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Editorial

The number of pages in this and other issues of *Leprosy Review* devoted to reports on various surgical aspects of leprosy is to be taken as an indication of interest rather than as a recommendation of emphasis. The importance of adequate medical treatment following early diagnosis of leprosy remains unchanged, and the theoretical ideal—at present generally unattainable—of prevention of preventible deformity must ever be in the forefront of the thinking of health planners and practical leprologists.

It is only in rare instances, however, that the men, the means and the vision are concurrently available for leprosy programmes that enshrine the ideal. Most readers who have to grapple with the day-to-day problems of diagnosis and management, of organizing and supervising, are facing both a regrettable repetition of the sad story of neurological deficit resulting in neuropathic atrophy and ulceration, and a sizeable backlog of physical handicaps of one sort and another due to untreated leprosy. It is hoped that the publication of good work in research, treatment and prevention may prove helpful and stimulating to the specialist reconstructive surgeon and the "jobbing surgeon".

The earlier enthusiasms and popularizings that surfaced after the pioneering efforts of Brand had received their due acclaim, have given place to a more sober appraisal of the place of reconstructive surgery in the whole programme of leprosy treatment and control. However attractive and technically challenging the problems posed by deformity in leprosy, and however valuable to the leprosy campaign the "before-and-after" visually convincing results of reconstructive or plastic operations, leprosy is still basically a medical and an epidemiological problem (with, of course, its attendant social repercussions), and the continued occurrence of "surgical" complications and sequelae is a measure of our medical ignorance or administrative short-sightedness. We can see the value to the individual sufferer, and to the community, of some kind of surgically-orientated rehabilitation scheme, incorporated into a leprosy control programme, but we can also see the importance of so treating leprosy as to obviate the need for surgical and social rehabilitation. The amplitude of the swinging pendulum is much less, and also much less jerky, than it was.

Here and there, the backlog of deformity has been tackled with commendable competence and determination. In Carville, Louisiana, a succession of surgeons, drawing on consultative skills at nearby Tulane, have been at the disposal of the handicapped. Hay Ling Chau is coming to the end of its rôle as a reconstructive agency as the Hong Kong Government takes over the irrecuperably deformed and the manageable accession of patients with new infections. The excellent work of Carayon and his colleagues at Dakar, Bamako, Marseilles and elsewhere is becoming more widely known, and elsewhere in this issue (p. 122) we refer to the prize-winning report by Van Droogenbroeck of his work in Korea. Similarly, the

government-sponsored and mission-aided surgical rehabilitation programme in Papua and New Guinea, which owes much to the inspiration of Clezy, has made commendable inroads on the accumulated deformities due to leprosy.

These situations, however, are rare and atypical. The more usual problem is the volume, often unsuspected, of deformity due to leprosy and the dearth of means available for tackling it. The average leprosy programme planner has not yet grasped what can be done, within the imposed limitations of time and staff and money, to adopt and adapt the basic principles of reconstructive surgery and prev ntive rehabilitation.

There is evident, too, a certain disillusionment, a kind of rebound phenomenon, in the application of surgical techniques to the deformities of leprosy. The over-enthusiasm of a few has resulted in a misplaced emphasis that views leprosy as a "surgical disease". Not only has attention been diverted from the gnawing problem of new infections, but the improvements resulting from surgical interventions have often been illusory or short-lived: the continuing incubus and tragedy of unrelieved sensory deficit has not always been appreciated by patient and surgeon alike. A good anatomical result does not necessarily mean perfect functional restoration. Careful selection of cases, consideration of the patient's real needs and the enlistment of his co-operation at all stages, adequate physiotherapy and good n rsing both before and after operation, and the timely provision of prostheses these very obvious desiderata have not always been respected, despite the act that the workers at Karigiri, Addis Ababa, Hong Kong and elsewhere have for years been emphasizing their importance.

What, then, is the outlook for today? Where lies the middle way between an extensively equipped Surgical Rehabilitation Unit dealing with a mere handful of patients whose physical deformities are due to neglected leprosy, and a leprosy control programme integrated into the general health services whose resources do not appear to permit of even the sketchiest attempts at reconstructive surgery? Wherever possible some kind of expertise should be available at every central hospital of every leprosy scheme. It may be that one of the doctors in charge (or the only doctor) will attempt to become proficient at the more ordinary surgical tasks–dealing with such conditions as neuropathic foot ulceration, and to perform tibialis transfer for drop-foot deformity, operations on peripheral nerve trunks, tarsorrhaphy for lagophthalmos, etc. With the help of such a manual as Fritschi's *Reconstructive Surgery in Leprosy* [see *Leprosy Review* (1971) **42**(4), 290], and a short apprenticeship under an experienced surgeon, the average medical practitioner can become reasonably competent. Such a pattern obtains in L PRA'S project in Malawi, and would be applicable elsewhere.

For more complicated surgical procedures, such as operations for flail foot, tendon transfer operations for the various degrees of claw hand, temporalis transfer for severe lagophthalmos, and the more demanding techniques of plastic surgery, longer training is necessary, and not all doctors have the requisite flair or potential. This training may be had in such institutions as Karigiri (South India), and ALERT (Addis Ababa), and individual surgeons with special interest and experience have from time to time taken pupils under their wing. On-the-job training has been given by surgeons well versed in the techniques of reconstructive surgery as applied to leprosy, during extended visits paid to different centres; surgical techniques have been demonstrated, and physiotherapeutic and prosthetic services have been inaugurated. Special courses have occasionally been given to groups of young general orthopaedic surgeons hoping to devote time to the surgery of leprosy.

Although many of the problems of reconstructive surgery in leprosy require rather special knowledge and techniques, the bulk of them may be handled satisfactorily in a Rehabilitation Unit dealing with other crippling diseases and conditions, such as congenital deformities, poliomyelitis, tuberculosis, accidents (road, domestic, factory, mine or forest). The "segregation" of leprosy should not be perpetuated or fostered by the provision of facilities tending to take leprosy out of the main stream of surgery and rehabilitation.

Many of the practical problems confronting the surgeon may be seen either as a challenge to his technical and operative skill, or as a stimulus to his enquiring mind. The pathology of nerve damage, the histopathology and immunology of tissue response in nerves and muscles and bones, the patterns of motor, sensory and sudomotor deficit—all pose unsolved problems with intensely practical sequelae. The pathways pioneered by Antia, Brand, and Carayon are now being trodden by Ranney, Warren, and their colleagues. There is plenty of room for others.

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News and Notes

ARMAUER HANSEN CENTENARY

Plans are afoot in various countries to commemorate the centenary of Hansen's discovery of *Mycobacterium leprae* and identifying it as the cause of leprosy.

In Norway, the Tenth International Leprosy Congress (to be held in Bergen from 13 to 18 August, 1973) will mark the occasion by special ceremonies both at the Jorgen Hospital (where Hansen worked) and at the commemorative bust displayed in a central park. It is hoped that His Majesty the King of Norway will grace the occasion with his presence. In addition, two postage stamps will be issued (0.80 kr. and 1.20 kr.) bearing the likeness of Hansen and a representation of acid-fast bacilli. These stamps will be issued on first day covers on 28 February, 1973, and a special dated cancellation design will be in use during the Congress for mail posted from the Congress.

In India, a stamp will be issued in July, 1973, and the Hind Kusht Nivaran Sangh will be distributing publicity material at the same time.

In Argentina, thanks to the inspiration and drive of Drs L. M. Balina, J. E. Cordama and J. C. Gatti, the centenary is to be marked by special lectures and seminars on Hansen, and an essay competition open to residents in Argentina: the prize will be announced during the International Leprosy Congress. A bust of Hansen will be unveiled in a prominent place, and a street named after him.

DR GRACE WARREN, MASTER OF SURGERY

The University of Sydney has accepted the thesis submitted by Dr Grace Warren entitled "Patterns of Tarsal Disintegration in Leprosy" as of sufficient merit to warrant the award of the degree of Master of Surgery.

Leprosy Review sends to Dr Warren its hearty congratulations. The thesis embodies research, spread over several years and adequately documented with serial radiographs, into the varieties of tarsal disintegration occurring in leprosy, the factors involved and the management advocated. It is hoped that the essentials of the thesis may find their way into the literature at an early date, so that all those concerned with these problems may profit from the unique experience of Dr Warren. Perhaps in view of the forthcoming closure of the Leprosy Mission's institution on Hay Ling Chau (The Isle of Happy Healing), Hong Kong, founded by Dr Neil Fraser, the specialized services of the newly-appointed Master of Surgery may be made available to other centres in South-east Asia.

THE BRODEN-RODHAIN PRIZE, 1969-70

We learn with pleasure that the Broden-Rodhain Prize, which is granted on the recommendation of the Belgian Society of Tropical Medicine, has been awarded for the years 1969-70 to Dr J. B. A. Van Droogenbroeck in respect of the work

presented in the article entitled "The surgical treatment of lower facial palsy in leprosy", which appeared in the *Annales de la Société belge de Médecine tropicale* (1970) **50**, 653-688 [see abstract in *Leprosy Review* (1971) **42**, 2, 140]. This first-class work, ably presented, was done in connection with the Leprosarium at Sorokdo, South Korea.

Leprosy Review extends its warm congratulations to Dr Van Droogenbroeck, and is gratified to see that good work done in the field of leprosy does not go unnoticed.

LEPROSY IN MALTA

The Annual Report for the year 1971 of the Chief Medical Officer of the Department of Health, Malta, provides up-to-date figures for leprosy. In St Bartholomew Hospital, there were 41 in-patients, 24 of them males; one only was admitted during the year, and none discharged. A total of 182 patients (159 males) are receiving out-patient treatment, in Malta (159 patients) and in Gozo (23). Of 223 patients under treatment for active disease, 36 are classified as having lepromatous leprosy, 30 the indeterminate, and 19 the tuberculoid form.

The Report embodies a certain scepticism regarding the possibility of ever eradicating the infection from the patient, and advocates life-long treatment for apparently cured patients who have had lepromatous leprosy. Due emphasis is given to the importance of social factors in the persistence of leprosy on the island.

LEPROSY IN GUYANA

The Annual Report of the Guyana Leprosy Control Programme for the year 1971 gives evidence of a "new look" advocated with enthusiasm and conviction, and accepted and adopted wholeheartedly. In a population of about 714,000, the estimated prevalence of leprosy may be as high as 2.4 per 1000. Hitherto the difficulties of control in a multi-racial population, unaccustomed to persisting with treatment for a chronic disease and subject to various taboos and misconceptions regarding leprosy, have rendered almost impossible any serious attempt at early diagnosis, the tracing of contacts, and laboratory cover.

Lady (Dr) Patricia Rose has tackled the problem with courage. She has enlisted the help of patients (including the chronically sick inmates of the "Mahaica Community"), volunteers and lay well-wishers. A Public Health Clinic has been built and furnished in the grounds of the Georgetown Hospital. A new spirit has shattered the complacency and fatalism of the 300 patients at Mahaica. The domiciliary treatment programme, with its laboratory confirmatory investigations, contact examination, records, and regular medical control, has got off to an excellent start, and strenuous efforts are being made to trace the numerous defaulters and those "lost to control" over the years.

LEPROSY IN THE REPUBLIC OF SOUTH AFRICA

According to the Annual Report of the Department of Health of the Republic of South Africa, 749 notifications of leprosy were received during 1970. All occurred in people classed as "Bantu", except for 4 seen in "coloured", 2 in

"whites" and 1 "Asian". In-patient facilities are provided at the Westfort Leprosarium, near Pretoria, but the majority of patients receive treatment near their homes.

In the Bantu Homelands, we note, "planning was commenced on a comprehensive community-based and hospital-centred health service to provide complete health care for the individual, combining both the preventive and the curative aspects of health". It is hoped that those suffering from leprosy may profit from the facilities when they are created.

LEPROSY IN IRAN

Since the publication of the news item in a previous issue of *Leprosy Review* (1971) **42**, p. 153, under the above title, word has been received of the death of His Excellency Dr A. H. Radji, Acting Director, *Bureau de l'Association d'Assistance aux Lépreux* in Tehran. The cause of leprosy in Iran owes much to the vision, energy and essential friendliness of Dr Radji, and he will be much missed. Dr N. A. Siyadat has taken over the functions of Executive Director of the *Bureau*.

A contract has recently been signed with the *Compagnie Internationale de Développement Rural* (of France), whereby the services of six expatriate medical workers will be made available for work in the Mehrabkhan Sanatorium at Mashad, their salaries and local expenses being a charge on the Iranian Association.

So far, no leprologist or ophthalmologist has been found to join the team. Any readers, preferably French-speaking, who by their experience and availability might be interested in a two-year contract, are invited to get into touch with

Dr R. G. D. Garrigue,
Maison Médicale de l'Ermitage,
60 Autreches,
France.

LEPROSY NEWS FROM UGANDA

The first meeting of the newly-appointed Leprosy Advisory Committee, whose duty is to consider and co-ordinate all leprosy measures in the country, took place in March, 1972.

AN ANTI-LEPROSY SCHEME FOR PAKISTAN

Following the First National Pakistan Leprosy Congress of February, 1971 [*Leprosy Review* (1971) **42**(2), 85], Dr Ruth Pfau, Dr Zarina Fazelbhoy and their colleagues at the Marie Adelaide Leprosy Centre in Karachi have drawn up a comprehensive report on the state of leprosy in Pakistan, including estimated prevalence rates, and existing treatment facilities. The gaps in knowledge and in coverage are indicated. The earlier estimates of prevalence in the former "West Wing" of Pakistan were probably too high, and a figure of 40,000 to 50,000 is now considered to be more realistic. Since 48% of patients presenting for treatment in Karachi are immigrants from highly endemic areas of India, the prevalence in the rest of the country—apart from two small endemic foci in the sparsely-populated mountainous northern region—is probably similar to that in neighbouring Punjab.

Tremendous strides have been made to ascertain the real prevalence of leprosy in all the States, and itinerant treatment programmes have been established, but still the coverage is far from complete.

Voluntary agencies have played a significant rôle in fostering and financing the outreach from the Marie Adelaide Centre. There are some indications that both Government and the medical schools are taking an interest in leprosy.

LEPROSY IN VIETNAM

Despite the overwhelming stresses of war in Vietnam, health officials are making great progress in their efforts to control the serious public health problem of leprosy in that country, according to Dr Oliver W. Hasselblad, President of American Leprosy Missions, Inc., who has just returned from a month spent as leprosy consultant there.

There are more than 25,000 registered cases of leprosy in the country. The prevalence rate varies widely: in some areas it is as high as 50 per 1000.

One of the encouraging advances in the Vietnam control programme is the trend towards integrating leprosy into the public health services. The official leprosy programme of the Health Plan calls for this integration, initially at the provincial hospitals and later extending to the district health services. Regional health inspectors, province medicine chiefs, and hospital directors are co-operating with the new leprosy programme, and a number of provincial hospitals have already set up leprosy out-patient clinics.

