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Editorial

VACCINATION AGAINST LEPROSY; RECENT ADVANCES AND PRACTICAL IMPLICATIONS

Leprosy control, using the current approach of mass treatment, has important limitations which are well recognized. The long incubation period of the disease, the insidious onset, the chronic course, and the need for prolonged treatment have made control a formidable task, bringing out the urgent need for improved tools. Primary prevention through immunization has thus attracted considerable attention in recent years, and efforts are being made to develop a vaccine against leprosy with high efficacy, acceptability and cost-effectiveness.

BCG itself was the first vaccine to be considered against leprosy following the report of Fernandez in 1939 on lepromin conversion among lepromin negative healthy children following BCG administration. Shepard later provided the first experimental evidence in favour of BCG in the mouse foot-pad model. However, it was not until the 1960s that major field trials on the value of BCG were started in Uganda, Burma, Papua New Guinea, and India. The trial in Uganda involving over 60,000 children showed an overall protective effect of 80% during the 8 years of follow-up. The Burma trial involving over 28,000 subjects showed a protective effect of about 20% at the end of 14 years of follow-up. In Papua New Guinea, the protective effect observed among 5000 subjects over a 12-year period of follow-up was about 46%. The Indian trial, which is still in progress, involves over 180,000 subjects and has so far shown a protective effect of 28%. Thus it can be concluded that the protective effect of BCG has generally been modest except in Uganda. The factors that might have contributed to the observed variations remain to be explained.

A major impetus to research on antileprosy vaccines was the possibility in the 1970s of obtaining large quantities of *Mycobacterium leprae* through the then discovered model of the nine-banded armadillo and preparing a vaccine based on killed *M. leprae*. Partly as a result of this development, a Scientific Working Group on the Immunology of Leprosy (IMMLEP), a component of the UNDP/World Bank/WHO Special Programme for Research and Training in

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Tropical Diseases, came to be established in 1975 with vaccine development as one of its major goals. Since then IMMLEP has made substantial progress.

An important premise on immunization in leprosy is that induction of cell-mediated immunity will lead to protection against the disease. This premise is based on the wide spectrum of disease that leprosy manifests, and the relationship of the different types in the spectrum to cell-mediated immunity. The next premise, which is based on experimental evidence, is that *M. leprae* and certain other cultivable mycobacteria are capable of producing cell-mediated immunity to antigens of *M. leprae.*

The availability of adequate quantities of *M. leprae* being a major prerequisite for vaccine development, IMMLEP has been able to produce large quantities through its armadillo colonies, store and distribute them through an *M. leprae* bank in London. This dependence on armadillos is expected to continue until other methods, such as production of *M. leprae* antigens in *E. coli* or other bacterial hosts through use of recombinant DNA technology, become possible.

As the vaccine preparation requires *M. leprae* in a purified form, IMMLEP has been able to develop an optimal method of purification of the organisms from host tissues which gives maximum yields of tissue-free bacteria with minimum damage to the organisms. Extensive *in vitro* and *in vivo* testing of the preparation has shown no loss of identifiable mycobacterial antigens. The vaccine preparation itself has involved both irradiation of the infected tissue and autoclaving of the final product.

Studies so far have established that the killed *M. leprae* preparation, even in the absence of adjuvants, is capable of producing good delayed-type hypersensitivity in mice as well as guinea-pigs. In addition, the preparation has been found in the mouse foot-pad model to be capable of protecting against challenge with live *M. leprae*.

The next vital step in vaccine development is testing of the vaccine preparation in human beings. Before considering any field trial it is essential to demonstrate that any preparation has the capability of converting normal individuals from non-endemic countries to positive and lasting immunological reactivity for delayed-type hypersensitivity or cell-mediated immunity, and that optimal doses for skin test conversion can be arrived at with minimal side-effects. Similar studies are also necessary among healthy individuals in leprosy endemic countries. IMMLEP has been able to initiate activities on this step, and the preliminary results appear to be encouraging.

Even as the original concept of developing a prophylactic vaccine against leprosy through the step-by-step approach was evolving, Convit and his co-workers demonstrated that a vaccine consisting of a mixture of killed *M. leprae* plus BCG was capable of upgrading the immune status of CMI deficient lepromatous and borderline patients, and suggested that such a vaccine should be capable of doing the same in susceptible but healthy individuals and thus prevent the occurrence of manifest disease. Such a study is currently under way in

Venezuela and is expected to involve ultimately about 30,000 contacts. The approaching of immunoprophylaxis through immunotherapy appears to be unique to leprosy. The same approach has been used in studies carried out in India with cultivable mycobacteria, which are slightly different from, and cross-react with, *M. leprae*. Deo and Bapat have used a cultivable mycobacterium designated as the ICRC bacillus for preparing a killed vaccine preparation and have reported on skin test conversion and immune upgrading in lepromatous and borderline patients. Lepromin conversion in lepromatous patients has also been reported by Talwar with a vaccine preparation derived from another cultivable organism designated as *Mycobacterium W*.

It is important to realize that while evaluation of side effects, acceptance and immune response could be studied in small groups of human subjects, the evaluation of the vaccine in terms of its protective capability in the individual, and its capacity to bring about disease control in the community can be effected only through large-scale prospective studies in populations. There appears to be no viable alternative to this approach. The implication of this is that a vaccine that could become available for public health practice is at least 1 decade away. Meanwhile, the tremendous progress that is being made in newer technologies such as DNA recombinant techniques promises even better vaccine preparations.

From the public health point of view, an ideal vaccine should be able to prevent leprosy, particularly the forms responsible for the spread of the disease, among those exposed and susceptible. While the concept of vaccination of selected groups of susceptible subjects is very attractive, the public health practice of this will be closely related to the ease with which such groups can be identified and reached and the proportion of disease in the community that occurs within such groups. The implication of measuring the protective effect of any vaccine against occurrence of multibacillary leprosy is that field trials will have to involve very large populations over long periods of time, in view of the very low incidence of multibacillary leprosy occurring *de novo* in most situations.

It should be pointed out at this stage that no matter how promising are the newer tools such as vaccines, they do not automatically guarantee that leprosy control will be achieved. Experience has shown that the problems in the application of even the most efficient tools for effective control are often more difficult to surmount than the problems in the development of the tools themselves. The implication is that leprosy control programmes should learn to use the existing tools such as modern chemotherapeutic regimens to the maximum effect through improved operational performance and be in a position to accept even better tools and apply them efficiently as and when they become available.

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Untreated borderline-leprosy in the ulnar nerve: light and electron microscopical studies

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Summary A case of a 41-year-old Indian patient with an untreated neuritis of multiplex type is presented. Clinical and microscopical examination revealed borderline-leprosy.

The difficulties in discriminating between changes due to the primary inflammatory process and secondary changes such as oedema, fibrosis, vascular occlusion and compressive factors, are discussed. Detailed morphological data from both light and electron microscopical studies are presented.

Introduction

Early lesions in leprosy, concerning especially the role of Schwann cell, have been studied to evaluate the exact mode of the spread of infection.[1,2] Apart from reactional states, secondary changes of the nerve like oedema, fibrosis, vascular occlusion and compressive factors in untreated borderline-patients may complicate the clinico-pathological picture, which itself is unstable due to the labile immunological response.

The present report demonstrates the difficulties in discrimination between the primary inflammatory process and the above secondary changes in peripheral nerves. Morphological data, from both light and electron microscopy in an untreated patient with borderline-leprosy, are presented.

Case report

A 41-year-old Indian physician noted tingling and prickling in the right 4th and 5th finger ten days after he had arrived in Germany. Some days later, increasing

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pains occurred together with a progressive weakness of those fingers. The patient observed a thickened *N. ulnaris* in the upper arm region. Pressure on this nerve caused painful paraesthesias, especially in the finger tips. Later flushing, itching and swelling occurred in the mid region of the 5th finger. No previous neurological illness was known except for a right hemianopia since childhood. No previous antileprosy treatment was given.

On admission the right ulnar nerve was palpable as a thickened, indurated cord extending 15 cm upwards from the *sulcus n. ulnaris* to the upper arm. Distal pressure of the sulcus caused intense, irritating pain diffusely in the lower arm and hand. There was a hypaesthesia for all modalities in the ulnar part of 4th and the entire 5th finger extending up to the wrist. A dissociated perception disorder also on the tip of the 3rd finger was found. Muscle weakness was severe in the ulnar Mm. lumbricales, the Mm. interossei, and the M. abd. dig. V, less severe in the M. flex. carpi uln., M. flex. dig. prof., M. opp. dig. V, M. add. poll., and M. flex. poll. brev. The M. ext. carpi uln. and M. ext. dig. comm. showed moderate weakness. There was a flush of the ulnar region of the dorsal right hand and the area of metacarpo-phalangeal joint of the 5th finger was swollen. On the back, a 5:5 cm hypo-pigmented area with irregular outlines was seen above the right buttock.

Nerve conduction velocity was normal in the right *N. medianus* and the left *N. ulnaris*. In the right *N. ulnaris* it was moderately reduced in the lower arm region, but severely reduced in the sulcus and upper arm region. EMG showed complete denervation of Mm. interossei. Severe neurogenic change was observed in the M. abd. dig. V. and less pronounced in the M. flex. carp. uln. Some neurogenic change was also seen in the M. pronator quadr. and the M. ext. carp. uln.

Eight weeks after onset an extended epineurial neurolysis of the right *N. ulnaris* was performed over a length of 20 cm from the proximal lower arm along the sulcus to the upper arm. Macroscopically the nerve appeared normal only at the most distal and proximal ends of the examined region. Intervening nerve tissue was grossly swollen; several fascicles were distended, yellowish-brown in colour; more proximally they appeared darkened and apparently necrotic. Tissues were taken for histological examination.

Methods

For light microscopy tissue was fixed in formalin (1:9) and embedded in paraffin wax. Sections of 18 μ were examined by the following methods: Haematoxylin–Eosin, Elastica-van Gieson's, PAS, Sudanblack-Nuclear Fast Red, Palmgren-Luxol Fast Blue, Gram's, Ziehl–Neelsen's, Wade–Fite's, Ladewig's, and Congo Red.

For electron microscopy specimens were fixed in phosphate buffered glutaraldehyde. They were postfixed in osmiumtetroxide, dehydrated in acetone

and embedded in araldite. Thin sections were stained with lead citrate and uranyl acetate.

Araldite-embedded semithin-sections of 1 μ were stained with Methylene Blue-Azur II, 45 min with 2·5% basic Fuchsin at room temperature and dried on a hot plate.

LIGHT MICROSCOPICAL FINDINGS

Epineurial tissue was diffusely infiltrated by lymphocytes, few plasmocytes, and histiocytes, occasionally in perivascular arrangement.

The perineurial sheath of some preserved fascicles was sometimes slightly thickened, but otherwise normal. The perineurial sheath of the major part of the

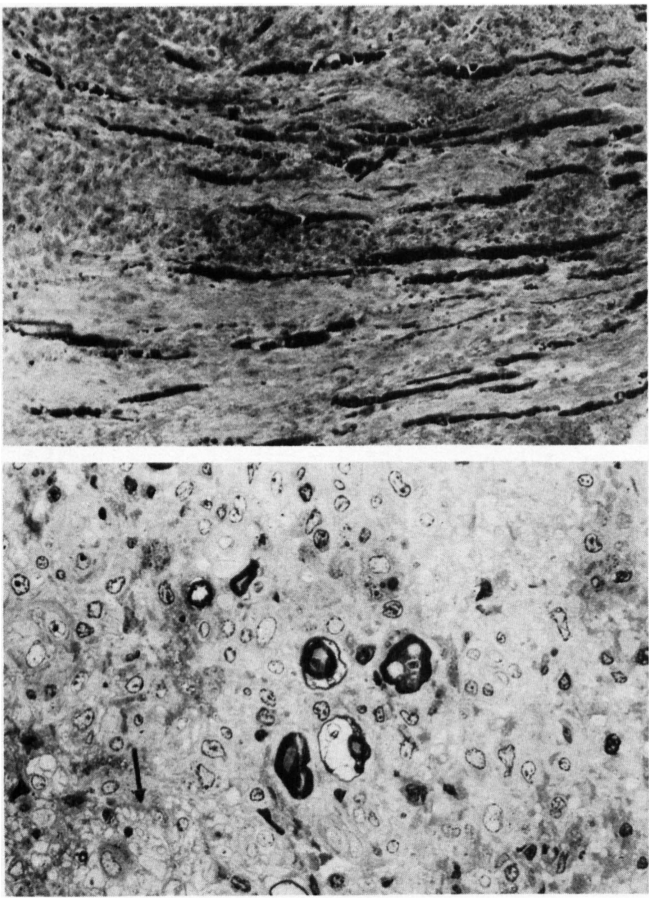

Figure 1 (a) Remnants of myelinated axons distended by strands of inflammatory cells. Balls of myelin (→). Sudanblack-Nuclear Fast Red, (× 160). (b) Semithin-section of myelinated axons surrounded by inflammatory cells and proliferated Schwann cells. Bands of Büngner (→). (× 700).

fascicles was largely destroyed. Alongside these areas inflammatory granulomatous tissue stretched into the remnants of endoneurial tissue.

Neural elements were extensively distended or replaced by fibrous tissue with few scattered portions of surviving myelin sheaths and axons. The larger proportion of myelin was fragmented and disaggregated in lumps, granules, and 'balloons' (Figure 1). The majority of the remaining axons showed degenerative changes. Definitely unaffected axons were not seen. Alongside the demyelinated fibres dense infiltrates of lymphocytes, rarely plasmocytes, and histiocytes occurred, the latter often appearing as foam cells. Rarely solitary epithelioid cells were diffusely spread.

Mycobacteria were often seen in clumps in Schwann cells, and in macrophages also arranged in globi. Frequently the bacteria showed a convoy-like arrangement along the remnants of myelin sheaths. The clumps of bacteria were not usually associated with surrounding inflammatory cells. Definitely extracellular mycobacteria were not detected.

Some remyelination as well as onion-bulb-formation was observed. The number of Schwann cell nuclei and endoneurial collagenous tissue were augmented. There was no abscess or amyloid formation. One large area of focal necrosis of fibrous tissue was encountered with degenerated inflammatory and endothelial cells and the remnants of vessel walls (Figure 2a).

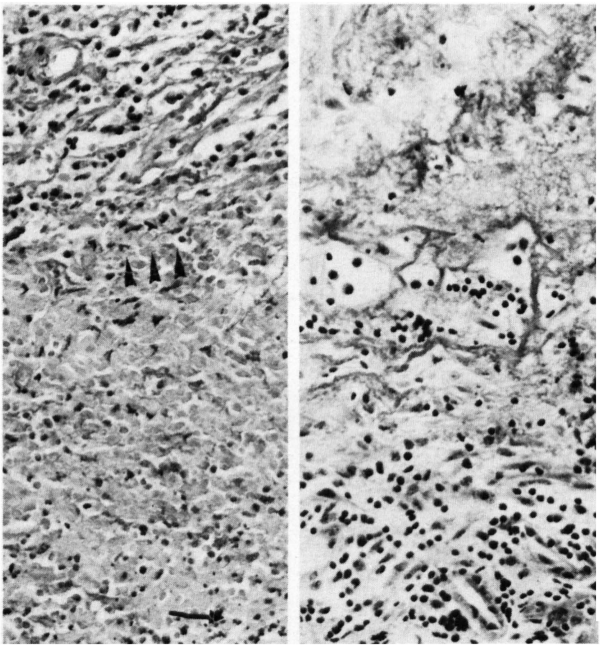

Figure 2 (a) Recent necrosis of inflammatory tissue with remnants of pycnotic nuclei (→). Border of the necrosis ( ). Elastica-van Gieson's, (× 320). (b) Fibrinous exudate in subcutaneous tissue. PAS, (× 320).

Inside and outside the fibrous tissue the number of endothelial cells of arterioles and capillaries was raised. Their nuclei were swollen. The vessel walls often appeared thickened. To some extent this was also seen in endoneurial vessels of fascicles with a normal perineurial sheath. Lumina of endoneurial vessels within regions of destroyed perineurial sheath sometimes appeared largely narrowed or even occluded by swollen endothelial cells (Figure 3). Thrombosis was not seen. Bacteria were not aggregated in or around peri- and endoneurial vessels.

Subcutaneous areas of the specimen were partly distended by masses of fibrin which to some extent showed signs of organization (Figure 2b). Some predominantly lymphocytic infiltrates in epineurial distribution were seen. Nerve fibres and their sheaths were largely inconspicuous. No acid-fast bacilli were observed.

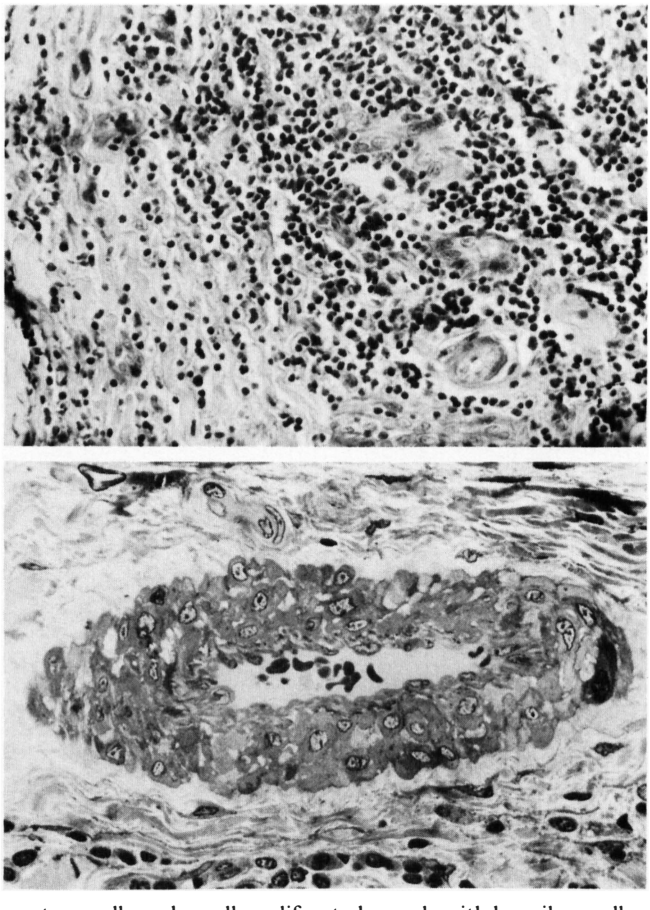

Figure 3 (a) Inflammatory cells and small proliferated vessels with heavily swollen endothelial cells. PAS, (×320). (b) Semithin-section of a larger epineurial vessel with swelling and proliferation of endothelial cells. (×700).

Endothelial cells appeared to be swollen. Skin biopsies from other parts of the body revealed a non-specific dermatitis with no bacilli visible.

ELECTRON MICROSCOPICAL FINDINGS

Few nerve fascicles had an intact perineurial sheath with well-preserved myelinated fibres. The larger proportion of nerve fibres was scattered and destroyed by inflammatory cells and fibrous tissue. Breakdown and phagocytosis of myelin were frequently encountered as were swelling of cytoplasm and proliferation of Schwann cells. Their processes were frequently intertwined with bands of endoneurial collagen in a complex fashion which sometimes presented as bands of Büngner (Figure 1b and 4a).

Wallerian degeneration, mostly in early stages, was sometimes conspicuous. Few large unmyelinated axons were seen, that appeared to be previously myelinated. The number of mitochondria was raised in myelinated more than in unmyelinated axons. Sometimes mitochondria were swollen. There were no pathological changes in axons from areas with an intact perineurial sheath.

Acid-fast bacilli were frequently observed in Schwann cells of myelinated and unmyelinated nerve fibres, in macrophages, and in histiocytes forming globi (Figure 4a). Few bacteria were detected in endothelial cells. Rarely bacteria in vessel lumina, fibroblasts and extracellularly were seen. The bacilli were mostly arranged parallel to the course of the nerve fibre like cigarettes in a tin can, sometimes in an immediate adaxonal position. Occasionally they appeared as rods, hooks, or dots. Solitary bacteria were rare, mostly clumps of 5–15 were encountered, often engulfed by a lysosome. With only few exceptions the bacteria themselves showed degenerative changes. Their surrounding electron-transparent zone (ETZ) had an ill-defined phagosome membrane and this often was confluent with that of neighbouring bacteria. Solid staining, viable organisms were mainly seen in Schwann cell processes.

Intra-axonal bacteria, viable or degenerated, were rarely observed. The electron-dense wall of the ETZ either completely separated the axoplasm from the organism or was slightly irregular. The adjacent axoplasm looked otherwise normal (Figure 4b).

The basement membrane of vessels was swollen and partly damaged. Extraluminal erythrocytes and intraluminal macrophages harbouring mycobacteria were observed (Figure 5). In accordance with light microscopy, endothelial cells were often swollen to such an extent that they appeared to occlude the vessel lumen.

