Editorials

SYMPOSIUM ON DAPSONE RESISTANCE

This Number of *Leprosy Review* is devoted to a single and highly relevant theme, namely, dapsone resistance. For over 25 years dapsone has been standard first line treatment for leprosy almost everywhere, its advent a turning point in the history of the disease. Millions of patients have been benefited by it and large numbers restored to health and strength. Equally important are the changes in outlook it initiated, so that leprosy treatment and control began to figure in the health programmes of many nations, and numerous leprosy control schemes were developed, based on chemotherapy with dapsone. At the same time the interest of research workers was awakened, leprosy became an attractive sphere of study, and enormous progress in our understanding of the disease has resulted. This process has culminated in the acceptance by the World Health Organization of leprosy as one of the 6 diseases selected for intensive research and attack.

Mercifully and quite empirically, for over a decade dapsone was administered in high dosage, and in contrast to experience in the chemotherapy of tuberculosis, drug resistance to dapsone was not encountered. The euphoria then generated tended to gloss over what might happen with small dosage and irregular treatment. These conditions have arisen and are widespread. A vogue for low dosage followed experimental work in the mouse. The very expansion of leprosy control programmes inevitably introduced situations of diminished oversight and poor patient co-operation. Dapsone resistance is now a rapidly growing problem full of menace for future chemotherapy in leprosy.

The Editorial Board, very aware of the importance, dangers and impact of this problem, decided to allocate a whole Number of *Leprosy Review* to it, and experts in the field and those with most experience were invited to co-operate. The response was most generous. In the pages of this Number there is to be found a unique consensus of experience and reflection on the problems involved, extending geographically from S. E. Asia, through India to Africa and the Near East. It includes the first authenticated reports of primary dapsone resistance. Appropriately the list of distinguished contributors is headed by our Consulting Editor, who as Chairman of the WHO Expert Committee on Leprosy and Secretary-Treasurer of the International Leprosy Association is in touch with developments everywhere and was invited to contribute the opening Editorial. Without doubt this Number of *Leprosy Review* will be the standard reference on dapsone resistance in leprosy for some time to come.

T. F. DAVEY

DRUG RESISTANCE IN LEPROSY—MYTH OR MENACE?

The papers that comprise this issue of *Leprosy Review* will provide sombre reading for field workers and Ministries of Health alike. They bring together within a convenient compass a mass of factual and experimental evidence that must affect the whole strategy of leprosy control throughout the world, with its implications for finance and staff, for training programmes and the integration of leprosy treatment/control schemes into the general health services. Furthermore, the findings here set forth will necessarily affect the fund-raising and propaganda activities of voluntary agencies.

For practical purposes, these papers are concerned with bacilli resistant to dapsone, but cross-resistance between dapsone and the sulphonamides, and between thiambutosine and thiacetazone provides interesting (though less important) clinical and experimental data.

Ever since doctors and medical auxiliaries dared to try to treat with a single drug patients suffering from multibacillary forms of the chronic mycobacterial infection that is leprosy, they were really asking for this to happen, in the light of experience painfully acquired over the years in many countries with the sister-disease, tuberculosis.

The only surprising feature in this sad story is the time factor—20 years were to elapse after the initiation of an essentially monotherapeutic treatment before the first cloud, "no bigger than a man's hand", appeared on the Malaysian horizon, and then another dozen years or so before the real threat of the emergence of drug-resistance on a wide scale became apparent. Workers in the early days of the sulphone era may perhaps be forgiven for their optimistic assumptions. After all, the introduction of the sulphones did mark the dawn of a new day for leprosy sufferers, especially in the African continent. Leprosy did seem to be different in many respects from infections with related organisms, and the sulphones in extremely low serum concentrations seemed to be mycobacteriostatic.

Having been privileged to examine clinically the first patients (at Sungei Buloh, Selangor, Malaysia) whose relapse, it was reasonably suspected, was due to the emergence of sulphone-resistant organisms, and having seen the microscopical evidence in smears containing numerous morphologically normal organisms, the writer was early alerted to the possibility that this initial observation might be the precursor of many more. By that time (1963), clinical suspicions could be confirmed by the elegant mouse foot-pad technique brilliantly adapted to demonstrate the stepwise development of resistance. The rest is history.