In Saigon the large Government institution, Cho-Quon Hospital, has transformed its leprosy out-patient department into a skin clinic in which all diseases affecting the skin, including leprosy, are diagnosed and treated. Some 6000 cases of leprosy are registered at the clinic. The trend toward accepting leprosy as an integral part of medical science is also apparent in teaching institutions. Both the University of Saigon School of Medicine and the National Institute of Public Health will include leprosy in their curricula.

In May, 1972, Dr Olaf K. Skinsnes gave the second of an annual lecture series on all aspects of leprosy at the Saigon Medical School. He also lectured and led seminars and clinical demonstrations for a specially chosen group of regional, provincial, and military personnel. Nurses and health technicians in hospitals and clinics in the provinces are also getting instruction about leprosy at the Cho-Quon Hospital.

One of the gravest problems of the civilian health services, and especially of the leprosy control programme, is the shortage of qualified personnel. To help provide the needed additional man-power, a plan to train former leprosy patients as auxiliary workers is being considered in some areas. Such training would not only fill an urgent need, but would help to rehabilitate unemployed ex-patients.

In addition to working with the Health Ministry on plans to implement the recommendations he made after his 1970 survey, Dr Hasselblad visited many major leprosy centres, government hospitals and clinics, despite the difficulties, and saw a large number of patients in their homes. A pilot project of leprosy control is to be initiated in Ba-Xuyen Province as a result.

Another encouraging development in leprosy control is the increasing co-operation of voluntary and mission agencies with the Government's control programme. American Leprosy Mission Inc., besides providing Dr Hasselblad's services to the government programme, has helped in many other ways.

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Comments on the Chemotherapy of Leprosy as Influenced by Present Knowledge of *Mycobacterium leprae**

S. R. PATTYN

Professor of Bacteriology,
Instituut voor Tropische Geneeskunde Prins Leopold,
Antwerp, Belgium

The chemotherapy of leprosy can now be based on firm laboratory knowledge about the responsible agent, *Myco. leprae*, and the general principles applied in the management of tuberculosis. First-line and second-line drugs may be distinguished. At present there is no need to change the existing dosage of 600 mg of dapsone (DDS) per week for mass campaigns.

Efforts should be made to find new treatment schedules leading to increased supervision by the application of intermittent therapy. In lepromatous cases, this intermittent schedule will probably have to be preceded by a preliminary course of continued therapy. It is possible that the use of rifampicin will appreciably shorten the period of treatment.

Introduction

Although an increasing number of new drugs have been introduced in the therapy of leprosy during the last three decades, their choice has been largely empirical, due to lack of knowledge about the responsible organism, *Mycobacterium leprae*, and the pathogenesis of the disease.

In the last 10 years, however, as a result of laboratory investigations, our knowledge and understanding of leprosy have increased more than in the 87 years between 1873 (when *Myco. leprae* was discovered) and 1960. In the latter year Shepard (1960a, b, 1962) demonstrated, using precisely defined conditions, that *Myco. leprae* multiplied in the footpads of mice. The second important discovery—the cellular type of immunity involved in leprosy—was made by Rees (Rees, 1966; Rees *et al.*, 1967) who showed that a generalized infection resulted when thymectomized and irradiated mice were inoculated with *Myco. leprae*. Several authors have since shown that a cell-mediated type of immunity is involved in the human disease (Dierks and Shepard, 1968; Shepard, 1968; Turk and Waters, 1969).

These discoveries revealed new features about *Myco. leprae*, such as its long generation time (Shepard and McRae, 1965), the interpretation of irregularly stained organisms (Rees *et al.*, 1960; Rees and Valentine, 1962; Shepard and McRae, 1965) and their quantitative assessment, using the Morphological Index

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(M.I.). Moreover, a more accurate histo-pathological classification of the various forms of human leprosy was evolved by Ridley and Jopling (1966) by including immunological features of the disease. Finally, for the first time a rational approach to the evaluation of antileprosy drugs in mice and man was developed by including all these new parameters.

In mice, antileprosy drugs can be assessed in three ways: (1) by the continuous method (Shepard and Chang, 1962; Pattyn and Rooyackers, 1965; Rees, 1967a; Gaugas, 1967); (2) by the kinetic method; and (3) by treatment of an established infection (Shepard and Chang, 1967). In man, the activity of antileprosy drugs can be monitored by the regular inoculation into mice of *Myco. leprae* obtained from human biopsies taken during treatment (Shepard *et al.*, 1968, 1969; Levy *et al.*, 1969; Rees *et al.*, 1970). These methods have revealed: (a) the time necessary for drugs to kill *Myco. leprae* (Shepard *et al.*, 1968; Rees *et al.*, 1970); (b) the existence of drug-resistant strains of *Myco. leprae* (Pettit *et al.*, 1964, 1966a, b; Rees, 1967b; Pearson *et al.*, 1968; Shepard *et al.*, 1969); (c) the correlation existing between irregularly-stained forms of the bacilli and their inability to multiply, proving that non-solid *Myco. leprae* are dead.

There has been some divergence of opinion, and even scepticism, about the significance of the percentage of non-solid forms of the bacilli (Convit *et al.*, 1970). Indeed, all morphological assessment is subjective. Therefore standard techniques in fixation, staining, observation and scoring must be used for determining the M.I. Perhaps some future histochemical method will supersede the counting of solidly staining (living) bacilli. At present the morphological criterion can only be checked by mouse inoculation, a technique that is entirely reliable (Levy *et al.*, 1970).

This newly acquired knowledge about *Myco. leprae,* together with advances made in the management of tuberculosis, another chronic infectious disease, now provide a rational basis for studying leprosy therapy. In the chemotherapy of tuberculosis, experience has shown that successful or unsuccessful therapy, relapse, or drug resistance, is determined by the biological behaviour of the causative organism and the pharmacokinetics and pharmacology of the drugs used. Studies of all these aspects, together with controlled clinical trials, have led step by step to the development of completely successful therapeutic regimens, of which the latest is based on intermittent therapy (after an initial continuous period) allowing complete supervision (Stradling and Poole, 1963, 1970). While the importance of maintaining the prescribed therapy throughout for the successful treatment of chronic infections has been particularly appreciated and employed in tuberculosis, similar considerations seem to have been less rigorously applied to the treatment of leprosy.

There are three factors to be taken into account in planning a rational approach to drug therapy of chronic infections in general, and leprosy in particular. These are discussed below under the headings: the bacillus, the host, and the drug.

The Three Interacting Factors in Drug Therapy

THE BACILLUS

For a correct interpretation of events during the therapy of leprosy, the notion that non-solidly staining bacilli are incapable of multiplication is of great importance. It is now certain that, while a population of *Myco. leprae* may be killed by treatment within a few weeks or months, it may take 5 years or more

for the bacilli to disappear from the skin or nasal mucosa. Thus the M.I. (if necessary checked by inoculation of bacilli from treated patients into mice) is of primary importance for following the effect of treatment (Shepard *et al.*, 1968, 1969; Levy *et al.*, 1969; Rees *et al.*, 1970).

Since multiplication of *Myco. leprae* in the mouse footpad is limited to inocula of 10^4 to 5×10^4 bacilli and the minimal infectious dose is between 3 and 10 organisms (Shepard and McRae, 1965), the sensitivity of the technique is of the order of 1/1000 living bacilli.

The total bacillary population of a patient at the start of treatment not only determines the severity of the disease but also the number of pre-treatment drug-resistant bacilli. Indeed, in every bacterial population there exist resistant mutants to any drug, but these spontaneous mutants ("pre-treatment resisters") have an advantage over the larger, sensitive part of the population only when exposed to the drug. For most pathogenic organisms, such as *Myco. tuberculosis*, the frequency and level of drug-resistant mutants can be measured *in vitro* by counting the number of colonies in media containing known concentrations of the drug and seeded with known numbers of organisms (Canetti *et al.*, 1961). In general, the frequency of such pre-treatment resistant organisms is of the order of 1 in 10^6 to 10^8. However, although similar *in vitro* determinations are not possible for *Myco. leprae*, drug resistance can be expected to arise in multi-bacillary types of leprosy (LL-BB) with between 10^{10} and 10^{12} organisms; but this is unlikely in the paucibacillary types (BT-TT).

The level of drug resistance of the "pre-treatment resisters" is also unknown for *Myco. leprae*. However, the large population of bacilli obtained in the immunologically deficient mouse might be sufficient to determine the level of drug resistance of these mutants. From available clinical data it appears that the degree of drug resistance is variable (Rees, 1967a, b; Pearson *et al.*, 1968).

THE IMMUNOLOGICAL COMPETENCE OF THE HOST

In the chemotherapy of most infectious diseases, the drug used accounts for the killing of the majority of the bacteria, while the defence mechanisms of the host deal with the remainder. In tuberculosis (Canetti, 1965), these residual organisms (drug-sensitive or drug-resistant) may persist, sometimes apparently in a dormant state, for a long time. In this situation, these organisms may begin to multiply again at any moment after treatment has ceased, and the patient relapses with a drug-sensitive or a drug-resistant infection.

In the patient with the lepromatous type of leprosy, the host has little or no capacity to destroy bacilli, and therefore *all* persisting and viable organisms will multiply again when treatment is stopped. This accounts for the high relapse rates reported in lepromatous leprosy: 12% in India (Vellut, 1968) and 25% in Latin America (Bechelli *et al.*, 1970), and Hemerijckx (personal communication) recommends that lepromatous patients should be treated for life.

THE DRUG

(a) *Minimal Inhibitory Concentration* (M.I.C.). The M.I.C. of many drugs against *Myco. leprae* can now be determined by the mouse footpad technique. The results (Table 1) show that there is no correlation between the antibacterial activity of drugs against *Myco. tuberculosis* or *Myco. lepraemurium* and *Myco. leprae*.

(b) *Serum concentration and half-life of the drug.* This may show considerable individual variation, and therefore the lowest figures known are given (Table 1).

TABLE 1

M.I.C. for several antileprosy drugs compared with serum concentrations obtained after current dosage

Drug	M.I.C. (μg/ml)	Dosage	Frequency	Serum concentration (μg/ml)	X
DDS	0.02-0.002	100	Daily	2	100
DADDS	id.	225 mg	1/77 days	0.06	3
Sulfadimethoxine	20	1.5 g	Daily	150-300	4-15
Sulfadoxine	20	1.5 g	1/week	150-300	4-15
Sulfamethoxypyridazine	0-35?	750 mg	1/2 days	30-40	4-15
Clofazimine	Current dosage is 100-200 mg per day Minimal effective dosage in man calculated to correspond to 7 mg per day				
Thiambutosine	?	3 g repository 2 g	Daily 1/week	?	
Ethionamide	25	250 mg	Daily	20-30	1

Genetic polymorphism in man has recently been described for the acetylation of dapsone (=inactivation) comparable to that shown for isoniazid (INH) (Gelber *et al.*, 1969) and may be of practical importance when intermittent or low dosage DDS is administered, as was the case in intermittent treatment of tuberculosis with INH (Tuberculosis Chemotherapy Centre, Madras, 1970).

Another important point is the rate at which drugs kill *Myco. leprae*, for which the following results are available:

DDS: 90 days (Shepard *et al.*, 1967, 1968)
Clofazimine (including DDS-resistant strains): more than 105 days (Levy *et al.*, 1969)
Rifampicin: 3 to 24 days (Rees *et al.*, 1970).

Thus, if a patient is treated with a drug having a high therapeutic activity, and he does not improve, or after some period of improvement there is clinical and bacteriological deterioration, there are only two explanations: either the infecting organism was or has become drug-resistant, or the patient failed to take or absorb the prescribed treatment (Poole and Stradling, 1960). This leads to the rather astonishing conclusion that in many cases the only advantage to be gained from determining the drug sensitivity of bacilli during treatment may be to demonstrate that the patient is taking the drug (McDermott, cited in Canetti, 1965). The persistent failure of leprosy patients to take their drugs regularly has been particularly well investigated by Pettit *et al.*, (1966); some patients with lepromatous leprosy still active after more than 10 years' residence and treatment in a leprosarium, improved when the treatment was adequately supervised.

The Possible Application of Principles Used in the Chemotherapy of Tuberculosis

In the chemotherapy of tuberculosis a distinction is made between first-line drugs (low M.I.C., sustained serum levels many times higher than the M.I.C., minimum toxicity, and low incidence of pre-treatment resistant organisms) and

second-line drugs (high M.I.C. and relatively low serum levels of shorter duration, resulting in more frequent resistance and/or higher toxicity). Treatment of multibacillary cases of tuberculosis with cavitation should always be initiated with 2 (preferably 3) major drugs in order to diminish the risk of the emergence of drug resistance, the frequency of double or triple drug resistance being of the order of 10^{-12} to 10^{-18}. After a preliminary period of continuous double or triple treatment, reducing bacterial numbers drastically and thus the possibility of drug resistance, long-term monotherapy can safely be given (Canetti, 1968). To ensure that the drugs are being taken treatment should be supervised, and for practical purposes this is easier to achieve by an intermittent, rather than a daily, regimen (Poole *et al.*, 1960; Stradling *et al.*, 1963, 1970). Moreover, intermittent therapy has a theoretical advantage, because contact between the micro-organism and the drug is discontinuous. Thus the surviving organisms do not multiply again immediately, but only after a lag phase. This phenomenon has been demonstrated experimentally both *in vitro* and *in vivo* (Dickinson, 1968; Canetti, 1968). Experimental studies with *Myco. leprae* on intermittent therapy in mice (Rees, 1965, 1967), using Shepard's kinetic methods (Levy, 1970), suggest that this phenomenon applies equally to leprosy.

Treatment of Leprosy

DAPSONE

The activity of substituted sulphones is entirely due to dapsone (4,4-diamino-diphenylsulphone, DDS), either liberated after administration or occurring as an impurity in some preparations (Shepard, 1969a; Shepard *et al.*, 1969). The M.I.C. of dapsone for *Myco. leprae* is of the order of 0.02 μg per ml serum, as determined by means of the mouse footpad model (Shepard *et al.*, 1966; Shepard, 1967b; Rees, 1967). Because the metabolism of dapsone is similar in mouse and in man, the results obtained in the mouse are directly applicable to man. Experiments in man have shown this to be the case. Thus, the administration of 1 mg of dapsone daily, or the intramuscular injection of 225 mg of acedapsone (acetyl-diaminodiphenylsulphone, DADDS) every 77 days, produced respectively serum levels of 0.02 and 0.06 μg per ml of dapsone and proved effective in the treatment of leprosy in man (Shepard *et al.*, 1968; Waters *et al.*, 1968).

When dapsone was introduced for the treatment of leprosy 30 years ago the dose chosen was based on the maximum amount tolerable (100 mg daily), because then the mouse model was not available (Lowe, 1954a, b). It is now proven that this dose produces serum levels of dapsone 100- to 300-fold the M.I.C. for *Myco. leprae*. Present results in mouse and man suggest that therapeutically the dose of dapsone could be reduced, but lower doses might increase the incidence of drug resistance.