Discussion

Clinically the patient presented with a neuritis of multiplex type, the main nerve involved being the right *N. ulnaris*. To a lesser extent the right median and radial

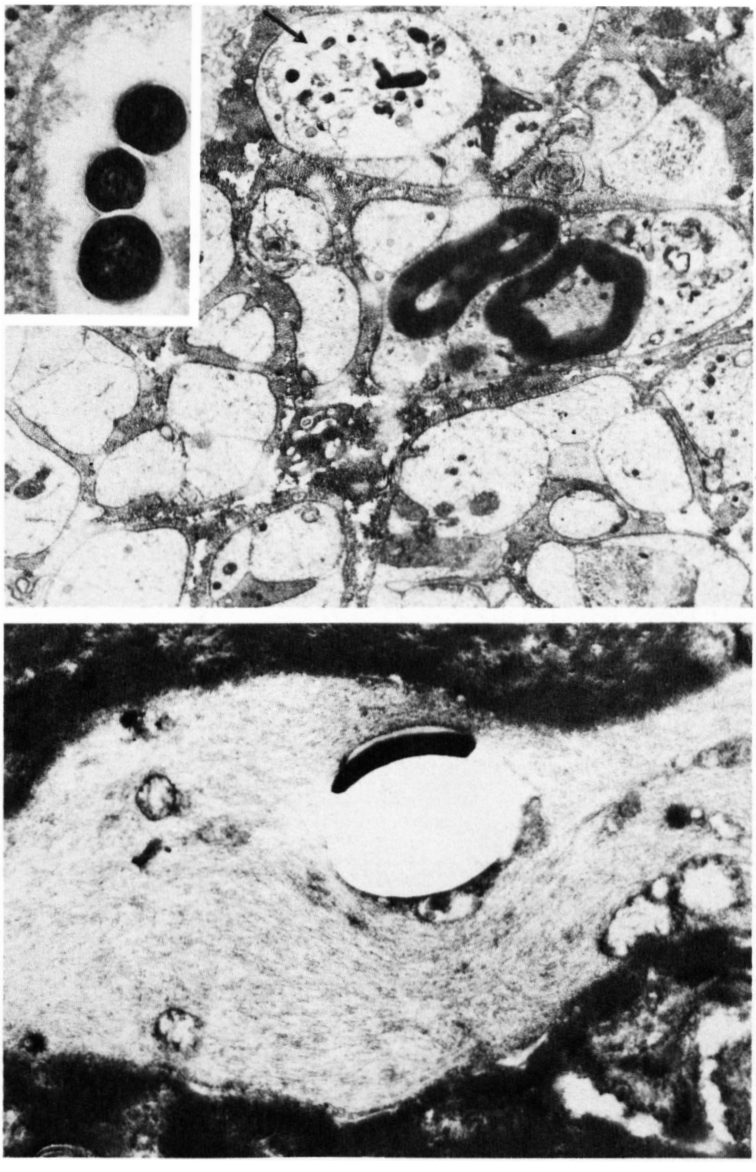

Figure 4 (a) Electron micrograph of a Schwann cell process with Mycobacteria inside. One Schwann cell process with two myelinated axons and debris (→). Proliferation of Schwann cell processes forming bands of Büngner, (× 11,200). Inset: Cross-section of viable Mycobacteria in a Schwann cell process (× 24,000). (b) A viable Mycobacterium with its electron-transparent zone (ETZ) inside a myelinated axon. (× 28,000).

nerve were also affected. Light and electron microscopical findings of the macroscopically most severely altered nerve regions revealed a borderline leprosy.[3] Both tuberculoid changes (exudation of fibrin, epithelioid cells, segmental demyelination) and lepromatous changes (diffuse spread of lympho-

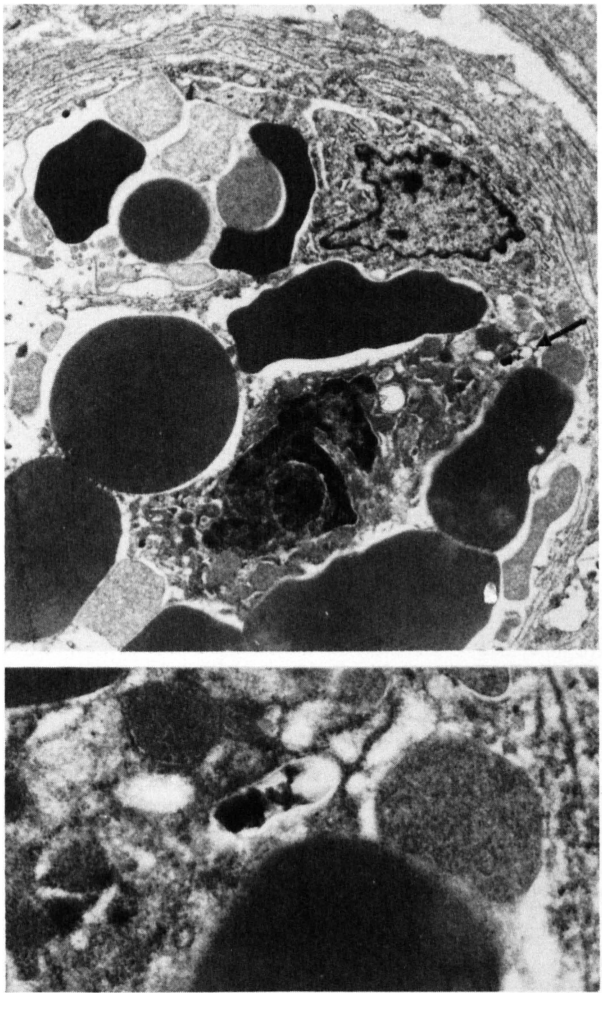

Figure 5 (a) Electron micrograph of a small vessel. Between erythrocytes and extruding from the vessel wall a large cell with a degenerated Mycobacterium (→). (× 7200). (b) Larger magnification of the above bacillus. (× 32,000).

cytes through the granuloma, foamy change of histiocytes, considerable bacterial load with intraaxonal bacilli) were present. Non-specific dermatitis in other body regions does not conflict with the classification, because even pure neural infections, in which there was as yet no apparent skin lesion, have been reported in all types of leprosy except LL.[3]

While the clinical history appeared to be short, histology indicated a rather advanced lesion. Neural elements were extensively destroyed and replaced by fibrous tissue. Preserved fascicles were distended by inflammatory cells, fibrin, oedema, and fibrous tissue.

In any type of leprosy the Schwann cell is considered to be the primary target

of the mycobacteria.[1] Also in the present case the vast majority of them was found in these cells. Proliferation of Schwann cells and their processes was striking. In contrast, Wallerian degeneration was scarce. The prevailing segmental degeneration affected both unmyelinated and myelinated fibres. Thus an advanced stage of infection was indicated too.[2]

Despite the considerable bacterial load only few mycobacteria were seen in endothelial cells or in macrophages lying freely in vessel lumina. In a report on BB/BL-cases intraendothelial bacilli were commonly found in skin granulomata, but in endoneurial vessels they were observed in only 25% of the patients. Macrophage-enclosed bacilli in the lumina were not seen.[4] Their occurrence in this advanced case suggests that up-take of mycobacteria in endothelial cells of endoneurial vessels is a late-stage phenomenon. An intact 'blood-nerve-barrier' in earlier stages may prevent bacillary entrance to the endoneurial vessels, except as a rare event.

If endoneurial cells extruded into vessel lumina to such an extent that even platelet passage appeared impossible, luminal occlusion, as rarely seen in the present case, may take place.[4,5]

After experimental focal occlusion axonal swelling, oedema, patchy fibre degeneration, and endoneurial fibrosis have been observed.[6,7] These changes, therefore, may also occur to some extent in leprous nerves, which already suffer from the non-specific vascular responses due to inflammation. The damage may be accentuated, if pressure by inflammatory cells inside the fascicles leads to further occlusion of vessel lumina.[8,9]

Inadequate nutrition by these vascular changes impairs regeneration of nerve fibres. This in our case is illustrated by only a few regenerative sprouts. Further inhibition is due to extensive endoneurial oedema. In an advanced case, like this, it is impossible to discriminate, to which proportion oedema is subsequent to leakage of 'blood-nerve-barrier'[10,11] or to inflammatory exudation. But its pertinent inability to be properly drained by lymphatics leads to swelling of the nerve, distension of endoneurial fibres, and to endoneurial fibrosis later on.[12]

Swelling of the ulnar nerve by these processes may cause entrapment at its elbow sulcus as in the present case. This may aggravate the previous inflammatory lesion by further segmental demyelination and, in long-standing cases, also by axonal degeneration.[13] As in general, pressure lesions may be either mechanical or ischaemic in leprosy too.

A mechanical factor is strongly suggested in our patient. In one area there was necrosis not only of neural tissue, but also of granulomatous and fibrous tissue. As there was no indication of a necrotizing reactional state, this necrosis, therefore, seems to be due to mechanical occlusion of supply vessels. This is an additional vascular contributor in leprosy, apart from the lumen occlusion mentioned above.

Leprosy bacilli have been observed in various cells: Schwann cells of unmyelinated and myelinated fibres, histiocytes, macrophages, fibroblasts,

endothelial cells, and perineurial cells.[2,14–17] In the present case the majority of bacilli were seen in Schwann cells and macrophages. On electron microscopy they were often degenerate and present within lysosome-like bodies.[18] At times, these membrane-bodies only showed osmiophilic debris, suggestive of a previously viable form, which was taken up by a phagolysosome.

The electron-transparent zone (ETZ) around a bacterium, sometimes confluent around a clump of them, is most conspicuous and well defined in viable organisms. Thus, it is considered to be a product somehow dependent on an intact bacillary metabolism, since degenerative appearance of bacteria is usually associated with irregularity of the outer membrane and the ETZ itself.[19] Bacterial degeneration must be due to the patient's immunological response. It cannot simply be attributed to treatment effects. For none of the borderline cases reported have received any antileprous treatment in the ten years before biopsy.[14–16]

Intra-axonal mycobacteria have been found to some extent in BL- and LL-patients.[2,4,19–24] None of these received any continuous treatment over a longer period of time. Early intra-axonal retrograde spread of bacteria has been correlated with disease untreated for more than one year.[4] Our case, however, suggests that a considerably shorter clinical history may present with intra-axonal bacteria.

In agreement with the data of others intra-axonal bacilli were observed here in an advanced stage of borderline-leprosy with a heavy bacterial load.[24] There must presumably be some damage to continuity of the axon so as to permit entrance of mycobacteria.

This is more probable in advanced lesions without previous therapy. The intra-axonal route might then be a mode of spread by sideways propagation: indeed, this may be inferred from the findings in the present case, since bacilli had apparently not affected the surrounding axoplasm.

Acknowledgments

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Leprosy—the Moslem attitude

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Summary Some of the Islamic principles and teachings regarding health and diseases and specific attitudes towards leprosy patients are outlined. The underlying aetiology for the beliefs prevailing in the Moslem communities is discussed and the need for giving due consideration to the social aspects in the control programmes is stressed.

Introduction

Leprosy is a disease well known for the strong stigma associated with it.[1–3] In spite of all the scientific information available today about leprosy, the fear and prejudices regarding leprosy and the leprosy patient remain ingrained and persistent. In many societies leprosy is associated with the idea of guilt, rejection and isolation.[4,5] These concepts were no doubt influenced by religious beliefs and local traditions, as well as by the medical pathology of the disease which gives leprosy its identity.[6]

It is known that disease control activities are not likely to be effectively carried out without understanding the values and beliefs of the communities affected.[7] This is particularly important in leprosy and it is lamentable that in most control programmes these important social and psychological aspects of the disease are overlooked and emphasis laid only on early detection and treatment. Failure to appreciate the importance of the social and psychological factors has resulted in the failure of otherwise well conceived control programmes.[8]

There is no reliable information about the Moslem view of leprosy patients. The beliefs, attitudes and practices prevailing in most of the Moslem countries thought to have religious origin in fact do not but are an outcome of complex indigenous traditional beliefs. Most of these beliefs antedate Islam and are thus unrelated to the proper Islamic teachings.

In the following pages an attempt is made to give the Moslem views about health and diseases in general and the specific attitude towards leprosy and the leprosy patient. These are mainly derived from findings in the Holy Qura'an and the Prophet's 'Hadiths' (sayings) and the historical perspective. This information is hoped to be of help to leprosy patients, their communities and leprosy workers.

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Leprosy in pre-Islamic Arabia

The Arabic word for leprosy 'Judham' is derived from the word Jadham which literally means cutting,[9] and denotes the outcome of the disease. The leprosy patient is called 'Mujdhum'. The word has the same origin and could be used to describe objects which are cut. The word was used in Arabic poetry before Islam.[10] There is no similar linguistic confusion as with the word lepra in the New Testament which was wrongly translated from the Hebrew word 'Tsara'ath' mentioned in the Old Testament.[6,11,12]

It is obvious from the use of the word that leprosy as characterized by its clinical complication was known in pre-Islamic Arabia. As the name for leprosy 'Judham' is more related to its medical and pathological complications, the reaction to the disease is more likely to be mainly to its physical effects. It is possible that there was then a stigma associated with this disease that mutilates though there is little information recorded.

The Moslem's concept of health and disease

It is of prime importance to mention some of the religious principles that influence the Moslem's attitude towards health and disease. In principle a Moslem accepts the concept of cause and effect as far as diseases are concerned. However irrespective of causes, to the Moslem, all events including diseases are caused by the will of God irrespective of causes.[13]

The second principle, which follows from the Prophet's Sayings, is that there is a cure for every disease; except for the inevitable ageing and death.[14] That the specific remedy for the disease is not known does not exclude the possibility of its discovery. In practice several medicines were used for the treatment of different diseases. Important among these is bee's honey which was mentioned as a cure in the Holy Qura'an.[15] With this understanding the Moslem is obliged to seek treatment wherever and whenever possible.[14] The deeply-rooted and long-held misunderstanding that leprosy is incurable is actually foreign to the Islamic beliefs, concepts and teachings about health and disease.

Thirdly, diseases are not considered as punishment by God for sins or wrong-doings as it is held in some communities.[5,6,10] However, the Prophet said that some diseases may be remitted in absolution of some sins (the concepts of Kaffarah). It is the duty of a Moslem to visit and console the ill and be merciful to them.[14]

The fourth principle, is that all necessary precautions should be taken to prevent transmission of infection from the diseased to the healthy.[13] Within this context plague was considered as infectious and the Prophet explained that if it appears in a certain area people should not go to it and people within the affected area should not leave it.[15,16]

History tells us that outbreaks of plague which appeared during the early Moslem era were treated accordingly.[13]

Leprosy in the Qura'an and the Hadiths

Leprosy was not mentioned in the Holy Qura'an. The disease mentioned in the Qura'an[17] and which was cured by Jesus was Vetiligo, the Arabic word for which is 'Baras' and not leprosy as wrongly translated by Gills.[18]

There are several 'Hadiths' by the Prophet Mohamed about leprosy. However, some of these 'Hadiths' are not authentic according to the lines of study of the 'Hadiths' and are not discussed here. There are three 'Hadiths' mentioned in more than one of the main books of 'Hadiths' and which are considered as reliable. In one 'Hadith' the Prophet was quoted to have said: '. . . Escape from the leper as you escape from the lion'.[14] In another 'Hadith' it is said that a leprosy patient who was coming to the Mosque to swear his fealty to the Prophet was asked by the Prophet to stay away and the Prophet told him that his allegiance was accepted.[13] In the third 'Hadith' it is said that the Prophet asked a leprosy patient to eat with him and he actually took the patient's hand and put it in the dish.[14,19] In the first two 'Hadiths' emphasis was laid on the precautionary measures to be taken to prevent the spread of the disease to the individual and to the community. In the third 'Hadith' the Prophet is stressing the principle of full belief and confidence in God's will.

The Arabic name (Judham) has no ritualistic connotation and does not carry the sense of defilement or uncleanness as associated with the Hebrew word 'Tsara'ath'.[6] The behaviour of the Moslem community at the time of the Prophet and the attitudes towards the leprosy patient are well illustrated by the Prophet's wife's behaviour. Asha (The Prophet's Wife) mentioned that they used to have a servant who was a leprosy patient and who lived and ate with them.[14] This shows the attitude of the most religious community during the early days of Islam.

Discussion

Leprosy is unique in its medical characteristics and this is reflected in the community's attitudes towards the leprosy patient. The foul smelling chronic ulcers, deformities and crippling that may follow from untreated disease lead to the repulsive response and the expulsion of the leprosy patient. It is believed that the strong stigma associated with leprosy is partly due to a religious fear, in addition to the primitive and irrational fear which results from the physical effect of the disease.[20] The social reaction of most communities is largely derived from a wrongly perceived picture of a contagious, incurable disease which progresses and eventually results in deformities and mutilation. This casts doubt on the

contention that social reaction to leprosy is the result of biblical teachings, including possible mistranslations.[21]

Apart from the physical deformities of leprosy, the disintegration of human dignity and the distortion of the patient's personality also results.[4] This is mainly the consequence of a complex of attitudes and behaviour by the community towards the leprosy patient and the patient's reaction towards these behaviours. Most of the wrong beliefs and practices noted in some of the Moslem communities regarding leprosy have no religious justification. There is no religious basis for the prevailing concepts of leprosy being a retribution for some moral sin committed. Moreover according to the Islamic teaching it is part of a Moslem's responsibilities to console the ill and to help them whenever possible.[14] In actual fact in most Moslem communities a medieval type of persecution is still practised. The leprosy patient is not accepted as a member of the community and even his family tend to isolate him.

Leprosy is no doubt one of the most trying diseases that man has to endure. Besides the medical treatment, the leprosy patient needs moral support and reassurance so that he can gain self-confidence and self-respect. In this context medicine has a duty that should extend beyond its avowed responsibility of preventing and curing diseases. It is one of the duties of the health worker to alleviate the anxiety of the leprosy patient and to give him all possible moral support. The grievous effect of the disease could be greatly tempered by sympathy and kindness. To show this responsibility successfully it is necessary for the health worker to have a clear understanding of the religious beliefs and practices prevailing in the community in which he is working. This understanding will help him to appreciate the rationale behind both the patient's and the communities' behaviour, and would facilitate communication. The change in attitudes could be partly attained through the provision of correct religious information as well as appropriate scientific information. This necessitates the collaboration of the health authorities, the religious elites and the communities' political leaders.

In conclusion more attention needs to be paid to the long neglected and underrated effect of the social and cultural factors which determine the success and failure of leprosy control programmes. Leprosy as a public health problem has medical as well as far reaching social, psychological and economic ramifications. To disentangle this multitude of problems and solve them there is a need for a multidisciplinary approach involving the medical, social and religious professions.

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Social aspects of leprosy: a case study in Zaria, Northern Nigeria

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Summary This is a study of the socio-economic impact of leprosy on a group of 129 patients under treatment in Zaria, Northern Nigeria, with additional notes on their views about leprosy, their reasons for delays in seeking medical advice, their expectations from Government, and the role of patients in a leprosy control programme.

Introduction

Leprosy holds a unique position among communicable diseases because of the incidence of deformity, physical handicap, and ostracism due to social stigma. The attitude of patients to leprosy control is influenced by widely held traditional beliefs about the disease and its causes, and it is important for those engaged in leprosy work to be informed about social aspects. The objectives of this study were to learn about the socio-economic effects of the disease and to discover what views were held about leprosy and its causes.

Materials and methods

A cross-sectional study was conducted in 29 leprosy clinics of Zaria Local Government Area between September 1983 and January 1984, where 1556 leprosy patients were registered in a population of approximately 667,000. A systematic sample was taken (every 10th patient amongst those above 15 years of age) consisting of 129 patients over the age of 15 years, with 84 males and 45 females. Ninety-three were in the age group 15–44 years, and 36 were 45 years or above. All 129 patients were interviewed according to a pre-designed and pre-tested schedule.

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Results

(1) *Personal characteristics.* The majority belonged to the Hausa tribe and were Muslims. Their standard of education was low, as was their socio-economic status. Sixty-three had one or more deformities.

(2) *Socio-economic impact of leprosy.* (a) *Migration.* Of the 33 patients who migrated to Zaria, 21 did so for reasons directly connected with their disease: the majority did so in order to be near a treatment centre, and a very small minority migrated because they were not wanted in the family or in order to beg. (b) *Effect on occupation.* Apart from 7 who resorted to begging, the remainder continued in their way of life, whether as agriculturalists, petty traders, etc. The few employed persons were able to continue in employment, although in some cases the employers objected to their deformities and had to be persuaded to allow them to continue in work. (c) *Effect on income.* The majority suffered only a marginal reduction in income, but 43 lost one-half to two-thirds of their income, and 8 became paupers and either resorted to begging or to being sustained by their families. (d) *Effect on marital and family life.* Of the 129 patients interviewed, 82 were living married lives, 16 were divorced (10 males and 6 females), 13 were living alone although married, 2 had become widowers, and 16 were still unmarried. Eleven of those leading married lives said that their disease was responsible for lack of harmony, making a total of 40 who had marriage problems. As regards the effect of leprosy on family life, 18 had experienced worsening.

(3) *Patients' views on leprosy.* Apart from 10 patients, all the remainder accepted that they were suffering from leprosy. As to causes of leprosy, 46 held supernatural causes responsible, 31 blamed poor living conditions, 9 blamed contact with leprosy sufferers, 4 mentioned germs, and the remainder said they did not know. On the subject of curability, 78 believed leprosy to be curable, 31 believed it to be partially curable, 3 had no faith in cure, and 17 did not know.

