. Its practical importance can readily be demonstrated.

If a single smear of the nasal septum had been undertaken as routine in these patients, the chances that it would have included the most heavily involved site were 8 out of 53. (In these 8 patients, both sides of the septum were equally involved with a B.I. of 6.0, also found simultaneously in the inferior turbinates.) The smearing of both sides of the septum would have yielded a true sample in 28 cases (53%), leaving 25 cases (47%) in whom smears of the anterior septum would not have given a true picture of the situation.

The inferior turbinates give a better result. A single smear of the anterior end of one inferior turbinate would have given a true picture of the whole in 15 cases (18%). The smearing of both inferior turbinates would have yielded a correct result in 41 cases (80%).

A combination of the two, i.e. the smearing of both anterior septum and inferior turbinate on both sides would have yielded a true index in 47 cases (90%).

(iii) It is also noticeable from Table 2 that at a depth of 6 cm from the nasal orifice, involvement was frequently heavy on both septum and inferior turbinate. In most cases this was part of a broader area of heavy involvement in the structure concerned, the anterior parts also being implicated, but in 6 patients (11%) the nasal infection was concentrated on these deeper levels only, and anterior smears would not have revealed it in its full intensity.

(iv) *Middle turbinates*

In the small group of patients tested, the middle turbinates were also an important focus of involvement by *Myco. leprae.*

DISCUSSION

(1) The origins of this study go back to 1971, when Dr J. C. Pedley drew the attention of one of us (TFD) to the very large number of *Myco. leprae* being discharged from the noses of some of his patients in Nepal. Experience has shown that the same situation exists in central India. This study is an introduction to a much wider investigation of the role of the nose in leprosy which is now in progress.

(2) Two significant findings arose out of this study. The first is the association between early lepromatous leprosy and a very heavy involvement of the nose by *Myco. leprae.* This is not a generally recognised phenomenon. Involvement of the nose has of course been accepted as a feature of lepromatous leprosy for almost 100 years, but for a long time it has been thought that the nasal infection developed proportionately with the general advance of the lepromatous condition elsewhere in the body. In this series, 45 out of 58 untreated cases of early lepromatous leprosy were found to have concentrations of *Myco. leprae* in their nasal mucosa between 10 and 100 times as heavy as could be found at any skin site. This is a matter of importance because the bacilli do not simply remain in the nasal mucosa. Many escape in the nasal discharge.

(3) Is this a peculiarity of leprosy in central India, or has it a wider relevance? Certainly in the experience of one of us (TFD) in Nigeria, nothing comparable was found, though the type of study here described was never undertaken there. If the relative prevalence of the different types of leprosy is any guide, there certainly is a difference in genetic and immunological background between Nigeria and central India. Here, the dominant presentation of leprosy is the

unstable, indeterminate, dimorphous or borderline forms of the disease, the degeneration of which to the lepromatous form is a frequent occurrence, and often manifests itself first in the ears and face. The nose too may be important at this stage. Twelve patients in this series, all of whom had recently experienced a downgrading exacerbation of their disease, firmly related the onset of this to their noses, in the shape of blocking of the nostril and bleeding. This opinion was volunteered, not elicited by direct questioning.

(4) The second interesting finding was the variation between one part of the nasal cavity and another in the frequency and intensity of invasion by *Myco. leprae*. The anterior portion of the nasal septum was the area least likely to offer a fair sample of the bacteriological situation in the nose. The inferior turbinates gave a decidedly better picture. At a depth of 6 cm from the nasal orifice, both septum and inferior turbinates were also frequently and heavily involved, while the middle turbinates were also important in the small group of patients in whom they were tested. In this part of India, nasal smears from the anterior septal area could give rise to highly misleading judgments regarding the role of the nose in leprosy.

(5) Is this another finding of local interest only, or are we here too confronted with something of wider importance? In the latter case, the implications are considerable. In established lepromatous leprosy, a more or less uniform involvement of the nasal mucosa is to be expected. Dutz, Chen and Wen-Hsiang (1972) have drawn attention to the continuous bacillaemia which is inseparable from established lepromatous leprosy. It means that every tissue is continuously exposed to the bacillus, and the nasal mucosa, with its rich blood supply can be no exception. The finding of intense concentrations of the bacillus in nasal smears in the early stages of the disease must have meaning. Does it signify that the infection started there, or that bacilli grow there more vigorously than in skin, or that they are selectively filtered from the blood at this site? These are pregnant questions, to which nasal smears by themselves can provide no answer. They are a pointer to underlying pathological processes which are as yet insufficiently understood. The coming together of Bacteriologists, Immunologists, Ear, Nose and Throat specialists, and Leprologists in joint studies will alone find the answers.

(6) The practical question immediately presents itself as to how far nasal smears should be undertaken by leprosy workers as routine, especially in field conditions. There can be no doubt that nasal smears, especially if both septum and inferior turbinates are included, will sometimes give an indication of the severity of an early lepromatous infection in a way that skin smears will not reveal. On the other hand, in unskilled hands, more harm than good may be done to the patient. Certainly whoever undertakes this type of examination must be conversant with the internal anatomy of the nose, and be able to recognise a pathological situation when he sees it.

A few further notes on technique may not be out of place.

All the tests in this series were undertaken by the light of a good but ordinary torch, held by an assistant standing immediately behind the examiner, himself seated close to, and on the same level as, the patient. A preliminary inspection of each nasal cavity is necessary, with the nasal orifice dilated by a speculum, and the examiner himself using the torch to illuminate the different parts of the cavity. Before undertaking the actual smears, the area of mucosa to be examined must be seen to be clear from adherent crusts. In the dry climate of central India hard adherent crusting is frequently encountered, and must be removed. Easily

the best way of doing this is for the nose to be irrigated with warm normal saline, when the patient can usually blow out the softened crusts himself. Gentleness in the examination is essential. The mucosa in many patients is very friable and liable to bleed. After a preliminary wipe with a sterile pledget of cotton wool, the instrument, sterilized by flaming immediately before use, is introduced under direct vision with its blade downwards, and then rotated through 90 degrees when the site to be examined is reached. A gentle scrape up and down a few times is quite enough to obtain the tiny fragments of mucosa and accompanying exudate needed. A faint trace of blood is a certain indication that these objectives have been achieved. A smear on a carefully labelled slide is then made immediately. This technique is easily learned, and if reserved for patients whose nasal cavities show abnormality, and whose leprosy is towards the lepromatous side of the spectrum, will have a positive usefulness.

(7) If this study induces colleagues in India and elsewhere to look once again into the noses of their patients and question the meaning of what they see there, its primary purpose will have been achieved. To our patients the nose is supremely important, for the threat of disfigurement of the nose lies behind much of the anxiety and depression to which people with lepromatous leprosy are prone. Clinical examination of the nasal cavities is an essential part of the assessment of any patient with overt of incipient lepromatous leprosy, and will often destroy any illusions the examiner may have regarding the extent of the disease in that patient. It is then and in the subsequent follow-up that nasal smears are of practical value.

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The Leprosy Mission A Century of Service

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During the past hundred years, The Leprosy Mission has played a significant role in all the major advances in the treatment of sufferers from leprosy. Sympathetic custodial care was at first the only way of helping the individual and of alerting the conscience of Christendom and of governments. Workers of The Mission have been foremost in the use of modern medication, reconstructive surgery, domiciliary treatment schemes, rehabilitation, and vocational training, and have made important contributions to the literature of leprosy. The emphasis throughout has been compassionate caring for the individual afflicted by leprosy.

"The Leprosy Mission, as it is now known, has probably made a greater contribution to the cause of leprosy in its hundred years' existence than any other organization" (Day, 1974).

The centenary of The Leprosy Mission affords a fitting occasion for a salutary review of this "greater contribution", particularly in respect of the influence exerted by the Mission down the years on the attitude of men and women the world over to leprosy and its victims. Far from being an insignificant collection of sentimental do-gooders, actuated albeit by high principles of altruistic service, The Leprosy Mission has been the pioneer and catalyst in practically every major field of activity on behalf of the leprosy sufferers (Askew, 1973).

Out of a wealth of historic detail, a selection will be made of those events and policies that have proved to be of prophetic or potential importance.

It may be difficult for modern research workers surrounded by complicated investigative apparatus in their air-conditioned laboratories to picture the grim harsh world of leprosy in which the Mission first saw the light of day in 1874. Contemporary descriptions of neglect and cruelty and callousness, of deep-seated fear and helplessness in the face of an incomprehensible terror—increase one's admiration for the handful of Christians who risked misunderstanding and ridicule by daring to help.

Despite ingrained beliefs concerning leprosy and its differences from conditions regarded as "diseases", it is remarkable that as early as 1875 Wellesley Bailey, the schoolmaster-missionary founder of the Mission, ordered from the Andaman Islands a 54-gallon cask of Gurjan oil, since he had read that it might be a good treatment for leprosy and that leprosy might indeed prove to be treatable in the same way as other diseases. It is not surprising to learn that after an initial stage

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of apparent improvement, this remedy—like hundreds that were tried subsequently—had to be abandoned.

The Mission—then known as "The Mission to Lepers in India"—soon embarked on a policy of encouraging by means of financial grants any medical worker who was interested in leprosy. Thus, Neve of Kashmir applied his not inconsiderable surgical skills to the relief of nerve trunk pain in leprosy, and the Mission in 1883 backed his efforts with grants of financial assistance. It was not only in the operating theatre that Neve broke new ground: he was among the first to admit leprosy patients to the general wards of a hospital, making the most of the opportunities afforded to instruct his medical staff and to attack the unwarranted prejudice of fellow-patients against the victims of leprosy.