The 5th Expert Leprosy Committee of the World Health Organization meeting October 1976 (whose Report should be appearing shortly), examined the evidence accruing from many sources of the emergence of dapsone-resistant *Mycobacterium leprae* and of the apparent appearance of resistance in wild strains (indicating some kind of decrease of susceptibility to drug concentrations, formerly mycobacteriostatic) isolated from newly-diagnosed patients, and made recommendations for therapeutic regimens that would, it was hoped, postpone indefinitely the emergence of such forms on an unmanageable scale and treat

successfully those patients whose clinical relapse is due to drug-resistant bacilli. Meanwhile, the consequences of these findings have to be accepted by those responsible for leprosy treatment/control programmes, and steps taken urgently to forestall the imminent threat of a pandemic of patients with drug-resistant bacilli.

One curious observation is the patchy reporting of such cases. Much depends, naturally, on the length of time that the sulphones have been used in any given area and the lepromatous/tuberculoid (or, better, the multibacillary/paucibacillary) ratio, which may be as low as 1 : 10 or even 1 : 20 in some African countries where regular whole-population examinations are done. Much more depends on the degree of awareness or suspicion shown by doctors and medical auxiliaries. Ignorance of the clinical presentations of skin lesions due to drug-resistant bacilli, misdiagnosis of clinical and bacteriological relapse (as erythema nodosum leprosum), and a failure to use the investigative laboratory procedures that are (or should be) generally available in field-work would account for the non-recognition of such cases. It cannot be too strongly emphasized that bacteriological relapse frequently precedes clinical evidence of relapse: therefore regular and frequent slit-smear examinations should be performed on patients whose multibacillary leprosy is apparently quiescent after adequate periods of treatment.

For most countries, clinical confirmation of clinical suspicion of the emergence of resistance will be the norm, with field laboratory work of the highest possible standard—for the recognition and enumeration of "solid staining bacilli". The experimental confirmation by the mouse foot-pad technique is beyond the reach—or the financial and operational resources—of the majority of countries where the problem is certainly occurring now. It is here that offers of international co-operation would be most welcome—Japan to South-East Asian countries, United States of America to Central and South America, England and Belgium to Africa. *Noblesse oblige* when the threat is global. Typical cases could be selected for laboratory confirmation—as a convincing demonstration of the actual occurrence of relapse due to resistant bacilli.

Treatment

Fortunately, the great majority of leprosy sufferers in the world may still be treated with a single drug—the cheap and effective dapsone. The more intensely case-finding surveys are done, the greater the proportion of cases of paucibacillary and self-healing leprosy that will be detected. In these, cell-mediated immunity will suffice, with a single drug, to overcome the infection, and the risk of the emergence of dapsone resistant bacilli is negligible. Perhaps a greater use could be made of the lepromin reaction in those cases of indeterminate leprosy that may really be pre-lepromatous. A persistently negative Mitsuda reaction would ideally indicate the need for prolonged, multidrug therapy.

It is in those patients suffering from multibacillary forms of leprosy that real therapeutic and financial difficulties will arise, and problems associated with controversial public relations aspects. In theory, more than one drug should be given: which drugs and for how long? are questions that may evoke different answers in different countries. Dapsone is a *sine qua non*. In addition, rifampicin for a few weeks at a dose of 600 mg a day, or at a higher dose (900 mg) on 2 successive days every month for some months, or even a single dose of

1500 mg—all regimens are on trial. Dapsone is given concurrently and then continued alone.

Clofazimine has its advocates, given at a dose of 100 mg every other day (with daily dapsone) for 3-6 months, to be followed by dapsone alone. Other drugs, such as thiacetazone and ethionamide, will have to be investigated further in this context. The general recommendation to continue treatment "for life" for patients with multibacillary forms of leprosy, itself contains the seeds of resistant bacillary forms, since a small but definite proportion of persister organisms—once they leave the dormant stage and begin multiplying again—will be potentially resistant mutants.

Whether we like it or not, we must assume that for some time to come—because of expense and the logistic difficulties of implementing multi-drug regimens—many countries will continue to favour monotherapy with dapsone for all patients suffering from leprosy whatever the form of the disease.