(4) *Delays in seeking medical advice.* Although there was an average delay of $1\frac{1}{2}$ years between onset of symptoms and seeking medical advice, 73 delayed for 4 or more years. Illiterate patients had the longest delays. Reasons for delay were: the taking of traditional medicine (47%); ignorance (31%); belief in self-healing (6%), and non-availability of diagnostic services (16%).

(5) *Expectations from Government.* When asked if they expected more from Government, 81 answered in the affirmative; 48 wanted more effective medicine, 24 wanted more clinics and leprosy workers, 3 expected financial help, 3 expected jobs, 2 thought that hospital transport should be provided, and 1 wanted food to be provided. Twenty-seven did not expect more from Government, and 21 had no ideas to express.

(6) *The role of patients in leprosy control.* When the 129 patients were asked what role they could play in leprosy control, 25 said that if they came across untreated leprosy sufferers they would advise them to report for treatment, 21

wanted to educate the public about leprosy, 6 said they would bring family contacts for medical examination, 1 patient wanted to donate money to the clinic, and 1 young man wanted to become a doctor in order to treat leprosy, but 24 were quite negative about their role, and 51 did not know what they could do.

Discussion

The majority of patients interviewed in this study had a low educational and socio-economic status, suffered no social ostracism because of their disease and were able to continue their various occupations, but had to accept a reduced income due largely to physical handicap from deformity and to phases of lepra reactions. Nearly 50% had one or more deformities. A minority experienced marital disruption due to their leprosy, and one-half of those leading married lives had marriage problems. One-third of the group believed that their leprosy was due to supernatural causes, and nearly two-thirds believed that the disease could be cured. The main reason for delay in diagnosis and treatment was the time spent receiving ineffective treatment from traditional practitioners, and consideration should be given to the proposition that such practitioners should be given training in the diagnosis and treatment of leprosy. The need for more effective chemotherapy, expressed by more than one-third of the group, will be met by the introduction of multidrug therapy.

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Immunological status of histoid leprosy

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Summary The first report of the immunological profile in histoid leprosy revealed an impaired cell-mediated immunity because of the low percentage of early and total T-lymphocytes, and negative lepromin test. The humoral immunity, however, was greatly increased, this was shown by the increased percentage and absolute count of B-lymphocytes and the raised levels of IgG, IgA and IgM. Hypocomplementaemia (C3) was another significant complement.

Introduction

Histoid is a unique expression of leprosy so far as the clinical, bacteriological and histopathological features are concerned. The immunological status of the entity is, however, not known. It was, therefore, thought worthwhile to investigate this aspect in detail, the observations made form the subject matter in this paper.

Materials and methods

Twenty-three histoid leprosy patients, comprising 21 males and 2 females formed the subject material for the study. The diagnosis in each was established on detailed morphological characteristics.[1–4]

Fifteen millilitres of blood was collected under aseptic conditions. The technique of 'E' rosette[5] was used for quantification of T cells, while for B cells the method of 'EAC' rosette[6] was followed. A preliminary total and differential leucocytic count was done from each blood sample in order to obtain the percentage, and absolute count of lymphocytes. The lymphocytes were separated from the heparinized blood by using histopaque solution (Stock No. 1077-1,

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Sigma Chemical Company, P O Box 14508, St Louis, USA) containing Ficoll type 400 (5·7 g/100 ml) and sodium diatrizoate (9 g/100 ml) for gradient centrifugation. After cell separation, their viability was checked with 0·25% Trypan blue (A G Fluka, S F Buchs, Switzerland) and more than 90% of cells were confirmed to be viable. A final cell suspension between 1000 and 10,000 cells mm^3 was obtained. For T cell estimation, an equal quantity (0·2 ml) of adjusted lymphocyte cell suspension and 0·5% sheep red blood cells were mixed and incubated at 37°C for 15 min in two sterile glass test tubes. These were centrifuged at 1000 g for 3 min and kept at 4°C. Early and total rosettes were estimated after an incubation period of 2 and 24 h respectively. For estimation of B cells, equal quantities (0·2 ml) of lymphocyte cell suspension and erythrocyte amboceptor complement (EAC) were mixed and incubated at 37°C for 30 min in a sterile glass test tube. The B lymphocytes were counted immediately after incubation.

Immunoglobulins—IgG, IgA and IgM—were measured in the sera by radial immunodiffusion technique[7] using limit diffusion in agar gel. Undiluted sera were used for estimating IgA and IgM, while the serum was diluted 10 times with isotonic saline for IgG. Readings were recorded after 50 h for IgG and IgA and 80 h for IgM. The final value of IgG was calculated by the multiplication of the figure by 10, the dilution factor.

Complement component C3 was measured in the sera by single radial immunodiffusion technique[7] by limit diffusion in agar gel. Monospecific anticomplement C3 antiserum and its three reference standards were obtained commercially (Lallested Laboratories Inc., Lake Hazeltine Drive, USA) after a diffusion time of 48 h, followed by washing in isotonic saline for the same duration, the slide was stained by amido-black stain. It was then destained in rinsing solution, dried and the diameter of the precipitin rings measured. The reference curve was plotted for the values of the reference standard and the square of the ring diameters and the values were read from this curve.

For estimating circulating immune complexes (CIC), equal amounts of serum (0·2 ml) and 8% polyethylene glycol (PEG, mol. wt 6000, BDH, England) were mixed and the precipitate was separated by centrifugation in a clinical centrifuge. It was washed three times with 4% PEG. The composition of the precipitate was determined qualitatively by a double diffusion technique on agar gel using various monospecific anti-immunoglobulins and antihuman C3 and C4 antiserum.[8] Protein concentration in PEG precipitates was also estimated.[9]

Cryoglobulins were detected by keeping the fresh serum at 4°C for 7 days. The cryoprecipitate was harvested by centrifugation at 1500 g for 30 min at 4°C.[10]

A lepromin test—early (Fernandez) and late (Mitsuda)—was performed using lepromin A (armadillo derived, containing 40 million bacilli per ml, obtained from Dr W P Kirchheimer, Chief, Laboratory Research Branch, National Hansen's Disease Centre, Carville, USA, through WHO).

Ten normal individuals and 9 non-histoid, active lepromatous (LL) patients of corresponding age, sex and socio-economic background served as controls.

Observations

Histoid leprosy and healthy controls. The basic haematological profile revealed that the mean percentage of lymphocytes was 33·1% ($P > 0·4$) and the mean absolute lymphocytic count was 2375·1 mm^3 ($P > 0·2$) which was statistically insignificant in comparison to controls. The mean absolute counts of early (825·01 mm^3) as well as total (1514·78 mm^3) T-lymphocytes also had insignificant deviation ($P > 0·4$). The mean percentage of early T-lymphocytes was 34·9% ($P < 0·001$), while the total T-lymphocyte percentage was 64·3% ($P < 0·005$). Both these values were statistically significant.

The mean percentage of B-lymphocytes was 21·9% while their mean absolute count was 517·7 mm^3. On statistical evaluation, a significant increase was observed in both the percentage ($P < 0·001$) and the absolute count ($P < 0·001$) in the studied group.

The mean levels (Table 1) of all the three immunoglobulins—IgG, IgA and IgM—were higher in the patients as compared to the controls, but this was statistically significant only in IgG ($P < 0·01$) and IgA ($P < 0·025$). These values are depicted in Figures 1 and 2.

The mean level of complement component was much lower in the patients and this too was statistically significant ($P < 0·001$).

The mean of total protein concentration (1·636 mg/ml) in CIC was significantly higher ($P < 0·001$) in the sera of the patients. The detailed analysis of

Table 1. Immunological profile: immunoglobulins, complement C3 and immune complexes

Parameters	Patients	Healthy controls	Statistical evaluation
Immunoglobulin (mg/dl)			
IgG	1623·28 ± 401·98 (725–2064)	1225 ± 177·99 (975–1500)	S
IgA	317·62 ± 109·71 (113–642)	221·25 ± 37·56 (167·5–275)	S
IgM	193 ± 79·72 (98–389)	161 ± 33·23 (107·5–205)	n.s.
Complement C3 (mg/dl)	76·19 ± 14·82 (50–102)	146·05 ± 24·28 (117·5–188)	S
PEG precipitates (mg/ml)	1·636 ± 1·293 (0·358–5·0007)	0·097 ± 0·035 (0·052–0·164)	S

Values are expressed as mean ± s.d. (range); S, significant; and n.s., not significant.

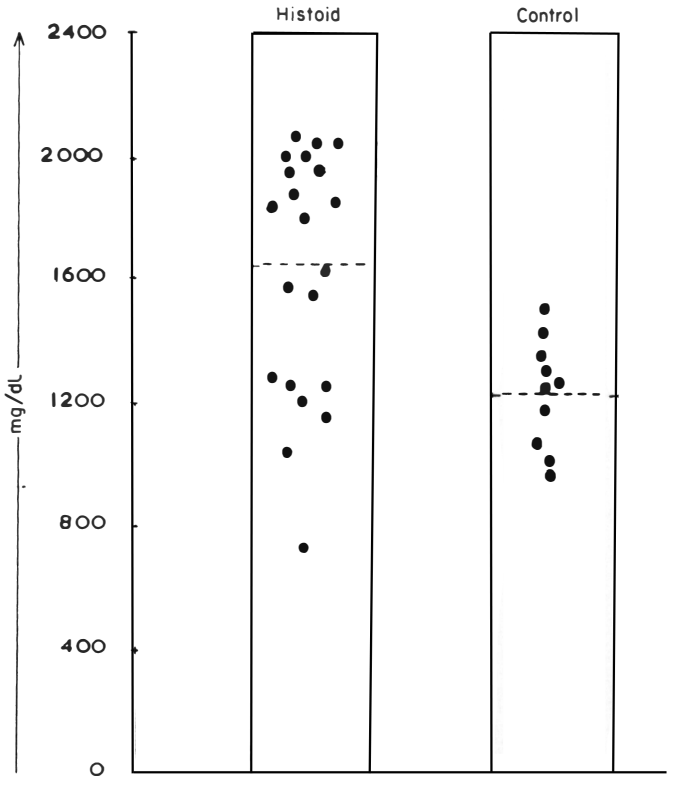

Figure 1. Scattergram of IgG, dotted line indicates the mean value.

PEG precipitates is shown in Table 2. The cryoprecipitate was observed in 9 (39·1%) patients and also 4 (40%) controls.

Histoid leprosy and non-histoid active lepromatous patients. Basic haematological profile revealed that although the total leucocytic count was statistically higher in histoid leprosy ($P < 0{\cdot}025$), the absolute lymphocytic count did not vary significantly ($P > 0{\cdot}04$) in the two groups. The percentages as well as the absolute counts of both early and total T-lymphocytes were significantly raised in histoid (Table 3). Furthermore, the percentage of B-lymphocytes was also raised significantly in the studied group ($P < 0{\cdot}025$). However, their absolute count did not reveal much variation ($P > 0{\cdot}4$). The levels of immunoglobulins IgG and IgA were significantly lowered in the histoid, while the levels of immunoglobulin IgM did not vary much in the two groups (Table 4). The complement C3 levels were grossly lowered in the studied group ($P < 0{\cdot}001$). Early and late lepromin test was uniformly negative in both the groups.

Discussion

The results of our study are indeed intriguing, because for the first time they focus attention on the immunological status of histoid leprosy. It is quite apparent that

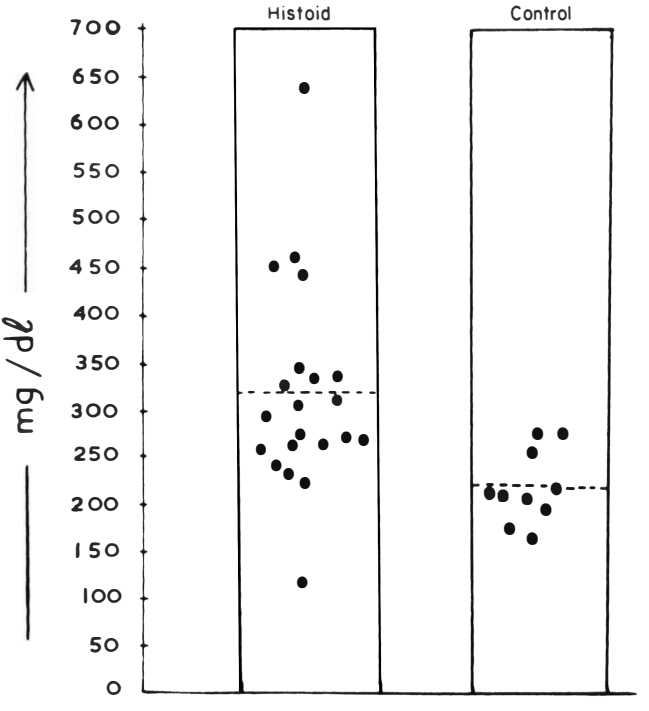

Figure 2. Scattergram of IgA, dotted line indicates the mean value.

Table 2. Analysis of polyethylene glycol (PEG) precipitates

Components	Patients	Healthy controls
IgG	21	6
IgA	3	1
IgM	16	3
C3	1	3
C4	13	—

the cell-mediated immunity was considerably impeded in this entity. This was revealed through the low percentage of early and total T-lymphocytes. It was complemented by negative early and late lepromin test. Furthermore, when results of our study were compared with those of non-histoid active LL, it was found that there was a relative increase in cell-mediated immunity in the studied group which may suggest an attempted focalization of the lesion to only limited regions of the body in histoid leprosy.

The humoral immunity too was considerably increased in histoid leprosy. It

Table 3. Immunological profile: T and B lymphocytes

Parameters	Patients	Active LL controls	Statistical evaluation
Early T cells			
Percentage	34·9 ± 4·5 (25–40)	29·7 ± 7·3 (20–45)	S
Absolute count	825·01 ± 254·1 (537·4–1344)	618·1 ± 243·6 (269–1080)	S
Total T cells			
Percentage	64·3 ± 5·7 (50–72)	55·2 ± 10 (40–70)	S
Absolute count	1514·7 ± 427·9 (940·8–2402·4)	1163·6 ± 444·3 (538–1824)	S
B cells			
Percentage	21·9 ± 2·9 (16–25)	18·9 ± 7·2 (10–30)	S
Absolute count	517·7 ± 142 (336–813·2)	504·9 ± 328·3 (162–896)	n.s.

Values are expressed as mean ± s.d. (range); S, significant; and n.s. not significant.

Table 4. Immunological profile: immunoglobulins and complement C3

Parameters	Patients	Active LL controls	Statistical evaluation
Immunoglobulins (mg/dl)			
IgG	1623 ± 401·98 (725–2064)	1714·4 ± 373·9 (1210–2700)	S
IgA	317·62 ± 109·71 (113·5–642)	405·3 ± 75·9 (131–350)	S
IgM	193·48 ± 79·7 (98–389)	236·1 ± 42·8 (170–265)	n.s.
Complement C3 (mg/dl)	76·19 ± 14·82 (80–102)	189·4 ± 75·4 (110–280)	S

Values are expressed as mean ± s.d. (range); S, significant; and n.s., not significant.

was reflected as the increased percentage and absolute count of B-lymphocytes and also by the increased levels of IgG, IgA and IgM. IgG and IgA in particular, were much raised. Interestingly, the findings in non-histoid active lepromatous (LL) patients were more or less identical except for a conspicuous rise in the levels of immunoglobulins IgG and IgA which are largely complementary to our preceding observations (*vide supra*). In addition, a gross hypocomplementaemia (C3) was another salient feature in histoid.

The immunological profile may, thus, indicate that histoid leprosy is a relatively stable component of multibacillary leprosy.

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Thalidomide induces imbalances in T-lymphocyte sub-populations in the circulating blood of healthy males

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Summary Lepromatous leprosy patients experiencing erythema nodosum leprosum (ENL) have been reported to have an increase in the ratio of circulating T-helper to T-suppressor cells (H:S ratio). Thalidomide is an effective drug in the management of ENL. To determine if thalidomide affected cells of the immunoregulatory system, B cells, T cells, T-suppressor cells, T-helper and natural killer cells in the blood of the healthy males were enumerated. Thalidomide induced a decrease in the T-helper to T-suppressor cell ratio. The decrease was due to a significant reduction in the percentage and absolute number of T-helper cells and an apparent increase in the percentage and absolute number of T-suppressor cells. B cells and natural killer cells were not affected.

Thalidomide's ability to decrease the H:S ratio in healthy individuals suggests that it may act in ENL by reducing an elevation of that ratio.

Thalidomide is well documented as being an effective treatment for erythema nodosum leprosum (ENL) occurring in lepromatous leprosy.[1,2] The full pathogenesis of this syndrome is unknown and it has been proposed that ENL is precipitated by, or at least is associated with, an acute imbalance in immunoregulatory T-lymphocyte subsets.[3]

To determine if thalidomide affected the balance of immunoregulatory T cells, we enumerated the percentage and absolute numbers of lymphocyte subsets in the blood by direct fluorescence microscopy. T cells, T-suppressor cells, T-helper and natural killer cells were determined using the fluorescein-conjugated mouse monoclonal antibodies Leu-1, Leu-2a, Leu-3a and Leu-7, respectively. B cells were enumerated using a fluorescein conjugated $F(ab')_2$ fragment of a rabbit anti-human IgG $F(ab')_2$.

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Materials and methods

HUMAN SUBJECTS

Thalidomide (Grunenthal GMBH 5190 Stolberg/Rhld, Federal Republic of Germany), was administered to 6 healthy males after obtaining their informed consent. The volunteers were employees of the National Hansen's Disease Center in Carville, Louisiana; their ages ranged from 26 to 56 years with a median age of 36 years. Thalidomide was taken orally in doses of 100 mg every 12 h for 4 days. The subjects were taking no other medications immediately prior to, or during the study.

CELL SEPARATIONS

Leukocytes were enumerated using a Coulter counter (Coulter Electronics, Inc, Hialeah, Florida), and differential counts were performed on peripheral blood smears stained with Wright's stain. Heparinized venous blood was drawn and diluted 1:2 with normal saline, and 20 ml of the dilution was layered over 6 ml of Ficoll–Hypaque (Lymphoprep®, Gallard-Schlesinger Chemical MFG, Co, Carle Place, New York). After centrifugation at $400 \times g$ for 45 min at 20°C, the mononuclear cells were collected.

DETERMINATION OF LYMPHOCYTE CELL SURFACE MARKERS

B-lymphocytes were identified by direct fluorescence microscopy as previously described[4] using fluorescein conjugated $F(ab')_2$ fragment of rabbit anti-human IgG $F(ab')_2$ (Cappel Laboratories, Cochranville, PA). T-lymphocyte phenotype markers were determined as described for B-lymphocytes, using monoclonal antibodies Leu-1 (T cells), Leu-2a (cytotoxic/suppressor), Leu-3a (helper/inducer), and Leu-7 (natural killer cells) (Becton Dickinson, Sunnyvale, CA).

Absolute levels of lymphocytes bearing a given phenotype or surface immunoglobulin were calculated from the product of (a) leukocyte counts, (b) the percentage of lymphocytes on differential counts, and (c) the proportion of mononuclear cells, corrected for monocytes by peroxidase staining, that fluoresced with a particular fluorescein conjugated antibody.

Results

Table 1 summarizes the effects of ingestion of thalidomide by healthy male volunteers on T cells, T cell subsets, and B cells. Using the paired t-test analysis to compare baseline values determined prior to ingestion of 200 mg of thalidomide

Table 1. T cells, T cell subsets and B cells enumerated by direct fluorescence microscopy

	Mean percent ± standard deviation (N) fluorescent cells[a] among peroxidase negative mononuclear cells (lymphocytes)						Absolute count/ml × 10^6				
Days[b]	Leu-1	Leu-3a	Leu-2a	Leu-7	Ig^+	Leu-3a: Leu-2a	Leu-1	Leu-3a	Leu-2a	Leu-7	Ig^+
0	76·8 ±9·1 (6)	48·1 ±6·4 (6)	33·2 ±13·2 (6)	25·3 ±8·7 (6)	8·4 2·9 (5)	1·64 ±0·62 (6)	2·55 ±0·85 (6)	1·53 ±0·26 (6)	1·05 ±0·5 (6)	0·83 ±0·37 (6)	0·29 ±0·12 (6)
4	76·5 ±14·9 (6)	40·5 ±9·5 (6) **	45·3 ±13·1 (6) ***	24·7 ±15·4 (6)	8·4 2·1 (5)	0·99 ±0·47 (6) ****	2·19 ±0·72 (6)	1·14 ±0·40 (6) **	1·29 ±0·53 (6) *	0·71 ±0·49 (6)	0·27 ±0·11 (6)
18	83·3 ±8·8 (5)	51·8 ±13·6 (5)	32·0 ±7·8 (5)	21·3 ±7·1 (3)	8·2 ±2·9 (5)	1·84 ±0·59 (5)	2·51 ±0·77 (6)	1·75 ±0·65 (5)	0·93 ±0·10 (5)	0·59 ±0·17 (3)	0·25 ±0·14 (5)

[a] Leu-1 directed against all T-lymphocytes.
Leu-3a directed against helper/inducer lymphocytes.
Leu-2a directed against cytotoxic/suppressor lymphocytes.
Leu-7 directed against natural killer cells.
Ig^+ directed against surface immunoglobulin and identifying B-lymphocytes.