Soon after this, in 1888, we read of trials of chaulmoogra oil being conducted in the Mission's hospital at Purulia in West Bengal. Years before Leonard Rogers popularized this ancient Indian and Burmese remedy, the physicians at Purulia were reporting good results in certain forms of leprosy.

The policies of the Mission reflected the changing patterns of knowledge (or of ignorance and prejudice) current at the time. After the discovery by Hansen of *Mycobacterium leprae* in 1873, the concept of leprosy as a contagious disease gradually gained acceptance. The emphasis was thus increasingly placed on segregation of leprosy sufferers, and the separation of infants from mothers who had the disease. The Mission's influence was exerted to ensure that the panic measures of government were tempered by humanitarian kindliness, and that education and care were provided for the "orphaned" children of patients. The obvious and only logical way of controlling a contagious disease seemed to be the exclusion from the community of the mutilated and ulcerating victims of leprosy.

At this stage, the Mission—now established as a serious organization with a reputation for cooperation with government—offered to set up in every State in India a model institution for the care of leprosy sufferers. On its part, the local and central administrations showed their appreciation by making financial grants available—a happy augury for future cooperative working.

In the early days of this century, Purulia was the leading centre for drug trials—chaulmoogra oil and its derivatives, Nastin (also investigated at Chiengmai in Siam, and Canton), guaiacol and other remedies with short-lived vogue. The Indian government aided the research at Purulia with encouraging grants-in-aid.

As the Mission's sphere of activity widened to include China and Japan, its title was changed to "The Mission to Lepers of India and the East" (1893), and then to "The Mission to Lepers" (1914). Similarly, its influence on government policies was becoming more apparent. In Japan and Korea, the public conscience was aroused, and in the United States of America the Mission was influential in establishing Carville as a Leprosy Hospital and in fostering the passage of legislation in aid of leprosy sufferers.

At the first International Leprosy Congress, held in Berlin in 1904, the only non-medical delegate was Wellesley Bailey, Founder-Director of the Mission, and he was actually invited to read a paper to the participants. Five years later, at the second Congress, held in Bergen under the Presidency of Hansen himself, Bailey was an honoured visitor. He afterwards reported that "the belief is induced that the disease is not incurable"—prophetic words in the light of the synthesis of diamino-diphenyl-sulphone in Germany the previous year.

In the early years of the century, solid, unspectacular work was undertaken in many lands as the Mission extended its sphere of helpfulness, aiding doctors and

nurses of an increasing number of missionary societies and establishing more centres in its own name. But it was in the years following World War II that the Mission saw its biggest development. Retaining its spiritual ideals of compassionate assistance for the individual, it added new dimensions of service for the "whole man". It encouraged Ernest Muir, Robert Cochrane and others in their early investigations of the sulphones at Purulia, Chingleput, Vellore and elsewhere. It backed Paul Brand and his colleagues in their application of the principles of orthopaedic surgery to the deformities of leprosy. In cooperation with the American Leprosy Missions, Inc. (originally an auxiliary of the Mission to Lepers), it founded the teaching and research centre at Karigiri in association with the Christian Medical College and Hospital at Vellore, where surgeons, physicians, pathologists and research workers in many branches of medicine profited from courses and in-service training.

Occupational therapy, shoes and prostheses, a small factory for making microcellular rubber, farming, cookery classes—were all developed at Karigiri. A huge and highly populous area in Gudiyatham was selected for epidemiological investigations.

A succession of high-quality scientific papers came from Karigiri, Vellore and other Mission centres.

Medical auxiliaries, nurses, laboratory technologists and shoemakers were not forgotten in the teaching activities at Karigiri, nor was the provision of suitable literature.

In the Far East, the Isle of Happy Healing (Hay Ling Chau) was demonstrating that government and Mission could cooperate happily, to the benefit of the patient and the community.

The Mission was also responding to other calls—in many countries in the African continent, in Thailand, and elsewhere. Invitations from Nepal, Indonesia and Bhutan met with a ready acceptance from the Mission, its workers and its supporters in an ever-widening international family.

A change in the Mission's name to "The Leprosy Mission" in 1966 reflected a growing feeling that the old name might suggest an outmoded attitude to those suffering from a specific mycobacterial infection. Later, a change in the constitution enabled The Leprosy Mission to diversify its activities and treat patients suffering from other diseases than leprosy—a change consonant with the newer ideas on the integration of leprosy into general programmes of health care.

One of the founders of ALERT in Addis Ababa (the All-Africa Leprosy and Rehabilitation Training Centre), of ELEP (the Federation of European Leprosy Associations), and of ULAC (the United Leprosy Aid Committee) and a consistent supporter of the International Leprosy Association, The Leprosy Mission is showing its capacity for cooperation and adaptability to the changing patterns of knowledge and resources.

The teaching activities of the Mission have been extended by the organization of seminars in various countries by the Mission's Medical Consultant, Dr Stanley Browne, and (in reconstructive surgery) by Dr Grace Warren.

In the past 25 years, the old "Homes" have become hospitals; the "asylums" are now centres for out-patient programmes; "lepers" are "leprosy patients". Amid all the changes, however, the Mission and its growing band of national and expatriate colleagues insist that the most important person in all its activities is the individual suffering from leprosy who must be helped in all ways, in the context of his family, his work and his community. This salutary emphasis is still

needed today, in the mass treatment/control schemes and the integrated programmes.

At present, the Mission is responsible for the treatment of about 240,000 sufferers from leprosy in 30 countries, and assists in the leprosy programmes of about 90 Protestant missionary bodies—a far cry from the handful of pathetic beggars that moved Wellesley Bailey to action a century ago.

As long as governments cannot or will not realistically and adequately face the problem of the leprosy sufferer, a Christian Mission furnished with the expertise and experience of a hundred years, and motivated by high standards of medical competence and compassionate caring, will still play a significant role in the struggle against leprosy.

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Lepr. Rev. (1974), **45**, 170-172

Father Damien: Centenary Commemoration

T. N. Jagadisan, formerly Professor at Annamalai University, and an authority on English literature, came through profound personal tragedy to devote himself to the cause of sufferers from leprosy in India, and over many years has rendered distinguished service both through the Hind Kusht Nivaran Sangh, and at a very personal level. He has made a special study of Father Damien. A commemorative speech made at the Annual Meeting of the Hind Kusht Nivaran Sangh, was published in *Leprosy in India* **XLIV**, 191-3. His address on the same subject at the All India Leprosy Workers' Conference at Sevagram in October 1973, will long be remembered by those priveleged to hear it. There is no one more appropriate to write on this theme, and we are happy to include the following abridged version of his Sevagram address which he has kindly contributed to the *Leprosy Review*.

Father Damien: His Life and Work

T. N. JAGADISAN

Joseph De Veuster was a man of destiny. Born at Tremelo, Belgium, in 1840, he was the youngest of 8 children. He grew up in the peace and quiet of rural life, and at an early age displayed a spirit of good neighbourliness and compassion towards others. The combination of solitude with sociability, of prayerfulness with brotherliness, marked him out for a religious life, in which he found divinity in the loneliest and most abandoned of men, and like a second Jesus bore a cross in order to redeem his fellow-men.

Joseph's father had intended that he should be a trader, but the boy had already heard the call of God and set his heart upon the religious life. The vocation of the Picpus Fathers, with its hidden life of prayer, public life of service, and sacrificial life of daily mortification appealed to Joseph's heart, and hard though it was for his father and his family, he entered the congregation of the Picpus Fathers.

In 1863, The Bishop of Hawaii asked urgently for missionaries to work in the South Sea Islands. Damien's flaming ardour so prevailed on the authorities, that although he had not yet been ordained, his wish to serve there was granted. It was a decision which was to affect not only the history of leprosy but the story of civilization.

While working as a missionary in Hawaii Island he came to know at close quarters the misery of those afflicted with leprosy. A compulsory and cruel system of segregation had come into force, imposing a lifetime of exile for leprosy patients, who were removed to the island of Molokai. The sufferings of these

unfortunate people so touched the heart of the Bishop that he made the decision to send a resident priest to Molokai. His dilemma was, could he demand such a sacrifice of anybody, especially as according to the new regulations of the Board of Health, anyone who went to Molokai in the future would have to remain there for the rest of his life. Four priests offered to go. Among them was Damien, glowing with eagerness and sincerity, and insisting that he should be the one to be chosen. Again the hand of destiny was at work. The Bishop chose him. With one extra shirt and his breviary, which was all he had, he decided to go to Molokai that very instant. The Bishop himself sailed to Molokai and left him on the shore to embark on his sublime mission. One would fain know what were the thoughts that passed through Dámien's mind on that first fateful night under the pandanus tree. No doubt tenderness and resolution were mixed in his feelings, but waver he never did. For his unbelievable sacrifice was built on the impregnable rock of Faith.

Father Damien found Molokai in a condition of unimaginable squalor and filth. The disease had robbed its victims not only of their physical features, but of what is even more important, their morale, and that hope for the future which is so essential to continued living and progress. With a faith that leapt all bounds, with courage undaunted, with perseverance indomitable, with a physical strength matched only by his courage, he set about his task of bringing some kind of order into the island, and some kind of hope into the hearts of the abandoned, neglected, patients. With his own hands he made coffins and dug graves. He acted as carpenter and built houses, he became their engineer and brought water to the settlement from the mountains. He was doctor, nurse, compounder, priest, teacher and friend—all rolled into one. He did everything he could to improve the lot of his parishioners. He waged many a battle with the Board of Health in Honolulu, and got supplied, medicines, clothing and food for the colony on Molokai.