Ideally, and in order to forestall—or indefinitely postpone—the emergence of dapsone-resistant bacilli, many leprologists now recommend that a high daily dose of dapsone be given from the outset of treatment to all patients suffering from leprosy. Herein lies a snag. It is common experience that a high dose of dapsone, administered from day one to all patients suffering from multibacillary forms of leprosy, will be followed within a few days in many patients by the lesions of erythema nodosum leprosum or, in the case of borderline-lepromatous leprosy, by the signs of polyneuritis (reversal reaction). In some countries, this proportion has been so high as to imperil the acceptance of the leprosy programme. Our French colleagues have done much work on what they call the "reactogenic" properties of the different drugs used for leprosy. Before such findings are dismissed as "anecdotal" or "uncontrolled", we should do well to remind ourselves of the considerable variations in the clinical pattern of leprosy in different countries and the differences in response to anti-leprotics. Insomnia and manic hyperactivity not infrequently follows every dose of 100 mg dapsone in some individuals. Fixed eruption following sulphone therapy may vary between 0.1% and 3.0% in different communities, and dermal fibrosis may vary from the negligible to the enormous; some communities show unduly high prevalence rates of kebid, ainhum, juxta-articular nodules, paratrochanteric fibrosis, and palmar and plantar hyperkeratosis, framboeisial or following friction. Some patients with leprosy seem especially prone to the rapid development of intraneural fibrosis and a dense fibrous sheath around peripheral nerve trunks that may even be the site of deposit of calcium salts. However, the local situation, including the ready availability of facilities for diagnosing and treating such episodes—however precipitated—must determine the posology of anti-leprotics, and the immediate risks involved must be nicely balanced against the remoter benefits (to the patient himself and the community) of the relegation to the distant future of the emergence of dapsone-resistant bacilli.

The treatment of patients with reasonably ascertained dapsone-resistant disease has hitherto been simple—monotherapy with either rifampicin or clofazimine. But, by the same token, multidrug therapy (with both rifampicin and clofazimine) must henceforth be recommended, especially since rifampicin-resistant bacilli have

to these cripplingly costly proposals?

The question is far from academic or theoretical in the light of the discovery that some recently diagnosed patients are suffering from multibacillary forms of

leprosy attributable to bacilli primarily resistant to sulphones. And if such cases exist now (suggestive of the pathogenicity and invasiveness of these organisms), it will not be long before, in the same community exposed to the same bacilli, some people will succumb to forms of leprosy which, by reason of innate degrees of cell-mediated immunity, will declare themselves as "tuberculoid" leprosy. The possibility that such cases are in reality infected with dapsone-resistant bacilli will doubtless be overlooked until lack of the expected response to monotherapy with dapsone alerts the clinician.

The implications of all these serious observations for governments and voluntary agencies will not be lost. The future of public relations regarding leprosy bristles with difficulties; awkward questions will be asked about published claims for rapid and cheap "cure", about the real extent of the menace of drug resistance and the cost of available antileprotic drugs: and patient resistance may be matched by official disillusionment and resignation to the "inevitable".

Another implication concerns the desirability and practicability of integrating leprosy programmes with the general health services: since the antileprosy campaign is likely to prove more difficult and more protracted (and more expensive) than hitherto imagined, Ministries of Health will still need to be able to call upon expert advice at all levels. The delicate balance between the advantages to be gained by integrating leprosy into the general health programme will have to be examined against the risk of perpetuating the stigma of the disease and incurring the expense of organizing separate services for several diseases.

This whole question of drug-resistance in leprosy underlines the urgent necessity for developing new anti-leprotic agents. Perhaps some derivatives of hydnocarpic acid may show the way forward in attacking the multiplying organism at a novel and vulnerable site.

It also implies that the whole question of infection with *Mycobacterium leprae* must be taken much more seriously than it has been. Clinical standards and laboratory cover must likewise be raised, and more resources made available by all possible means so that we may do what we can while we can to control this most challenging of diseases.

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Dapsone-resistant Leprosy and Its Implications for Leprosy Control Programmes

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The incidence of suspected dapsone-resistant leprosy in the Addis Ababa area is now about 3% per annum of all lepromatous patients under treatment, and this figure may not be atypical of other areas of the world. New (and expensive) treatment programmes are needed to prevent the emergence of dapsone-resistant leprosy; and training programmes and administration of leprosy control programmes need revision to make possible the early diagnosis and correct management of dapsone-resistant cases. This paper suggests some ways in which the problems of diagnosis, treatment and prevention of dapsone-resistant leprosy can be tackled under field conditions. If measures of this type are not undertaken, there is serious risk that the spread of primary dapsone-resistant leprosy will make leprosy control by chemotherapy unattainable.

Introduction

Patients who have developed dapsone-resistant leprosy are now being diagnosed in increasing numbers, and are indeed becoming one of the major sources of anxiety in the management of leprosy control programmes. Even one patient with progressive disease despite regular treatment will lower the morale of a whole clinic, encourage the belief that leprosy is indeed incurable, and so make case holding more difficult. Also there is an obvious risk that such patients could be a source of new leprosy cases which will be dapsone-resistant from the start. Prompt identification of patients with *prima facie* evidence of dapsone resistance, facilities for proper investigation and management, and availability of second line drugs for treatment of resistant cases are therefore now essential parts of a leprosy control programme.