[b] 0 = Baseline prior to ingestion of 100 mg of thalidomide.
4 = 4th day after ingestion of 200 mg of thalidomide/day.
18 = 18th day after baseline study and 2 weeks after thalidomide stopped.

*–$P < 0{\cdot}05$ one tail paired t-test, compared with day 0.
**–$P < 0{\cdot}01$
***–$P < 0{\cdot}005$
****–$P < 0{\cdot}001$

per day, the drug induced a significant decrease ($P < 0{\cdot}001$) in the circulating T-helper (Leu-2a) to T-suppressor (Leu-3a) cell ratio after 4 days (Figure 1). The post-treatment helper:suppressor (H:S) ratio returned to baseline levels 2 weeks after thalidomide was stopped. The decreased helper:suppressor ratio (H:S) was due to a highly significant decrease ($P < 0{\cdot}01$) in the percentage and absolute numbers of circulating T-helper cells and an apparent increase ($P < 0{\cdot}05$) in the percentage and absolute numbers of T-suppressor cells (Figure 1). The percentages and absolute numbers of natural killer and B cells were not altered.

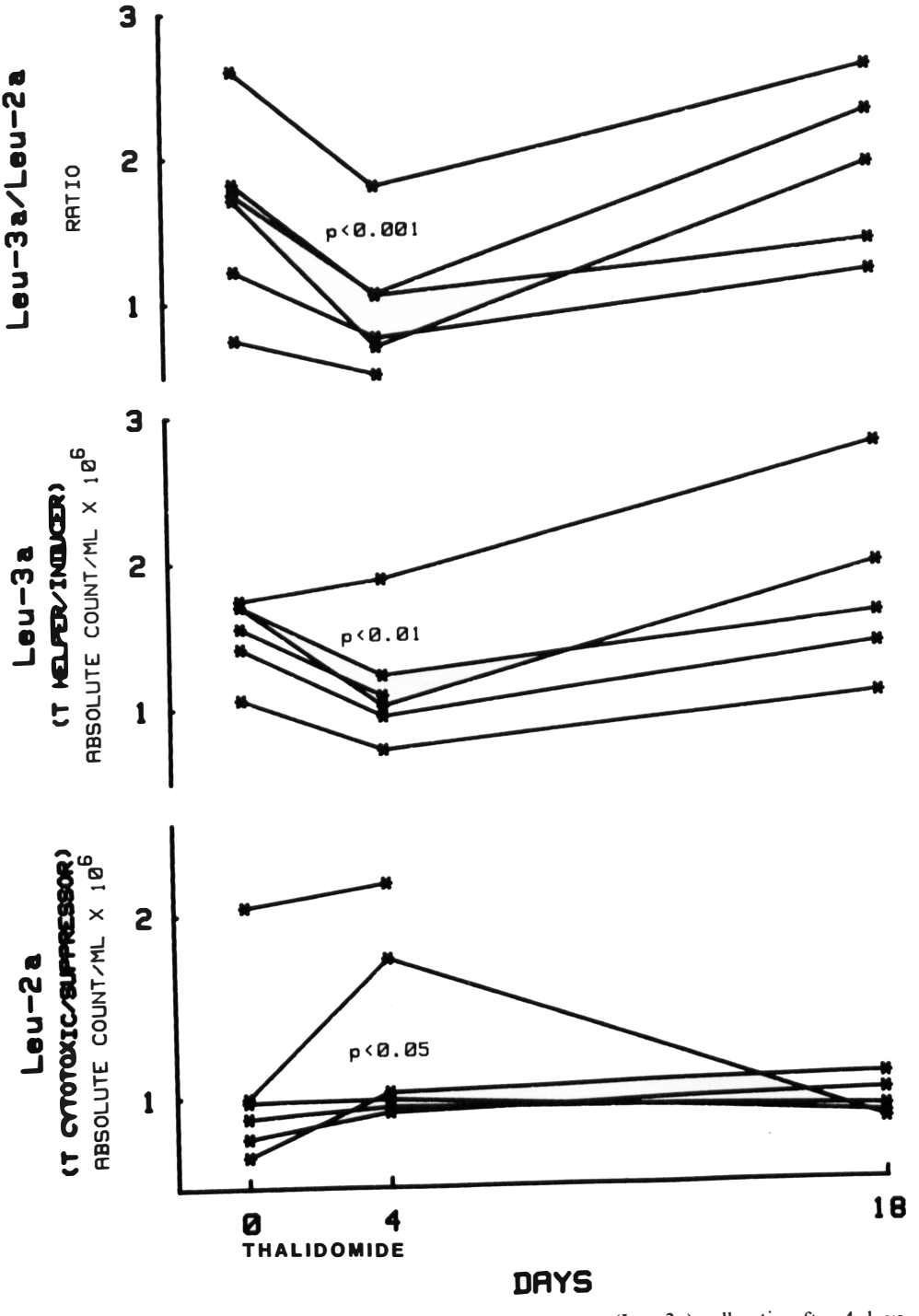

Figure 1. The circulating T-helper (Leu-2a) to T-suppressor (Leu-3a) cell ratio after 4 days.

Discussion

Lepromatous leprosy patients experiencing ENL have a significant increase in their H:S ratio.[5–7] Thalidomide's ability to decrease the H:S ratio significantly in healthy individuals suggests that it may act in ENL by reducing an elevated H:S ratio. This site of action would explain many of the immunosuppressive activities of thalidomide in a variety of both humoral and cell mediated immune systems.

Acknowledgments

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Reconstruction of the heel with chronic ulceration with flexor digitorum brevis myocutaneous flap

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Summary The management of chronic non-healing plantar ulcers on the heel in leprosy is a difficult and challenging task. It represents a defect on the heel, the reconstruction of which has been an enigma to most reconstructive surgeons, the problem being compounded by plantar anaesthesia and intrinsic paralysis inherent in leprosy. Recent advances in closure of heel defects by flexor digitorum brevis myocutaneous flap, as presented in this article have been applied by us to the chronic non-healing ulcers on the heel in leprosy. Surgical anatomy and the technique of flap elevation is described in brief. The short-term evaluation up to $1\frac{1}{2}$ years following the operation has shown its value in durability, weight bearing and prevention of recurrent ulceration.

Introduction

In leprosy, total recovery from plantar anaesthesia and intrinsic paralysis is generally unlikely due to the very nature of the disease. At the same time it is not possible to avoid the stress and strain of locomotion. Although damage due to all these factors can be minimized by health education and care of the feet, it is not uncommon to see the occurrence and chronicity of plantar ulcers on the heel.

The uncomplicated chronic ulcer is diagnosed by its appearance (punched out, heaped up with hyperkeratotic margin, floor covered with thin slough or pale granulation, and discharging thin seropurulent material) and absence of any active infection in the bones and joints as seen clinically and in radiographs.[1] While infection can be controlled, the major contribution of reconstructive surgery is in providing adequate local tissue which will be able to bear stress and strain. The ideal tissue is the fibrofatty layer as found in the normal foot.

In a comparative study[2] it was also observed that no form of distant sole replacement was satisfactory. The local transposition of the specialized plantar skin was preferred. Another study[3] mentions that transposition flap elevated superficial to plantar facia requires 'delay' owing to precarious blood supply, thus produce fibrosis and scars tend to violate the weight-bearing area.

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To provide an additional blood supply one study[4] described the neurovascular island which not only requires sacrifice of a toe but provides a small skin area with a long scar in the centre of the foot. In another study[3] an arterialized myocutaneous island flap has been used incorporating the abductor hallucis muscle and the medial plantar artery. One study[5] has used the flexor digitorum brevis muscle flap with skin graft in 5 cases, but have also used flexor digitorum brevis as myocutaneous island flap in a difficult heel reconstruction. Our design of flexor digitorum brevis myocutaneous flap is similar to that of Curtin's[6] 'delayed' local transposition flap. By incorporating muscle there is no need to 'delay' the flap. The muscle fills the 'gap' between calcaneus and the skin, thus eliminating the dead space providing the most important substitute for the fibrofatty layer which bears the stress and strain of locomotion.

Surgical anatomy

The flexor digitorum brevis (Figure 1) takes its origin from the medial process of the calcaneus and the plantar aponeurosis. It is a flat muscle traversing the mid-plantar region, gaining insertion in the middle phalanges of the 2nd, 3rd, 4th and 5th toes through 4 separate tendons. The musculotendinous part is at the centre of the instep. The flexor digitorum brevis muscle is bordered by the abductor hallucis muscle medially and the abductor digiti minimi laterally. It is

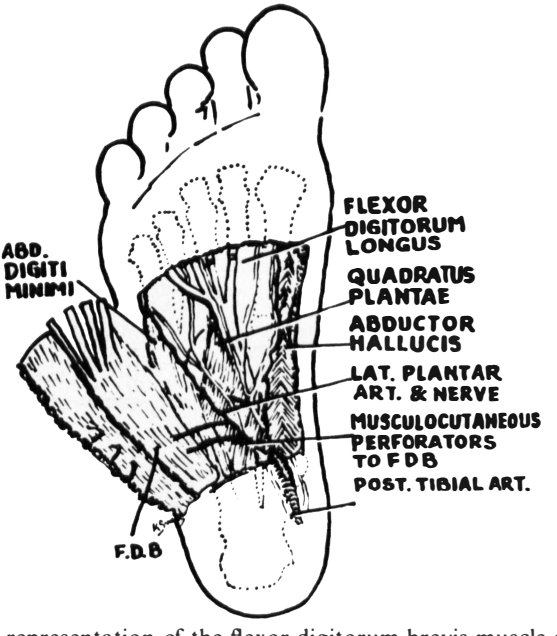

Figure 1 Schematic representation of the flexor digitorum brevis muscle and its relations.

intimately related to the quadratus plantae on its superior surface (deep surface during dissection of flap) but is easily separated from it by the presence of a thin areolar tissue. It derives its major blood supply from the lateral plantar artery, pedicles of which enter the muscle in its proximal third. There are also minor pedicles from the lateral plantar artery distally and a small pedicle from the medial plantar artery. The lateral plantar nerve supplies the musculocutaneous unit proximally, and a large sensory branch from the lateral plantar nerve supplies the area of the mid-plantar region of the foot.

Technique

The operation is carried out under spinal anaesthetic or general anaesthetic, with a tourniquet applied to the thigh, the ulcer on the heel is palpated to find the extent of induration and its fixity. A generous mass of hyperkeratotic callus skin and fibrosis is excised, down to the calcaneus. If there is a projecting spur from calcaneus it is osteotomised and excised till a smooth bony surface is obtained. This liberal excision creates the true defect on the heel for which the flap is marked out as shown in Figure 2. The dissection to raise the flap starts distally where the

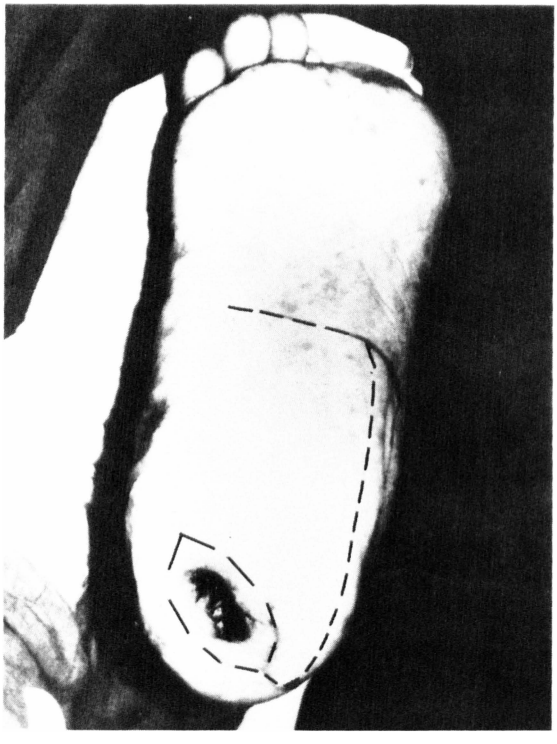

Figure 2 A chronic ulcer on the heel with markings for flexor digitorum brevis myocutaneous transposition flap.

plantar aponeurosis is incised, immediately below which the tendons of flexor digitorum brevis are seen. It is lifted over an artery with forceps and tested for the movement of the middle phalanges of the lateral 4 toes. Having confirmed it, the tendons are divided by a sharp cut. Proceeding with the medial skin incision and working down, adjacent to the abductor hallucis muscle the flap is raised. We generally prefer to suture the cut ends of the muscle to the dermal edge of the skin to prevent its retraction and bunching. As the flap is being elevated the minor pedicles in its distal part are ligated and divided (Figure 3). The lateral plantar artery and nerve are identified and protected (Figure 1). In our experience, unless the calcaneal origin of the muscle is divided the flap does not move well and transposition is very difficult. So the calcaneal origin of the flexor digitorum brevis is divided carefully while protecting the neurovascular pedicle of the flap. The flap is adjusted to the defect and if necessary a 'back cut' is made at the lateral distal edge of the flap to release the tension. The heel skin with its fibrofatty padding is mobilized. The tourniquet is released and haemostasis established. The flap is sutured in 2 layers over a 'glove' drain. The triangular defect over the distal donor area on plantar aspect skin is grafted with a medium thickness skin graft from the thigh (Figure 4). A firm elastocrepe bandage is applied and the foot is elevated on a Bohler splint. The drainage tube is removed after 48 h. The sutures of the skin graft are removed on the 10th day and the sutures of the flap are removed on the 14th day. The patient is gradually allowed to bear weight after 3

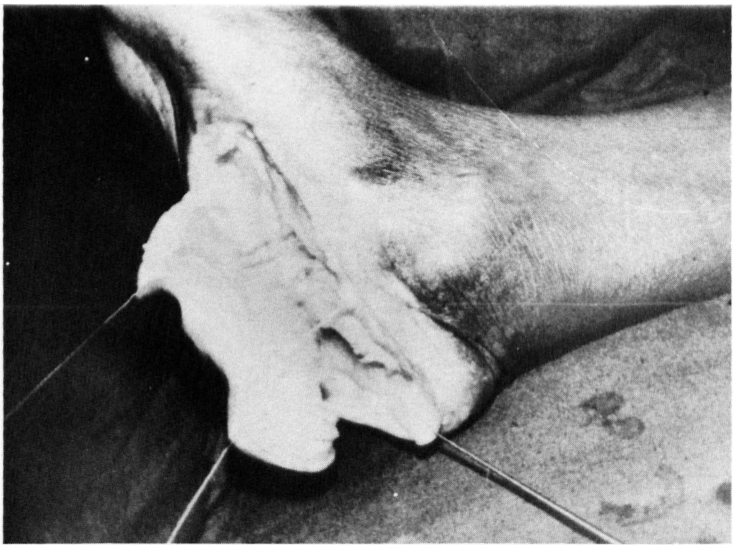

Figure 3 The flexor digitorum brevis myocutaneous flap dissected out, the distal minor pedicles and a proximal pedicle from medial plantar artery stands out during dissection. In between these are the major pedicles from lateral plantar artery. (In this case it was not necessary to sacrifice any of these pedicles.)

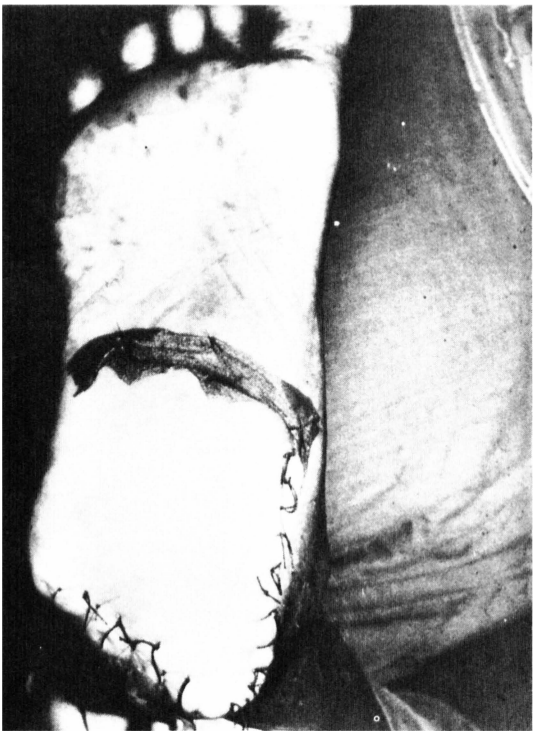

Figure 4. The flap in position, and the donor area is skin grafted.

weeks. Customary special chappals with microcellular rubber insole are provided. During the hospitalization and on discharge he is taught and advised to take care of his anaesthetic feet. (No procedure is a substitute for health education in leprosy.)

Results

Six patients were operated by this procedure. The duration of chronicity of ulcers of the heel varied from 6 months to 9 years. In 2 patients the ulcers were recurrent within 3 to 6 months. In 1 patient (1st case) there was wound dehiscence which responded to secondary suturing. Another patient had a loss of skin graft on the donor area and required regrafting. Four patients healed well without any complications. During follow-up it was observed that a skin graft contracts so much that a very narrow area of it is visible after 6 months in the non-weight bearing area (Figure 5). On enquiring in to their walking habits it was found that each patient was travelling an average distance of 1·5–2 km/day.

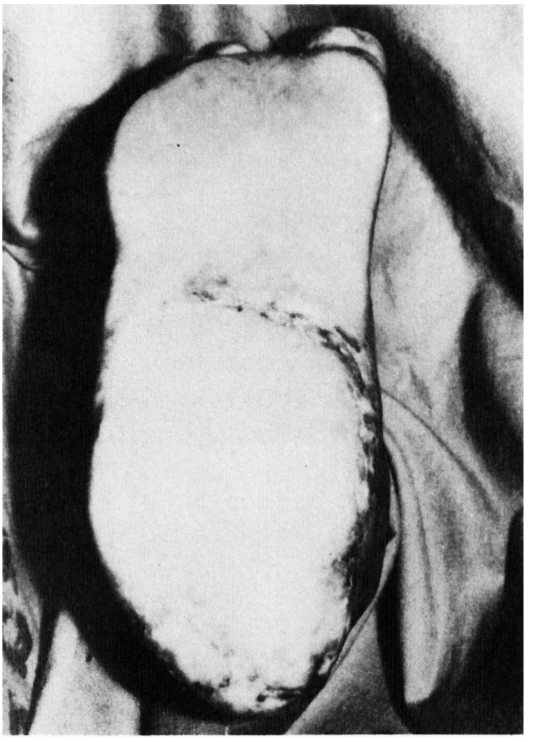

Figure 5. Post-operative result after 4 months. Note the contraction of the graft.

Discussion

Treatment of chronic non-healing ulcers of the heel is a difficult problem particularly if the ulcer is large with hyperkeratotic and callus margins or if it is associated with periostitis, spur in calcaneum or osteomyelitis. Although in this study no patient had deep seated osteomyelitis, almost all of them had a hard fibrous ring and periostitis. The precarious blood supply due to heavy scarring limited the efficiency of the natural healing process. It is also well established that the fibrofatty layer of the sole is the padding between bony weight-bearing areas and the skin. Its replacement by non-resilient scar tissue which may permit weight-bearing to some extent but does not tolerate stress and strain of walking is the main hindrance in prevention of recurrence. The flexor digitorum brevis myocutaneous flap affords the advantages that it is a well vascularized flap, provides a substitute for fibrofatty layer to take the stress of walking, does not require 'delay' and the scars do not violate the weight-bearing areas of the sole of the foot. The donor area is chiefly non-weight-bearing skin (except in flat foot). The skin graft does not cause any problem as only a thin line remains following graft contraction after 6 months and that too is in a non-weight-bearing area

(except a little area on the lateral edge). This is a single procedure and does not require more than three weeks (maximum) of hospitalization. In leprosy, even if the muscle is paralysed it is vascular and seldom totally fibrosed. However, the quality of plantar skin in front of the ulceration also must be good. The cases with frank osteomyelitis and also with poor tissues in front are unsuitable for this technique.

We will conclude the discussion by contemplating the combining of this procedure with nerve release since the elevation of this flap offers good visualization for medial and lateral plantar nerves. Palande[7] has demonstrated the effectiveness of posterior tibial nerve decompression in prevention of plantar ulcers particularly calcaneal branch for heel ulcers. Shall we extend the decompression of the posterior tibial nerve to its terminal branches, while reconstructing the heel pad is an interesting thought for the future.

Conclusion

The flexor digitorum brevis myocutaneous flap for the treatment of chronic non-healing ulcers on the heel has proved to be viable and a reliable one-stage reconstructive procedure. It replaces the specialized fibrofatty layer of the sole of the foot at the ulcer site and allows normal weight-bearing and also the stress and strain of walking. There has been no recurrence in any of the 6 patients followed up for a period of 4–18 months.