One day to a hushed congregation in the church he said, "My brethren". He stopped and cleared his throat and went on, "We lepers". That was his simple announcement that he had contracted leprosy. The disease grew rapidly, and the story of his suffering spread quickly round the world bringing with it pity for the priest, admiration for his heroism, and compassion for leprosy workers. In his last years, he had a widening circle of co-workers, Brother Dutton, the "Soldier-saint" who worked in Molokai for 40 years, Dr. Mouritz, Mother Marianne, and Franciscan Sisters, none of whom contracted leprosy.

Damien's last years were full of the radiance of tenderness and friendship from his co-workers and from admiring visitors. Foremost among friends from abroad who brought Damien the sweet voice of affection and the soothing balm of consolation were 2 English non-catholics, Rev. Hugh B. Chapmen, who raised monies for Damien's work on Molokai, and Edward Clifford, the English painter who has left the world an immortal painting of Molokai and Father Damien. Indeed, even after his death visitors came to the famed Molokai of Father Damien. One such visitor, the English author R. L. Stevenson, has left an immortal literary masterpiece in his letter vindicating Father Damien against unjust slander.

Damien was no cold, aloof servant of God, regarding his service for his beloved leprosy patients as just only a means to reach the feet of the Lord. Indeed, to him God dwelt in his abandoned brethren. Hence his great warm-hearted love to his chosen parishioners, and his human tenderness and human impatience which he

revealed in his busy life of serving them. It is remarkable in Damien—this incredible mixture of melting tenderness and grim determination, human grumbling and sublime acceptance of God's decree, of rebellion with acceptance, of impatience with resignation. We do not know which to love more, the hero in the man or the man in the hero. His letters home to his parents, brothers and sisters were human documents. They reveal the strength and tenderness of love which he had for the homeland and his kindred, and how in the midst of the devastating loneliness of spirit he looked up to the Blessed Sacrament as his sustenance and support. He wrote, "Without the Blessed Sacrament, a life like mine would be intolerable, but with the Blessed Sacrament I am always gay and work cheerfully for the relief of the poor leprosy patients" In that one sentence we see the humanity of this very human saint—his strength, his high resolve, and his terrible craving for friendship and human understanding. How Damien comes so near to us in his human-ness thereby giving us the hope that we too in our own humble way, weak as we are, can rise above our selfishness to high resolve and noble action!

Father Damien died in his 49th year, mourned not only in Molokai, but by the wider world of his admirers in many countries. The impact of his martyrdom was in the nature of a sudden, worldwide awakening to the needs of leprosy patients. Above all, he set an example that the civilised world has followed. Indeed, he lit a torch that burns for ever. Truly can it be said of him: "Not worldly deeds, not progeny, not wealth, but sacrifice and renunciation alone can confer immortality".

Lepr. Rev. (1974), **45**, 173-175

News and Notes

RESEARCH IN COMMUNICABLE DISEASES—SEMINAR IN BOMBAY

It was a happy thought to celebrate the Platinum Jubilee of the Haffkinke Institute, Bombay, with an international seminar entitled "Guidelines for Research in Communicable Diseases". A score of invited scientists from other countries met for three very full days with their opposite numbers from India to review a selected and necessarily limited number of topics having some bearing on the problems facing India today.

The parasitic diseases—helminthiases, amoebiasis, etc.—came in for major consideration. Tuberculosis, viral diseases, plague and toxoplasmosis called forth some excellent papers and discussions.

Leprosy was not omitted. Dr S. G. Browne read a paper on "Some Epidemiological problems of Leprosy in the Indian Context", and took part in a Panel Discussion in which the therapy of leprosy figured prominently. Profiting from Dr Browne's presence, the Health Minister, Dr Rafiq Zakaria, organized a meeting of doctors interested in leprosy control in Maharashtra State and in India generally, at which the present situation was critically reviewed and recommendations made.

Sponsored by Sandoz, the Basle pharmaceutical complex, and the Haffkinke Institute, and organized by Dr E. Jucker, the Seminar proved a real success, suggesting as it did lucunae in knowledge and in effective therapeutic agents. The general impression gained was of the huge size of Indian problems, and the necessity for a greater emphasis on mass treatment and mass prevention of the major endemic diseases. Sanitary engineering and health education must play their part if the problems are to be successfully tackled.

XVTH INTERNATIONAL CONGRESS OF DERMATOLOGY

The Executive Committee of the International League of Dermatological Societies, in official relation with the World Health Organization, are making preparations for the XVth International Congress of Dermatology, which will take place on 16 to 22 October 1977, at Mexico City. A comprehensive programme will include invited papers on the latest developments in clinical dermatology and dermatological aspects of basic sciences, symposia and workshops devoted to specific subjects, educational courses, discussion groups, free communications and demonstrations. The inclusion of several names well known in leprology in the list of distinguished members of the Executive Committee will ensure that leprosy will receive the attention it merits in this International Congress. We have much to learn from one another, and it is hoped that leprosy workers will note the date of the Congress in their diaries now. The Secretary of the Congress is Professor Felix Sagher, Department of Dermatology, Hadassah University Hospital, P.O. Box 499, Jerusalem 91000, Israel.

ZEITSCHRIFT FÜR TROPENMEDIZIN UND PARASITOLOGIE

The widespread interest in leprosy, evoked by the centenary of the discovery of *Myco. leprae,* receives further distinguished impetus in the December 1973 number of the *Zeitschrift fur Tropenmedizin and Parasitologie* which is devoted to New Advances in Leprology. Dr Browne on Epidemiology leads a series of ten valuable contributions, six of which are devoted to problems of research in chemotherapy and the use of chemotherapeutic drugs in combination. An account of leprosy in the nine-banded armadillo, the Leprosy Eradication Project of Malta, and antigenic studies of *Myco. leprae* completes the series. Abstracts of papers presented are included in the appropriate section of this number of the *Review.*

"CELLULAR AND HUMORAL IMMUNITY IN LEPROSY"

Following successful prize essay competitions in 1972 and 1973, the British Leprosy Relief Association in London (LEPRA) is again offering a prize of £100 for an essay on the above subject. This sum may be awarded to one, or divided between several candidates at the discretion of the judges. Entries should be of not more than 10,000 words, but length is not important and in previous years awards have been made for essays of only 2000 to 3000 words. While handwritten essays will be accepted, preference may be given to typed manuscripts. References should be included as in standard scientific publications. Existing knowledge of cellular and humoral immunity in this disease should be summarized, but no credit will be given for mere repetition of material already published in books or journals. Particular attention will be given to entries offering constructive criticism of present trends in research in the immunology of leprosy, and to ideas for future work which might benefit the individual leprosy patient, and also be of value in world leprosy control.

This essay requires neither clinical experience nor original work; *entries from junior students in the early years of study will be most welcome.*

Essays should be on quarto paper, double spaced, and submitted before 31 December 1974 to

Dr Colin McDougall,
Room 207,
Department of Human Anatomy,
South Parks Road,
Oxford OX1 3QX,
England

bearing the candidate's full name, college, home address and year of study.

OPENING OF INTERNATIONAL LEPROSY CENTRE AT CARACAS, VENEZUELA

The Pan-American Health Organization in collaboration with the Government of Venezuela have established an International Leprosy Centre at Caracas, Venezuela, with Dr Jacinto Convit, Head of the Venezuela National Institute of Dermatology as Director. Priority will be given to training and to the epidemiology of leprosy. The centre will strive to develop ways of improving data

based on standard indicators such as the number of cases reported and the age and sex of patients, and will also search for new indicators that might help to predict trends and aid in evaluating national control programmes. Research activities will primarily be devoted to drug trials, immunological studies, and bacteriological studies. A colony of 100 armadillos has been established. We wish the centre every success.

ELEP

During the meeting of the Medical Commission of ELEP (the Federation of European Leprosy Associations) held in Berne, Switzerland, on 29 and 30 March 1974, Professor Michel F. Lechat, Professor of Epidemiology at the University of Louvain, Belgium, was unanimously elected as Chairman. He replaces Dr S. G. Browne who has served in this capacity for the past three years. During this time, the standing of the Medical Commission within ELEP has increased, and the projects sponsored and financed by Member-Organizations (amounting to over £2½ million annually) have increasingly assumed an orientation in keeping with modern ideas on the treatment and control of leprosy.

The president of ELEP for the year 1974-75 is Dr L. Hartegen of Germany, well known for his interest in the Chiengmai (Thailand) Leprosarium.

LEPROSY SYMPOSIUM IN NIGERIA

The first West Africa Leprosy Symposium was held at the Bagauda Lake Hotel, Kano, Nigeria, from 1 to 4 April 1974. Sponsored by the Swiss Nigeria Chemical Company (a filial of Ciba-Geigy), the symposium attracted leprologists and dermatologists from several States in Nigeria itself, and from Ghana, Liberia and Zaire, as well as doctors responsible for the coordination of medical services in some States of Nigeria. Ample time was allowed for discussion on the various subjects presented under the general theme "Recent advances in the management of leprosy".

Some of the newer work on the immunological basis of leprosy, particularly as it impinges on our understanding of the disease and the treatment of patients undergoing episodes of acute exacerbation, was ably dealt with by Dr Anthony Bryceson and Dr G. J. Steenbergen.

The "father" of the symposium, Dr S. G. Browne (of the Leprosy Study Centre, London) gave three papers and guided the deliberations of the symposium out of his wide experience. At the conclusion, some recommendations were drawn up for presentation to the Nigerian Federal Ministry of Health. The Federal Minister had sent a message for the inaugural ceremony, outlining a forward-looking policy for leprosy control in Nigeria.