The observations of Pettit *et al.* (1966), Shepard *et al.* (1969), and Browne (1969) have shown that DDS resistance can occur in some lepromatous patients on standard, irregular, or smaller (50 mg twice weekly) doses of dapsone. Resistance may well arise if acedapsone, 225 mg every 77 days, is used on a large scale. However, because of the long generation time of *Myco. leprae*, it may take 3 or more years before dapsone-resistant mutants give rise to clinical evidence of relapse. The rarity of dapsone resistance noted during the 30 years of standard dapsone monotherapy is probably because there are very few high-resistant mutants capable of growing at the high concentrations of dapsone obtained.

For the treatment of tuberculoid leprosy, in which there is a small bacterial population and therefore fewer resistant mutants than in patients with lepromatous leprosy, lower doses of dapsone (1/10th of the standard dose) could be adequate. However, because of the low cost and low toxicity of dapsone in the standard dosage, smaller doses would have no practical advantages, whereas one standard dose for all types of leprosy would be advantageous.

For the treatment of lepromatous leprosy, lower doses of dapsone are much more likely to give rise to resistance, particularly if taken irregularly. Therefore lower doses of dapsone in lepromatous leprosy could be justified only when preceded by an initial period of standard doses (100 mg) intended to diminish the bacterial load considerably without danger of selection of resistant organisms. Lower doses are also justified when they are attained by intermittent therapy and therefore increase the possibility of supervised treatment. It is possible that, in the past, standard doses of dapsone (100 mg daily) were curative even in those patients who, after an initial period of regular treatment, became irregular, but took sufficient dapsone to produce active drug levels in the serum. This possibility is based on the fact that serum levels of dapsone obtained from standard treatment are 100- to 300-fold greater than the M.I.C. of dapsone for *Myco. leprae*.

Thus it would seem important to initiate controlled clinical trials in patients with lepromatous leprosy, with 4 to 6 months high dose (100 mg) continuous dapsone therapy, followed by supervised intermittent therapy, for example, 25 mg dapsone twice weekly *per os*, or once weekly long-acting sulphonamides, or injections of acedapsone (DADDS) every 77 days (Shepard *et al.*, 1968).

As has already been mentioned, relapses can be due either to drug-sensitive persisters multiplying after therapy has been stopped, or to the emergence of drug-resistant mutants. To determine the cause of such relapses, the sensitivity of the organisms can be tested in the mouse. However, the patient who has relapsed should also be put on a supervised test-period for 3 months on full-dose dapsone and any change in the morphological index used as an indirect method to detect a dapsone-sensitive or dapsone-resistant infection. This clinical method is more rapid than the mouse test. If it is confirmed that the histoid type of leprosy is always associated with dapsone-resistant organisms (Rodriguez, 1969), histopathological examination would rapidly resolve the question.

LONG-ACTING SULPHONAMIDES

Sulphones and sulphonamides both interfere with folate metabolism (Shepard, 1967) and cross-resistance between the two types of drug exists (Adams and Waters, 1966). Some sulphonamides were tried in the treatment of leprosy before the sulphone era (Schneider *et al.*, 1959); they were reintroduced as a result of a chance observation (Schneider *et al.*, 1959). The dose of sulphonamides for leprosy was chosen empirically and resulted in serum levels of 30 to 40 μg per ml (Schneider *et al.*, 1959; Languillon, 1964; Languillon and Carayon, 1969). Ellard *et al.* (1970) found the M.I.C. against *Myco. leprae* in the mouse for sulphadimethoxine and sulphadoxine to be 20 and 35 μg per ml respectively, and the calculated serum levels attained in man with these two drugs to be 150 and 300 μg per ml respectively. Since these serum levels are only 4 to 15 times higher than the M.I.C., Ellard *et al.* (1970) warned that sulphonamide resistance and, because of cross-resistance, sulphone resistance might result from treating patients with lepromatous leprosy with these drugs. Sulphonamide resistance has been

observed in man (Merklen *et al.*, 1968) and most authors (Schneider *et al.*, 1959; Litalien *et al.*, 1961; Languillon, 1964) consider sulphonamide treatment to give better results in tuberculoid than in lepromatous leprosy. The laboratory findings indicate that the use of long-acting sulphonamides should be limited to the treatment of tuberculoid leprosy, and, in lepromatous leprosy, as intermittent therapy following initial treatment with a bactericidal drug.

CLOFAZIMINE (B663)

Current dosage, again empirically determined, has been between 100 and 200 mg per day. Since this drug has different affinities for different tissues, dosage cannot be based on the M.I.C. and serum levels. However, Shepard (1969b) calculated the minimal effective dosage in man to be 7 mg per day. Studies by Levy *et al.* (1969) on the killing rate of *Myco. leprae* by clofazimine showed it to be somewhat slower than that of dapsone. Clofazimine is an important drug because of its low toxicity, high activity, and absence of cross-resistance with the sulphones or sulphonamides. Its great disadvantage is the skin pigmentation it induces, which is unacceptable to many patients. Some patients, however, appreciate this discoloration (Renders, 1968), and on the other hand it confirms that the patient is taking the drug.

Where skin pigmentation is a major obstacle, a dose of 200 mg per week (Waters *et al.*, 1968) would probably be adequate for patients with tuberculoid leprosy or as a secondary drug for patients with lepromatous leprosy following initial therapy with a bactericidal drug. Controlled trials along these lines seem indicated.

RIFAMPICIN

The M.I.C. of rifampicin for *Myco. leprae* has not yet been determined. However, its extraordinarily rapid killing effect on *Myco. leprae* is well known. Thus, it has been observed both in man (Rees *et al.*, 1970; Leiker *et al.*, 1970, and our own unpublished observations) and in the mouse (Shepard, 1971) that 2 days' treatment with rifampicin is as effective as 2 to 3 months of dapsone. Grumbach *et al.* (1969) considered that, for tuberculosis, rifampicin, in spite of its price, would be advantageous by shortening the duration of therapy. Future studies will determine whether a relatively short course of rifampicin will cure tuberculoid leprosy. In lepromatous leprosy, rifampicin might with advantage be given initially and continuously for a relatively short period, say 3 months, followed by intermittent treatment with either acedapsone, a sulphonamide, or clofazimine. Laboratory controlled treatment schemes along these lines are recommended.

THIAMBUTOSINE (DPT)–THIACETAZONE (TB1)–ETHIONAMIDE

The appearance of resistance to these drugs after 1 to 2 years of treatment is a regular phenomenon (Lowe, 1954b; Davey, 1955, 1960) and many resistant strains have been isolated in mice (Shepard, 1969; Rees, 1967b; Pattyn *et al.*, 1965). This must be due to the low serum levels attained with the current dosages and these cannot be increased because of the high risk of toxic side-effects (Cochrane and Davey, 1964). Thus thiambutosine is only a "second line drug" for leprosy; it took many years to reach this conclusion, despite the fact that thiambutosine was the second antileprosy drug discovered. The delay was due to the lack of suitable laboratory techniques which are now available. Ethionamide is also a "second line drug" that develops cross-resistance with related drugs (Floch

et al., 1966). The M.I.C. of ethionamide for *Myco. leprae* in the mouse is 25 μg per ml (Shepard, 1969b). This value is very close to the serum levels calculated to attain 20 to 30 μg per ml when given at a dosage of 250 mg daily, as was done by Floch *et al.* (1966). These authors found ethionamide to be active, but the duration of the trial was manifestly too short (4 to 18 months). Moreover, with the additional knowledge that ethionamide is rapidly excreted, that inhibition of the growth of *Myco. leprae* is of short duration (Shepard, 1969), and that the dosage cannot be increased for long-term treatment (because of toxicity), it is clear that ethionamide will remain at best a second-line drug.

Treatment of Patients with Drug-resistant Organisms

The occurrence of drug resistance to thiambutosine and dapsone is well-established. Because thiambutosine is a second-line drug in leprosy, it should not be administered alone at the start of treatment of patients with multibacillary disease. Cases resistant only to thiambutosine are not a therapeutic problem, since first-line drugs will still be effective. However, patients who are resistant to dapsone need special attention for two reasons. The first is the potential danger of spread of dapsone-resistant strains of *Myco. leprae* in the community, although nothing is yet known about their infectiousness for man. For the present, dapsone-resistant strains should be considered infectious for man; for the mouse, they are as infectious as dapsone-sensitive strains. The second reason is psychological. If dapsone resistance appears in a patient for whom high dosage dapsone (500 to 600 mg per week) has been prescribed, then he has probably taken the drug irregularly and not in the way prescribed. He may well be irregular with any new therapy and therefore will relapse again. Such patients present individual and community problems. Moreover, their apparently "uncured leprosy" may be quoted or used by others to prove, wrongly, that "leprosy is incurable".

Rifampicin and clofazimine are fully effective against dapsone-resistant strains of *Myco. leprae* in the mouse, and therefore are the drugs of choice for the treatment of patients with dapsone-resistant bacilli. Determination of the level of dapsone-resistance is only useful for identifying patients with intermediate levels of resistance, still capable of responding to full doses of dapsone (100 mg per day). However, for such patients dapsone should be given only in combination with one or two other antileprosy drugs.

References

Adams, A. R. D. and Waters, M. F. R. (1966). Dapsone resistant lepromatous leprosy in England. *Br. med. J. ii*, 872.

Bechelli, L. M. and Guinto, R. S. (1970). Some recent laboratory findings on *Mycobacterium leprae*. *Bull. Wld Hlth Org.* **43**, 559.

Browne, S. G. (1969). Dapsone resistant *Mycobacterium leprae* in a patient receiving dapsone in low dose. *Int. J. Lepr.* **37**, 296.

Canetti, G. (1965). Present aspects of bacterial resistance in tuberculosis. *Am. Rev. resp. Dis.* **92**, 687.

Canetti, G. (1968). Experiments with long-term intermittent chemotherapy in advanced tuberculosis in mice. *Tubercle (Lond.)* **49** (Suppl.) 70.

Canetti, G. and Grosset, J. (1961). Teneur des souches sauvages de *Mycobacterium tuberculosis* en variants résistants à l'isoniazide et en variants résistants à la streptomycine sur milieu de Loewenstein-Jensen. *Ann. Inst. Pasteur* **101**, 28.

Cochrane, R. G. and Davey, F. T. (1964). *Leprosy in Theory and Practice*, 2nd ed. Bristol: J. Wright & Sons Ltd.

Convit, J., Browne, S. G., Languillon, J., Pettit, J. H. S., Ramanujam, K., Sagher, F., Sheskin, J., De Souza-Lima, L., Tarabini, G., Tolentino, J. G., Waters, M. F. R., Bechelli, L. M. and Martinez Dominguez, V. (1970). Therapy of leprosy. *Bull. Wld Hlth Org.* **42**, 667.

Davey, T. F. (1955). Editorial. Leprosy treatment in East Nigeria. *Lepr. Rev.* **26**, 8.

Davey, T. F. (1960). Some recent chemotherapeutic work in leprosy. *Trans. R. Soc. Trop. Med. Hyg.* **54**, 199.

Dickinson, J. M. (1968). *In vitro* and *in vivo* studies to assess the suitability of antituberculous drugs for use in intermittent chemotherapy regimens. *Tubercle (Lond.)* **49** (Suppl.) 66.

Dierks, R. E. and Shepard, C. C. (1968). Effects of phytohemagglutinin and various mycobacterial antigens on lymphocyte cultures from leprosy patients. *Proc. Soc. exp. Biol. Med.* **127**, 391.

Ellard, G. A., Gammon, P. T. and Rees, R. J. W. (1970). The minimal inhibitory concentrations of sulphadimethoxine and sulphadoxine against *Mycobacterium leprae*. *Lepr. Rev.* **41**, 223.

Floch, H., Rist, N. and Jacobi, J. C. (1966). Intérêt de l'éthionamide en thérapeutique antilépreuse. *Bull. Soc. Path. Exot.* **59**, 715.

Gaugas, J. M. (1967). Antimicrobial therapy of experimental human leprosy *(Mycobacterium leprae)* infection in the mouse footpad. *Lepr. Rev.* **38**, 225.

Gelber, R., Glazka, A. J., Peters, J. H. and Levy, L. (1969). A comparison of dapsone and isoniazid acetylation in humans. *Int. J. Lepr.* **37**, 463.

Grumbach, F., Canetti, G. and Le Lirzin, M. (1969). Rifampicin in daily and intermittent treatment of experimental murine tuberculosis, with emphasis on late results. *Tubercle (Lond.)* **50**, 280.

Languillon, J. (1964). La sulfamidothérapie dans la lèpre. *Méd. Trop.* **24**, 520.

Languillon, J. and Carayon, A. (1969). *Précis de Léprologie.* Paris: Masson et Cie.

Leiker, D. L. and Kamp, H. (1970). First results of treatment of leprosy with Rifadin. *Lepr. Rev.* **41**, 25.

Levy, L. (1970). Death of *Mycobacterium leprae* in mice and the additional effect of dapsone administration. *Proc. Soc. exp. Biol. Med.* **135**, 745.

Levy, L., Murray, L. P. and Shepard, C. C. (1970). A comparative study of mouse footpad inoculation of skin biopsy specimens from patients with lepromatous leprosy in San Francisco and Atlanta. *Int. J. Lepr.* **38**, 54.

Levy, L., Shepard, C. C. and Fasal, P. (1969). Killing of dapsone-resistant *Mycobacterium leprae* during treatment with B663. *Int. J. Lepr.* **37**, 466.

Litalien, F., Harter, P., Trinkhthikim-Mong-Don and Nguyen-Thi-Lau (1961). Essai de traitement de la lèpre lépromateuse par la sulfaméthopyrazine. *Bull. Soc. Path. Exot.* **54**, 219

Lowe, J. (1954a). The chemotherapy of leprosy. Late results of treatment with sulphone and with thiosemicarbazone. *Lancet ii*, 1065.

Lowe, J. (1954b). The late results of sulphone treatment of leprosy in East Nigeria. *Lepr. Rev.* **25**, 113.

Merklen, F. P., Cottenot, F. and Egger, L. (1968). Reprises et aggravation d'une lèpre tuberculoide à la suite d'arrêts thérapeutiques répétés. *Bull Soc. Franc. Derm. Syph.* **75**, 188.

Pattyn, S. R. and Rooyackers, J. (1965). Traitement de l'infection expérimentale à *Mycobacterium leprae* chez la souris. *Ann. Soc. Belge. Méd. Trop.* **45**, 27.

Pearson, J. M. H., Pettit, J. H. S. and Rees, R. J. W. (1968). Studies on sulfone resistance in leprosy. 3. A case of partial resistance. *Int. J. Lepr.* **36**, 71.

Pearson, J. M. H. and Pettit, J. H. S. (1969). Chemotherapeutic trials in leprosy. 7. Trial of 50 mg DDS twice weekly in the treatment of lepromatous leprosy. *Int. J. Lepr.* **37**, 40.

Pearson, J. M. H., Rees, R. J. W. and Weddell, A. G. M. (1970). *Mycobacterium leprae* in the striated muscle of patients with leprosy. *Lepr. Rev.* **41**, 155.

Pettit, J. H. S. and Rees, R. J. W. (1964). Sulphone resistance in leprosy. An experimental and clinical study. *Lancet ii*, 673.

Pettit, J. H. S., Rees, R. J. W. and Ridley, D. S. (1966). Studies on sulfone resistance in leprosy. 1. Detection of cases. 2. Treatment with a riminophenazine derivative (B663). *Int. J. Lepr.* **34**, 375, 391.