Acknowledgment

The authors are thankful to Mr Daniel, physiotherapist of the Bombay Leprosy Project, for referral of cases. Mr G Krishnaswamy, medical photographer, Tata Department of Plastic Surgery for illustrations and Miss Rosita Wymess for typing the manuscript.

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Lepr Rev (1985) **56,** 49–50

Mycobacterium leprae in seminal fluid: a case report

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Introduction

Testicular involvement leading to impotence, sterility, and gynaecomastia is well documented in lepromatous leprosy.[1–3] Rogers & Muir[4] described the presence of *Mycobacterium leprae* in the seminal vesicles. Bacteria were also demonstrable in the form of globi in seminiferous tubules of lepromatous patients.[5] This report concerns a patient with lepromatous leprosy who showed the presence of *M. leprae* in seminal fluid.

Case report

A 36-year-old married man of Yemeni nationality was seen in the clinic. He complained of pain in joints and body associated with loss of sensation in both the hands for a period of 6 years. For about a year, he had noticed the loss of hair on eyebrows and felt pain in both testicles. At the same time he became aware of a lesion in the mouth.

Cutaneous examination showed infiltrated nodules on the right forearm which were not tender, and sensation was intact. There was a marked loss of hair from the eyebrows on the lateral side. A white, rough granulomatous lesion was noticed on the palate which was neither tender nor interfered with routine feeding. Bilateral testicular atrophy and epididymitis were noticed during examination. Gynaecomastia was not present.

The patient's complete blood picture was normal. Erythrocyte sedimentation rate was 30 mm in the first hour (Wester-Green method). Serological test for syphilis was negative. Urine analysis and chest X-ray were also normal. Ziehl–Neelsen staining of nasal and seminal fluid smear showed numerous acid-fast bacilli. Spermogram showed low count of sperms.

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The treatment given to the patient comprised a daily oral dose of dapsone, 25 mg and rifampicin 600 mg. Within 2 weeks of starting the therapy, the oral lesion disappeared. After about 6 months, the cutaneous lesions responded satisfactorily and the seminal fluid smear no longer showed acid-fast bacilli.

Discussion

It has been reported earlier that half of the male patients with lepromatous leprosy develop testicular atropy with direct invasion of seminiferous tubules and Leydig cells by *M. leprae*.[5,6] Epididymitis and azoospermia are also common complications in these patients.[2] Although the presence of *M. leprae* in seminal vesicles has been demonstrated by previous investigators, they have only rarely been reported in seminal fluid.[4] The presence of acid-fast bacilli in the semen of this patient was therefore of particular interest. Although the bacilli were not inoculated into mouse foot-pads, their morphology resembled that of *M. leprae* and the morphology of acid-fast bacilli from other leprosy lesions in the patient and was completely different from the morphology of *M. smegmatis* (R J W Rees, private communication).

Acknowledgment

We wish to thank Dr R J W Rees for his assistance, guidance and continuous encouragement.

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Lepr Rev (1985) **56,** 51–55

Relationship between the loss of maxillary anterior alveolar bone and the duration of untreated lepromatous leprosy in Malaysia

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Summary Alveolar bone loss and the duration of untreated disease were compared in 31 patients with lepromatous leprosy. In general, those patients with the longest confirmed untreated disease also had the greatest alveolar bone loss in the anterior maxilla. These data, taken together with previous observations, suggest that early detection and uninterrupted treatment of lepromatous patients will reduce the osseous deformities of the disease.

Introduction

Skeletal involvement is a serious complication of leprosy manifested as a net loss of skeletal mass,[1–5] probably due to an acceleration of bone resorption mediated by osteoclasts and osteolytic osteocytes.[6]

Resorption of alveolar bone was first noted by Moller-Christensen[2,7,8] in maxillae from skeletal remains of Danes with leprosy in medieval Denmark. These observations have been confirmed and extended in contemporary populations of patients with leprosy by several investigators.[9–15] These studies have shown that resorption of the alveolar process in the maxilla is a characteristic manifestation of leprosy.

Previously we have examined alveolar bone loss in leprosy and shown that it is greater in the anterior maxilla than other areas of the jaws, that the amount of bone resorption is greater in patients with lepromatous disease, and that the rate of bone loss in treated patients is surprisingly low.[13,15] These data suggest that the

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greater reduction in alveolar bone height in patients with lepromatous disease is the result of bone lost before treatment is initiated. This investigation compared the magnitude of such bone loss and the duration of untreated disease in 31 patients with lepromatous leprosy.

Material and methods

Thirty-one patients with lepromatous leprosy were selected from the patient population at the National Leprosy Control Centre, Sungei Buloh, Malaysia. Lepromatous disease was determined by smears and clinical examination.[16] All patients were under treatment with dapsone, and none were among the 10% of lepromatous patients in Malaysia whose relapses were due to dapsone resistance (MFR Waters, personal communication). All procedures were explained in detail to each patient who gave written informed consent in advance.

Each patient was questioned exhaustively by us and colleagues at Sungei Buloh and the University of Malaya as to the time and form of the first appearance of signs and symptoms of leprosy, the time and form of first treatment and the regularity of treatment. We noted the time of appearance of the earliest signs of disease [nasal stuffiness, crust formation and discharge and oedema of the legs and ankles at the end of the day[16]], as well as indications of more advanced disease such as anaesthesia, paralysis and cutaneous ulcers. Some of these data were available from the patient's chart and served as a measure of the reliability of each patient's memory. Dapsone therapy was first used at Sungei Buloh in 1947, and by 1949 all patients were being treated with this drug. Using this information and that derived from a detailed medical history, we were able to establish for most patients a reasonable record of the length of recognized but untreated disease and the type and continuity of treatment to the present.

Alveolar bone loss in the anterior maxilla, was measured radiographically[17] as described previously[13] using periapical radiographs taken with the paralleling long-cone technique.[18] This method permits the reduction in alveolar bone height interproximally to be expressed as a percentage by subtracting the current bone level, related to the root length of the maxillary incisor, from that present initially, presumed to be the full length of the root to the level of the cemento-enamel junction.[15]

These data from the detailed medical and treatment histories and measurements of alveolar bone height were used to examine the potential correlation of alveolar bone loss and the duration of untreated lepromatous disease.

Results

Our observations on each patient are presented in Figure 1, where the mean maxillary anterior alveolar bone resorption is plotted against the duration of

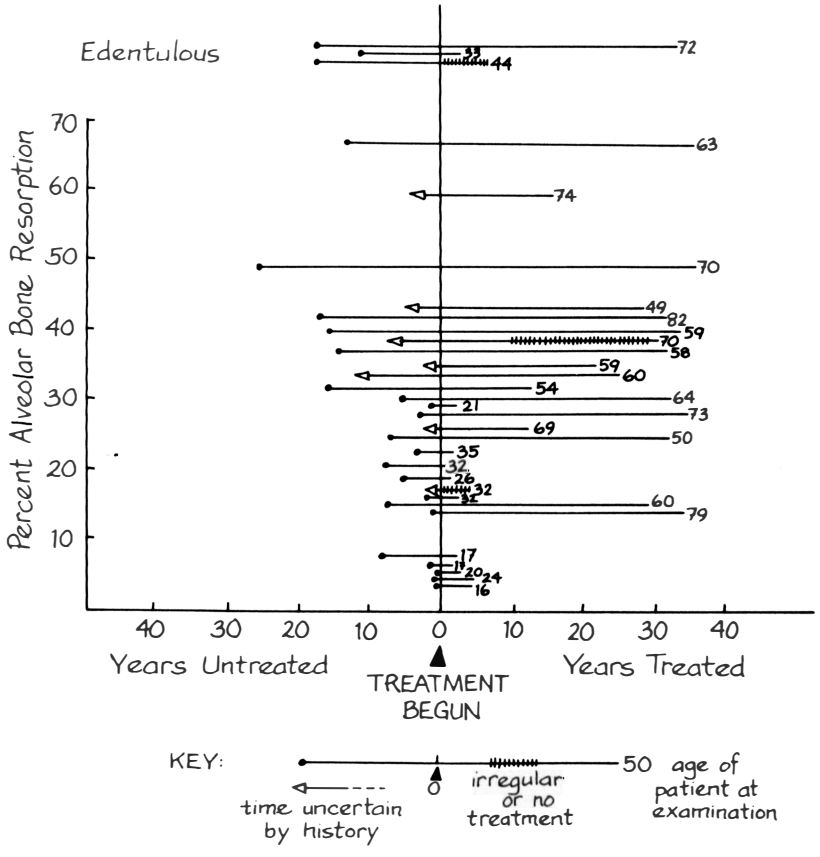

Figure 1. Graphic illustration of the relationship between magnitude of alveolar bone loss, first signs of the disease and treatment record of patients with lepromatous leprosy. Each patient is represented by a single horizontal line, whose vertical position corresponds to the reduction in height of alveolar bone in the anterior maxilla. The total length of the line represents the known duration of the disease. An arrowhead at the left of the line indicates that the time of initial signs and symptoms of disease is uncertain by patient history or record. Interruption of treatment is indicated by short vertical bars.

untreated and treated disease. Uncertainty about the time treatment began, as well as regularity of treatment, are indicated by individual symbols. Notice that there is a tendency for greater bone loss to be associated with a longer period of untreated disease. This is best illustrated by the 5 individuals aged 79, 60, 73, 70 and 70 whose bone loss was 14, 15, 28, 38 and 48% and length of untreated disease was 2, 8, 4, greater than 8 and 26 years, respectively. However, this association is not without exception.

These data are summarized in Table 1. In general, patient age and duration of untreated disease increase with bone loss in categories with more than 1 individual. Edentulous patients were untreated for longer than 10 years.

Table 1. Summary of observations

Alveolar bone resorption (%)	Number of patients	Mean age of patients	Mean duration untreated disease (years)
0–10	5	19	3
11–20	5	46	4·5
21–30	7	49	5·3
31–40	6	60	17
41–50	3	67	21
51–60	1	74	>4
61–70	1	63	13
Edentulous	3	50	16

Discussion

Previous work has shown that resorption of alveolar bone in the anterior maxilla is a characteristic skeletal deformity of leprosy,[2,8,9] that is probably caused by a local activation of osteoclasts.[14] This bone loss is most pronounced in patients with lepromatous disease[13] and in patients in Malaysia is as advanced in the fourth decade as is bone loss in the sixth decade in patients without leprosy in the general population.[13]

Nevertheless, alveolar bone loss in patients under continuous treatment is very low in spite of general poor oral hygiene.[15] The present report suggests that the amount of alveolar bone loss in patients with lepromatous leprosy is related to the duration of untreated disease.

These data taken together suggest that early detection and treatment of leprosy are effective ways to minimize bone loss and skeletal deformities and that immune dysfunctions in patients with leprosy may protect them from the alveolar bone loss that accompanies the periodontal diseases.[15]

The cause of the local activation of osteoclasts in alveolar bone of these patients, be it the leprosy bacillus itself or its metabolic products, deserves further study.

Acknowledgments

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SPECIAL ARTICLE

The search for new drugs for the treatment of leprosy

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Summary The reasons for wanting to develop completely novel antileprotic drugs are stated. A number of promising lead compounds are identified from a consideration of the biochemistry and structure of *M. leprae* and the natural product, oil of chaulmoogra. Their structures provide a rational basis for the development of programmes of research which could lead to new antileprotic agents. Some early success in one such programme is reported.

The first-line drugs currently used in the treatment of leprosy are dapsone, the highly bactericidal rifampicin and clofazimine. Prothionamide (or ethionamide) is also widely used especiaily in the recently advocated multidrug regimens. Other second-line drugs are thiacetazone and thiambutosine[1] but the latter is already obsolete. *Mycobacterium leprae* resistant to all of these drugs[1,2] and multidrug combinations (reported to XIIth International Leprosy Congress) have been reported. The widespread emergence of both primary and secondary dapsone resistance is of particular concern.[1,3] Another cause for anxiety is the range of side-effects associated with some of the drugs available.[4] The potential for chronic damage is considerable and the need for clinical monitoring especially with rifampicin is now well known. Nevertheless effective treatment of leprosy is possible and the use of multidrug and pulsed therapy may require much shorter periods of treatment than was at first thought especially for multibacillary cases.[5] Why then the need for new chemotherapeutic agents? In the first place multidrug resistant strains of *M. leprae* are now a real possibility. Secondly, none of the existing drugs clear the 'persister' organisms. Thirdly, drugs with fewer side-effects are required for extensive treatment requiring less intensive clinical oversight. Fourthly, the cost of rifampicin and clofazimine in some countries is still too high for them to be used on the scale necessary to achieve control of the disease. Fifthly, the development and testing of an effective vaccine and its use in the field is still a long way off despite intensive efforts in this area.

Antileprotic drug research has, until recently, been concerned in the main, with the development of new agents derived from or based on the current drugs.[3,6] Seydel and co-workers have demonstrated in a series of elegant experiments that dapsone and some novel sulphonamides act at the uniquely sensitive pteroate synthetase enzyme of 'M. lufu' and *M. leprae*.[7] Interestingly they have shown that dihydrofolate reductase inhibitors, which have no antileprotic activity of their own, exhibit a pronounced synergistic effect with dapsone. Dapsone and bromdiaprim (a dihydrofolate reductase inhibitor) in combination have been shown to be effective clinically.[8] Dapsone has however been shown, in a recent quantitative structure—active study, to have the

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optimum structure for antileprotic activity.[9] It also has a good pharmacokinetic profile. Any significant improvement in the sulphone series therefore appears unlikely. Ansamycin, an analogue of rifampicin, has also been shown to possess high activity.[10] Its longer half-life in man would be of advantage provided this was not associated with a greater incidence of undesirable side-effects. Recently analogues of thiacetazone, lacking the sulphur atom, thought to be responsible for toxicity, have been prepared.[11] They have yet to be fully evaluated but could provide useful alternative therapeutic agents.

A major problem, with all these compounds, is that they would not be expected to be effective against organisms which are resistant to current drugs.

The problem with attempts to develop completely new drugs is to identify new lead compounds as quickly as possible. Only recently have good *in vitro* test systems, which would allow screening of new compounds on a moderate scale, become available.[12] The characteristics of any new agents which are desperately needed[13] are that they should be: (i) bactericidal rather than merely bacteriostatic and destroy persister organisms; (ii) effective orally; (iii) parasite specific and therefore have few side-effects; (iv) cheap to produce and formulate.

Potential lead compounds may be identified in several ways. Random screening is not possible due to the limited facilities and in any case is uneconomic and no longer necessary. Useful clues about new compounds can come from an understanding of the biochemistry of *M. leprae*. It is only recently, with the increased availability of bacilli from armadillos, that such studies have been possible. There is still much to learn in this area. Other leads could come from natural products which have proved effective in leprosy. Prabhakaran[1,13] has identified a unique melanin producing tyrosinase enzyme system in *M. leprae* which utilises L-dopa as its substrate, and although this work was, and remains, controversial it suggests that new drugs related to the enzyme substrate, dopa(1), or its products 5,6-dihydroxyindole(2) could be developed.[1] Since the principles of drug design and irreversible enzyme inhibition are now well established[14] it should be possible to design compounds which are selective enzyme-activated irreversible inhibitors of this system. Such compounds would be expected to be bactericidal rather than simply bacteriostatic. The recent disclosure[15] of antileprotic activity of the fructose derivative of serotonin(3) agrees with this line of reasoning. This compound is a natural metabolite of serotonin with few side-effects in man. It is active orally in man and the mouse, but unfortunately is only bacteriostatic. Recently *in vitro* tests on a series of indole compounds specifically designed as antileprotic drugs have demonstrated significant activity (M Hooper, PR Mahadevan—unpublished data). Since man also possesses tyrosinase enzymes the question of parasite/host selectivity is a real one. However biochemical studies have indicated that the putative enzyme in *M. leprae* is stereochemically and electronically less selective than the host enzyme. This is consistent with the more primitive phylogenic status of *M. leprae*.[1,13]

Recent studies of the cell wall structure of mycobacteria generally and *M. leprae* in particular have identified novel elements not present in other species of bacteria.[16] The structure of the peptidoglycan of mycobacteria shows that *meso*-diaminopimelic acid(4) plays an extensive part in both the individual chains of the peptidoglycan and in their cross linking. The cross-linking of the peptidoglycan chains in other bacteria involves a D-alanyl—D-alanine terminus and a glycine residue. The transpeptidase which utilizes D-alanyl—D-alanine as its substrate is a major site for the action of penicillins and cephalosporins which are now known to function as active-site irreversible inhibitors of this enzyme. The weak activity of β-lactam antibiotics against mycobacteria may be a reflection of the low incidence of such sites in these organisms. However there has recently[17] been a report of amoxicillin in combination with clavulanic acid (a β-lactamase inhibitor) showing significant *in vitro* activity against *M. tuberculosis*. The resistance of mycobacteria to penicillins may therefore be due to lactamase activity.

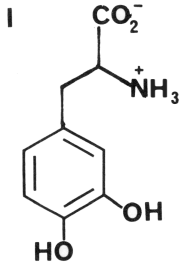
The unusual glycolyl muramic acid derivative in mycobacteria may provide another site for drug design.

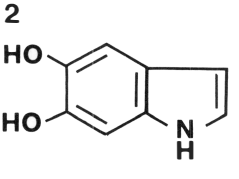
Since mammalian cells lack a cell wall comparable with that of mycobacteria it is reasonable to expect that new drugs derived from such structures will be highly parasite specific.

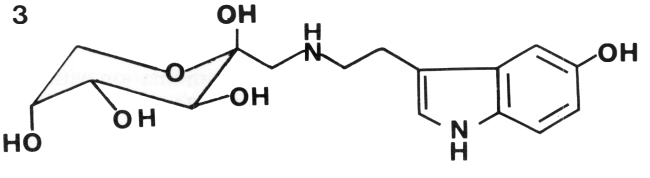
M. leprae also has present in its cell wall a variety of novel lipids, fatty acids and their complex derivatives.[18] Some of these are covalently bound into the wall whilst others are more labile. Any disturbance of the organism's metabolism of these compounds would be expected to cause some defect of cell wall function resulting in loss of viability of the bacillus. Indeed thiacetazone, thiambutosine and ethionamide are thought to act in this way. Recently chaulmoogric acid(5), a major constituent of oil of chaulmoogra, has been shown to be incorporated into the cell wall lipids of various mycobacteria.[19] The resultant changes in the cell wall structure could be the basis of the known bacteriostatic activity of the compound. Once again, since these lipids are unique to mycobacteria, there is a possibility of selectively active analogues of chaulmoogric acid being developed.

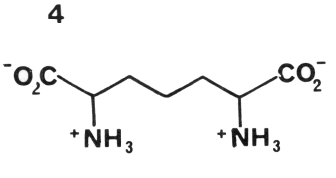
Electron micrographs of *M. leprae* in sections of host tissue show distinctive electron transparent zones round the bacilli. This now appears to be due to large quantities of potent antigenic glycolipids with unique structural features.[20] The production of large amounts of this compound by the bacillus provides another possible target for drug design. The electron transparent sheath may disguise many other antigenic features of the bacillus and thereby render it less susceptible to the host's immune system. Its removal by chemotherapeutic agents would be expected to increase the effective recognition and destruction of the bacillus.

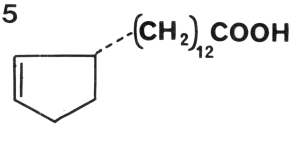
The structure and biochemistry of *M. leprae* and the physiology of leprosy are being vigorously studied at present. From these studies other targets for drug development would be expected to emerge. The major requirement will then be for that discernment which will identify new structures which will best meet the above criteria for new antileprotic agents. The future prospects for the development of new antileprotic drugs are good given modest funding to support this kind of work.











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SPECIAL ARTICLE

References to 'Side-effects of antileprosy drugs in common use'* (Jopling WH. Editorial, *Lepr Rev* 1983; **54:** 261–70)

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Dapsone

For general reviews of dapsone's side-effects, see (1) Graham WR. Adverse effects of dapsone. *Int J Dermatol*, 1975; **14:** 494–500; (2) Leading Article. Adverse reactions to dapsone. *Lancet*, 1981; **2:** 184–5.

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Lepr Rev (1985) **56,** 71–73

Domiciliary and Field Work

Books for Health Workers; AMREF, Nairobi, Kenya

This 89 pp manual, approximately A4 size, describes the selection and use of books for health workers, based on a vast experience in the writing, printing and distribution of such material in East Africa. Under 'How this book came to be written', the opening paragraphs read as follows: 'The selection and provision of appropriate learning materials—making them known and useful and affordable to those who need them—is clearly a fundamental requirement in the training of all cadres of health workers. Without learning materials, the health worker embarks on a difficult career handicapped from the outset. And yet, despite the acknowledged need for relevant, usable books and other materials, there is an acute shortage of these resources throughout East Africa, and indeed throughout the whole developing world.'

Following a workshop in the AMREF headquarters in 1976, participants ' . . . noted that there are 4 types of problem associated with books for health workers in the developing world: 1. To begin with, an appropriate book may not exist at all. 2. If the appropriate book does exist, it may not be known to the person who needs it. 3. If the book is known, it may not be available at a price and in a currency that the student can pay. 4. Finally even if the book exists and is known and is available, the student may not know how to study from books.