During the symposium, the Association of West African Dermatologists was created, under the Presidency of Dr A. N. Okoro (of Enugu), and preliminary discussions were held on the formation of a West African Leprosy Association.

Lepr. Rev. (1974), **45**, 176-187

Leprosy and the Community

TEACHING AIDS IN LEPROSY

The Institute for Child Health, London, has been inspired, particularly by Dr David Morley, to produce 23 sets of colour slides for teaching purposes on various aspects of tropical medicine, especially as it applies to children, together with authoritative commentaries. Among these sets is one on leprosy, recently prepared by Dr Colin McDougall, Leprosy Consultant, The Slade Hospital, Headington, Oxford, and formally Leprosy Specialist, Ministry of Health, Lusaka, Zambia. The 24 slides cover all important aspects of leprology, and are of excellent quality. The illustrations have an African background, but this in no way restricts the usefulness of this series of slides for teaching purposes. A tape recording of the commentary is available. The set is produced at a very low price, and further information may be obtained from 'TALC', Institute of Child Health, 30, Guildford Street, London WC1N 1EH, England.

PRIZE ESSAY

In order to stimulate interest in leprosy among the younger members of the medical profession, LEPRA instituted an annual prize essay competition on some aspect of leprology. The winning entry for 1973 came from a medical student, Miss Celia Moss, whose essay is here presented. The views expressed are those of the author, and publication of the essay does not mean that they are necessarily the views of the Editorial Board.

The subject of the 1974 Essay is announced under Notes and News in this Journal.

THE TRANSMISSION OF HUMAN LEPROSY

CELIA MOSS

It seems probable that a necessary requirement for the transmission of leprosy is the passage of the bacillus *Mycobacterium leprae* from one person to another. An obvious way of studying the transmission of leprosy would therefore be to study how *Myco. leprae* passes from one individual to the next. However, the validity of this approach is doubtful since Koch's Postulates have not been fulfilled for *Myco. leprae,* i.e. this organism may not be the sole and sufficient cause of leprosy. *Myco. leprae* is certainly identifiable in every case of the disease; leprosy can be introduced into experimental animals by injecting bacilliferous material from patients; and the organism can be recovered after serial passage through several animals. But *Myco. leprae* has not yet been isolated in pure culture: it has been grown in certain tissues *in vitro* with variable success, but nobody has yet developed a reliable cell-free culture medium.

There are several plausible explanations for the notorious obstinacy of *Myco. leprae* in satisfying Koch's Postulates. It could be simply that some chemical constituent of susceptible cells is absent from all media so far tried; alternatively, since *Myco. leprae* is an obligate intracellular parasite, perhaps some specific feature of the intact cell is necessary (e.g. membranes) which would preclude growth in a cell-free medium. On the other hand, it is conceivable that some symbiotic organism is required, i.e. *Myco. leprae* alone cannot cause leprosy.

For this reason alone, there must be more to the study of leprosy transmission than bacteriological studies: but besides this theoretical objection there are more obvious practical ones. Many people have tried to piece together the route of transmission by searching for *Myco. leprae* in various sites. The trouble with this apparently sensible approach is that it has been embarassingly productive: nasal mucus, ulcer exudate, hair follicles and milk have all been shown to contain viable bacilli. The louse, the flea, the cockroach and the mite have all been incriminated. In short, if *Myco. leprae* is to be found almost everywhere it is sought, how can we ever unravel its route of transmission? Susceptibility to leprosy seems to involve factors other than exposure alone to the bacillus. Some people contract leprosy after minimal exposure, while others may remain healthy after living for years with an actively lepromatous patient. To take into account other variable factors such as human resistance and bacterial pathogenicity, and thus to clarify the relationship between exposure to *Myco. leprae* and transmission of leprosy, one must use epidemiological methods.

In conclusion, neither the bacteriological nor the epidemiological approach alone can answer the question "How is leprosy transmitted?" but together they can be applied to the problem formulated in the following way:

(a) What epidemiological variables determine the distribution of leprosy?
(b) How can the effects of these variables be explained in terms of a mechanism of transmission of *Myco. leprae*?

Epidemiological Studies

Dr T. W. Meade has discussed in detail the application of epidemiological studies of leprosy to the identification of high-risk groups, i.e. people to whom leprosy is easily transmitted. There are four essential conditions for a useful study:

(i) The study must be prospective, not retrospective.
(ii) One should measure incidence, not prevalence, of leprosy.
(iii) A multivariant technique of analysis should be used.
(iv) The population studied must not have been subjected to prophylactic measures.

These requirements present great practical problems which no study to date has overcome. In addition there is the theoretical difficulty of knowing what data to collect. One must clearly be selective, and yet not hampered by preconceived ideas. For instance, the classical view of transmission of leprosy is that skin to skin contact is necessary, so investigations have focused on that rather than nose-blowing, eating and defaecation habits, which may be equally relevant to transmission.

Therefore, epidemiology has so far cast little light on the mode of transmission. What is needed is an intensive survey satisfying the requirements laid down by Meade. This would require a large insular and static population where leprosy is endemic and where there have been no control measures. After exclusion of all

those already affected, the rest should be examined for signs of leprosy at least once a year. Each person should be asked a series of questions, with multiple-choice answers suitable for computer analysis. Information collected should include:

(1) Data concerning factors which might influence host resistance to infection: i.e. age, sex, race or tribe, past illnesses, lepromin reaction, etc.
(2) Opportunity for contact with the bacillus: relationship to known patients, nature and duration of contact with them, level of hygiene in the household, e.g. presence of parasites and domestic animals; whether overcrowded, sanitation, treatment of minor skin wounds, method of disposal of nasal secretions, etc.
(3) Examinations of bacilli from known patients for differences in pathogenicity.

In addition, those who develop leprosy during the study should be asked *about contacts,* the site of first lesion, and whether they have had ulcers and if so whether they were dressed. Bacillary load of nasal mucus, as well as skin, should be assessed quantitatively. Finally, values for all these variables could be fed into a computer and correlated independently with the occurrence of leprosy. Those environmental factors thought to influence transmission of leprosy by affecting the opportunity for transfer of bacilli, rather than either of the other variables, might then be revealed. Their effects could then be interpreted in terms of theories of the route of bacterial transmission.

This ideal experiment is clearly ambitious. Much preliminary work would have to be done: sociological studies, as well as a preliminary estimate of incidence, so that a suitable population size could be defined. However, in view of the gravity of the situation at present, and the uncertainty of the pattern of spread (e.g. sudden epidemics arising in non-endemic areas) it is clearly a matter of great urgency to identify the people at risk, and to analyse the predisposing factors, so that the mechanism of transmission can be recognized and blocked.

Direct Studies on the Mechanism of Transmission of *Myco. leprae*

There is a very wide range of possible routes of bacterial transmission, and these can be investigated in several ways. One can search for the bacillus in various sites and try to piece together the route of transmission; or one can select the more likely routes and test them on experimental animals (Rees *et al.,* 1967; Rees, 1969, 1970). When lepromatous material is injected into the footpad of a normal mouse *Myco. leprae* will multiply locally for about six months and then die. If an immunologically deficient (thymectomised, irradiated) mouse is used, the disease becomes progressive: after initial local multiplication bacilli spread, via lymphatics and blood, to cause lesions in many other sites. There is a remarkable similarity between the histological manifestations of *Myco. leprae* infection in the mouse with the disease process in humans.

(A) ROUTE OF EXIT OF *MYCO. LEPRAE* FROM AN INFECTIVE PERSON

Most work on this, the first stage in transmission, has been on lepromatous patients. There is obviously a potential exit from the heavily bacilliferous dermis when the overlying epidermis is cut or ulcerated. An interesting question is whether viable bacilli can also find their way out of unbroken lepromatous skin, as patches usually cover a far larger area than ulcers.

Pedley (1970*a,b*) found very few *Myco. leprae* on lepromatous patches (only 20 on 300 cm^2) using his Composite Skin Contact Smears (CSCS) technique. The method involved pressing a glass slide firmly on ten different areas of skin, heat-fixing it after every second or third smear, and then examining it for bacilli, suitably stained. As a control he showed that the CSCS method would pick up bacilli (a) from nasal mucus on the skin, (b) shed from nearby sores, and (c) from skin smeared with tissue from positive slit scrapings. His conclusions were that *Myco. leprae* does not emerge through intact epidermis, and that therefore skin to skin transmission is unlikely.

Periaswami (1968) found considerable numbers of acid fast bacilli on the skin of lepromatous patients. His method was to smear a few drops of egg-albumin on a closed lesion and transfer it to several other similar sites, thus concentrating anything lying on the surface. Control smears were taken from healthy individuals: no bacilli were found in these.

These positive findings of Periaswami are incompatible with the common observation that bacilli are hardly ever present in the epidermis, even when the whole dermis is replaced by bacilliferous granuloma. Reasoning that there are three possible routes out of the skin (sweat duct, sebaceous duct and hair follicle), Periaswami went on to show how bacilli can emerge through intact skin, by electron-microscopy. In skin biopsies of lepromatous patches he found a concentration of bacilli in the hair follicles, far less in the sweat glands, and hardly any in the sebaceous glands. He also showed, in transverse sections, bacilli apparently spilling out on to the skin around hair follicles, and concluded that infection could occur by this route. Seabra Santos (1965) made the same observation, and concluded that the apparent affinity of *Myco. leprae* for hair follicles could account for alopecia in leprosy. Desikan and Iyer (1972) have confirmed this finding in skin biopsies from 100 lepromatous and borderline patients: they found bacilli in nerves in all cases, in the epidermis in 8 cases, and in hair follicles in 38. There were none at all in sweat or sebaceous glands.