Poole, G. and Stradling, P. (1960). Chemotherapeutic pitfalls in the treatment of tuberculosis. *Brit. med. J. i*, 160.
Rees, R. J. W. (1965). Recent bacteriologic and pathologic studies on experimental human leprosy in the mouse footpad. *Int. J. Lepr.* **33**, 646.
Rees, R. J. W. (1966). Enhanced susceptibility of thymectomized and irradiated mice to infection with *Mycobacterium leprae*. *Nature (Lond.)* **211**, 657.
Rees, R. J. W. (1967a). A preliminary review of the experimental evaluation of drugs for the treatment of leprosy. *Trans. R. Soc. Trop. Med. Hyg.* **61**, 581.
Rees, R. J. W. (1967b). Drug resistance of *Mycobacterium leprae*, particularly to DDS. *Int. J. Lepr.* **35**, 625.
Rees, R. J. W. (1969). New prospects for the study of leprosy in the laboratory. *Bull. Wld Hlth Org.* **40**, 785.
Rees, R. J. W., Valentine, R. C. and Wong, P. C. (1960). Application of quantitative electron microscopy to the study of *Mycobacterium lepraemurium* and *Mycobacterium leprae*. *J. gen. Microbiol.* **22**, 443.
Rees, R. J. W. and Valentine, R. C. (1962). The appearance of dead leprosy bacilli by light and electron microscopy. *Int. J. Lepr.* **30**, 1.
Rees, R. J. W., Waters, M. F. R., Weddell, A. G. M. and Palmer, E. (1967). Experimental lepromatous leprosy. *Nature (Lond.)* **215**, 599.
Rees, R. J. W., Pearson, J. M. H. and Waters, M. F. R. (1970). Experimental and clinical studies on rifampicin in treatment of leprosy. *Brit. med. J. i*, 89.
Renders, A. (1968). Essai d'un lèprostatique récent (B663) dans le traitement de la lèpre léprostatique. *Ann. Soc. Belge Méd. Trop.* **48**, 625.
Ridley, D. S. and Jopling, W. H. (1966). Classification of leprosy according to immunity. A five-group system. *Int. J. Lepr.* **34**, 255.
Rodriguez, J. N. (1969). The histoid leproma. Its characteristics and significance. *Int. J. Lepr.* **37**, 1.
Schneider, J., Languillon, J. and Clary, J. (1959). Traitement de la lèpre par un nouveau sulfamide: la sulfaméthopyrazine. Premiers résultats. *Bull. Soc. Path. Exot.* **52**, 47.
Shepard, C. C. (1960a). The experimental disease that follows the injection of human leprosy bacilli into footpads of mice. *J. exp. Med.* **112**, 445.
Shepard, C. C. (1960b). Acid-fast bacilli in nasal excretions in leprosy and results of inoculation of mice. *Am. J. Hyg.* **71**, 147.
Shepard, C. C. (1962). Multiplication of *Mycobacterium leprae* in the footpad of the mouse. *Int. J. Lepr.* **30**, 291.
Shepard, C. C. (1967a). A kinetic method for the study of activity of drugs against *Mycobacterium leprae*. *Int. J. Lepr.* **35**, 52.
Shepard, C. C. (1967b). Activity of repository sulfones against *Mycobacterium leprae* in mice. *Proc. Soc. exp. Biol. Med.* **124**, 430.
Shepard, C. C. (1968). Immunologic suppression in leprosy and its relation to lepromatous disease. *Int. J. Lepr.* **36**, 87.
Shepard, C. C. (1969a). Chemotherapy of leprosy. *Am. rev. Pharmacol.* **9**, 37.
Shepard, C. C. (1969b). Minimal effective dosages in mice of clofazimine (B663) and of ethionamide against *Mycobacterium leprae*. *Proc. Soc. exp. Biol. Med.* **132**, 120.
Shepard, C. C. (1971). Rifampicin vs *Mycobacterium leprae*. Proc. VIth Annual Leprosy Research Conference, Atlanta, Ga. **10-12**, 3.
Shepard, C. C. and Chang, Y. T. (1962). Effect of several anti-leprosy drugs on multiplication of human leprosy bacilli in footpads of mice. *Proc. Soc. exp. Biol. Med.* **109**, 636.
Shepard, C. C. and Chang, Y. T. (1967). Effect of DDS on established infections with *Mycobacterium leprae* in mice. *Int. J. Lepr.* **35**, 52.
Shepard, C. C., Levy, L. and Fasal, P. (1968). The death of *Mycobacterium leprae* during treatment with 4-4′-diaminodiphenylsulfone (DDS). *Am. J. Trop. Med. Hyg.* **17**, 769.
Shepard, C. C., Levy, L. and Fasal, P. (1969). The sensitivity to dapsone (DDS) of *Mycobacterium leprae* from patients with and without previous treatment. *Am. J. Trop. Med. Hyg.* **18**, 258.
Shepard, C. C. and McRae, D. H. (1965). *Mycobacterium leprae* in mice: Minimal infectious dose, relationship between staining quality and infectivity, and effect of cortisone. *J. Bact.* **89**, 365.
Shepard, C. C., McRae, D. H. and Habas, J. A. (1966). Sensitivity of *Mycobacterium leprae* to low levels of 4-4′-diaminodiphenylsulfone. *Proc. Soc. exp. Biol. Med.* **122**, 893.

Shepard, C. C., Tolentino, J. G. and McRae, D. H. (1968). The therapeutic effect of 4-4′-diacetyldiaminodiphenylsulfone. *Am. J. Trop. Med. Hyg.* **17**, 192.

Stradling, P. and Poole, G. (1963). Towards foolproof chemotherapy for tuberculosis. *Tubercle (Lond.)* **44**, 71.

Stradling, P. and Poole, G. (1970). Twice weekly streptomycin plus isoniazid for tuberculosis. *Tubercle (Lond.)* **51**, 44.

Tuberculosis Chemotherapy Centre, Madras (1970). A controlled comparison of a twice-weekly and three once-weekly regimens in the initial treatment of pulmonary tuberculosis. *Bull. Wld Hlth Org.* **43**, 143.

Turk, J. L. and Waters, M. F. R. (1969). Cell-mediated immunity in patients with leprosy. *Lancet ii*, 243.

Vellut, C. (1968). Ten years follow-up of lepromatous leprosy patients and DDS treatment. *Leprosy in India* **40**, 111.

Note added in proof. Since the submission of this manuscript, Holmes and Hilson (*J. med. Microbiol.*, 1972, **5**, 251) have published the results of rifampicin treatment of the experimental infection of mice by *Myco. leprae*. The results indicate that rifampicin is very rapidly bactericidal and that the MIC is around 0.3 μg/ml whereas the serum concentration attained in man during rifampicin treatment with 600 mg/day "fluctuates through the day from about 15 μg/ml to 0.5 μg/ml". The bactericidal effect of rifampicin on *Myco. leprae* was confirmed in the mouse model.

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Management of Tarsal Bone Disintegration*

GRACE WARREN

Hay Ling Chau Leprosarium, Hong Kong

Tarsal bone lesions may occur in as high a proportion as 25% of leprosy patients. Some of these lesions develop into a progressive disintegration that results in marked deformity and increasing disability. For years this was considered to be part of the specific leprosy process and to be unresponsive to routine treatment methods. Recent investigations show that these lesions will heal in response to simple treatment methods, but require a considerable length of time. This paper describes these lesions, their diagnosis and treatment, with special reference to the clinical signs and symptoms for those who do not have facilities for radiographic examination.

Many leprosy patients, when the disease is first diagnosed, already have marked deformity and disability of the feet. The leprosy worker is confronted with the problem of making the best of what is left in order to try and give the patient feet that are ulcer-free and useful. However, when reviewing patients who have been under medical treatment for years, one realizes that although on admission the patient had "good feet" they are now deformed and require special care. Why does this progressive deformity occur, and what can we do to prevent it?

The common causes of progressive deformity are:

(1) Repeated minor ulcers and other trauma which slowly result in the loss of the tissue of the foot, especially the toes and the front of the foot. This trauma can usually be prevented in the co-operative patient by adequate education in the care of the feet and the use of suitable footwear.

(2) Gross sepsis and osteomyelitis; these may result from an accident, a burn, or neglected minor trauma, and cause marked loss of tissue, with scars that may contract and distort part of the foot. Education of the patient and instructions to report and treatment of all infections as soon as possible will minimize resultant deformity and loss of tissue. Treatment must include *adequate* rest, which is often neglected because of the accompanying diminution of pain perception.

(3) Progressive breakdown of bone (Paterson, 1961); this is not of necessity associated with sepsis but gradually allows increasing deformity to occur. For long it has been thought that these lesions are a part of the specific leprous process and that they are difficult or impossible to treat (Harris and Brand, 1966). However, recent investigations have shown that early diagnosis and active treatment will result in bone healing without deformity. The bones most commonly affected are the tarsal bones, though the adjacent metatarsal bases and the lower ends of the tibia and fibula may be secondarily involved. The condition is hereinafter referred to as tarsal bone disintegration.

The first two conditions are well known and articles on them are legion. The remainder of this paper is on the third cause, and is specifically written, bearing in

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mind that many leprosy workers do not have radiographic facilities readily available.

Tarsal Bone Disintegration

In some leprosy patients progressive disintegration of bone appears to follow comparatively minor trauma. This usually occurs in persons who have a diminution of pain perception and so continue to retraumatize the bone during everyday usage. Having no warning of the increasing damage they do not rest the traumatized bone and thus encourage the body's attempts to repair the damage. This disintegration may be progressive until there is complete destruction of part of the foot. If the repeated trauma is prevented, healing of the damaged bones can occur (Warren, 1971b).

Clinical Findings

The earliest lesions present as a minimal swelling of the foot, with some heat over the affected area (Lennox, 1964); there is no obvious deformity of the foot and the patient does not usually complain of any pain or discomfort, but an abscess may be suspected (Fig. 1a, b) (Price, 1960).

Careful history-taking may reveal:

(1) An accident causing unusual trauma to the foot (tripping in a drain or over a stone is common) (Paterson and Job, 1964).

(2) A period of relative inactivity such as occurs during prolonged bed rest for intercurrent disease or chronic lepra reaction.

(3) A period of immobilization of a foot in plaster, such as is used for the treatment of ulceration of the foot in leprosy, followed by rapid resumption of walking. The immobilization may have been of the unaffected foot, nevertheless resulting in relative inactivity during the use of a plaster cast, but is more commonly of the affected one (Harris and Brand, 1966).

(4) A recent area of sepsis on the foot, though this may have already healed.

(5) The use of corticosteroids for leprosy, or intercurrent disease. In many countries corticosteroids can be purchased easily and are taken as analgesics, so that their use may not be immediately obvious.

(6) Recent lepra reaction, including neuritis, and commonly associated with paralysis or paresis of the affected foot, or with swelling of the foot.

However, in many instances none of these factors is obviously present and the patient denies any possible cause for the heat and swelling.

In more advanced cases some crepitus (Lennox, 1964) may be palpated over the point of maximum heat and swelling and a flattening of the arch of the foot may be observed when the two feet are placed sole to sole. This flattening of the arch is a very useful sign (Fig. 2a, b).

Further bony disintegration may result in abnormal mobility of the affected area—usually the talo-navicular area. If excessive mobility (Lennox, 1964) has been present for some time there may be no obvious heat, though residual swelling and deformity may be present. The patient could still walk on the ankle illustrated in Fig. 3, but he complained of some instability! In these later cases there is usually little doubt regarding the diagnosis, and full treatment should be instituted without delay if a functional foot is to be achieved after healing.

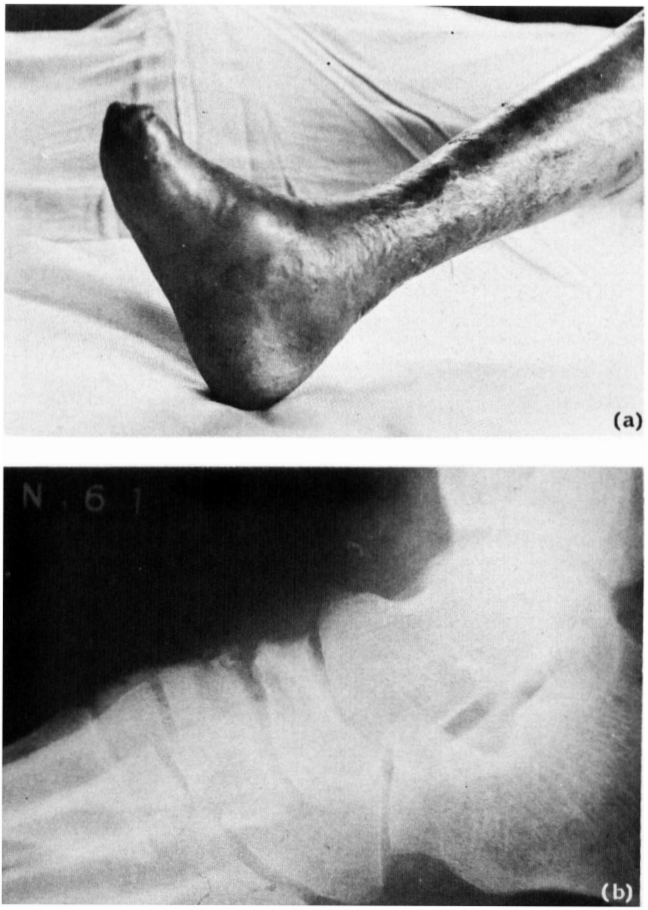

Fig. 1(a). Swelling of the foot that may occur with an early naviculo-cuneiform lesion; (b) radiograph of (a). The lesion commenced as a fracture of the talus and calcaneum 5 years illustrated in Fig. 1(a).

The progress of disintegration varies greatly in different patients. In one patient with a known fracture sustained 6 months earlier there was still no appreciable deformity and minimal bone disintegration. In another, there was complete loss of the talus, with disorganization of the ankle within 6 months of his initial complaint of "slipping into a gutter".

If radiographic examination is possible, it is the ideal method of diagnosing and controlling the treatment of this condition, but in its absence adequate treatment that will prevent permanent disability is still possible.

For radiographic diagnosis two views are really necessary.

First, AP or preferably APO (which more clearly defines the anterior tarsal bones). The film should be placed and the exposure adjusted so that a clear view of the talus head is obtained. This means the phalanges of the toes will be over-exposed and not well visualized.