Accordingly, Workshop participants undertook to accomplish the following objectives: 1. To define remaining gaps in available books and determine which gaps need to be filled most urgently. 2. To prepare a list of recommended books, so that students and teachers can be apprised of what *is* available. 3. To explore ways of producing relevant, low-cost books locally. 4. To discuss how books can be used most effectively.'

The present book (1984) comprises a list of recommended and available books by subject, but it includes books for the medical, nursing and environmental health cadres, books for dental, laboratory, pharmaceutical, physiotherapy and radiographic cadres as well. Apart from a comprehensive list of titles and authors, this publication is a model of assessment technique for books in this context. It also contains: l, addresses of publishers and distributors, 2, a section on 'Writing of health learning materials', 3, 'How a book is produced', 4, 'How to use books effectively', 5, 'How to run a school library', and book assessment form. Apply: African Medical and Research Foundation (AMREF), PO Box 30125, Nairobi, Kenya.

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The Director of the Schieffelin Leprosy Research and Training Centre has drawn our attention to the availability of stocks of MCR at Karigiri:

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Since then it has been in regular use all round the world for the insoles of ulcer preventive footwear for leprosy patients.

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We commend our product to you as standard, of high quality and available from immediate stock.

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Portable McArthur microscope in plastic

The Eritrean Relief Association, a British Registered Charity, inaugurated an extensive public health programme in 1981 as part of its attempt to provide a framework for longer term development in its programme area, where the population have been afflicted by war for over 20 years and for the last 5 years by a severe drought. In May 1982, a decision was taken in the Eritrean Public Health Programme (EPHP), that a considerable input of microscopes and microscopy skills would be required, in order to change disease patterns in the areas of Eritrea where the programme was operative. A large number of instruments were reviewed, and the McArthur design was chosen as the most suitable.

Technical data on the basic instrument. The miniature microscope is equipped with three high quality objective lenses (10 ×, 40 × and 100 × oil immersion) and a 10 × monocular eyepiece—allowing a maximum magnification of approximately 1000 times. It has a flat metalized milar mirror and single-lens moulded aspheric condenser with an iris diaphragm. Fine adjustment is added to its automatic focus mechanism (automatic by virtue of the inverted specimen always being a fixed distance from the lens), while firm stops allow easy alignment of the lenses which are seated in a spring-loaded slide. A simple stage is fitted and a small mechanical stage is under development. Two high quality mirrors in a moulded light tube bend the light path through 180 degrees, which reduces the size of the instrument to 4 × 2·5 × 2 in. The plastic parts are moulded in light grey copolymer acetal resin which is very durable, and resistant to heat and most chemicals. The instrument weighs 200 g. The basic instrument is supplied with a 'lying drop' slide, the special slide used for examining fluids.

This plastic microscope has the same magnification as the ordinary hospital bench instrument and the same abilities for diagnosis, but it has the advantage that it can be carried in a little case on the belt or even in the pocket. The WHO's Laboratory

0305-7518/85/056071+03 $01.00

Technology recently coordinated an 8 country laboratory evaluation of the optical quality and handling of the instrument.

All enquiries and orders can be made to Dr N Andersson, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1; or, EPHP, BCM Box 865, London WC1V 6XX, UK.

Zenith binocular microscope

The following is extracted from 'Laboratory equipment—where are the tools to do the work?' Monica Cheesbrough. *Brit Med J* (1984) **288,** 30 June:

'A low priced, ruggedly built range of microscopes is the Zenith range, available from Primary Health Equipment Ltd. The binocular quadruple nosepiece model is shown in figure 1. It is equipped with a mechanical stage, condenser and iris, and range of optics to give magnifications up to × 1350. It costs £247 complete with case and three objectives. Available accessories include a dark ground condenser (price £19), a lamp unit for mains electricity supply, a 60 × oil immersion lens, and other optics. Monocular instruments are also available from £150, complete with optics, mechanical stage, mirror, and case'

Primary Health Equipment Ltd, Machno, Church Street, Stilton, near Peterborough, Cambs PE7 3RF, UK, was formed and is managed by Mr Alan Riley, a qualified design engineer and member of the consultative group for appropriate technology in the field of health laboratory technology.

Correspondence course for leprosy technicians, Marie Adelaide Leprosy Centre, Karachi

Dr Ruth Pfau, Adviser on Leprosy to the Ministry of Health in Pakistan, has recently started a correspondence course for leprosy technicians in Pakistan. The course consists of six lectures spread over a period of one year. The first subject is the treatment of leprosy. The object is to keep paramedical staff abreast of new developments and to reinforce and broaden knowledge gained at annual workshops. The information issued on Multiple Drug Therapy covers the selection of patients, classification, precautions before starting drug treatment, health education, side-effects, procedure after stopping MDT, referral to hospital, and record keeping. There is also a questionnaire.

[Although carried out within one country, this approach amounts to 'distance learning'. David Morley and Felicity Savage-King have recently drawn attention to the enormous (untapped) potential of this approach. ('Appropriate teaching aids'; *Brit Med J*, **289,** 20 October 1984, pp 1057–8.) To quote from their closing paragraph, such an approach '. . . could train the whole health team and provide a continuing training programme for health workers who have had practical experience of the problems that they are expected to deal with and need some feedback. Above all, distance learning is a way to get ideas about how to improve health outside academic institutions and in the community.' Editor].

Damien Foundation, India, organizes workshops

As a part of their in-service training policy, the Damien Foundation, India, has organized three workshops. Two of these workshops were meant for leprosy workers employed either in the Damien Foundation Leprosy Control Programmes or in private programmes sponsored by the Damien Foundation, one for Government non-medical supervisors. The objectives of these workshops, which lasted six days each, were threefold: to acquaint the leprosy workers with multidrug therapy—its scope and dangers, and with other specialized care needed by leprosy patients; to help leprosy workers realize the complexity of village communities and the need to integrate leprosy control with other problems of the community; and to help leprosy workers realize the need to function as a team, in which each member having its own function works with all the others to realize a common goal.

The three workshops were held in SBD Hospital, Kanpur. Altogether 63 workers participated in these workshops. Forty-two, of them came from eight private centres belonging to five different States (Bihar—Rajasthan—Gujurat—Uttar Pradesh—Maharastra). Each of these centres were asked to send the medical officer, their physiotherapist and one paramedical worker for the first workshop, and their non-medical supervisor, laboratory technician and one paramedical worker for the second one.

The first workshop was held from October 15 to 20 and the second one from October 29 to November 3 1984. The third workshop was held from November 26 to December 1 and was attended by 21 Government non-medical supervisors belonging to 5 districts of UP State (Kanpur—Varanasi—Lucknow—Jaundpur—Unmao).

The six days of the workshop were spent in discussions on subjects chosen by the participants which are important to them in their daily work.

Some of the patients of Kanpur contributed to the success of the workshops by agreeing to be examined by the participants and allowing their disease management to be discussed by all.

Mr P Antony, physiotherapist from Hemerijckx Government Leprosy Centre, Polambakkam (TN), spent a few days with each group of participants of the first two workshops. During the first workshop he demonstrated how to apply plaster of Paris and dress different types of ulcers. In the second workshop, practical demonstration could not be done, due to the sad demise of Ms Indira Gandhi and consequent difficulties in our country. But time was spent discussing these subjects. In the third workshop, Mr Bagwandas, physiotherapist attached to SBD Hospital, Kanpur, gave demonstrations of plaster of Paris, dressings and exercises.

The need for better Health Education Programmes in the areas around the centres was deeply felt by all the participants. In the second workshop the possibility of each centre having a Health Education Team, composed of a few workers from the Centre, was discussed and found practical. One of the Centres (Kanpur), as an outcome of the workshop, organized their Health Education Team and held an exhibition on leprosy in a local fair on the 13 November.

The Damien Foundation, India, plans to have one more workshop in Kanpur in the near future. It is intended for UP Government Leprosy Control Doctors.

The Damien Foundation, India, is particularly grateful to all the workers of SBD Hospital who worked hard to make these workshops a success.

(Source: Simone Liégeois, Consultant, Damien Foundation, Andal Apartments, AL-189 1st Street, 12th Main Road, Annanagar (West), Madras 600–040, India.)

Gandhi Memorial Leprosy Foundation, India

We are most grateful to Mr S P Tare, the Director of GMLF (Hindinagar, Wardha 442103, Maharashtra, India) for sending a copy of the 1983–84 Report of this Foundation. This includes sections on—leprosy control units; health education units; leprosy referral centre and hospital; training centre; WHO workshop on health education; other activities and visitors. As the Preface says '. . . GMLF has pioneered a number of experiments in its existence for 33 years now, and some of the concepts introduced by the Foundation have now become components of the National Leprosy Eradication Programme.'

Medical student education in leprosy: Indian Association of Leprologists

The 13th Biennial Conference of the Indian Association of Leprologists was held in Bombay in November 1983 and the facilities offered by the medical colleges in the city (Grant Medical College and TN Medical College in particular) were largely responsible for the success of this Conference. The object of exposing medical students and staff to recent advances in leprosy was amply fulfilled by holding the Conference in the auditorium of the TN Medical College.

The Organizing Committee of the 13th Biennial Conference decided to donate a set of books and journals on leprosy to all medical colleges in the city so as to expose both undergraduate and postgraduate medical students continuously to recent developments in the field of leprosy. This function was arranged in collaboration with LTM Medical College, Sion, with the help of the Dean, Dr N A Dhabolkar, and Dr (Mrs) Gopa Kothari, Professor and Head of the Department of Preventive and Social Medicine, on 11 October 84, in the college premises. Mr D K Afzulpurkar Additional Municipal Commissioner was the Chief Guest, who handed over the donation to the Deans of the different colleges.

On this occasion the Bombay Leprosy Project screened a few video cassettes on leprosy to mark the beginning of a massive programme contemplated by the Project to continuously expose the medical fraternity to the subject of leprosy through attractive audiovisual equipment, kindly donated by LEPRA. Mr Afuzulpurkar inauguarated this programme by switching on the audiovisual equipment. Dr R Ganapati, Vice-president of the Indian Association of Leprologists, requested the Deans of all medical colleges to make use of this equipment for the benefit of their students by sending them in small batches to the Project Office, by prior arrangement. Dr M V Yellapurkar, Vice-Chairman of the Conference stressed the need for removal of the social stigma and fear about leprosy—prevalent even amongst the medical profession.

Dr Gopa Kothari while proposing a vote of thanks welcomed this new approach and suggested that leprosy teaching should be included in the mdical curriculum from the pre-clinical stage.

Karigiri Video: Medical Teaching Programmes, South India

This programme, which is producing informative videotapes, will soon cease to have outside funding and so is hoping to become self-sufficient from the sale of tapes. To date the following videotapes (available in VHS or Betamax format of the PAL system) have been produced:

Painless feet, Dr E. P. Fritschi: Progressive destruction of the feet is one of the commonest and most crippling complications of leprosy. This video describes how this can happen, and how one can protect the ulcer prone foot using very simple methods to avoid both internal and external pressures on the foot. 16 min/Rs. 800/- (plus post & packing); £60; US$75 (postage paid). Also available in French/Spanish.

Mice against leprosy, Dr Joel Almeida: Leprosy research was transformed by the discovery that mice could be infected with *Mycobacterium leprae.* This video, which is aimed at physicians, demonstrates some of the more important uses of mice in leprosy research and treatment. The tape is accompanied by a multiple choice questionnaire. 9½ min/Rs. 500/- (plus post & packing); £38; US$48 (postage paid). Also available in Spanish.

Healing while walking, Dr E. P. Fritschi: Only a small minority of leprosy patients can afford to spend 6 weeks in a hospital bed. This video shows 3 applications of plaster-casts for different types of ulcers on the feet that provide local rest while the patient remains ambulatory. The plasters applied are: a full length below knee plaster, a window plaster and a double rocker moulded shoe. The video follows the treatment from the time of diagnosis to recovery; and it shows some of the complications which can occur during that period. 45 min/Rs. 850/- (plus post & packing); £60; US$75 (postage paid).

Keep blinking, Dr N. Suryawanshi. One of the complications of leprosy is damage to the zygomatic branch of the facial nerve. This leads to paralysis of the orbicularis oculi muscle causing inability to blink. This condition, lagophthalmos, can result in blindness if left untreated. The video demonstrates the medical and surgical treatment of lagophthalmos. 20 min/Rs. 750/- (plus post & packing); £55; US$70 (postage paid).

Slide-audio cassette programmes:

An introduction to leprosy control, Dr K. Jesudasan. This programme is an introduction to the field of leprosy control for medical students as well as general audiences. It provides the basic information about what causes the disease and how it can be treated and controlled.
The presentation shows what is actually being done to control the disease in the highly endemic area of southern India, with emphasis on the work of the Paramedic, and the importance of early detection. 20 min/78 slides/Rs. 475 (plus post & packing); £38; US$48 (postage paid).

Leprosy: the great imitator, Dr S. Arunthathi. In endemic areas, purely cutaneous diseases will tend to be mistaken for leprosy. The reason for these mistaken diagnoses is that leprosy can imitate many diseases both clinically and histopathologically. The conditions which always should be considered in a differential diagnosis of leprosy are shown. 45 min/150 slides/Rs 850 (plus post & packing); £65; US$80 (postage paid).

For further information contact: **Sanjay Agrawal**, Director/Cameraman, Karigiri Video, Schieffelin Leprosy Research and Training Centre, Karigiri 632 106 Tamil Nadu, India. Orders from within India will be sent by VPP (payment on delivery). For foreign orders the payment should be made in advance by money order or demand draft at any Indian bank in Madras or Vellore, North Arcot District in favour of 'SLR & TC, Karigiri'.

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Reports, News and Notes

Robert Cochrane Fund for Leprosy

The fund, in memory of the great leprologist Robert Cochrane, is administered by the Royal Society of Tropical Medicine and Hygiene. It is to be used to finance up to 2 travel fellowships each year to a maximum value of £1000 each.

The intention is to enable leprosy workers to travel for practical training in field work, or in research, or to enable experienced leprologists to travel in order to provide practical clinical training in a developing country. There is no restriction on the country of origin or destination providing the above requirements are fulfilled.

Application forms are available from the Society and must be received by the Society at least 6 months ahead of the proposed trip. All applications must be sponsored by a suitable representative of the applicant's employer or study centre, and agreed by the host organization. A 2 page report on the travel/study should be submitted to the Society within 1 month of the recipient's return. Apply: The Administrator, Royal Society of Tropical Medicine and Hygiene, Manson House, 26 Portland Place, London W1N 4EY.

Medical Research Council Tuberculosis and Related Infections Unit

The MRC's new unit, directed by Dr J Ivanyi, was opened at the Royal Postgraduate Medical School, London, on 1 October. It replaces the Unit for Laboratory Studies of Tuberculosis, which closed last month when the director, Prof. D A Mitchison, retired. The Tuberculosis and Chest Diseases Unit at the Brompton Hospital will continue to function until 30 September 1986, when the director, Prof. Wallace Fox, retires.

Handbook of Leprosy, W H Jopling, 3rd edition, now also in ELBS

In a recent issue (Number 4, 55, 1984) we drew attention to the advantages of the English Language Book Society (ELBS) system, whereby selected books are available to students in developing countries at between one-third and one-half the normal price. An ELBS edition of Dr Jopling's invaluable handbook will be available from 1985 onwards. Enquiries to William Heinemann Medical Books Ltd, 23 Bedford Square, London WC1B 3HH or ELBS, The British Council, 11 Portland Place, London WIN 4EJ.

Tropical Diseases Chemotherapy Research Unit, Sunderland Polytechnic

We are grateful for the First Annual Report of this Unit in Sunderland, which was inaugurated in November 1982, with a lecture on 'Chemotherapy and Tropical Disease' given by Dr L G Goodwin, formerly Director of the Nuffield Institute of Comparative Medicine. The following are extracts from Professor Hooper's report: *The aims of the Unit* are the design and development of novel effective chemotherapeutic agents for the treatment of tropical diseases. At present the major areas of interest are leprosy and tuberculosis, trypanosomiasis and leishmaniasis. The area of activity is being extended to include filariasis.

The TDCRU brings together members of academic and research staff in the Faculties of Pharmaceutical Sciences and Science with a common interest and commitment to the study of tropical diseases and the development of effective new chemotherapeutic agents for their treatment.

The Unit has well-found research laboratories for synthetic work, for a range of biochemical investigations and for *in vivo* biological studies. These include a grade B pathogen laboratory.

In particular the Unit has established *in vitro* and *in vivo* screening procedures for testing potential trypanocidal compounds. The screen can accommodate compounds from external organizations in addition to those from the Unit's own research programmes. A screen for anti-leishmanial compounds is presently being established and this facility will also be available to outside organizations. *Enquiries*: TDCRU, Sunderland Polytechnic, Sunderland, SR2 7EE.

CIBA–GEIGY; cassette on Lamprene and Rimactane

We are grateful for this excellent tape on clofazimine and rifampicin from Basle, which describes the development and clinical use of these drugs in leprosy. Enquiries to Dr J P Heiniger, CIBA–GEIGY, Medical Department, CH-4002, Basle, Switzerland.

OXFAM, Oxford; *Questions and answers on the implementation of multidrug therapy (MDT) for leprosy*

This is a 32-page booklet, A5 size, in question and answer form, produced by OXFAM as Number 3 in its 'Practical Guide' series. Starting with 'What is MDT?' and ending with 'Will the implementation of MDT lead to the control, and perhaps even to the eradication of leprosy?', 15 questions, all of a practical nature, are posed, and an attempt made to answer them in the light of existing knowledge about a fast-expanding subject. Price: £1.50 per copy, with a 25% discount on orders of more than 10, plus postage charges on bulk orders. Enquiries: OXFAM, Health Unit, 274 Banbury Road, Oxford OX2 7DZ.

0305-7518/85/056074+06 $01.00

International Symposium on Mycobacteria of Clinical Interest

Date: 27–28th September, 1985. Themes—immunopathology of leprosy and tuberculosis; modern methods for the rapid diagnosis of tuberculosis; human mycobacteriosis; therapy of leprosy and tuberculosis; experimental chemotherapy, etc.

Apply to Secretariat, International Symposium on Mycobacteria of Clinical Interest, Department of Microbiology, School of Medicine, University of Čordoba, CORDOBA-4, Spain.

Tropical Health Technology; *Medical Laboratory Manual for Tropical Countries*; Vols 1 and 2

These 2 volumes are now available, at remarkably low cost, from Tropical Health Technology Ltd, 14 Bevills Close, Doddington, Cambridgeshire, England PE15 0TT.

Volume 1 covers—introduction to the laboratory; anatomy and physiology and explanation of clinical terms; medical parasitology; clinical chemistry. There are appendices on the preparation of reagents; addresses of manufacturers; useful tables, index and loose sheets.

Volume 2 is on microbiology, including bacteriology; virology and mycology. The UK cost of Volume 1 is £9.35, inclusive of postage and of Volume 2 £9.95, inclusive of postage. Rates to Europe, North America and other countries are available from the above address. (These volumes are produced and distributed on a non-profit-making basis and they are of exceptional value. They include full and extremely well-illustrated sections on the taking of split-skin smears in leprosy, and the examination of sputum for tuberculosis).

Coordination Bureau for Tropical Medicine and Hygiene, Copenhagen

The descriptive booklet reads as follows:

Denmark has for many years been engaged in all aspects of health care in developing countries. Enquiries among aid organisations and private firms have shown the need for an advising and coordinating body in that field.

The Danish Society of Tropical Medicine has therefore decided to set up a Coordination Bureau for Tropical Medicine and Hygiene in agreement with the Danish Medical Association's Working Group on Health Care in the Developing Countries, and with the cooperation and understanding of Statens Seruminstitut, the Medical Faculties, the Centre for Development Research, and the Department of Infectious Diseases, Rigshospitalet.

By utilising the existing experience, the Bureau has the following aims: to train Danish personnel in the solving of health problems in developing countries, using an integrated approach with other disciplines; to support and advise Danish health workers in the field by building useful contacts; to mobilise the experience from ongoing projects by offering advice with relevant evaluation; to contact previous and present health workers with the purpose of computing and canalising the existing experience; to offer this experience to private and public aid organisations as a help to planning, carrying out, and evaluation of health related projects; to stimulate health education and research both abroad and at home; to establish national and international contacts with organisations engaged in health projects in developing countries, in order to promote a better coordination of effort.

Enquiries to: Department of Infectious Diseases M 7701, Rigshospitalet Tagensvej 20 2200 Copenhagen N, Denmark.

Medical Education Newsletter; Centre for Medical Education, Dundee

The Newsletter for Summer 1984 from the Centre for Medical Education, The University, Dundee, DD1 4HN, Scotland, UK, is, as usual, packed with items of information on all aspects of medical teaching and includes a form on the back page for requesting further details, and even copies of the material described. This is an invaluable source of information for all engaged in teaching. Enquiries to the above address.