The nasal mucosa may remain bacteriologically positive even after skin smears have become negative, so bacilli might be disseminated in sneezes, nose-blows, sputum or exhaled droplets. Recent experiments of Rees on hospitalized lepromatous patients, in which a 24 h sample of nasal mucus was collected in a sputum-pot left at the patient's bedside, showed that the total bacillary content was of the same order as that of *Myco. tuberculosis* in sputum from patients with active pulmonary T.B. This supports the idea that infected nasal mucus may transmit leprosy.

Milk could also be a medium for transfer of bacilli (Pearson, Rees and Weddell, 1965; Pedley, 1967) provided they can be absorbed from the gut. However, this cannot be more than a subsidiary route: the index case in a family is by no means always the mother. The same applies to findings of *Myco. leprae* in seminal fluid: the frequency of conjugal infection is very low indeed. In conclusion, the predominant route of exit of bacilli is likely to be via nasal secretions or sputum, ulcer exudate, or the hair follicle. Only in the case of nasal mucus is there evidence that this could be quantitatively adequate.

(B) ROUTE OF ENTRY OF *MYCO LEPRAE* INTO SUBSEQUENT HOST

Theoretically, *Myco leprae* might enter the body at any interface with the environment. It is generally assumed that there is a single site of entry and the

discussion below is based on this assumption. However, there could be multiple routes. Perhaps people susceptible to tuberculoid leprosy are more vulnerable to bacilli on the skin, while people tending towards the lepromatous form are more vulnerable to bacilli in the lungs or gut. Another possibility is that the site at which bacilli enter predisposes the subject to one form or the other.

Some light might be cast on the portal of entry if one knew how the bacillus is subsequently disseminated throughout the body. Conversely, the mode of dissemination might be elucidated if one knew the portal of entry. Unfortunately neither of these problems has yet been solved, so inevitably this field of leprology is fraught with circular arguments.

(1) Evidence for entry through the skin

The main reason for the popular belief that leprosy is transmitted by skin to skin contact is, of course, that it is a predominantly cutaneous disease with a peculiar affinity for the peripheral nervous system. This alone does not prove the cutaneous route of entry: it could be that chemotactic influences attract *Myco. leprae* from other parts of the body, or, particularly in tuberculoid leprosy, that bacilli are not particularly concentrated in the skin, but tend to cause damage in sites exposed to cold or other trauma. Some arguments for cutaneous entry are:

(i) Epidemiological evidence, especially site of first lesion. But the inadequacy of these studies has been stressed above.

(ii) Evidence for the primary involvement of cutaneous nerves. The nerves most frequently affected (ulnar, peroneal, greater auricular, etc.) appear to be those containing mainly sensory fibres. Even when large mixed trunks are involved, the long time-lapse between the appearance of sensory and motor changes suggests that at first bacilli are confined to sensory nerves. *Since both motor and autonomic nerves are eventually affected it would seem that these fibres enjoy no special resistance: it merely takes longer for the infection to reach them. This again supports the idea that the infection starts in the skin.

(iii) Evidence for the centripetal spread of bacilli (Lumsden, 1964). Gerlach (1891) showed that the earliest changes are in the most peripheral branches of cutaneous nerves. Soon sensory branches in the larger nerve trunks are affected, and the process can advance as far proximally as the spinal cord. He concluded that the earliest and most extensive degeneration occurs at the site of entry of bacilli (i.e. the skin). This has been taken a step further by recent histological studies of Ridley (1970). In the earliest recognisable tuberculoid lesion there is infiltration of the epidermis by lymphocytes and epithelioid cells, before any infiltration of nerves occurs or any AFB's can be seen. This picture is interpreted as a stage of maximum immunity, *Myco. leprae* being arrested on entry into the epidermis. If resistance is lower they may reach the dermis and get a more secure hold on nerve and muscle: in this case a few AFB's are seen and there is a non-specific cellular infiltration around nerve bundles and other dermal structures.

The most potent argument against cutaneous entry is that *Myco. leprae* is very rarely found in the epidermis. This makes inunction through the skin unlikely, so if *Myco. leprae* does enter through the skin it must be through breaks in the epidermis. Experimental attempts to transmit leprosy to volunteers have been remarkably unsuccessful, but there is circumstantial evidence that leprosy can be transmitted in this way. There are one or two cases of lesions developing around

* Autonomic nerves may be involved very early. Ed.

the site of a pin-prick, and although many of these might be explained in terms of unrecognised contact with a leprosy patient, there is still the classic case of two sailors who were both tattooed on the forearm at the same place, and both developed leprosy around the site of the tattoo some years later (Porrit and Olson, 1943).

Since the theory of cutaneous entry of bacilli rests partly on evidence for centripetal neural spread, another counter-argument is that haematogenous spread of bacilli undoubtedly occurs. Visceral foci are common post-mortem findings in humans and in irradiated mice injected with leprosy bacilli. However, supporters of the theory of neural spread claim that it is the relative infrequency of internal (compared with cutaneous) lesions that calls for explanation, not their occasional occurrence.

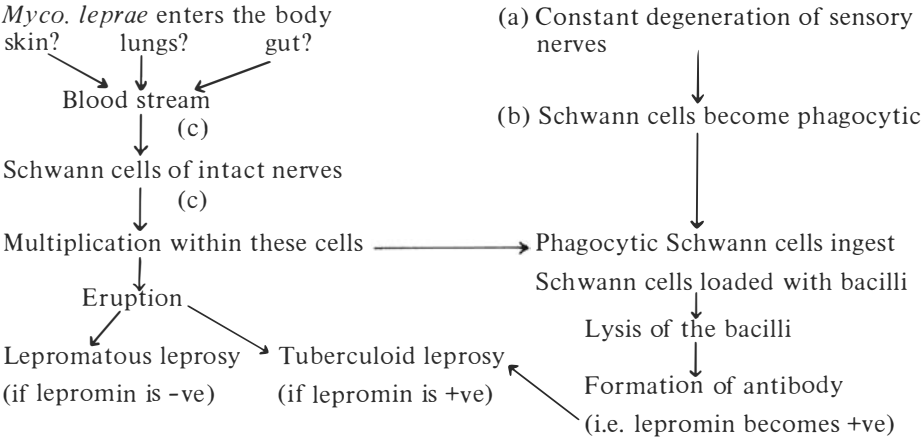
(2) Evidence for entry through respiratory and gastro-intestinal tracts

If one could show blood-borne bacilli at an early stage in the disease, and a positive attraction of *Myco. leprae* to cutaneous nerves from other sites, it would not be necessary to postulate cutaneous entry of bacilli to account for the findings mentioned above. More positive evidence for entry at other surfaces would be the demonstration of early accumulation of bacilli around capillaries in these sites.

(i) *Evidence for haematogenous transport.* The occurrence of visceral foci in all clinical forms of leprosy has already been mentioned, and frank bacillaemia is often found in the lepromatous form. In some cases lymphatic transport may be responsible for internal lesions (Desikan and Job, 1966). However, there is often no lymphatic connection between cutaneous and visceral foci, and transport must be via the blood stream. It would be interesting to know whether visceral lesions can precede skin lesions. Further support for haematogenous transport is provided by observations on mice: even in immunologically intact mice the capillary endothelium is a site of preferential accumulation and multiplication: sometimes electron-micrographs show bacilli apparently bursting out of endothelial cells into the lumen. In irradiated mice, bacilli injected intradermally proliferate locally and may cause alopecia at that site: 8 weeks later they are found in lymphatics draining that area, and involvement of the viscera, particularly the spleen, is found commonly within 18 weeks.

(ii) *Evidence for the attraction of* Myco. leprae *to the skin from other sites.* If it could be shown that the injection of *Myco. leprae* could produce a typical cutaneous lesion at a completely separate site, all the evidence for cutaneous entry would be invalidated. This has not yet been carried out in a healthy human being. However, Cochrane once demonstrated, in a single splenectomized monkey, that implantation of lepromatous tissue into the splenic stump followed by daily intradermal injections of lepromin, resulted 1 year later in a tuberculoid lesion on the forehead. This has not been repeated. In contrast, it is a common finding that intravenous injection of bacilli into thymectomized, irradiated mice causes lesions predominantly in cutaneous sites: the skin of the ears, paws, nose and tail.

Dr Weddell has proposed that *Myco. leprae* is attracted by the Schwann cells of cutaneous nerves (Weddell and Palmer, 1963; Weddell, Jamison and Parker, 1964). His theory of transmission, and some of the relevant experimental observations are summarized below.



(a) There is normally continuous degeneration and regeneration of all cutaneous nerves.
(b) The debris is removed by macrophages which originate from within the perineural sheath. Carbon particles injected into the skin of lepromatous patients are found, 5-7 days later, in Schwann cells related to degenerating axons. Moreover this phagocytosis shows some degree of specificity for *Myco. leprae:* heat-killed bacilli injected into the radial nerve of an infected person are found later in Schwann cells whereas *Myco. lepraemurium* injected into the other side as a control are found in the connective tissue sheaths of nerve bundles rather than inside Schwann cells.
(c) In lepromatous leprosy, bacilli have been found in Schwann cells of intact nerves suggesting that *Myco. leprae* is attracted to, and can multiply within, non-phagocytic Schwann cells without lysis.