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These requirements in themselves, however, are insufficient. Properly implemented, they will deal with new cases of dapsone-resistant leprosy as they arise; but prevention is better than cure. The application to leprosy of the principles of prevention of drug resistance which have been established in the field of tuberculosis is long overdue, and treatment policies for leprosy control programmes need revision with this end in view. Furthermore, the possible presence of cases of primary dapsone resistance may require investigation: should it prove to be a significant problem in any particular area, treatment regimens will need yet further modification.

These innovations will affect both patient care and also many aspects of training, supervision and administration. (It is possible that this is one reason for hesitation over their introduction.) The purpose of this paper is to review the findings of dapsone-resistant leprosy in Ethiopia, where it has been possible to study the problem more fully than in most centres, and where there is greater awareness of its extent and potential dangers, and suggest some principles which can be applied to the diagnosis, treatment and prevention of dapsone resistance in leprosy control programmes.

Findings in Ethiopia

Dapsone therapy was introduced to Ethiopia during the early 1950s, and the first patients with clinical evidence of dapsone-resistant leprosy were seen during the period 1965-1970. By the end of 1972, 41 patients had shown sufficiently clear evidence of clinical deterioration despite continued and reasonably supervised dapsone therapy to require transfer to treatment with another drug. At that time mouse foot-pad tests could only occasionally be undertaken; the clinical diagnosis was, however, confirmed in all 4 cases in which they were performed.

From 1973 onwards patients with clinical evidence of dapsone-resistant leprosy have been seen in increasing numbers in both city and rural clinics, though they have been very uncommon in clinics established for shorter periods than about 10 years. It is not possible to give accurate figures for the country as a whole; facilities for diagnosis are not fully developed, and not all suspected cases are referred to the central leprosy hospital in Addis Ababa. However, from a total in 1976 of about 65,000 registered patients (about a quarter of them lepromatous–LL or BL) about 350 have been reviewed in Addis Ababa for suspected dapsone resistance. Results of mouse foot-pad tests were available in only 82 cases, but only in 4 of them was the clinical suspicion disproved. It appears, therefore, that when, on sympathetic questioning, these patients stated that their disease was getting worse in spite of continued and reasonably regular treatment with dapsone, they were usually telling the truth.

In Addis Ababa itself the problem of dapsone-resistant leprosy can be more accurately defined. Since early 1973 all patients receiving treatment in Addis Ababa and suspected of developing dapsone-resistant leprosy have been referred to a single unit, the Medical Research Council Leprosy Project, for investigation and management. The figures of this group of patients are therefore more complete and more susceptible to analysis.

During the 4 years 1973-76 the number of registered patients attending clinics in Addis Ababa and classified as lepromatous has remained fairly stable at about 1500. From this population 50-60 patients per annum have shown evidence of

dapsone-resistant leprosy (Table 1). Thus the incidence of suspected cases in these clinics is about 3% per annum.

The results of mouse foot-pad tests, in patients in Addis Ababa and those from elsewhere in Ethiopia, are shown in Table 2. (About 60% of the tests were performed in Ethiopia, the remainder in the National Institute for Medical Research, London. Duplicate tests demonstrated good agreement between the results from the 2 laboratories.) Patients changing treatment without trial were those whose leprosy was sufficiently severe (i.e. damaging eyes, larynx, testes or nerves) as to make the risk of further deterioration unjustifiable. Such patients were given priority for mouse foot-pad tests which, when performed, always showed dapsone resistance. The other group of patients receiving priority were those from outside Addis Ababa. For patients living in Addis Ababa, who could be more fully supervised, reliance was chiefly placed on the results of a period of trial treatment with dapsone.

TABLE 1

Number of patients in the Addis Ababa area with suspected dapsone-resistant leprosy

Year	Number of patients	
	New cases	Total cases
1972		41
1973	56	97
1974	63	160
1975	53	213
1976	63	276

TABLE 2

Results of mouse foot-pad dapsone sensitivity tests according to clinical status of 361 patients with suspected or proven dapsone-resistant leprosy

Clinical status	Number of patients			
	Mouse foot-pad tests performed			Not tested
	Dapsone resistant	Dapsone sensitive	Results awaited	
Patients in Addis Ababa				
Changed treatment without trial	40	0	1	61
Changed treatment having deteriorated during trial	9	1	2	27
Still under trial	9	1	2	147
Patients elsewhere in Ethiopia				
Changed treatment without trial	4	0	2	8
Changed treatment having deteriorated during trial	2	0	1	2
Still under trial	14	2	3	23

With such large numbers of patients with acquired dapsone resistance the risk of primary dapsone-resistant leprosy is obvious. A small scale study including patients from Addis Ababa and other areas where dapsone has been in use for 10 years or more has shown that of 8 patients with previously untreated lepromatous leprosy, 5 have shown dapsone resistance on mouse foot-pad testing (Pearson, Haile and Rees, 1977).