Medical Journals from China

On an exchange basis with *Leprosy Review*, we continue to receive 3 journals from the Republic of China—1) *Chinese Medical Journal*, 42 Dongsi Xidajie, Beijing, 2) *Chinese Journal of Dermatology*, c/o Institute of Dermatology, Chinese Academy of Medical Sciences, 100, Jiangwangmiao, Taipingmen, Nanjing, Jiangsu, and 3) *Journal of Clinical Dermatology*, Department of Dermatology-1, First Teaching Hospital, Nanjing Medical College, Nanjing, China. Both dermatological journals frequently carry articles on leprosy. Typical headings from recent issues include:

Urine test for monitoring regular self-administration of dapsone and its application *Department of leprology, Institute of Dermatology, Chinese Academy of Medical Sciences* . . .

HLA-linked control of predisposition of lepromatous leprosy . . . *Xu Keyu et al*

Histopathology of Blood Vessels and Skin Appendages in the Skin Lesions of Untreated LL and BL Forms of Leprosy Patients—A Light and Electron Microscopy Study . . . Zhu Wen-Yuan *et al*

Malignancy of Trophic Ulcer in Leprosy: Report of Two Cases . . . Dong Li-Wen *et al*

The Influence of Corynebacterium Parvum (C. P.) and M. Vaccae Vaccine on Leprosy Infection . . Ji Baohong *et al*

—all from the *Journal of Clinical Dermatology*. And the following—

Study in cultivation on M. leprae in vitro: II. Characteristics of 21 strains of acid-fast bacilli studied by means of 12 differential identification tests . . . *Wu Qinxue et al*. Further observation on histoid leproma by TEM and SEM . . . *Liu Lihe et al*—both from the *Chinese Journal of Dermatology*.

China Medical Abstracts, 1984

CHINA MEDICAL ABSTRACTS (Internal Medicine) is the first official publication of its kind of Chinese Academy of Medical Sciences (CAMS) published in English. It provides comprehensive sources of recent advances of the specialities of internal medicine, which were published in the major Chinese medical journals and acta academiae of medical schools all over China. Readers may comprehend rapidly and extensively what the Chinese medical workers have done in the field of internal medicine. The CHINA MEDICAL ABSTRACTS will come out 4 times a year. Subjects index will be prepared annually. Price US $40.00 (surface mail).

Apply: Export Department, China National Publications Import & Export Corporation, PO Box 88, 137 Chao-Nei Street, Beijing, People's Republic of China.

Video-tape: 'Chemotherapy of Leprosy for Control Programmes', Oxford

The Department of Medical Illustration in Oxford has produced a 14-minute video-tape (VHS PAL 625 system) describing recent regimens of drug treatment for leprosy, based on the Report of a WHO Study Group entitled '*Chemotherapy of Leprosy for Control Programmes*', published by WHO in Geneva in 1982 in the Technical Report Series, Number 675.

The intended audience includes—medical students, medically qualified doctors, senior personnel in ministries of health in leprosy-endemic countries, tutors and teachers in medical and para-medical schools, programme planners, leprosy control officers and supervisors, senior staff in pharmacies, drug supply and distribution.

The subject matter covers the classification of leprosy according to both Madrid and Ridley–Jopling systems; definition of pauci and multibacillary leprosy; unit dosage and regimens of dapsone, rifampicin, clofazimine and the thioamides for the treatment of both pauci and multibacillary cases. In order to ensure the safe and effective implementation of multiple drug therapy for as many patients as possible and with the minimum of delay, repeated emphasis is given to the importance of the training, retraining and supervision of the health personnel concerned.

Cost: £12 sterling ($16 US dollars), plus Value Added Tax (VAT), but inclusive of postage. Apply directly to: Department of Medical Illustration, the John Radcliffe Hospital, Headington, Oxford OX3 9DU, England.

Lower limb prosthesis for amputees in rural areas

We are grateful to Dr P K Sethi, FRCS, for information about a lower limb prosthesis which has already proved of great value in the rural areas of India. The 'Jaipur foot', named after the village in the state of Rajasthan where Dr Sethi tested his invention, is simple, inexpensive and easily made by local artisans. Wearing it, an amputee can return to normal activities—ploughing wet paddy fields, walking up and down rough terrain, pedalling a rickshaw tricycle or riding a motorcycle. If desired, the prosthesis fits easily into a normal shoe, and it enables the wearer to squat or sit cross-legged. Materials to construct the foot are commonly found in most developing countries. At its core is a universal joint made of virtually indestructible sponge rubber. This is enclosed in rayon cord (commonly used in tyres). The external surface is made of vulcanized rubber, moulded to size in a die produced by age-old sandcasting methods. It has the shape of a normal foot, complete with big toe. Discarded tyres can be used as raw material and the foot bleached and stained to match the skin tone of the individual. Bicycle axles replace expensive steel knee joints, and leather near the hips allows the sideways movement involved in squatting or sitting cross-legged. The amputee is ready to walk only 45 min from the time measurement of the limb begins. Following up on his patients, Dr Sethi has found that farmers are carrying out their usual work, which involves considerable wading in mud and water, for 3 or 4 years without a breakdown. The foot is being fitted at the Rehabilitation Research Centre at Sawai Man Singh Medical College and Hospital in Jaipur, which Dr Sethi heads. The centre handles over 700 patients a year, who come from all over India, some from as far as a thousand miles away. The Mahavir Society for the Physically Disabled purchases materials, identifies the disabled and helps them get to Jaipur and pays other costs. The foot itself is provided free of charge. Further information from: Drs P K Sethi, Vivekan and Marg, Jaipur 30200, India.

Erratum. *Editorial, LEPRA's Elective Period Student Programme, 1978–83*

In reference 4 of the above paper (*Lepr Rev* (1984) **55**, 321–325) both Davies RA and Ng YY were incorrectly listed as LEPRA Elective Period Students. They were in fact financed by The Leprosy Mission and the Medical Research Council, We apologize for this error.

Histopathology of leprosy course, Santa Margherita Ligure, Italy, September 1984

From 24 to 29 September 1984, in S. Margherita Ligure, Italy, a course on histopathology was held under the auspices and the contribution of the Italian Leprosy Relief Association 'Amici di Raoul Follereua' and the Department of Dermatology of the University of Genoa. The course was conducted by Prof D L Leiker and Drs D S Marion and Ridley. The 14 participants of the course came from six Mediterranean countries, from Bulgaria and from the USSR.

Raoul Follereau Grant 1984 for leprosy research

The Raoul Follereau Grant of 20.000 US$ is offered every two years by the Italian Leprosy Relief Association 'Amici di Raoul Follereau', for leprosy research. The first grant was allocated on the advice of an international committee of experts to a young scientist, Dr Teunis Eggelte, in Amsterdam, for a study on: 'Synthesis and evaluation of artificial *Mycobacterium leprae* antigens for serodiagnosis of leprosy infection'. The name of the winner of the 1984 Grant was made known during the working session of ILEP in Venice in June 1984.

NLO Bulletin: National Leprosy Organization, India

We are grateful for 3 copies (Numbers 2 and 3 of 1983 and Number 1 of 1984) of this Bulletin, published by National Leprosy Organization, Hindinagar, Wardha, Maharashtra, 442103, India. The original articles cover: the Indian classification of leprosy; prevention of deformities; mode of transmission; bacteriological status of fingers; contact examinations; epidemiology of leprosy; health education in rural areas. Other sections deal with reprinted material and reports from WHO and other agencies. This publication, essentially for India, contains a great deal of information which will surely be of interest to leprosy workers in other parts of the world.

Pan American Health Organization (PAHO) publications

The PAHO Office of Publications publishes: the Scientific Publications Series, which consists of almost 500 numbers on a broad spectrum of subjects—in English, Spanish, and Portuguese—in health and biomedical fields; the Periodicals Series, which includes the *Boletín de la Oficina Sanitaria Panamericana* (published regularly since 1922), the *Bulletin of the Pan American Health Organization, Educación médica y salud*, and the *Epidermiological Bulletin/Boletin epidemiológico*; and the Official Documents series, which consists of the *Annual Report* and *Quadrennial Report of the Director, Basic Documents, Handbook of Resolutions*, and the *Financial Report of the Director* and the *Program and Budget*.

Catalogues of these publications and the publications themselves can be obtained by writing to either of the following:

Distribution and Sales, Pan American Health Organization, 525 Twenty-third Street, Washington, D.C. 20037, USA or BIREME—Latin American Center for Health Sciences Information, Rua Botucatú 862 Vila Clementino, Caixa Postal 20381, CEP. 04023 São Paulo, SP Brazil. These publications can also be obtained from any of the PAHO/WHO Country representatives.

Leprosy and tropical dermatology

Leprosy was certainly not overlooked at the Fifth World Congress of Tropical Dermatology, which was held in Mexico City, 16–20 October 1984.

Dr Stanley Browne, a founder-Member of the Society, had been invited to organize a Teaching Seminar on Leprosy under the title 'Leprosy: the new look'. Thanks to the willing cooperation of leprologists from Mexico itself, the USA, Malaysia and Brazil, the well-attended meeting listened with interest to a rapid review of modern ideas on leprosy and its treatment.

Because half of the participants were attending a concurrent session at the time of the Teaching Seminar, Dr Browne was asked to give an unscheduled Lecture on the general theme 'What every dermatologist should know about early leprosy'.

Medicines, health and the poor world; Office of Health Economics, London

This book of 37 pages, plus references, was written by David Taylor and published by the Office of Health Economics, 12 Whitehall, London, SW1A 2DY in 1982. It is a nextension and up-dating of the 1972 paper from this Office on 'Medical Care in Developing Countries', '. . . taking into account the events of the last decade and extending the analysis provided to include an examination of the distribution and use of modern medicines in the Third World'. It is packed with valuable information under the following main headings—introduction; development and demographic transition; ill health and its causes; the provision of health care; choices for health; medicines for the poor world; pharmaceutical policies for the future; conclusions. There are 9 tables, including a large one on medical and nursing manpower in the countries of the world, grouped as low income countries, middle income countries, industrial market economies, capital surplus oil exporters and non-market industrial economies. Obtainable from the above address in London at £1.50.

XIII International Leprosy Congress, The Hague, Netherlands, 1988

The President and Secretary of the International Leprosy Association are happy to announce that the XIIIth International Leprosy Congress will be held at The Hague, Netherlands, from 11 to 17 September 1988. The Pre-Congress Workshops will be held on 8, 9 and 10 September 1988. The Inauguration of the Congress has been tentatively fixed for the evening of 11 September 1988 and the Scientific Sessions will start on 12 September. The concluding session will be on the forenoon of 17 September 1988.

Mr H E M De Bok of the Netherlands Leprosy Association is making the arrangements for the Congress and the first Information Brochure will be sent to you by September 1985.

If you have any suggestions, please contact: Dr R H Thangaraj, Secretary—ILA, No. 5 Amrita Shergill Marg, New Delhi 110003, India.

II Congress of Hansenology of the Endemic Countries, December 1985

This congress is scheduled for 3–5 December 1985 at the Baton Rouge Hilton Hotel and the National Hansen's Disease Center in Carville, Louisiana. The College of Hansenology of the Endemic Countries is an international organization of health professionals, physicians, social and paramedical workers concerned with the microbiology, immunology, experimental animal models, pathology, clinical aspects, therapy, physical and psychosocial rehabilitation, and the epidemiology of Hansen's disease. Panels, working groups, and free communications are planned, addressing these themes. One-half day will be devoted to a visit and tour of the National Hansen's Disease Center in Carville.

For further information contact: Dr R Azulay, President, College of Hansenology of the Endemic Countries, Rua Nascimento Silva, 16/201, CEP-22.421-IPANEMA, Rio de Janeiro-R.J., Brasil; or Dr R Hastings, President, II Congress of Hansenology of the Endemic Countries, National Hansen's Disease Center, Carville, LA, 70721, USA.

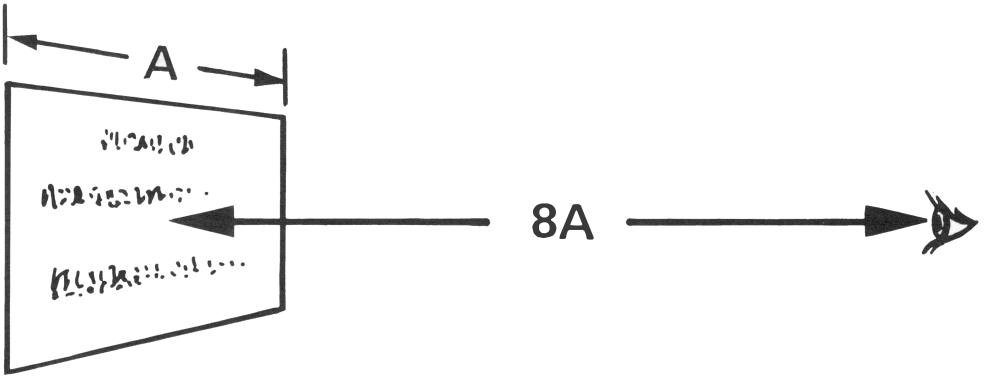
***ILEP Catalogue on Training*, 1985**

ILEP (International Federation of Anti-Leprosy Associations) has issued a catalogue of training centres in various parts of the world, which gives full details of the courses offered, main subjects taught, etc., English and French text. The centres include those in ALERT, Ethiopia; Bamako, Mali; Bauru, Brazil; Carville, USA; Fontilles, Spain; Karigri, India; Mexico City, Mexico; Yaounde, Cameroon; and Dakar, Senegal. Copies are available from ILEP, 234 Blythe Road, London W14 OHJ, or from ILEP representatives.

Artwork for transparencies; a useful rule of thumb

The Department of Medical Illustration in Oxford has kindly supplied the following practical advice:

If you are preparing material for presentation as a slide, there is only one rule to follow.
When you view the artwork from 8 times its longest dimension you must be able to read it easily.
It will then produce a legible slide when projected.



Further hints on the production of written material and tables in transparencies

The Royal College of Physicians of London has supplied the following advice, which should be of considerable value (and might profitably be distributed to all intending speakers at the next International Leprosy Congress): 1, On any given slide (transparency), use the *minimum* of information; no more than can be typed on a postcard. 2, Check legibility with a rule such as that given above, and remember that a part of any audience *does not have normal vision.* 3, Remember that tables which are suitable for publication *are not necessarily suitable for projection* (and are frequently much too complicated for this purpose). 4, The content of your message should fit the *shape* of the slide. 5, Writing should in general occupy not more than *7 lines* in height. 6, Do not use more than about 12 characters to the line. 7, Keep the number of words in the title of each slide down to *about 5*. 8, Slides for projection should be marked with a spot at the *lower left-hand corner* when viewed in the hand. 9, Write your *name*, the title of the talk or lecture, the *session* and *time* clearly on the box or folder which you hand in to the projectionist.

Council for International Organizations of Medical Sciences

The CIOMS arranged an International Conference in Athens, 29 October–2 November 1984 on the theme 'Health Policy, Ethics and Human Values'. About 120 participants from 40 countries—health planners, ethicists, cultural and religious leaders, as well as eminent medical men and women—joined in lively discussion and debate around the subject 'The non-medical aspects of health policy making'.

The International Leprosy Association (a founder-Member of CIOMS) was represented by its present and past Secretaries, Drs R H Thangaraj and Stanley Browne. Dr Thangaraj was invited to address the Conference on 'Hinduism' while Dr Brown was Rapporteur of one of the Working Groups.

The Conference stressed the importance of the social cultural and religious components that were essential if the WHO slogan 'Health for All by the year 2000' is to become an actuality.

Under the firm and genial chairmanship of Dr J H Bryant (the main organizer) and thanks to the excellent preparation of Dr Z Bankowski (the secretary of CIOMS), the participants thrashed out many of the implications of health policy as it affects the peoples of the world.

XII World Conference on Health Education, 1985

Trinity College in Dublin will be the venue for the XIIth World Conference on Health Education which will be held 1–6 September 1985. The theme chosen is 'Health for All—Meeting the Challenge'. Five sub-themes will focus on a particular aspect of meeting the challenge of health for all: 'Have we all a choice? What are the constraints? What progress so far? Who first? Is it the same everywhere?' For information please write to Mary D'Ardis, Conference Coordinator, Health Education Bureau, 34 Upper Mount Street, Dublin 2. Tel.: 76 11 16.

AHRTAG, London, 1985

We are most grateful to Ann Darnbrough, Disability Prevention and Rehabilitation Unit, AHRTAG (Appropriate Health Resources and Technologies Action Group Ltd, 85 Marylebone High Street, London WIM 3DE) for information about the following:

1, *How to make hand grips*; an extremely well-illustrated 4-page guide to the production of grips for patients with various kinds of hand disability, by Don Caston. 2, Details of free newsletters, posters and resource lists from AHRTAG. 3, Details of publications on aids for disabled children; looking after a health centre store; personal transport for disabled people; 'How to make an illuminator'. Further details and costs from the above address.

WHO intensifies research in tuberculosis (1984)

WHO has recently expanded its research efforts in the immunology of tuberculosis to take advantage of recent progress in the basic biomedical sciences. The new methods now available, such as recombinant DNA technology, T-cell cloning and monolconal antibodies, should open up fresh opportunities for devising better immunoprophylaxis and other control methods. Yet, so far they have not led to a concerted effort in the control of tuberculosis, a disease that remains a great public health problem in developing countries despite the application of the control methods already available.

A comprehensive research programme was outlined at a planning meeting convened by WHO in Boston, USA, earlier this year. It was realized that such an effort requires a stepwise approach, and the meeting focused on the initial activities to be carried out. Priority was given to the following areas, where activities and resources at present are too limited.

—Molecular biology of *Mycobacterium tuberculosis*: the goals in this area include establishing the genetic and biochemical bases for the pathogenicity of *M. tuberculosis* and developing methods to identify strain heterogeneity.
—The production of monoclonal antibodies to various components of *M. tuberculosis* to help detect mycobacterial antigens in clinical specimens; the identification of the most suitable serotypes of *M. tuberculosis* and *M. bovis* for epidemilogical use; and the devising of more sensitive and specific serologica tests.
—Studies of the cellular immune response to *M. tuberculosis* and its regulation in different population groups, including patients with different types of tuberculosis and subjects living in areas where BCG has been found to give insufficient protection against tuberculosis.
—Studies in experimental animals to identify by T-cell cloning the antigens involved in protective immunity, to determine the optimum means of eliciting local immunity in the lung, and to identify the mechanisms of antibacterial action in host cells, especially macrophages. (Source: *WHO Chronicle*)

Lepr Rev (1985) **56,** 80–87

Letters to the Editor

HIGH SCHOOL STUDENTS IN INDIA LEARN ABOUT LEPROSY THROUGH HANDBILLS AND 'QUIZ' CONTEST

Sir,

On the occasion of the Anti-Leprosy Week in India in 1983, a handbill, carrying information about leprosy in either basic English, Telegu or Urdu, as appropriate, was distributed to 10th class students in 623 schools throughout the State of Andhra Pradesh. The handbill carried simple, clear information on the nature of leprosy as a disease, its drug treatment and control. No fewer than 42,700 handbills were distributed and on the next day we followed this up with a questionnaire to approximately one third of all the students in each school. We set multiple choice questions covering: the cause of leprosy, infectiousness, transmission, the reasons for fearing it, deformities, treatment, control. We allowed 10 days for the completion and return of the questionnaire forms, through headmasters of schools, to the District Leprosy Officers, who were responsible for correction and marking. The final results were sent to this office and prizes were awarded for the best entries.

This project was uncontrolled and it would clearly be of importance to repeat the exercise in another area, without the use of handbills, and to attempt a comparison. It is therefore difficult to draw definite conclusions from our preliminary study, but there is no doubt that the interest and enthusiasm shown not only by the school students, but also by the headmasters and teaching staff, was impressive. This approach to health education in leprosy in a vitally important section of the community requires a lot of hard work and planning, but it is simple in design, and inexpensive. We consider that it may be of value in other parts of India, and perhaps in other leprosy-endemic countries.

S N MATHUR & S HASAN

Hind Kusht Nivaran Sangh
Hyderabad,
India

OCCURRENCE OF LEPROSY IN MANY MEMBERS OF THE SAME FAMILY

Sir,

It was very interesting to read the article on a case report of an 8-member family affected by leprosy (*Lepr Rev* 1984, **55,** 47–50).

In 1982 while I was working at the Niramol Leprosy Clinic, Khon Kaen, Thailand, I had the opportunity to study a similar family with 7 of its members affected by leprosy. The father aged over 60 years and 6 children aged between 20 and 38 years (5 brothers and 1 sister) had the disease, but the mother and 1 daughter had no evidence of either past or present disease.

The cases were picked up when one of the sons was brought to the clinic for treatment of ENL reaction. He was a case of active BL leprosy with pustular ENL reaction. Since it was our practice to

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examine any accompanying contacts of patients, his sister who had accompanied him was examined too. She had lesions suggestive of resolving BT leprosy. Subsequently all other members reported to the clinic as instructed and all were examined.

The father and 2 other sons had lesions of inactive BT, the elder son was a case of inactive LL and another son had active TT lesion. Except the son with active TT, all others were already registered and treated elsewhere. Only the one with active BL was bacteriologically positive. Three of the sons had deformities of hands.