This theory is attractive in that it explains quite simply several odd characteristics of leprosy: the long incubation period, changes in lepromin reaction with exposure (it becomes positive) and the apparently higher susceptibility of children. More important in this context, it accounts for the sites of predilection of leprosy: the nerves usually affected are just those which are most exposed to trauma and undergo frequent degeneration and regeneration, i.e. contain a high proportion of phagocytic Schwann cells. If it is correct, there is no need to postulate that the peripheral sites of lesions reflect the sites of entry of bacilli (although cutaneous entry would not be ruled out completely).

(iii) *Positive evidence for entry via the lungs or gut epithelium* in humans is so far lacking. With regard to the gut, it could easily be shown whether bacilli remain viable in gastric juice: if not this route would be ruled out. Proof of entry at either of these sites would require demonstration of bacilli in the epithelial cells and capillaries some years before the manifestation of leprosy—clearly a difficult experiment to arrange. However, it would be feasible to collect samples of gastric, intestinal and respiratory mucosa from autopsies in an endemic area: if the bacillus is as ubiquitous as is commonly suggested, one would surely find *Myco. leprae* in a few sections, particularly those of close relatives of a leprosy patient.

This is a field where animal experiments could be very useful. In fact Rees has already attempted an experiment in which three groups of immunologically deficient mice were exposed to bacilli in different ways. One group received *Myco. leprae* in their food, a second in nose-drops, and a third in an aerosol spray. Unfortunately the results were largely negative because the experiment was terminated too soon: it would surely be worth repeating. Three questions need to be answered: firstly, do these mice acquire lepromatous lesions at all? Secondly, which method is the most successful in producing lesions? Thirdly, in which cells of the mucosa concerned do *Myco. leprae* settle and multiply?

(C) EXTRA-HUMAN SURVIVAL OF *MYCO. LEPRAE*

Any site where *Myco. leprae* can remain viable for long periods must be considered as a possible reservoir for infection, if not an essential step in transmission. Bacilli should be sought in fomites, droplets, nose-blows, sneezes, etc., and their viability estimated after various intervals by injection into mouse footpads. Studies on the bacillus *in vitro*, e.g. chemical and physical conditions incompatible with viability, are clearly relevant to this phase of transmission, but there is no room to discuss them here. However, this sort of data is inconclusive on its own. For instance *Myco. leprae* have been demonstrated in the gastro-intestinal tract of the flea which may be found in large numbers in endemic areas. Some have concluded from this that arthropods contribute to the transmission of leprosy, but this may well be just an incidental finding: considering the vast numbers of bacilli in a single skin smear it would be remarkable if a flea, which spends its life biting human skin, did not contain *Myco. leprae* in its gut.

Conclusions

No experiment has yet proved or disproved any theory of transmission of leprosy. Bacteriological studies can, at best, only rule out impossible modes of transmission. Epidemiological studies have contributed no concrete facts because the ideal conditions are so difficult to fulfil. It is disappointing to finish with no definite conclusions, although this can be rationalized in terms of the question set at the beginning: until the variables determining the distribution of leprosy are known (from the suggested large-scale epidemiological survey) their effects cannot be interpreted in terms of a mechanism of transmission.

In view of the likelihood that nasal mucus of infectious patients contains enough bacilli for transmission of leprosy, it might be worth emphasising this route a little more in research. In epidemiological studies one should record nasal load of *Myco. leprae* instead of just skin load. In the laboratory the viability of *Myco. leprae* in nasal secretions should be studied, and more attempts made to transmit leprosy to mice by methods other than injection, e.g. nose-drops and aerosol sprays. Finally, *Myco. leprae* should be sought in lung and gut epithelial cells and capillaries.

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Field Workers' Forum

INDICATIONS AND CONTRAINDICATIONS FOR RECONSTRUCTIVE SURGERY

GUIDELINES FOR FIELD STAFF

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Social and Psychological Considerations

Preference should be given to
(1) children and young people;
(2) people for whom reconstructive surgery may mean a definite improvement in their economical or social conditions;
(3) patients who actively desire reconstructive surgery;
(4) all patients with endangered vision.

General Medical Considerations

(1) The patient should have been on stable treatment for not less than 3 months prior to surgery.
(2) The bacterial index (B.I.) should be + 2 or less.
(3) The morphological index (M.I.) should be O. Inherent in No. 1 is the claim that
(4) the patient must have shown NO evidence of "reaction" during the last 3 months prior to surgery.
(5) The patient must have received NO corticosteroids or ACTH during the last 3 months.

Surgical Considerations

(A) INTRA-OCULAR OPERATIONS

(e.g. iridectomy, cataract extraction, intro-ocular drainages, etc.) Intraocular surgery in leprosy presents a number of difficult and potentially dangerous situations. Such patients should be treated either by an ophthalmologist with training in leprosy, or by a reconstructive surgeon with training in ophthalmology.
(1) B.I. and M.I. must have been O for at least 6 months.
(2) No clinical activity must have been detected during the last 5 months prior to surgery.
(3) No septic conditions must be present anywhere in the body.

(B) SURGERY OF THE TEAR CANALS

This is usually required in cases with chronic infection of the tear canals. Since it frequently is associated with corneal/conjunctival anaesthesia, its correction is a matter of urgency.

No special contraindications are recognized.

(C) SURGERY ON THE EYELIDS

This is usually required for entropion or for lagophthalmos. Since both conditions frequently are associated with corneal/conjunctival anaesthesia, and since both conditions, even in the absence of this complication constitute a serious risk to the preservation of an unimpaired vision, their correction is a matter of urgency. If the surgical considerations are fulfilled, patients may be referred to plastic surgeon or to ophthalmolgist for correction, or preferably to reconstructive surgeon. If the surgical considerations are NOT fulfilled they must urgently be sent to reconstructive surgeon, who in consultation with the medical team will decide on the plan of treatment.

(D) RECONSTRUCTIVE SURGERY OF THE FOOT

(1) Weakness of dorsiflexion or dropfoot of less than 3 months duration requires referal to reconstructive surgeon (the treatment may in certain cases be conservative).
(2) Dropfoot of more than 3 months duration requires referal to reconstructive surgeon for operative treatment.
(3) Clawing of toes will in most cases be associated with dropfoot at the moment when the patient presents his complaints. The surgical correction may be undertaken simultaneously with dropfoot correction.
(4) Conditions related to plantar ulceration and scarring: see guidelines on ulcers and scars.

(E) RECONSTRUCTIVE SURGERY OF THE HAND

(1) Clawing of fingers, paralysis of the thumb, and wrist drop of less than 3 months duration require referral to reconstructive surgeon (in many cases attempts at conservative treatment may be made).
(2) Uncomplicated clawing of fingers, paralysis of the thumb, and wrist drop of more than 3 months duration require referal to reconstructive surgeon.
(3) Hands with severe absorption, deformed and twisted fingers, contractures, or extensor tendon damage can with careful surgery and competent physiotherapy in many cases yield surprisingly good results. Consider the social and psychological situation, and if the patient is suitable, refer to reconstructive surgeon for assessment and possible surgery.

(F) PLASTIC AND COSMETIC SURGERY OF THE FACE

This is usually required for madarosis, correction of collapsed nose, correction of pendulous and and deformed ears, and correction of excessive wrinkling of the face.

(1) Consider the social and psychological situation.
(2) B.I. and M.I. must have been O for at least 6 months prior to surgery.
(3) No clinical activity must have been detected during the last 6 months prior to surgery.

It should be recognized that with increasing urbanization, more and more people will come to depend on jobs where their appearance is of great importance.

(G) NON-SPECIFIC SURGICAL CONDITIONS

(1) Gynaecomastia and hyperthelia may be treated surgically either at local general hospital or by reconstructive surgeon.
(2) Any other condition that may require surgery: (I) if general medical conditions permit, refer to local general hospital; (II) if general medical conditions do NOT permit, refer to reconstructive surgeon or to medical leprologist for advice.

(H) SPECIAL CONSIDERATIONS FOR PREGNANT OR LACTATING WOMEN

It is particularly important under these conditions to ensure an adequate diet, particularly in respect of protein intake. Treatment with iron preparations and multivitamins should invariably be given.

(1) If the woman is under regular treatment: (I) stop further increase in DDS dosage; (II) refer to medical leprologist for advice.
(2) If the woman has discontinued treatment for whatever reason: (I) do NOT initiate or re-start treatment with DDS; (II) refer to medical leprologist for advice.
(3) If the woman has never had anti-leprosy treatment (I) do NOT initiate anti-leprosy treatment; (II) refer to medical leprologist for advice.

Since reconstructive surgery in leprosy was initiated by Mr P. W. Brand, 25 years ago, tremendous advances have been made in the surgical techniques and in the related and essential field of physiotherapy.

It was fairly early recognized that the medical and social conditions of the patients who submitted themselves to surgery were of great importance. One should not brush aside the occasionally seen provocation of reactions by the surgical trauma. The very nature of this problem has rendered the surgeons wary of initiating double blind studies to ascertain the exact nature of indications and contraindications in this field. We, therefore—all of us—tend to work from experience and impressions, coupled with a knowledge of certain basic facts of biology.

The guidlines set out here represent the experiences of the author from a number of years of work in this field in various parts of the world and under varying conditions. Naturally discussions and information from many colleagues have influenced this. Equally naturally different surgeons may differ in details of opinion.

In different social, economic and cultural settings the relative priorities of surgery of the hand and of the foot tend to vary. However, vision-preserving surgery must always have the highest priority. Cosmetic surgery—such an apt and often misused term—tends to assume higher priority with increasing urbanization.

On all points the individual surgeon in consultation with his medical colleagues and local social services must make up his own mind.

It is the hope of the author that these guidelines may help to a better understanding and helpful service to the leprosy patients.