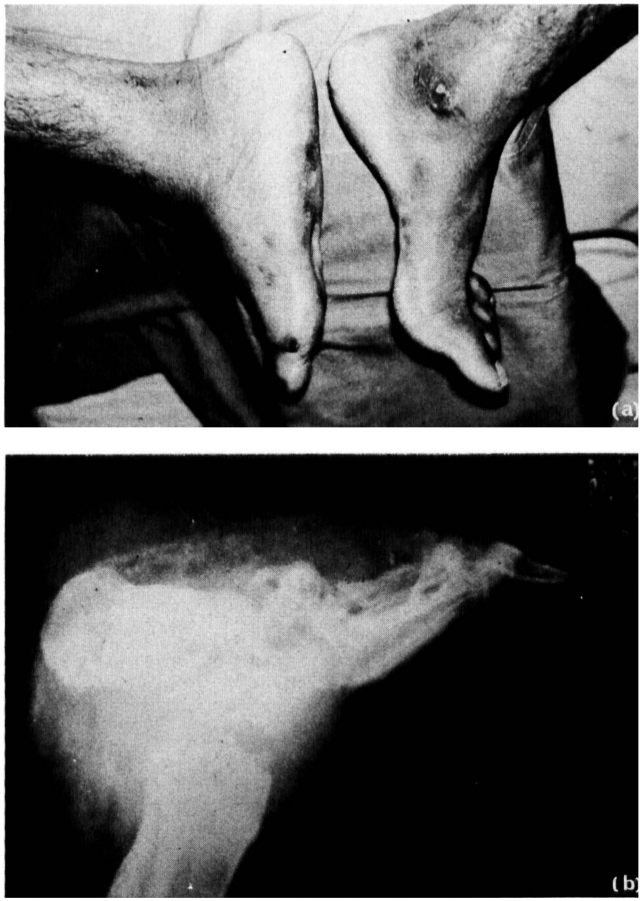

Fig. 2(a). Flattening of the arch of the affected foot; (b) marked radiographic changes of affected foot shown in (a).

Second, a true lateral view of the calcaneum, with the film placed so that all the tarsals and the lower portion of the tibia are visualized. A *standing* lateral view gives the best position for future comparisons. If deformity of the ankle is present care must be taken to get the true lateral of the calcaneum and not of the ankle joint. These two views should reveal all lesions, though in a grossly distorted ankle some adjustment of this position may be needed to define the affected bone and an AP view of the ankle may also be advised.

Early lesions of the talus and navicular are most easily diagnosed from the lateral view, but those of the middle and lateral cuneiforms and cuboid are seen earlier on the APO view. With careful placement it is possible to get the APO and lateral views of one foot on to one 8 x 10 in X-ray film (Fig. 4). If films are readily available, it is desirable to radiograph both feet so that the abnormality can be compared with the normal foot. Ideally, every patient should have his feet radiographed at the time of the diagnosis of leprosy in order that any early bone

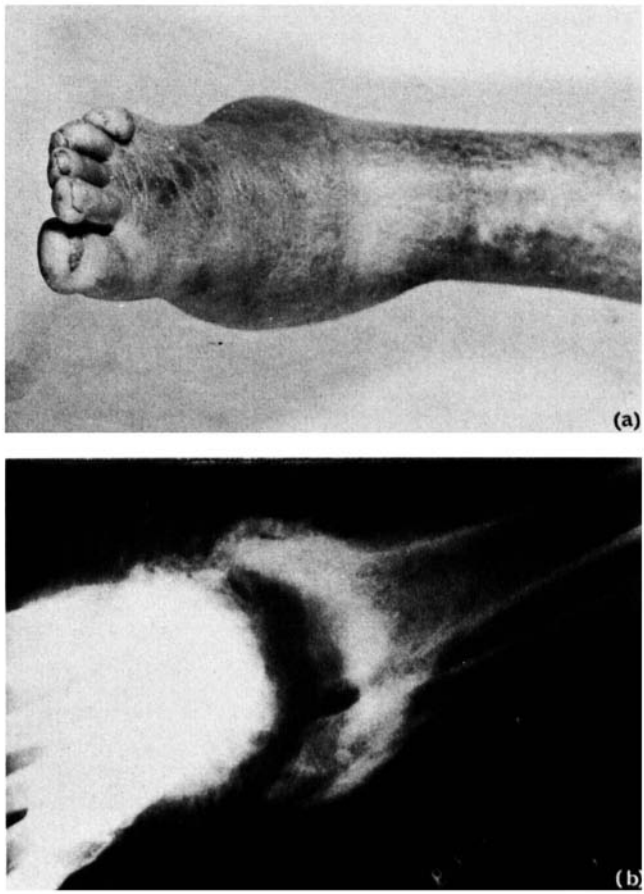

Fig. 3(a). Soft fluctuant swelling of the ankle area without heat or obvious inflammation; (b) radiograph of (a). The lesion commenced as a fracture of the talus and calcaneum 5 years earlier.

lesions can be detected and treated before real deformity occurs and to provide a base line for later comparisons.

The early and less disabling lesions may appear as:

(1) a vagueness of outline of one or more bones, with or without a definite change in shape; (2) a frank fracture (Paterson, 1961); sometimes attention is drawn to it by surrounding osteoporosis; (3) a portion of the medullary bone appearing to be squeezed out through the fracture line (Fig. 5); (4) a change in shape of a bone without any obvious break in the continuity of the cortex (especially the talus) (Fig. 6a, b).

Late lesions may appear as a gross change in the shape of one or more bones, with the loss of adjacent joint spaces. The residual bone may be fragmented and the stress of walking may have displaced the fragments, so that the remaining bones are impacted and the normal architecture of the foot is lost. Every degree

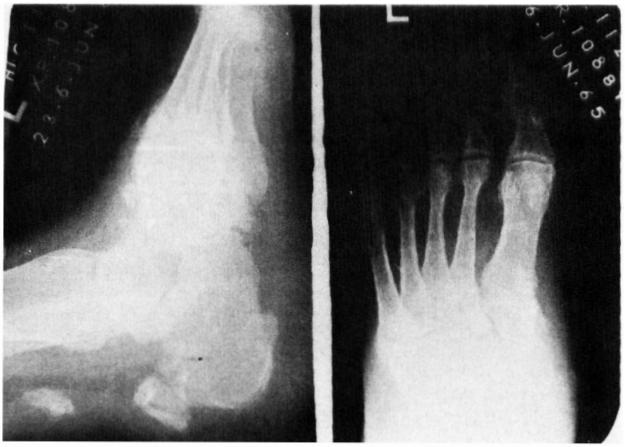

Fig. 4. Placement of APC and lateral views on one 8 x 10 in film. A deformity of calcaneum and another of the talo-navicular area (with pin *in situ*) are visualized.

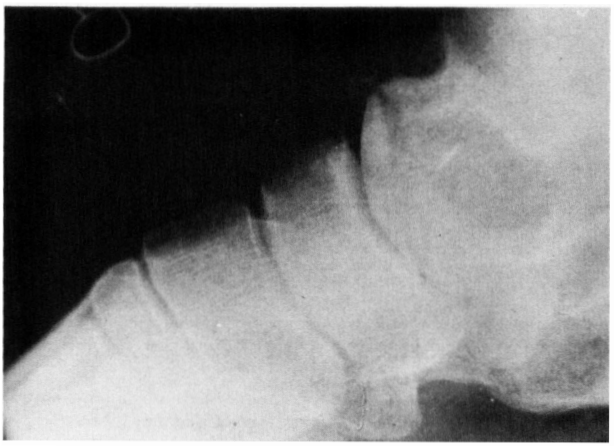

Fig. 5. Portion of medullary bone being squeezed out through a crack in the cortex of the talus. This lesion progressed to complete loss of the neck of talus and collapse of the head when unrestricted walking was allowed for 6 months after a short period of plaster immobilization. Healing eventually required 18 months' immobilization.

of deformity may be present. The still active bone lesions will have a hazy appearance. Healed lesions will usually appear sclerotic, with smoothed-off edges (Fig. 7a, b, before and after PoP). At surgery it has been found that this bone is very dense and hard. In practice this healed sclerosed bone has not been seen to fracture or to disintegrate.

Management

The treatment for all stages of tarsal bone disintegration is immobilization in the functional position for an adequate period of time to allow complete bone

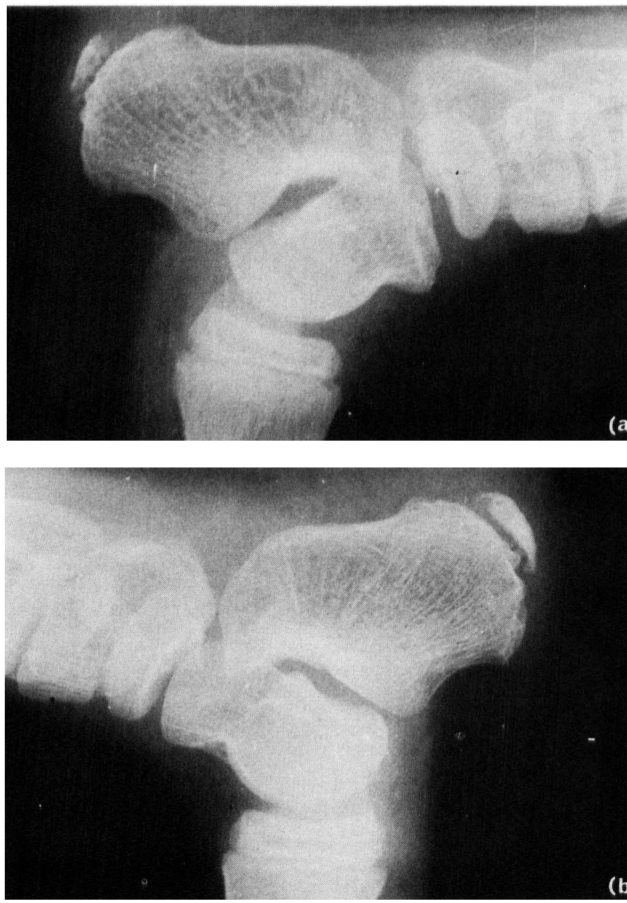

Fig. 6(a). Deformed talus navicular bone in foot of 8- to 10-year-old Chinese boy; (b) normal foot for comparison.

healing to occur. This is usually achieved by use of a below-knee plaster-of-Paris (PoP) walking cast. Ideally the length of time should be determined radiographically, but in the absence of this the following method will prove effective.

The earliest lesions are difficult to differentiate from fractures and sprains. Even radiographic evidence of a stress fracture may not be apparent for 4 to 6 weeks. If a patient presents with a slightly warm, swollen, undeformed foot and no definite history, it is advisable to support the foot with a crêpe bandage and give diuretics for a few weeks, while allowing the patient to continue reasonable activity. If the symptoms do not subside within 4 weeks, then it should be assumed that a bone lesion is present, even if radiographic examination is not possible. If radiographic examination is possible it should be done every 3 to 4 weeks until all symptoms have subsided, or a bone lesion is apparent.

Once it is decided to treat the lesion as a tarsal bone disintegration a well-fitted (PoP) walking cast should be applied, taking special care to mould the plaster to

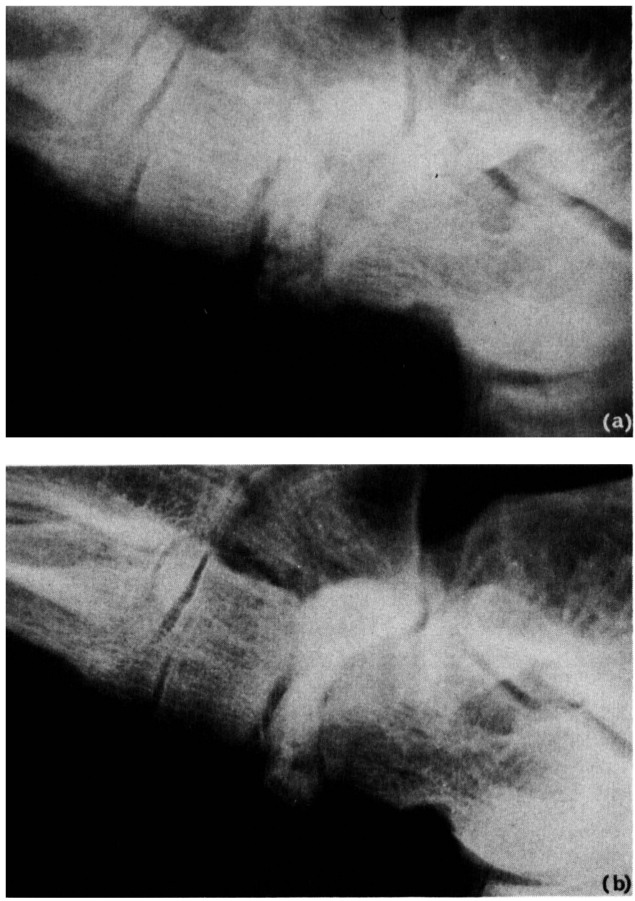

Fig. 7(a). Breakdown in navicular bone; (b) healing of navicular bone after 6 months' immobilization.

the shape of the foot and to hold the foot in a functional position (ankle at 90° without inversion of the heel) (Warren, 1971b).

If the bone lesions involve the body of talus and the calcaneum immediately below the talus, the weight should be carried through a Bohlers iron from the tibia. The leg portion of the plaster needs to be extra well fitted to do this (Warren, 1971). For bone lesions at other sites a standard wood or rubber rocker can be used, or a flat soled plaster can be applied to be worn in conjunction with a flat sandal. In the foot with a doubtful lesion, this plaster can be kept on for 2 to 3 months; at the end of this period trial walking should show if it was a true bone lesion or not. For a definite lesion, the plaster can be changed at 3 months to allow radiographic studies when these are available; the plaster can then be reapplied for another 2 to 3 months before further radiographic studies, and trial walking carried out if the radiographs are satisfactory.

The early lesion requires 4 to 6 months for full healing, so if radiography is not

available it is advisable to maintain plaster immobilization for about 5 months before allowing trial walking. Changing of the plaster should be well supervised. If radiographic studies are possible it is important to ensure that the patient does *not* walk while waiting at the X-ray department, as he may damage the healing bone and delay further healing. Also, if at all possible, the plasters should be applied by the medical officer in charge himself so that the optimum position may be achieved. This is especially important when there is mobility of the foot, as in the more advanced cases, and a poorly moulded plaster may increase the deformity.

Trial walking is a graded method of return to unsupported walking.

As it is impossible to assess, on radiological evidence alone, if healing after disintegration is complete, the following routine has been formulated. It does reveal most cases of incomplete healing and at the same time provides a gradual return to activity that assists in recalcification of the osteoporotic bones and helps reduce the possibilities of stress fractures and further episodes of disintegration. Trial walking is also used at Hay Ling Chau, with modifications, on all occasions when normal ambulation is being resumed after prolonged non-use of a foot, such as after ulceration, reaction, surgery, or complete bed rest.

Method

(a) The affected foot is firmly bandaged; (b) suitable shoes with resilient insoles are laced on to the foot; (c) walking around the bed is then allowed for 3 min on three occasions on the first day; (d) after walking the foot is checked for heat and swelling. This procedure is repeated daily, provided no heat or swelling develops, but the time is increased gradually, to 5 min on the second day and 10 min on the third day, so that at the end of a week the patient is walking about, in the hospital, for 30 min three times a day.

If swelling of the foot occurs, or there are other indications of impending trouble, the increases are taken more slowly and diuretics may be given, but if the swelling subsides before the next day it is usually only "travel oedema" and the use of the crêpe bandage support helps to prevent this. If heat over the damaged bones occurs and does not subside overnight the bones should be regarded as not fully healed and complete immobilization resumed for a further 6 to 12 weeks.