Surprisingly the father had non-infectious type of leprosy though he had the longest duration of disease (over 20 years). The children had the disease for durations varying from 5 to 10 years. There was no history of leprosy among the ancestors. No genetic study could be done.

Presently, I am treating a family of 8 members, 5 of whom have leprosy. The mother aged over 50 years, is a case of inactive LL and has had the disease for 30 years; 2 sons aged 27 and 20 years are cases of active LL with the duration of 13 years and 10 years, respectively; 1 son aged 13 years has had active BT for a duration of 5 years; another son who was said to have deformities has absconded from the family and so was not available for examination. The father and 2 sons have no evidence of leprosy.

These cases seem to support the idea that heredity plays a significant role in the transmission of leprosy.

Paradoxically however, I find that among the families in the colonies here, where most families have both the parents with leprosy (married after being settled here), the number of children affected is much less than what one would expect. There are very few families with 2 children affected and hardly any with more than 2 children with the disease.

MARY S JOSEPH

Nonsombun Leprosarium
Khon Kaen, Thailand

ULNAR NERVE CALCIFICATION AND ABSCESS FORMATION IN 2 CASES OF PRIMARY MONONEURITIC LEPROSY

Sir,

This is with reference to the article on 'Ulnar nerve calcification and abscess formation in 2 cases of primary mononeuritic leprosy', by Samuel *et al*., (*Lepr Rev* 1984; **55:** 173–6).

Case 1 indicates a neural involvement without sensory deficit, skin lesion or positive skin smears. The caseous material was negative for AFB.

Case 2 indicates similar findings with the exception of a sensory deficit.

It is generally agreed upon that a diagnosis of primary neuritic leprosy whether mononeuritic or polyneuritic, can only be confirmed by a report on the nerve biopsy, which was not reported in either of the cases cited above. One is therefore led to understand that there is every likelihood that these are *NOT* of a leprous aetiology, but could perhaps be abnormal calcification in nerves resulting in neurolysis.

Of course leprosy cannot be ruled out, especially in endemic areas, but we ought to be guarded in labelling a patient as having leprosy, and the proof must be convincing beyond doubt. A report on the nerve biopsies of these patients would certainly be interesting.

T OOMMEN

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LIPIDS AND LEPROSY

Sir,

I was very interested to read Sritharan's article 'High density lipoprotein cholesterol (HDL-C) analysis in leprosy patients' (*Lepr Rev* 1984; **55:** 167–71). On relatively small numbers of individuals they have been able to show a significant difference in HDL-C and the HDL-C/TC (total cholesterol) ratio between lepromatous patients (both treated and untreated) and controls. If these results can be repeated in other studies and in other parts of the world it would suggest that the area of lipid metabolism and immune response to *Mycobacterium leprae* might be a fruitful area for research. There is already considerable interest in mycobacterial lipids.[1,2]

It is interesting to note in Sritharan's study that there is a general rise in TC, HDL-C and the HDL-C/TC ratio with age. In western populations it has been consistently shown that while TC levels tend to rise with age,[3] the HDL-C remains static with the result that the HDL-C/TC ratio falls as age increases.[4]

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CLOFAZIMINE POTENTIATES THE SYNTHESIS OF PROSTAGLANDIN E2 BY HUMAN POLYMORPHONUCLEAR LEUCOCYTES *IN VITRO*

Sir,

In addition to its value as an anti-microbial agent, clofazimine (Lamprene, B663) in high dosage also possesses properties which are of established value in the treatment of erythema nodosum leprosum (ENL)[1–3] and possibly also in reversal (upgrading) reactions.[4,5] The exact mechanisms of clofazimine-mediated anti-inflammatory and immunosuppressive activity are unknown. We have suggested previously that they may be related to the pro-oxidative properties of the drug,[6] ie, the ability of clofazimine to stimulate polymorphonuclear leucocyte (PMNL) and macrophage membrane associated oxidative metabolism.[6–8] In this preliminary report the effects of clofazimine on both the spontaneous and leucoattractant-stimulated synthesis of the anti-inflammatory[9,10] immunosuppressive[11] prostaglandin (PG), PG E2, by human PMNL *in vitro* are described.

PMNL-enriched suspensions were prepared as previously described[5] and resuspended to a concentration of 1×10^7/ml in Hanks' balanced salt solution (HBSS). The synthetic chemotactic tripeptide N-formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP, Miles Laboratories Inc, Elkhart, Indiana, USA) at a final pre-determined concentration of 0·1 μM was used as the stimulant of

PG E2 synthesis. Clofazimine was completely solubilized using the following procedure: 10 mg of the drug was dissolved in 0·1 ml of 100% glacial acetic acid and 0·3 ml of 100% dimethyl sulphoxide (DMSO) and brought to 1 ml with 0·6 ml of distilled H_2O. The drug was diluted in distilled H_2O to a concentration of 200 μg/ml followed by addition of 0·1 ml of 1N NaOH, filtration through a 0·2 μm pore size micropore filter and $\frac{1}{10}$ dilution in HBSS to give a stock solution of 20 μg/ml which was brought to pH 7 and centrifuged in a microfuge at 12,000 rpm for 3 min. Solvent controls without clofazimine were identically processed. No residual particulate material relative to control systems could be detected in the clofazimine stock solution by a laser nephelometric procedure. The effects of clofazimine on the spontaneous and stimulated synthesis of PG E2 by human PMNL were measured at final drug concentrations of 1, 2·5, 5 and 10 μg/ml. Reaction mixtures contained 2×10^6 PMNL in a final volume of 1 ml HBSS. After incubation at 37°C/30 min, 1 ml of ice-cold HBSS was added to each tube and the tubes transferred to an ice-bath. After removal of PMNL by centrifugation the supernatants were assayed for PG E2 using a competitive binding radioimmunoassay (RIA) system (New England Nuclear Corp, Boston, Mass, USA). Results are shown in Table 1 and are expressed as p grams PG E2/10^6 PMNL/30 min.

Table 1

Clofazimine concentration	Spontaneous synthesis of PG E2 by PMNL	FMLP-stimulated synthesis of PG E2
Control (no Clofazimine)	5·2 ± 2·1†	13·0 ± 2·1
1 μg/ml Clofazimine	6·0 ± 2·8	25·0 ± 5·6*
2·5 μg/ml Clofazimine	8·6 ± 3·2	52·3 ± 6·5*
5 μg/ml Clofazimine	14·0 ± 3·5*	76·7 ± 6·7*
10 μg/ml Clofazimine	25·1 ± 5·0*	81·3 ± 6·3*

* $P < 0{\cdot}005$ by comparison with the corresponding control (without clofazimine) systems.

† Results as the mean value in p grams PG E2/10^6 PMNL ± SEM of 6 experiments.

Clofazimine at all concentrations tested increased the spontaneous and especially the FMLP-stimulated synthesis of PG E2 by PMNL. Ingestion of 200 mg of clofazimine daily gives peak serum levels of 0·7–1 μg/ml and probably higher tissue concentrations[12] indicating that these effects may be operative *in vivo*. Solvent control systems which were included for each clofazimine concentration did not affect PG E2 synthesis. Likewise clofazimine *per se* did not interfere with the RIA for PG E2 as shown by the inclusion of control systems containing clofazimine only (no PMNL or FMLP).

PG E2 inhibits T-lymphocyte proliferation and antibody production.[11] Likewise pharmacological amounts of PG E2 or its poorly metabolizable analogues relieve nephritis and adjuvant arthritis in animals and eliminate immune complex arthritis.[9, 10] Potentiation of PG E2 production by PMNL, monocytes and macrophages in response to pro-inflammatory stimuli such as leucoattractants and antigens, if operative *in vivo*, is a likely mechanism of clofazimine-mediated anti-inflammatory and immunosuppressive activity.

R ANDERSON

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ADHESIVE LABELS AND ARROWS FOR CLINICAL PHOTOGRAPHY IN LEPROSY

Sir,

Most departments of medical illustration and many others who are experienced in clinical photograpy have used various labels with measuring scales for many years. I have however been surprised to find that many people in the UK are not aware of the existence of adhesive labels and arrows which are ideal for this purpose. Prior to a visit to India on a LEPRA-supported elective period project in 1984, I happened to hear that such labels (originally developed for use in forensic medicine), were available commercially and I tried them out on the skin of patients under conditions of considerable heat and humidity. They adhere well for several minutes and this is more than enough for most purposes in clinical photography. The Standard label, in 'photographic grey', is shown in Figure 1; similar labels in white are also made. Orange-coloured adhesive labels are

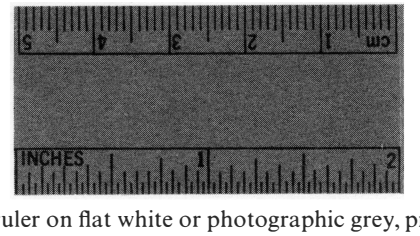

Figure 1. Two-inch/50-mm ruler on flat white or photographic grey, pressure-sensitive paper, with peel-away backing. The patient's name, number, the date and other details can be recorded between the rulings.

produced to draw attention to details. The cost of 50 such labels is £4.00 and they can be obtained in the UK from Wilcare London Ltd, 10 Linden Avenue, Ruislip Manor, Middlesex.

D ANSLEY

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INCUBATION TIME OF RELAPSES AFTER TREATMENT OF PAUCIBACILLARY LEPROSY

Sir,

I write this with reference to the article entitled 'Incubation time of relapses after treatment of paucibacillary leprosy' S R Pattyn (*Lepr Rev* (1984) **55,** 115–120. As the author has mentioned, information on the incubation time of relapse is important in order to plan the follow up period for 'cured' paucibacillary cases.

However, it is difficult to assess the usefulness of the median incubation time as calculated by the author. On one hand there is the influence of the annual increase in the number of discharges to be reckoned with. On the other there is a truncation effect which gives rise to an apparent increase in the number of cases which occur after a short incubation period. I shall attmept to demostrate this problem using the following model.

Table 1

Year of RFC	No. RFC's	No. relapsed 1981	1982	1983	1984	Total
1980	1000	10	10	10	10	40
1981	1000		10	10	10	30
1982	1000	—	—	10	10	20
1983	1000	—	—	—	10	10
Total						100

Table 2

Incubation time	No. replapsed
1 year	40
2 year	30
3 year	20
4 year	10
Total	100

Let us assume that the annual relapse rate among patients released from control is steady at 1% and that every year the same number of patients are released from control (RFC) (Table 1). If we just take into consideration the patients who have relapsed and ignore the population from which they are emerging the result will be as in Table 2.

Even though the annual relapse rate is steady this kind of analysis leads us to believe that 70% of the cases relapse within 2 years and that the median period for relapse is less than 2 years. At any given time there will be more RFC patients who have experienced their Nth year after RFC than those who have gone through their $N \div X$ years after RFC. Hence given a larger pool it is only natural that there will be a larger number of relapses occurring from those who have been released recently even if the relapse rate is the same throughout or increasing slightly. It can also be shown that relatively younger control programmes will show a shorter incubation time as compared to those units which have been going on for several years. Indeed if we were to take into consideration the variation in the number of patients released from a control programme annually the possible effect on the median incubation time calculated in the above manner would be considerable.

Perhaps it would be better to calculate the relapse rate using the person year concept. This would provide information on the probability of relapse for each year after release from control.

J MULIYIL

Leprosy Control Community Health Department
Vellore 632 002
South India

REPLY 'INCUBATION TIME OF RELAPSES AFTER TREATMENT OF PAUCIBACILLARY LEPROSY

Sir,

The comments made by Dr J Muliyil merit serious discussion, because they point towards a fundamentally different approach to the one we have taken.

Dr Muliyil argues that by a constant relapse rate, the median is determined by the truncation of the follow-up. In the artificial data set elaborated by him, the median is less than 1 year if the observation period is only 2 years; is between 1 and 2 years if the observation period is 4 years; and should be between 2 and 3 years if the follow-up is 8 years.

Thus far we agree with Dr Muliyil. But in fact this argument is not pertinent to our study: in a control programme that is running a long time, the relapse rate is exponentially distributed (as our data suggest).

It has to be kept in mind that the data do not come from a cohort study, but from a study in which the intake of patients was spread over many years. The Kaplan–Meier technique allows one to transform this study population into a study of cohort type. The underlying assumption of no cohort effect was made, and is necessary for the correct interpretation of this series.

The problem of truncation is thus virtually non-existent in our data. (We agree that we accepted the assumption of lack of selection bias of the relapsed cases, i.e. that the chance of a relapsed case being detected is not determined by the duration of the programme or by the time interval since the end of the specific antileprosy treatment.) Dr Muliyil suggests that we need to take into account the whole experience of all treated patients. We do not agree for two reasons:

1 The experience of non-relapsed patients does not contribute any information that is relevant to our problem, which is the average length of time between the end of treatment and the relapse. Figure 1 represents the experience of the relapsed patients only, while Figure 2 represents (hypothetically) the relapse experience of all treated patients.

As we are *NOT* interested in the relapse rate itself, Figure 2 is not relevant for our study.

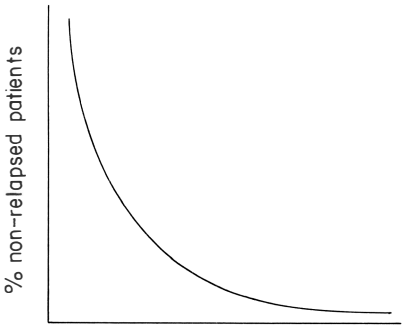

Figure 1. Relapsed patients.

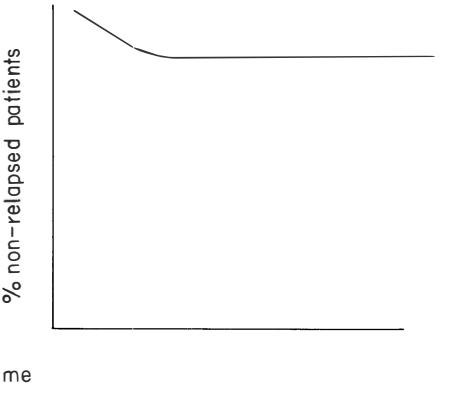

Figure 2. All patients.

2 The determination of the amount of person-years of exposure is NOT a measure of risk, but only of the incidence density of the force of relapsing.

We need the average cumulative incidence of relapsing (given by the median) and its time interval.

The MEDIAN is a good summary statistic of this time-series of relapsing and the determination of the 95% confidence intervals permits inference to a parent population that is similar to our study population. We are thus 95% sure that in any population, similar to our study population, the median relapse rate is not less than $1\frac{1}{4}$ years and not more than 3 years. The limits of the confidence bands would be narrower if the study population were bigger.

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++ A CIBA-GEIGY CONTRIBUTION + TO THE FIGHT AGAINST LEPROSY ++

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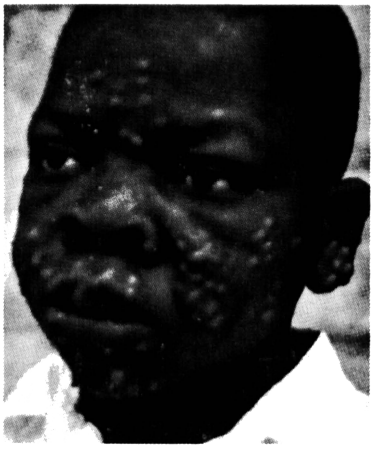

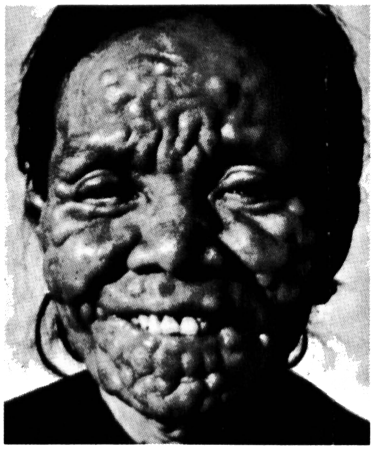

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Lamprene
Capsules of 50 mg and 100 mg

Composition: Clofazimine. *Capsules* of 50 mg and 100 mg. Indications: *Leprosy:* prevention of secondary resistance to sulphones, as well as of lepra reactions in patients with lepromatous (LL) and borderline (BL, BB) leprosy. Treatment for lepromatous (LL) and borderline (BL, BB) forms of leprosy resistant to sulphones. Suppression of lepra reactions, e.g. erythema nodosum leprosum (ENL). Administration and **dosage:** For the treatment of leprosy, Lamprene should be employed in combination with other suitable antileprosy drugs. The dosage of Lamprene must be adapted to the patient's body weight and to the state of activity of the disease. The capsules should preferably be taken during meals or together with milk. *For the prevention of resistance to sulphones and of lepra reactions in cases of lepromatous (LL) and borderline (BL, BB) leprosy:* 50–100 mg Lamprene daily, or 100 mg 3 times weekly, during the first 4–6 months of long-term treatment with dapsone (50–100 mg daily). *In cases resistant to sulphones:* long-term treatment with Lamprene in a dosage of 100 mg daily, combined during the first 2–3 months with rifampicin (®Rimactane, 600 mg daily). *In lepra reactions:* if lepra reactions (e.g. ENL) occur, the basic therapy given hitherto should be continued. To suppress the lepra reactions, Lamprene should be administered under surveillance in relatively large, individually determined doses. The dosage generally recommended is one of 300 mg daily for 3 months. As soon as the lepra reaction has been brought under control, the dosage should be gradually lowered to a level at which its suppressant effect is still just sufficient. Note: Treatment with Lamprene should be given under medical supervision. Daily doses of 300 mg or more should not be administered for longer than 3 months. If gastro-intestinal symptoms develop during treatment with Lamprene, the dosage should be reduced or the interval between doses prolonged. In the event of persistent diarrhoea or vomiting, the patient should be hospitalised. During long-term medication with Lamprene, as well as in patients with a history of liver or kidney disease, it is advisable to perform clinical examinations and tests of hepatic and renal function every 3 months. The use of Lamprene in patients complaining of recurrent abdominal pain, or suffering from damage to the liver or kidneys, should wherever possible be avoided. Unwanted effects: Lamprene is generally well tolerated. The following side effects have been observed: red to brownish-black discolorations. Dryness of the skin, ichthyosis, pruritus, photosensitivity, acneform eruptions, and non-specific skin rashes. Nausea, vomiting, abdominal pain, diarrhoea, anorexia, and loss of weight are encountered chiefly in the presence of accompanying gastro-intestinal diseases or in cases where large doses (> 300 mg) have been used for a prolonged period (> 3 months). Packages: *Lamprene 50:* 100 and 1,000 capsules of 50 mg. *Lamprene 100:* 100 and 1,000 capsules of 100 mg. Further information is available on request.

Rimactane
Capsules of 150 mg and 300 mg

Composition: Rifampicin. *Capsules* of 150 mg and 300 mg. Indications: *Leprosy:* in combination with other antileprosy drugs as treatment for lepromatous and dimorphous (borderline) forms of leprosy, as well as in patients with other forms of leprosy, in whom intolerance of, or resistance to, other antileprosy drugs is encountered. Administration: At least ½ hour before a meal on an empty stomach according to WHO recommendations. Contra-indications: Hypersensitivity to rifamycins. Jaundice associated with reduced bilirubin excretion. Note: Daily treatment with Rimactane is generally better tolerated than intermittent therapy. Resumption of treatment with Rimactane after termination of a course of long-term therapy with the drug involves risks and should therefore, if possible, be avoided. In patients with *liver diseases*, as well as in *severely undernourished patients*, treatment with Rimactane entails a higher risk and its therapeutic benefits should therefore be weighed against the possibility of its causing further damage. If such treatment is necessary, the dosage must be correspondingly reduced. During pregnancy the use of Rimactane should, if possible, be avoided. Rimactane passes into the breast milk. Mothers in whom its use proves unavoidable should refrain from breast-feeding their infants. Unwanted effects: Gastro-intestinal disturbances; disorders of hepatic function, e.g. mild transient elevation of the transaminase values, may occur–chiefly at the start of treatment–but do not generally necessitate discontinuation of the medication; isolated occurrences of jaundice, leucopenia, and eosinophilia; particularly in patients taking Rimactane intermittently or in patients in whom daily treatment is resumed after a temporary interruption, side effects–possibly of immunopathological origin–may take the form of influenza-like symptoms ('flu syndrome) and, in rare instances, of cutaneous manifestations, thrombocytopenia, purpura, and fever, as well as of acute renal failure, dyspnoea, or haemolytic anaemia. If serious complications occur, such as thrombocytopenia, purpura, renal failure, or haemolytic anaemia, treatment with Rimactane should be stopped at once and not reinstituted at a later date. Packages: 8, 16, and 80 capsules of 150 mg; 8 and 40 capsules of 300 mg. Further information is available on request.

1. Chemotherapy of leprosy for control programmes, Report of a WHO Study Group, WHO Technical Report Series 675, WHO, Geneva 1982.
2. S. J. Yawalkar, J. Languillon, S. K. Hajra, A. C. McDougall, S. Gosh, D. V. A. Opromolla, C. J. S. Tonello. Once-monthly rifampicin plus daily dapsone in initial treatment of lepromatous leprosy. Lancet 1199, 29 May 1982.

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