Lepr. Rev. (1974), **45**, 188

Book Review

Leprosy for Students of Medicine, by A. Bryceson and R. E. Pfaltzfraff. Edinburgh, Churchill Livingstone £1.50, 152 pp.

This book, written by two leprologists of great experience, could well be one which many leprosy workers have been seeking for a long time. Clear, concise, and comprehensive, it compresses into 152 pages the facts which every student of leprosy needs to know. At the same time it presents them with a scientific approach which not only places leprosy in the main stream of general medicine, but brings out its unique interest and importance.

As the authors state in the preface, the book is born of a course in leprosy run at Garkida for medical students of Ahmadu Bello University, Zaria, Nigeria. Students who have teaching of such distinction are fortunate indeed.

While the African setting is evident, the authors have made every effort to present the world wide picture of leprosy. Numerous diagrams, and 43 black and white plates enrich the text. The 15 chapters cover every aspect of leprology, with suggestions for further reading appended to each. Chapters dealing with immunological questions are particularly outstanding, and typical of the whole approach is a welcome chapter on ophthalmology, and also a chapter on experimental leprosy.

The inevitable emphasis on clinical leprosy as seen in Nigeria, and the approach to treatment and control appropriate in that area, does not sometimes take sufficient account of features which may be more apparent, for instance in Asia. I could not find any reference to the heavy involvement of the male external genitalia in lepromatous and borderline leprosy, or to the immunological downgrading associated with puberty in the male, and, more importantly, with parturition in the female. On the practical side too there are one or two points to be made. The suggestions for multiple smears on a single slide on p. 32 are admirable, but if the slide illustrated is the usual 1 in × 3 in size or thereabouts, he would be a remarkable technician who succeeded in making 6 to 8 smears in the area of the lines shown on the diagram. Surely they should be more widely spaced. This is a minor point. A more important one is the omission of the simple technique for testing thermal sensation. It was probably correct to include the pilocarpine test for loss of sweating, though the practical usefulness of this in preference to asking the patient to run for 100 m is debatable.

For the rest, two elements in the pleasure one had in reading this book were the confirmation of cherished points in personal clinical experience on the one side, and fine points about which one would like to argue on the other, as e.g. the placing of pin prick first in the modalities of lost sensation in lepromatous leprosy, and the statement that in tuberculoid lesions a macular phase precedes the raised phase.

These are minor criticisms when set against the tremendous positive value of this book, and can easily be reconsidered in the second edition which it is hoped will be called for. This book should be read and treasured by doctors involved with leprosy in five continents, and at a price of £1.50, should be within the reach of them all.

Frank Davey

Lepr. Rev. (1974), **45**, 189-190

Letters to the Editor

Dr Stringer's conclusion [*Leprosy Review* (1973) **44**, 70-74] that the word "leprosy" should be retained "particularly because of its value to fund-raising", testifies both to the tremendous power of that word and to the uniqueness of that disease. Nothing similar occurs in any other branch of medicine.

Those of us who really believe that it should be "like any other" preferred the educational and, consequently, the preventive possibilities of an emotionless non-stigmatizing "hanseniasis", although regretting that this "cold" term might hamper the fund-raising possibilities of the voluntary agencies in our area. We had to make a choice for the benefit of the patients and our programmes, and we chose enlightenment and destigmatization.

Evidently, this is not a problem for England, where there are neither "lepers" to be hurt (and abscond), nor control programmes to be hindered. But we still hope that in the so-called civilized era we live in, voluntary agencies will eventually find a way to raise funds for patients in Africa, Asia and the Western Pacific without contributing to the suffering of millions in the Americas and to the spread of the endemic in this part of the world.

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PROFESSOR A. ROTBERG

In the editorial, "How Do Leprosy Bacilli Leave the Body?" [*Leprosy Review* (1973) **44**, 47-49] the comment is offered that "In the Far East the genitourinary tract has for many centuries been associated in popular belief with the transmission of leprosy. . ." The concept of the transmission of leprosy by urine is also prevalent in central Africa.

During the period 1961-1973, I often asked inhabitants in various parts of what is now the Republic of Zaire about their thoughts on the mode of transmission of leprosy. In addition, each year in my dermatology course at the Institut Medical Evangélique, Kimpese, lower-Zaire, I would ask the students, who came from every province of the country, what were the prevailing beliefs in their home village areas on the contagion of leprosy (not necessarily the belief of the student). Transmission by contamination of the soil with urine from a leprosy patient was a popular concept. There were of course many other explanations such as consumption of the meat of elephants or spotted animals, especially red-skinned ones such as antelopes.

I am not certain of the basic reasoning behind the implication of urine, but there is an association of ideas between "leprosy" contaminated soil and the development of plantar ulcers, as if the neuropathic ulcers had been caused by organisms directly inoculated from the soil. In central Africa the stigmata of

leprosy are perhaps socially more acceptable than in certain other parts of the world. However, as the editorial suggests, the development of plantar ulcers seems to be especially unacceptable. We have observed patients with other deformities who were normally welcome in their village until plantar ulcers developed. The belief was that the soil was contaminated by "leprosy" from the open ulcers as well as by urine and thus transmitted the disease.

A sympathetic understanding of the popular ideas concerning any disease, and especially leprosy, is essential to a meaningful patient-physician-population relationship in any society.

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Lepr. Rev. (1974), **45**, 191-195

Abstracts

1. POWELL, S. & McDOUGALL, C. **Clinical recognition of leprosy: some factors leading to delays in diagnosis.** *Brit. med. J.* 1974, Vol. 1, 612.

Case histories of eight patients in the United Kingdom admitted to hospital for the diagnosis of leprosy are examined in detail to draw attention to sources of error in diagnosis which are easily made in countries where leprosy is not endemic. In this series, misdiagnoses included, syringomyelia, polyarteritis nodosa, allergy, mycosis, and erythema multiforme, and had led in two patients to treatment with cortico-steroids. All the patients did in fact present signs which should have led to a correct diagnosis, and the authors draw attention to the importance of nasal symptoms in patients with early lepromatous leprosy.

T. F. Davey

2. REES, R. J. W. & MEADE, T. W. **Comparison of the modes of spread and the incidence of tuberculosis and leprosy.** *The Lancet,* 12 January, 1974, 47.

An interesting comparison is made between the bacterial loads of *Myco. leprae* in single early morning nose-blows and 24 h collections of nasal discharge from patients with lepromatous leprosy, and loads of *Myco. tuberculosis* from 12 h collections of sputum from patients with open tuberculosis. Bacterial loads are of the same order in the two diseases. A comparison is also made between average annual age-specific and sex-specific attack rates for the two diseases in family contacts in two similar groups in areas of South India in close proximity. The rates in the two diseases are of the same order of magnitude, though actually higher for leprosy than tuberculosis in males aged 5-14. These important similarities are consistent with the possibility that modes of spread and routes of infection could be identical in the two diseases.

T. F. Davey

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3. HARTMAN, A. **The prevalence of leprosy at the coast of Kenya.** *E. Afr. Med. J.,* 1973, v. 50, No. 4, 181-8.

Twenty-one villages on or near the coast of Kenya, "selected at random", were visited by teams of teachers and students from the University of Nairobi, and the villagers examined for leprosy and "other diseases". "The object of our survey was not mentioned" and the author concludes that this method prevented "the hiding of suspect cases". In 4 villages the team first carried out a census. Of 8011 people examined, 62 were found to have leprosy, with ages ranging from 7 to 76. Twenty tribes or sub-tribes were identified and people with leprosy were found most frequently in the largest tribes; it occurred in some smaller tribes but not in others. In certain districts the prevalence was high (up to 1.5%) and more staff for leprosy clinics is recommended. The author estimates that, in a total coastal population of 800,126, there would be 6700 people with leprosy.

C. S. Goodwin

4. SAMUEL, D. R., GODAL, T., MYRVANG, B. & SONG, Y. K. **Behavior of *Mycobacterium leprae* in human macrophages *in vitro*.** *Infection and Immunity,* 1973, v. 8, No. 3, 446-9.

"Attempts have been made to cultivate *Mycobacterium leprae* in human macrophages *in vitro*. In 27 out of 55 experiments a two- to ninefold increase (mean 2.31 ± 1.46) in acid-fast organisms were observed over a period of 1.5 to 3 months of cultivation. No such increase was observed with heat-killed bacilli (mean fold increase 0.88 ± 0.19). Macrophages were necessary for obtaining increases. No multiplication was observed on artificial media. A close correlation between increases of acid-fast organisms and changes in viability as determined by the morphology of the bacilli (morphologic index) was found. The increases in acid-fast organisms could be inhibited by anti-leprosy drugs. It is concluded that multiplication of *Myco. leprae* may take place inside human macrophages *in vitro*. Multiplication appears not to be dependent on whether the macrophages are derived from lepromatous or tuberculoid patients or health individuals. Moreover, multiplication took place both at 33° and 37°C. The applicability of this method is at present limited by the restricted survival of human macrophages *in vitro*."

5. BULL WLD HLTH ORG., 1973, v. 48, No. 3, 345-54; *Ibid.,* No. 4, 483-91. **Immunological problems in leprosy research: 1 and 2.**

"This Memorandum reviews the present status of knowledge of the immunology of leprosy, with particular attention to development since the publication of a similar review in 1970. The different types of lepromin reaction and their significance in healthy contacts and in patients with tuberculoid and lepromatous leprosy are discussed. The immunological responsiveness of patients with leprosy is also considered, with special attention to *in vitro* methods for evaluating this response. . .