Trial walking also helps to prevent breakdown of the skin of the sole such as frequently occurs when a patient with an anaesthetic foot resumes walking after a prolonged period of complete immobilization or bed rest. If the patient has adequate muscle action, he can start using weights in conjunction with trial walking to stimulate movement and circulation without the risk of a fracture. This commences with half-pound (230-g) resistance to dorsiflexion and the weight gradually increased as strength returns.

Advanced Lesions

In more advanced disintegrations the diagnosis is more obvious. If heat and/or swelling are still present, healing can be expected. If mobility has already occurred it is wisest to allow 9 months of immobilization before trial walking when radiographic control is not available. The position of the foot during each plaster application is most important. If the foot cannot be moulded into a functional position it may be advisable to consider surgical reconstruction, using internal

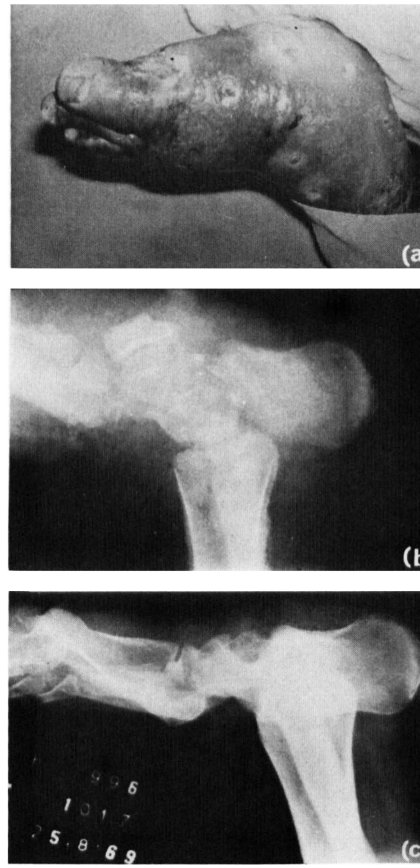

Fig. 8(a). External view on admission of foot shows multiple discharging sinuses; (b) radiograph on admission shows osteomyelitis and disintegration; (c) radiograph some 12 months later shows bone healing well advanced.

fixation. Healing of these bones does occur after surgery if complete immobilization is achieved. A period of 9 to 12 months is required for healing of a mid-tarsal wedge osteotomy, but a talo-calcaneo wedge will usually heal in 4 to 5 months.

If there is no sign of heat or swelling and the deformity and/or mobility has been present for a long time without change (over 6 months), it can be assumed that any lesions that were present have healed. On radiographic examination they will be seen to be smoothed off and sclerotic. Simple immobilization will do little, if anything, to improve stability and reduce disability unless surgical intervention precedes the immobilization. It may be necessary to use a bone graft from the iliac crest to make up for a deficit in bone bulk. The hard sclerosed bone must be chiselled out until a bleeding surface is displayed and complete immobilization maintained for up to 12 months, or possibly even longer. Any infection may lead to rejection of the graft and will delay fusion, but provided the foot is held completely immobilized at all times, in the position of function, a favourable final

outcome can be hoped for. This sometimes poses problems and requires some ingenuity to immobilize and yet at the same time allow for dressings of discharging sinuses.

In the foot in which bone disintegration is complicated by sepsis, the same principles hold. Immobilize in the optimum position while treating the infection with local packs and antibiotics, and a useful foot can often be salvaged (Fig. 8a, b and c). But REST is essential—and because of the diminution of pain perception the patient will not rest unless forced to. Even one weight-bearing step taken at a plaster change may fracture the newly formed callous and delay healing by many months.

Comments

Disintegration of the bones of the foot of a leprosy sufferer may progress until the foot is a useless member and a real disability. However, no matter how severe the lesion is when first diagnosed, it is usually possible to achieve healing of the remaining bones. Provided that destruction has not progressed too far, the remainder of the foot can become a useful member again, though this may require much time and ingenuity on the part of the medical workers.

Tarsal bone disintegration is no longer a condemnation to deformity or amputation, especially if detected and treated early.

Minor foot trauma is often unnoticed because of the diminution of pain perception, but we need to teach our medical personnel, and the patients themselves, to watch for early signs and symptoms so that early lesions of all types can be effectively treated and more severe deformity and disability prevented.

References

Harris, J. R. and Brand, Paul W. (1966). Patterns of disintegration of the tarsus in the anaesthetic foot. *J. Bone Jt Surg.* **48B**, 4-16.

Lennox, W. M. (1964). A classification of leprosy foot deformities. *Lepr. Rev.* **35**, 245-249.

Paterson, D. E. (1961). Bone changes in leprosy; their incidence, progress, prevention and arrest. *Int. J. Lepr.* **29**, 393-422.

Paterson, D. E. and Job, C. K. (1964). Bone changes and absorption in leprosy. *Leprosy in Theory and Practice*, 2nd ed., Chapter 26. (Eds R. G. Cochrane and T. F. Davey.) Bristol: J. Wright and Sons Ltd.

Price, E. W. (1960). Studies in plantar ulcers in leprosy. *Lepr. Rev.* **31**, 97-103.

Warren, Grace (1971a). Plaster casts. *Lepr. Rev.* **42**, 55-59.

Warren, Grace (1971b). Tarsal bone disintegration in leprosy. *J. Bone Jt Surg.* **53B**, 688-695.

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The Solar Bath*

R. FOSTER
Kafue, Zambia

P. KATUMBI
Mwami
and
D. SMITH
Blantyre, Malawi

In a rural centre where a continuous electricity supply is not available, but where the sun usually shines, the solar bath has proved useful in the pre-operative management of leprosy patients with ulnar damage.

Introduction

Stiffness and contractures of the interphalangeal joints are common complications of ulnar nerve damage in leprosy. If wax baths are to be used for this condition in centres where electricity is not available, or is available only intermittently, some other heat source must be used. Open flame methods may result in serious accidents. This report describes a method of heat treatment that takes the place of the conventional wax bath, using the sun as a heat source. This "Solar Bath" has been in use for the past 5 years at Mwami Leprosarium, in the eastern province of the Republic of Zambia.

Development

A container of suitable dimensions was constructed, triangular in cross section; the hypotenuse face of the triangle is of glass, which can be directed towards the sun (Figs 1 and 2). The average temperatures obtained for 100 treatments given to 8 patients are shown in Fig. 3. No untoward effects from the use of the solar bath have arisen.

Temperature Comparison with Wax Bath

Temperature measurements were made with Yellow Springs Instrument Co. Tele-Thermometer model 43TD, and with a conventional mercury laboratory thermometer.

Solar-bath treatments are given indoors through an open or closed glass window, or (less often) outdoors. The patient washes his hands with soap and water, then rubs in peanut oil, two or three finger-dips, at room temperature. Both hands are then placed in the solar bath for 25 min. The 100 treatments,

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Fig. 1. The experimental solar bath. Recording the temperature at 5-min intervals.

Fig. 2. Group of patients using a battery of solar baths.

which furnished the average temperatures, were taken from mid-morning to early afternoon during the months of October to December 1967, and January, February and July 1968–months that include both the warm and the cold seasons.

Comparative temperature readings were taken with the same measuring equipment at Malamulo Leprosarium where electricity supply is constantly available to heat the wax in a conventional bath. The thermocouple and glass thermometer were fixed to the finger with an Elastoplast band (a ruler being used to protect the glass thermometer). The hand was then dipped into the wax bath

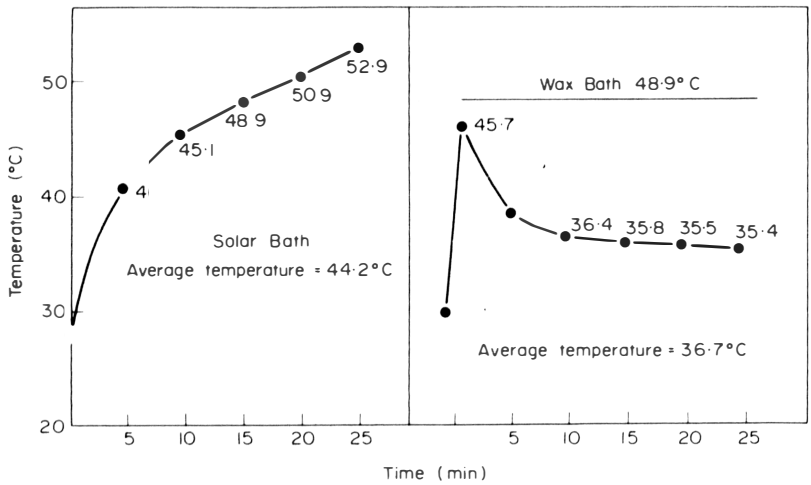

Fig. 3. Comparison between the average temperature of a solar bath and a wax bath.

10 times, wrapped in plastic covering, and covered with a pillow-slip. Temperature recordings were made before placing the hand in wax, the initial maximum temperature, and the temperature at 5-min intervals for a period of 25 min. The average temperatures for the 27 treatments given are shown in Fig. 3.

Discussion

The finding that the temperature in the solar bath continued to rise during the period of treatment caused some concern at first in case burns or blisters might occur in anaesthetic hands. Initially, therefore, a timer was used to ensure that the treatment was limited to 25 min. This is no longer considered necessary, however, since no blisters have occurred.

After treatment in the solar bath, a skin-tight plaster is applied to the fingers to mobilize them in maximum extension. Studies are in progress to ascertain if the solar-bath treatment has an influence on the time taken to mobilize the contractures.

The average temperature over the period of treatment is greater in the solar bath than that with the wax bath in our part of the world. This finding should be supplemented by studies of the blood flow in the forearm and fingers. Any softening effect of the wax on the tissues, and the rapidity with which the contracted tissues are mobilized, must also be taken into account.

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Mis-reinnervation in Leprous Neuritis Affecting the Facial Nerve*†

D. A. RANNEY

Chief of Surgery, The Schieffelin Leprosy Research Sanatorium P.O., via Katpadi, North Arcot District, Tamil Nadu, South India

M. A. FURNESS

East Arm Hospital, P.O. Box 1847, Darwin N.T., Australia 5794

and

C. K. SANTHANAKRISHNAN

Indian Airlines, Begumpet Airport, Hyderabad-19, Andhra Pradesh, India

Evidence for misdirection of fibres in severe and well-established leprous neuritis of branches of the facial nerve is presented. In the present study blinkbursts, twitches, and voluntary co-contractions were abundantly seen. Fibrillation and giant polyphasic potentials were rare. Leprous neuritis is contrasted with Bell's palsy in terms of site of involvement, and the significance of this is discussed. Misdirection as a source of re-innervation is one of several factors influencing recovery.

Introduction

Leprosy is the commonest cause of peripheral neuropathy in the world today. Paralysis of facial muscles occurs in approximately 2% of patients afflicted with this disease. Although often compared with Bell's palsy, the pattern of paralysis seen is quite different. This is because in leprosy the site of pathological change is one or more of the peripheral branches of the facial nerve, and not the main trunk (Fig. 1). At this site there is a reduction in temperature which has been shown by Brand (1964) and confirmed by Job and Desikan (1968) to be an important factor in the development of nerve lesions. The leprosy bacilli proliferate more readily at reduced temperature. The presence of osseo-fibrous tunnels in the region of the zygoma have been implicated specifically in the facial nerve by Dastur *et al.* (1966) as selecting factors in determining this site of involvement. Hence, unlike Bell's palsy, lower facial palsy is less frequently seen and varying degrees of paresis of the upper facial musculature is a feature. A variable degree of recovery may take place, and a better understanding of the processes of recovery is of more than academic interest.

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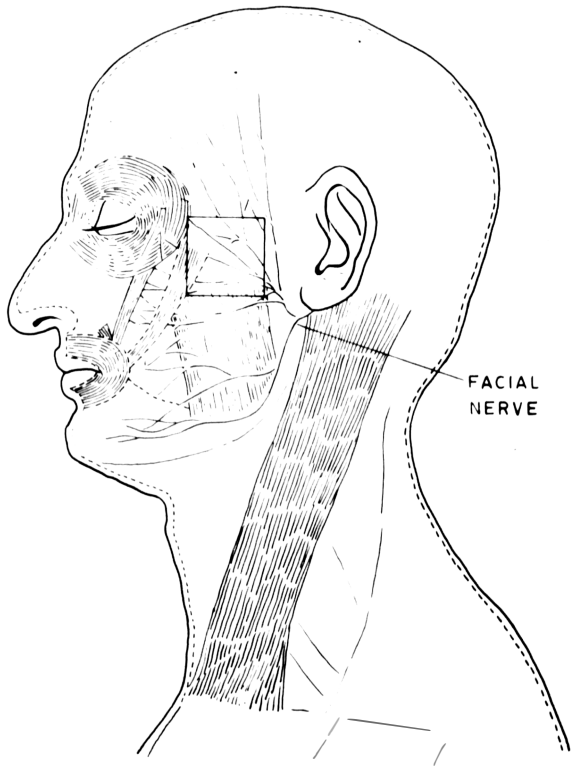

Fig. 1. Branches of the facial nerve. Any of these may be involved, either in isolation or together with other branches, but the commonest site of involvement is within the rectangular area shown in the diagram.

Materials and Methods

The frontalis, upper and lower halves of the orbicularis oculi (pars palpebralis) and levator labii superioris muscles were studied electromyographically, using a Medelec MS3R 2-channel model and concentric needle electrodes, in 22 patients as part of their postoperative assessment following temporalis transfer for lagophthalmos due to leprous neuritis. All had had, as prerequisites for surgery, severe established paralysis of 1 year's duration or more and medical control of the progress of the disease. In 5 of these cases bilateral operations had been performed so that 27 sites of the face affected by leprosy were studied. All cases were also studied in detail, clinically and by faradic stimulation, as part of a larger series to be reported elsewhere by Ranney and Furness (1973).

In addition to examining these 27 in detail, 1 patient with signs that resembled hemifacial spasm also had the other (normal) side examined for comparison, and in 2 other cases with visible contralateral co-contractions in the levator labii superioris muscle on the unparalysed opposite side the muscles concerned were also examined electromyographically. Also examined were the procerus and corrugator supercilii muscles in one patient and the levator anguli oris in another

when visible ipsilateral co-contractures were seen. Of the 22 patients 5 had lepromatous, 12 borderline, and 5 tuberculoid leprosy. Their ages ranged from 17 to 55, with an average of 38.7 years, and 20 were male and only 2 female.

Results

The general pattern of paralysis in the 4 muscles selected for study is shown in Table 1; it is not in any way related to the type of leprosy. Fibres of orbicularis oculi in the upper lid were the most severely affected. While the lower lid fibres were affected almost as often, partial paralysis was very much more common in this muscle. Consequently a remarkably larger number of incomplete patterns were seen in the lower lid as compared with the upper.