"Part 2 of this Memorandum covers possible mechanisms of altered immune response in leprosy (including a tentative scheme to explain the possible genesis of the lepromatous lesion); genetic, nutritional, and hormonal factors; the possibility of vaccination; attempts at immunotherapy; and areas in which further research is needed. A detailed protocol for evaluating the effect of transfer factor in leprosy is included as an annex."

(This memorandum was drafted by 17 experts in various aspects of leprosy research and immunology. There are 60 references.)

6. GODAL, T., LOFGREN, M. & NEGASSI, K. **Immune response to *Myco. leprae* of healthy leprosy contacts.** *Int. J. Lepr.,* 1972, v. 40, No. 3, 243-50.

Transformation of lymphocytes specifically by *Mycobacterium leprae* indicates an immune response and, in this study, was performed in parallel with BCG to assess the specificity of the reaction; lymphocytes incubated without any antigen were used as controls. In Addis Ababa, lymphocytes from 94 people were cultured: 16 were household contacts of patients with leprosy (group I), 36 had been workers among leprosy patients for more than one year (group II), 8 for less than one year (group III), and 22 had not been in household or occupational contact with leprosy patients (group IV). Twelve of the people tested were Ethiopian staff from a tuberculosis clinic (group V). The average response to BCG of lymphocytes from those in group IV was 7%, and to *Myco. leprae* was 0.51%, a "cross-reactivity" of 7.25%, while in group V the cross-reactivity was 14.7%. A response to *Myco. leprae* was found in the lymphocytes of one person in group IV, in 6 people in group III, in 84% in those in group II, and in 81% in group I. In group II the degree of lymphocyte transformation seemed to be related to the degree of contact. The authors discuss their findings at length, concluding that the absence of leprosy in the great majority of people attending patients with leprosy, and in household contracts, is due to the development of effective immunity, although this response does not

differ in degree from that of patients with tuberculoid leprosy. It is suggested that a response early after exposure to leprosy leads to immunity, but a delayed response may lead to disease.

C. S. Goodwin

7. THORSBY, E., GODAL, T. & MYRVANG, B. **HL-A antigens and susceptibility to diseases. II. Leprosy.** *Tissue Antigens,* 1973, v. 3, No. 5, 373-7.

"Thirty-nine leprosy patients (20 tuberculoid and 19 lepromatous) have been HL-A typed and compared to 36 non-leprosy individuals of the same ethnic group (Amharas). The most significant deviation was related to the W21 antigen, which was found only among leprosy patients (both tuberculoid and lepromatous), not in the control group. No deviation in antigen frequency was found to be specific to the lepromatous group."

8. SWIFT, T. R., HACKETT, E. R., SHIPLEY, D. E. & MINER, K. M. **The peroneal and tibial nerves in lepromatous leprosy. Clinical and electro-physiologic observations.** *Int. J. Lepr.,* 1973, v. 41, No. 1, 25-34.

"Clinical examination and segmental nerve conduction velocity studies of peroneal and tibial nerves were carried out on 25 patients with lepromatous leprosy and on 16 control subjects. Muscle atrophy and weakness occurred most often in the extensor digitorum brevis muscle (15 of 50 legs) and intrinsic foot muscles (12 of 50 legs), with lesser instances of weakness in other muscles. Nerve enlargement and nerve pain were common for the peroneal nerve and less common for the tibial nerve. Nerve conductions and latencies revealed significant slowing in the patients in the segment of the peroneal nerves from the popliteal fossa to the head of the fibula and in the latency from the ankle to the extensor digitorum brevis muscle. Tibial slowing occurred in the segment from the popliteal fossa to the ankle and in the latency from the popliteal fossa to the lateral head of the gastrocnemius. This study shows that clinical and electrical evidence of segmental involvement of both nerves is common in lepromatous leprosy, and points out the importance of performing nerve conduction velocity studies on the segment of the peroneal nerve between the popliteal fossa and the head of the fibula."

9. SU, D. W. P., YANG, H. Y. & SKINSNES, O. K. **The effect of neonatal thymectomy on *Mycobacterium leprae* infection in mice.** *Int. J. Lepr.,* 1973, v. 41, No. 1, 81-93.

"C_3H mice were thymectomized at birth and inoculated intraperitoneally with *Mycobacterium leprae.* The neonatally thymectomized and control sham-thymectomized and nonthymectomized mice were sacrificed at one month and bi-monthly through the tenth month. The total acid-fast bacillary content of their livers, spleens, lungs and kidneys were harvested and evaluated with respect to their total numbers and solid-form numbers. Neonatally thymectomized mice had higher total and solid-form bacterial counts than either the sham-thymectomized or nonthymectomized animals but both the total and the solid-form counts decreased after the sixth month. Thus, the animals recovered from the immunologic defect induced by neonatal thymectomy by the sixth month and this recovery is associated with an ability to alter the morphology of the bacilli to a form regarded as nonviable. The recovery of immune capacity was associated with redevelopment of follicles with profuse lymphocytes in the spleens of thymectomized mice after the fourth month. Oxytetracycline in the drinking water, in a concentration of 3 mg 100 ml, helps to prolong the lives of thymectomized mice and decrease the incidence of "wasting disease." The significant proliferation of solid-form bacilli in the viscera of the thymectomized mice during their period

of immunologic deficiency suggests that the lower tissue temperature postulated as necessary for the success of the proliferation of *Myco. leprae* in the mouse footpad may not be an obligate factor."

10. BECHELLI, L. M. *et al.* **Proposed method for estimating leprosy prevalence based on rates in children.** *Bull. Wld Hlth Org.,* 1973, v. 48, No. 4, 502-3.

An inexpensive and reasonably accurate indication of the prevalence of leprosy in a community is, according to the authors, to be gained by a survey of schoolchildren (aged 5–14 years), who are readily available for examination. In general, the total prevalence rate would be about 4 times as high as that found among children. The ratio remained the same after 10 years of leprosy control in central Burma.

S. G. Browne

11. FAZELBHOY, Z. A. **Leprosy control in Pakistan.** *J. Pakistan Med. Ass.,* 1973, v. 23, No. 5, 129-35.

This article mentions superficially many areas of Pakistan, with an indication of the prevalence of leprosy apparently based on either the numbers attending clinics or "random surveys". In 5 out of 34 areas in Karachi the prevalence ranges from 0.98 to 3.3 thousand, but in some small areas in other districts it is 40 thousand. Because rooms were not available in Government dispensaries, separate buildings have been built as leprosy clinics. Apparently most work among patients with leprosy is done by "voluntary agencies".

C. S. Goodwin

12. PRABHAKARAN, K. **A rapid identification test for *Mycobacterium leprae.*** (Correspondence.) *Int. J. Lepr.,* 1973, v. 41, No. 1, 121.

A drop each of phosphate buffer 0.5M, pH 6.8, and bacillary suspension "about 100 μg protein", and D-dopa solution "about 2 mg/ml in water, made up fresh" are placed in a cavity slide which is kept in a Petri dish with a moisture source overnight at 37°C. If a "deep purplish" colour develops which gradually turns black this indicates the presence of *Mycobacterium leprae.*

C. S. Goodwin

13. DASTUR, D. K., RAMAMOHAN, Y. & SHAH, J. S. **Ultrastructure of lepromatous nerves. Neural pathogenesis in leprosy.** *Int. J. Lepr.,* 1973, v. 41, No. 1, 47-48.

Interested workers will need to read the original of this detailed description of the ultrastructure of nerves in lepromatous leprosy, with its many electron micrographs. It is not suitable for abstraction, but some conclusions can be stated.

In three patients of lepromatous type and one of borderline type, *Mycobacterium leprae* constantly parasitized Schwann cells, endothelial and perineurial cells with equal facility, three cell types which have in common the possession of a basement membrane, although smaller numbers of organisms were found also in endoneurium and perineurium in cells without a basement membrane. Schwann cells, therefore, were not considered to be the sole target cell. It was confirmed that Schwann cells as well as myelin and axons might be heavily damaged. However, it was mainly the Schwann cells of non-myelinated fibres that were parasitized, and the axons not at all.

D. S. Ridley

14. MALAVIYA, A. N., PASRICHA, A., PASRICHA, J. S. & MEHTA, J. S. **Significance of serologic abnormalities in lepromatous leprosy.** *Int. J. Lepr.*, 1972, v. 40, No. 4, 361-5.

The sera of 50 Indian patients with lepromatous leprosy but without *erythema nodosum leprosum* were analysed. Hepatitis-associated antigen was found in 14%. Rheumatoid factor was detected in 26%, anti-thyroid antibody in 16%, antinuclear antibody in 26%, and C-reactive protein in 24% of the patients; these percentages are similar to those among patients with "autoimmune diseases". The authors suggest that depressed cell-mediated immunity in lepromatous leprosy may allow the development of autoantibodies.

C. S. Goodwin

15. NEBOUT, M. A propos d'un cas de lèpre tuberculoïde nodulaire chez un adulte africain porteur de scarifications rituelles. **(Report of a case of nodular tuberculoid leprosy localized, in an adult African male, on ritual scarifications.)** *Méd. Trop.*, 1973, v. 33, No. 5, 523-8. English summary.

The author reports the appearance of lesions of tuberculoid leprosy 3 years after ritual scarification of the forehead in an adolescent African male. The nodular lesions were initially confined to the lines of scarification, but subsequently extended to several areas of skin, particularly over the thorax. Histological examination of the nodules showed typical tuberculoid changes, and the response to standard treatment was good.

No conclusions can be drawn regarding the introduction of leprosy bacilli, but the occurrence of the visible lesion was obviously connected with trauma to the skin.

S. G. Browne