TABLE 1

General pattern of electromyographic activity in 27 halves of the face in 22 patients

	Upper lid	Lower lid	Frontalis	Lev. lab. sup.	Total
Full interference pattern	1	2	14	16	33
Incomplete interference pattern	6	16	8	10	40
No voluntary activity	20	9	5	1	35
Total	27	27	27	27	108

While the mass movements sometimes described in Bell's palsy were *not* seen, blinkbursts and periodic twitches were often obvious at first sight. Clinically visible blinkbursts were seen and confirmed electromyographically in the pars orbitalis of the lower half of orbicularis oculi in 2 cases, and in the levator labii superioris in 5 patients. One of these 5 had unilateral upper and bilateral lower facial involvement, but blinkbursts in levator labii superioris occurred only on the side with a full interference pattern in orbicularis oculi. On the other side this patient had 10-μV twitches in the same muscle; these were out of phase with blinking but synchronous with rhythmical twitch activity in the lower half of the orbicularis oculi on that side. Single twitches of up to 75 μV in amplitude in the levator labii superioris occurred in another patient with gentle voluntary eye closure and are therefore also listed as co-contractions. Still another patient had continuous twitch-like activity which could not be controlled voluntarily but which spread to the opposite levator labii superioris on tight eye closure.

Voluntary co-contractions were seen 21 times in 16 of the 22 patients studied; all but one of these were on the same side (Table 2). This type of synkinesis was seen in 3 out of 5 patients with lepromatous leprosy, 9 out of 12 with borderline, and in 4 out of 5 with tuberculoid disease, so that again no relationship was seen to exist between the type of leprosy and the incidence of co-contraction. Five occurred in orbicularis oculi of the lower lid in 4 patients—3 in pars palpebralis and 2 in pars orbitalis, and all were associated with voluntary activation of the levator labii superioris muscle of the same side. Five occurred in the frontalis of 5 patients; 4 of these co-contractions were observed on attempted closure of the eye (Fig. 2) and in 3 of these 4 this was the only type of voluntary activity possible. Surprisingly, contraction of frontalis occurred in the 5th case on

TABLE 2

Electromyographic abnormalities seen in 27 halves of the face in 22 patients

	Upper lid	Lower lid	Frontalis	Lev. lab. sup.	Procerus corrugator	Lev. ang. oris.	Total
Blinkbursts		2 (in pars orbitalis)	0	5			7
Twitches	0	1	0	3			4
Voluntary co-contractions	0	3 (pars palpebralis) 2 (pars orbitalis)	5	9	1	1	21[a]
Fib. potentials		0	1	0			2
Giant polyphasics	0	1	1	0			2

[a]One of these was contralateral, associated with complete ipsilateral paralysis (see text).

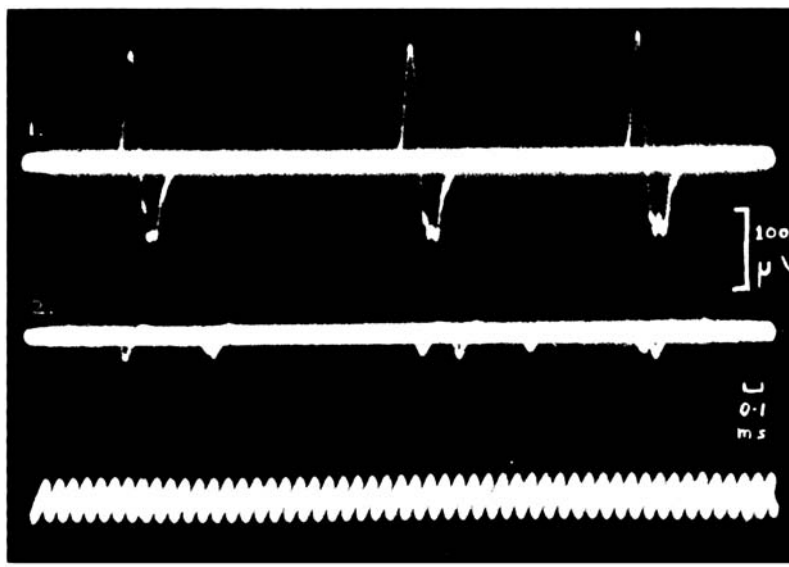

Fig. 2. Co-contraction in frontalis muscle (Lead 1) during spontaneous activity in lower lid orbicularis oculi (Lead 2).

activation of the ipsilateral levator labii superioris. Volitional activity was possible also in this particular case.

On closure or attempted closure of the eyes co-contractions were seen in the levator labii superioris in 9 patients; in 8 of them these were on the same side, but one, in which the ipsilateral lip musculature was also paralysed, occurred on the opposite side. In all cases the co-contractions occurred on gentle eye closure, and therefore were not a manifestation of attempts to "screw up" the face in order to facilitate closure of the eye in the presence of lagophthalmos. In one case, resembling hemifacial spasm, there was also spread of the ipsilateral co-contraction to the other side on tight closure of the eye.

Although it was not planned to study other facial muscles in so much detail, a careful inspection of all muscles, lasting 30 min, was made. During the course of this examination associated movements were also noted in the corrugator and procerus muscles in one patient and in the levator anguli oris in another, both on attempting gentle eye closure. The clinical impression of co-contraction in these muscles was confirmed electromyographically.

Fibrillation potentials and giant polyphasic potentials were uncommon. It is of interest, but possibly of no significance, that both were found only in patients with tuberculoid leprosy. Fibrillation potentials were seen on only two occasions: in the upper lid of one patient in whom no spontaneous activity was present, and in frontalis of the same patient where giant polyphasic M.U.P's of 3500 μV were also seen on voluntary activity. It should be noted in this case that 31 months previously i.e., 1 year after the onset of paralysis, frontalis was recorded as not responding to faradic stimulation. Two months later there was a slight response, and now there is a normal response.

Discussion

Following facial paralysis due to Bell's palsy, associated movement in physiologically unrelated muscles, clinically discernible blinkburst activity, and spontaneous twitching have been observed. Taverner (1955) has postulated that some, if not all, of these phenomena can be explained by misdirection of regenerating axons. Good support for this theory has recently been put forward by Teasdall and Salman (1971), who demonstrated by means of evoked muscle potentials that in 5 out of 8 cases of Bell's palsy with associated movements "during facial nerve regeneration some of the most rapidly conducting nerve fibres which originally innervated orbicularis oculi subsequently supplied orbicularis oris". Mis-reinnervation has also been reported in the forearm by Satoyoshi *et al.* (1971) following cervical nerve root trauma and has also been cited by Ford and Woodhall (1938) as occurring during recovery of certain cranial, spinal and autonomic nerves from trauma and from infection. So far it has not been reported in leprosy.

In leprous neuritis of the facial nerve the evidence here presented indicates that misdirection of regenerating nerve fibres occurs in this condition also, and often leads to a loss of regenerating axons which would otherwise innervate the orbicularis oculi. The blinkbursts activity seen in the levator labii superioris can best be explained on the basis of misdirection. Regenerating fibres originally destined for some part of orbicularis oculi seem to have been misdirected to levator labii superioris instead. A similar misdirection could explain the co-contraction of levator labii superioris seen on voluntary gentle eye closure. Similarly, axons which normally innervated orbicularis oculi but were misdirected to frontalis would explain the associated movement in this muscle. In 3 cases they were the only source of innervation, so that the patients could only raise the eyebrows when told to close the eye, while in a 4th case the frontalis muscle received some of its original axons also. In another case the source of re-innervation of frontalis appears to have been the nerve to the levator labii superioris. When this investigation was initiated it was felt that there might be some evidence of axon sprouting at the intramuscular level, for Dastur (1956) reported such an occurrence in leprosy in other muscles, although to a limited degree. But bridging of the gap between so widely separated muscles as frontalis

and levator labii superioris by axon sprouting at the sub-terminal level is incredible, and the rarity of giant polyphasic potentials also renders such a possibility even less likely. The concept of re-innervation by fibres misdirected at a more proximal level would seem to be the only rational explanation for the associated movements seen so abundantly in these cases.

It is possible that in Bell's palsy misdirection of axons occurs at the site of the lesion, since there, there is close proximity of all nerve fibres. However, in leprosy the site of involvement is almost always more peripherally situated, where the individual branches are exposed to low temperatures and possibly enclosed in osseo-fibrous tunnels. Where the branches are so isolated from each other re-innervation by misdirection seems hardly possible—yet it does seem to occur. Sullivan in 1939 showed that in experimental division of the facial nerve in monkeys there could be retrograde degeneration which would leave the neurolemmal tubes proximal to the site of the lesion open and receptive to in-growth from healthy axons, at least for a short distance. Antia *et al.* (1966) demonstrated at operative explorations that the facial nerve does not consist of a simple system of branches, but rather of a network or plexus of branching and re-anastomosing fibres. Is it not possible then that in some cases retrograde degeneration, or even the disease process itself, extends back at least to the level where it is in contact with such a branch? In some cases it need not extend very far.

Misdirection, being haphazard, might be expected to occur not only away from the external eye musculature but also in the reverse direction. Though less frequent, it did seem to occur in those patients in whom the lower half of the orbicularis oculi showed co-contraction on activation of the levator labii superioris. As a source of re-innervation of a paralysed orbicularis oculi a few branches of nerve fibres normally supplying muscles of the lower half of the face would account for the preponderance of incomplete interference patterns seen in the lower lid. This possibility deserves serious consideration, because Magora *et al.* (1965), Antia *et al.* (1966), and Margaret Brand in a personal communication, have expressed the view that the lower lid, not the upper, is more obviously denervated in leprosy, and yet in our series, while the frequency of involvement was almost identical, it was the upper lid that was the more completely paralysed. Perhaps some of the lower lids paralysed had partially recovered due to mis-reinnervation—although axon sprouting at the intramuscular level could also be a factor. It may also be that in the upper lid the axonal pathway is so completely blocked by the destructive process going on that sprouts originating proximally find their way into nerves destined for frontalis, levator labii superioris, and even orbicularis oculi of the lower lid to a much greater extent than can occur in the reverse direction.

The extent of recovery due to misdirection cannot be assessed on the basis of this study and may be less than these data would indicate. It is important to realize that the cases here reported represent a special group, and that there are other factors responsible for recovery of paralysed facial muscles which play an important rôle. The patients studied were those who had required a temporalis transfer operation for lagophthalmos, which in our series was never done until the paralysis had been present for 1 year, and the minimum follow-up period was 1 year; hence they all had established paralysis and of a severe degree, at least a far as the orbicularis oculi was concerned. Furthermore, clinical evidence of associated movements was not so frequent in those patients in the post-operative

study who were not also studied electromyographically. So the point being made here is, not that misdirection of fibres occurs often and is important as a source of re-innervation, but rather that it *does* in fact occur and may be one of several factors influencing recovery.

The mechanisms important in recovery of muscle function may be briefly summarized as follows:

(a) Recovery of the original nerve lesion may occur. In leprosy, as shown by Job and Desikan (1968), there may be segmental demyelination or axonal degeneration in funiculi invaded by the bacillus or there may be oedema of the nerves resulting from destruction of a few axons, causing neuropraxia in the adjacent non-infected funiculi. The view expressed by Ranney (1970) is commonly held, namely that there is often a combination of neuropraxia, segmental demyelination and axonal destruction, and that the spontaneous recovery frequently seen, especially in cases of lepra reaction, is often due to the recovery of the nerve lesion itself, particularly if it is neuropraxic in origin.

(b) Axon sprouting, whether at the sub-terminal level or, as described above, at a much more proximal level which can lead to misdirection of nerve fibres, is certainly a factor.

(c) Hypertrophy of muscle fibres in remaining motor units may occur following exercise. This has been commonly observed clinically in orbicularis oculi by the authors and by others such as Brand (1965) and Karat (1969, personal communication), and has been demonstrated in other muscles experimentally by Harreveld (1945). Edgerton (1967) has stated that over-stretching induces muscle atrophy, and therefore hypertrophy of surviving motor units can be facilitated by surgical means which prevent over-stretching of partially denervated muscles, e.g., the myofacial and static slings usually performed for treatment of lagophthalmos.

(d) Increased central excitation or recruitment is seen in hemifacial spasm, and in the cases here reported it seemed evident in one patient who showed also contralateral activity of levator labii superioris on tight eye closure but only ipsilateral co-contraction on gentle closure.

(e) The possibility of re-innervation through branches of other cranial nerves, especially of the 5th, as suggested by Martin and Helsper (1957), must not be forgotten. The possibility that this occurs through a direct take-over by motor neurons of the trigeminal nerve is excluded by the lack of associated movements in facial muscles on mastication. Conley (1964) has suggested that after resection of segments of facial nerve, regeneration into the terminal branches may occur from the intrapetrous portion of the facial nerve by way of the geniculate ganglion and superficial petrosal nerve. This could account for recovery of muscles in the area supplied by the maxillary division of the trigeminal nerve, notably the lower half of orbicularis oculi. However, it seems unlikely that the frontalis muscle could be re-innervated in this way. The same author (1971) has pointed out that such re-innervation is "smooth, has emotional control, and is often forceful in degree". While not denying this as a possible means of recovery in leprous neuritis, in general the blinkbursts and voluntary associated movements seen resemble more closely the phenomena seen in Bell's palsy, which have been attributed by Taverner (1955) to mis-reinnervation from other branches of the facial nerve.

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The authors wish to acknowledge the constructive criticism given during the writing of this paper by Dr John Pearson of Oxford and Sungei Buloh, Malaysia, Dr S. S. Pandya of the J.J. Group of Hospitals, Bombay and Dr G. M. Taori, Department of Neurological Sciences, C.M.C. Hospital, Vellore. Without the tireless and capable assistance of Mr Ramachandra Rao of S.L.R. Sanatorium, Karigiri, this investigation would not have been possible.

Requests for reprints may be made to D. A. Ranney, Chief of Surgery, S.L.R. Sanatorium P.O., via Katpadi, North Arcot District, Tamil Nadu, South India.

References

Antia, N. H., Divekar, S. G. and Dastur, D. K. (1966). The facial nerve in leprosy. I. Clinical and operative aspects. *J. Int. Lepr.* **34**, 103.

Brand, P. W. (1964). Deformity in leprosy. In *Leprosy in Theory and Practice*, 2nd ed. (Eds: R. G. Cochrane and T. F. Davey.) Bristol: John Wright and Sons Ltd.

Brand, Margaret (1965). *Watch Those Eyes: Eye Complications in Leprosy*, 2nd ed., p. 13. London: The Leprosy Mission.

Conley, J. J. (1964). Accessory neuromotor pathways to the face. *Trans. Am. Acad. Ophth. & Otol.* **68**, 1064.

Conley, J. J. (1971). Treatment of facial paralysis. *Surg. Clin. N. Amer.* **51**, 403.

Dastur, K. (1956). The motor unit in leprous neuritis: A clinico-pathological study. *Neurology (Bombay)* **4**, 1.

Dastur, D. K., Antia, N. H. and Divekar, S. G. (1966). The facial nerve in leprosy. 2. Pathology, pathogenesis, electromyography and clinical co-relations. *Int. J. Lepr.* **34**, 118.

Edgerton, Milton T. (1967). Surgical correction of facial paralysis: A plea for better reconstructions. *Ann. Surg.* **165**, 985.

Ford, F. R. and Woodhall, B. (1938). Phenomena due to misdirection of regenerating fibres of cranial, spinal and autonomic nerves. *Arch. Surg. (Chicago)* **36**, 480.

Harreveld, A. Van (1945). Re-innervation of denervated muscle fibres by adjacent functioning motor units. *Am. J. Physiol.* **144**, 477.

Job, C. K. and Desikan, K. V. (1968). Pathologic changes and their distribution in peripheral nerves in lepromatous leprosy. *Int. J. Lepr.* **36**, 257.

Magora, A., Sagher, F., Chaco, J. and Adler, E. (1965). An electrodiagnostic study of the lower motor unit in leprosy. *Int. J. Lepr.* **33**, 829.

Martin, H. and Helsper, J. T. (1957). Spontaneous return of function following surgical section or excision of the 7th cranial nerve in surgery of parotid tumours. *Ann. Surg.* **146**, 715.

Ranney, D. A. (1970). Peripheral nerve growth, regeneration and recovery of function. *Karigiri Review* **3**, 61.

Ranney, D. A. and Furness, M. A. (1973). A detailed study of the value of temporalis transfer for lagophthalmos due to leprosy. *Plast. Reconstr. Surg.* (in press–expected March 1973).

Satoyoshi, E., Kinoshita, M. and Doi, Y. (1971). Paradoxical mis-reinnervation phenomenon in cervical root lesions associated with myelopathy. Paper read at the 3rd Asian and Oceanian Conference of Neurology, Bombay.

Sullivan, J. A. (1939). Referred to in discussion by Fowler: Abnormal movements following injury to the facial nerve. *J. Am. Med. Assoc.* **113**, 1003.

Taverner, D. (1955). Bell's Palsy: a clinical and electromyographic study. *Brain* **78**, 209.

Teasdall, R. D. and Salman, S. D. (1971). Mass facial movements: Electromyographic evidence for misdirection. *Neurology (Minneapolis)* **21**, 652.

Abstracts

1. **Dapsone induced peripheral neuropathy**, by E. H. WYATT and J. CLARKE-STEVENS. *Br. J. Derm.*, 1972, **86**, 521.

Dapsone, unlike many other organic chemical compounds prescribed for human disease, is rarely suspected of directly causing peripheral neuropathy, although nerve damage not infrequently arises in the course of its use in leprosy.

The authors report a case in which dapsone was under strong suspicion of provoking peripheral neuropathy in a woman aged 24 who had received 8.6 g of the drug orally in 6 weeks for a condition at first considered to be dermatitis herpetiformis (later diagnosed as herpes gestationis). The neurological deficit was predominantly motor, with a small sensory element, and was mainly noted in the upper limbs. The patient continued to take dapsone at the dose of 200 mg daily until she had received 35 g in 139 days.

After dapsone was stopped, the patient reported improvement in the neurological condition; at the end of 16 months full muscular power had returned, and electromyography revealed no persisting abnormality.

S. G. Browne

2. **Comparison of B1912 and Clofazimine (B663) in *Mycobacterium leprae* infections (35654)**, by C. C. SHEPARD, L. L. WALKER, R. H. VAN LANDINGHAM and M. A. REDUS. *Proc. Soc. exp. Med.*, 1972, **137**, 728-729.

In the experimental infection of mouse footpads with *Myco. leprae*, the activity of a recently synthesized rimino-phenazine compound, B1912, was found to resemble very closely that of clofazimine (B663, Geigy) in such matters as the minimal effective dose and bacteriostatic range at different concentrations. Despite differences in the pattern of tissue deposition, as shown by a higher serum level and lower tissue levels (except in fat) in the case of B1912, the activity of the two compounds in the conditions of the investigation is very similar.

S. G. Browne

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Treatment with 4,4′-diacetyl-diaminodiphenyl-sulfone (DADDS) of leprosy patients in the Karimui, New Guinea, by D. A. RUSSELL, C. C. SHEPARD, D. H. McRAE, G. C. SCOTT and D. R. VINCIN. *Am. J. Trop. Med. Hyg.*, 1971, **20**, 495-501.

The authors report on the clinical and bacteriological results of the first 750 days of treatment of 28 patients with leprosy (out of 327 in a trial reported elsewhere) who had sufficient numbers of leprosy bacilli in their skin smears for appraisal of the proportion of solidly staining bacilli (Morphological Indices) during treatment. This investigation was carried out in the Karimui region of New Guinea, and patients were given an intramuscular injection of the diacetyl derivative of dapsone (DADDS) every 75 days, each injection consisting of 225 mg for adults and 150 mg for children under the age of 6 years.

Morphological Indices fell to near zero in 150 days, and there was a fall in Bacterial Indices compatible with that which would have been expected from standard dapsone therapy. Clinical

response and incidence of lepra reactions were also satisfactory. No drug resistance was noted, but the authors admit that continuing observation of these patients is necessary because of the small quantities of dapsone released by the depot injections (averaging 2.4 mg daily).

W. H. Jopling

4. **Physiopathologie de la névrite hansénienne et bases thérapeutiques (nouvelle approche).** (Physiopathology of leprous neuritis and bases for therapy—a new approach), by A. CARAYON. *Méd. trop.*, 1971, **31**, 503-523.

This detailed and well-documented study of the physiopathology of peripheral neuritis in leprosy embodies the investigations that the author has carried out over the past few years. In particular, the determinative rôle of constrictive fibrous tunnels and osteoligamentous narrowings on the whole pathology of leprous neuritis is supported by clinical observations, perineural lymphography and arteriography with micronized lipiodol, and operative exposure. The vascular and lymphatic occlusion, the slowing of the radio-opaque flow, the 10-fold retardation in the absorption of the injected lipiodol—all indicate the importance of the constriction. In addition, localized arterial spasm reduces the blood flow to the constricted nerve segment.

The commonly affected peripheral nerves are studied in turn, with a wealth of practical detail, and the importance in each case of the anatomical constrictions is demonstrated. Other germane factors, such as the elongation and hence compression of the ulnar nerve when the elbow is flexed, and the presence of a zone of non-inflammatory oedema distal to the site of constriction, are investigated and recorded.

The author attempts to correlate the sites of maximum observed damage in the peripheral nerves with the liberation of specific substances from dead *Mycobacterium leprae*, myelin and Schwann cells, together with enzymes released from leucocytes as the result of chemotherapy.

The bases for rational therapy of threatened or actual peripheral nerve damage are discussed in the concluding section. The author favours a bacteriostatic drug, coupled with surgical release of constricting bands if present.

(This paper covers a vast field in rather summary fashion, touching lightly and provocatively on such specialized realms as the biochemistry and immunology of neuropathology. Unfortunately, no references are given to the numerous works cited.)

S. G. Browne

5. **Prolonged survival of skin allografts in leprosy patients,** by S. H. HAN, R. S. WEISER and S. T. KAU. *Int. J. Lepr.*, 1971, **39**, 1-6.

The authors studied the fate of 30 skin allografts obtained from 10 healthy persons and grafted reciprocally, and on to the skin of 10 patients with tuberculoid leprosy and 10 patients with lepromatous leprosy. The survival times were significantly prolonged in both groups of leprosy patients, with means of 13.44 days in those with tuberculoid leprosy and 15.2 days in those with the lepromatous form, compared with a mean of 11.22 days for the healthy recipients. By the 11th day, the grafts had been rejected in all but 2 of the healthy recipients, whereas the grafts in all but 2 of the patients with leprosy were surviving. Only 2 of the grafts on patients with lepromatous leprosy were rejected by the 14th day. Graft survival was thought to be related, in the case of patients with lepromatous leprosy (all on treatment with dapsone), to the presence of organisms in the skin lesions.

The authors discuss these important findings of impaired allograft immunity in the light of current work on cell-mediated immunity and on specific and non-specific immunological deficiencies.

S. G. Browne

6. **Le traitement de la lèpre par la rifampicine. (The treatment of leprosy with rifampicin),** by J. LANGUILLON. *Med. Afr. Noire,* 1971, **18**, 765-770.

22 patients suffering from lepromatous leprosy were treated with rifampicin (Rimactane) at doses of 900 mg (6 patients), 600 mg (10 patients), and 300 mg (6 patients), daily for 12 months. In all three groups, the Morphological Index fell to zero within 6 months, and the Bacterial Index showed an average fall of between 1.22 and 1.35, no significant dose-related differences being discernible.

Clinical improvement appeared to be rather greater in the group taking the highest dose. Reaction occurred in 2 patients taking the highest dose, 2 in the next group, and 1 in the group given 300 mg daily. No instance of intolerance was seen.

The author recommends a daily dose of 900 mg.

S. G. Browne

7. **Fate of *Mycobacterium leprae* in macrophages of patients with lepromatous or tuberculoid leprosy,** by T. GODAL and R. J. W. REES. *Int. J. Lepr.,* 1970, **38**, 439-442.

Comparisons were made of the ability of cultures of macrophages from patients with lepromatous or tuberculoid leprosy to produce lysis of ingested *Mycobacterium leprae, Myco. lepraemurium* and *Myco. tuberculosis.* After 10 days observation, little or no lysis occurred in any of the preparations and there were no major differences between macrophages from the two groups of patients in respect of lytic ability. These results fail to confirm the findings of Barbieri and Correa [this *Bulletin,* 1968, v. 65, abstr. 919], and of Beiguelman [*ibid.*, abstr. 2523]. Possible reasons for this discrepancy are discussed.

G. R. F. Hilson

8. **Systemic sclerosis masquerading as leprosy in Ghana,** by J. ADDY. *Ghana med. J.,* 1971, **10**, 218-222.

This is a report on 2 Ghanaian males who were originally suspected of having leprosy because some areas of skin had become hypopigmented. In both cases subsequent developments led to a correct diagnosis of systemic sclerosis. After discussing the symptoms and signs of this disease, the author comments that, with regard to the skin, "All that is hypopigmented or depigmented is not leprosy" and, with regard to the fungus, "All that is trophic and clawed is not leprosy."

W. H. Jopling

9. **Does entrapment neuropathy contribute to nerve damage in leprosy?,** by H. SRINIVASAN and P. R. NAMASIVAYAM. *Indian J. med. Res.,* 1971, **59**(9), 1385-1391.

In leprosy, a disease in which intraneural damage is characteristic, transposition of the ulnar nerve (external decompression) is of limited value in treatment. However, a small proportion of those wih signs of ulnar nerve involvement may benefit from this operation; in this paper, based on a study of 192 adult patients suffering from lepromatous leprosy, the authors show that this small group can be selected on the basis of the following criteria: (1) a small interval between the olecranon and the medial epicondyle of the humerus (25 mm or less with the elbow extended), and (2) when this interval increases by more than 50% with the elbow fully flexed. Anatomical abnormalities of the arcuate ligament were investigated but were exonerated as causes of entrapment neuropathy.

W. H. Jopling

10. **Characterization of the cellular immune defect in lepromatous leprosy: a specific lack of circulating *Mycobacterium-leprae*-reactive lymphocytes**, by T. GODAL, B. MYKLESTAD, D. R. SAMUEL and B. MYRVANG. *Clin. Exp. Immunol.*, 1971, **9**, 821-831.

"The blastogenic response of leucocyte cultures from patients with tuberculoid and lepromatous leprosy has been studied. The leucocytes from the two groups were studied simultaneously and cultivated in the same pool of normal human serum. While the leucocytes from 28 tuberculoid patients responded quite strongly to *Mycobacterium leprae* after 7 days of culture (average lymphocyte transformation 11.1%), there was a complete lack of response in similar cultures from 27 lepromatous patients (average 0.1% transformed cells). These results were confirmed by studies on cellular incorporation of ^{3}H-thymidine in the cultures from four tuberculoid and four lepromatous patients."

"This lack of response was quite specific as leucocytes from several lepromatous patients responded to BCG. Furthermore, 4 patients with both lepromatous leprosy and tuberculosis responded as strongly to BCG and PPD as tuberculous patients without leprosy. In the mixed leucocyte reaction, between two lepromatous or two tuberculoid patients respectively, the lepromatous cells responded well (average 15%) and comparably to tuberculoid cells (average 12.1%)."

"The blastogenic response of purified lymphocytes to *M. leprae* revealed a similar pattern, i.e. the tuberculoid cells responded well, while again there was a lack of response in the lepromatous group."

"It is concluded that the lepromatous patients lack circulating lymphocytes responding to *M. leprae*, indicating that their immunological defect as observed in the present study has features in common with immunological tolerance."

Authors' summary

11. **Primeiros resultados do tratamento da lepra com a kanamicina. (First results of the treatment of leprosy with kanamycin)**, by D. V. A. OPROMOLLA and S. C. ALMEIDA. *Revta Bras. Leprol.*, 1970, **37**, 17-39.

10 patients with lepromatous leprosy were treated with kanamycin in a daily dose of 1 g for 90 days. In 6 patients there was transitory albuminuria and in 8 patients auditory involvement as indicated by audiometry. Only one patient showed gross symptoms such as giddiness, deafness and tinnitus and he was obliged to discontinue treatment. In the other patients the auditory damage occurred in the higher frequency above the level of social conversation and it was not perceptible to the patients themselves. The clinical results of treatment were similar to those seen with other antibiotics such as rifamycin and oxytetracycline, being clearly evident in the first 30 days especially in patients whose condition was deteriorating. In the cases studied bacteriologically there were morphological changes in the bacilli and 3 patients became bacteriologically negative. Kanamycin is endowed with bactericidal activity for leprosy bacilli, which is particularly evident in the elongated bacilli characteristic of patients who are deteriorating. Kanamycin is a drug with high toxicity for the auditory part of the ear, so that its administration requires careful clinical vigilance, and whenever possible, audiometric control. It is not suitable for mass campaigns, but its restrained use is recommended for patients who have not responded to classical treatments or who are clinically deteriorating. The period of treatment should not exceed 30 days. Further investigation is desirable in order to establish the optimal therapeutic doses and to diminish toxicity.

F. Hawking

12. **BCG oral e reacão leprominica (Oral BCG and the lepromin reaction)**, by J. ROSEMBERG and M. C. ROCHA PASSOS, Jr. *Revta Bras. Leprol.*, 1970, **37**, 51-60.

This is a review of previous work by Rosemberg and by other workers. For the details the original must be consulted.

The authors conclude that BCG vaccination exerts an indisputable effect upon the lepromin reaction, achieving in certain circumstances a conversion in 100% of cases. There is no difference whether the vaccination is administered orally or parenterally. Ingestion of BCG orally (a) transforms lepromin-negative persons into Mitsuda-positive ones; (b) produces positive lepromin reactions in persons who were negative when tested years earlier; and (c) can intensify lepromin reactions which are already positive. Oral vaccination with BCG shows clearly that positive Mitsuda reactions are produced independently of allergy; the reactions occur in the same form whether tuberculin allergy is previously present or absent. There is dissociation between allergy to tuberculin and the reaction to lepromin, the two phenomena being independent of one another. Immunity to leprosy (as measured by the Mitsuda reaction) can be created without the occurrence of sensitization to tuberculin. All the observations under review strongly suggest that BCG, whether given orally or parenterally, exercises a specific protection against leprosy.

F. Hawking

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