Discussion

To understand some of the problems of diagnosing dapsone resistance in leprosy, and to clarify the reason for the "lag phase" of almost a quarter of a century from the first use of dapsone to the appreciation of how potentially serious a problem dapsone resistance can be, it is necessary to review some of the properties of dapsone, and to define "dapsone resistance" as precisely as possible.

THE PROPERTIES OF DAPSONE

The most striking property of dapsone is its extreme effectiveness in inhibiting the multiplication of *Mycobacterium leprae.* Evidence both from experimental leprosy in the mouse and small scale clinical trial (Waters *et al.,* 1968) indicates that dapsone in a dosage as low as 1 mg daily will (at least initially) control the infection and lead to the death of the majority of leprosy bacilli in the patient. On the other hand, dosage levels of 100 mg daily are normally safe and free of toxicity, and even higher dosage can be used on occasion with few side effects. Thus the ratio of achieved to minimal inhibitory concentration in patients receiving dapsone in full dosage is unusually high for the chemotherapy of any infection; certainly it is much higher than that achieved by any drug used in the chemotherapy of tuberculosis.

It is this remarkable "safety margin" which accounts for the good results of dapsone used as monotherapy even in lepromatous leprosy. Other drugs are effective against leprosy, but their use as monotherapy against lepromatous leprosy almost always leads to the emergence of acquired drug resistance, usually within the first 3 years of treatment (Garrod and Ellard, 1968; Hastings *et al.,* 1969). These other drugs have "safety margins" against leprosy comparable to those of drugs used in the chemotherapy of tuberculosis. The multiplication times of *M. tuberculosis* and *M. leprae* are different, but clinical evidence of drug resistance takes approximately the same number of generation times to emerge. It is also this "safety margin", together with the long multiplication time of *M. leprae,* which accounts for the prolonged delay in the appearance of cases of dapsone-resistant leprosy. The first proven cases were reported by Pettit and Rees (1964), and it was more than a decade later that the extent of the problem in Ethiopia was analysed.

THE DEFINITION OF DAPSONE RESISTANCE

The remarkable sensitivity of *M. leprae* to dapsone was established by use of foot-pad sensitivity tests (Shepard *et al.,* 1969). It was shown that all strains obtained from previously untreated patients were inhibited from multiplying in the mouse foot-pad when mice were fed 0.0001% dapsone in the diet. Leprosy is therefore defined as dapsone-resistant when bacilli obtained from a patient multiply in mice receiving dapsone 0.0001% in the diet.

However, when patients showing clinical evidence of dapsone resistance began

to be observed, and strains of *M. leprae* from these patients were set up for drug sensitivity tests, it was shown that the degree of resistance could vary remarkably in different patients. Thus, strains of *M. leprae* have been isolated which multiply in the presence of 0.0001% 0.001%, 0.01%, 0.025% and even 0.1% dapsone (Pearson *et al.*, 1975; Pettit and Rees, 1964). The dapsone dosage in man equivalent to these levels in mice is shown in Table 3.

TABLE 3

Dapsone dosage in mouse diet and human therapy required to give similar blood dapsone levels

Dapsone concentration in mouse diet	Dapsone dosage required to give comparable blood levels in man
0.0001%	1 mg daily
0.001%	10 mg daily
0.01%	100 mg daily
0.1%	1 g daily

The implication of these findings is that dapsone resistance develops in a "stepwise" fasion rather than in a single step mutation. This complicates the clinical diagnosis of dapsone-resistant leprosy. For instance, some patients harbour bacilli which multiply in mice fed 0.0001% dapsone in the diet, but are inhibited at 0.001%. The latter concentration represents human dosage of about 10 mg daily. Such patients therefore could be expected to improve (and indeed do improve) at least for a period when treated with dapsone in maximal dosage; it is just possible that some of these patients might be curable with dapsone alone. However, such patients, when treated with dapsone in full dosage, improve for 1-4 years and then almost without exception deteriorate yet again; at this stage their bacilli have been shown to possess a higher degree of dapsone resistance. Thus dapsone monotherapy leads to further selective multiplication of the higher resistant mutants of *M. leprae*; the initial improvement due to higher or more regular dosage can, however, mislead a physician into thinking that the infection is not dapsone resistant.

THE DIAGNOSIS OF DAPSONE-RESISTANT LEPROSY

1. *History*

As in the case of other infections, the history of dapsone resistance is that, after initial clinical improvement there is recrudescence and progress of the disease even despite continued therapy. In the case of leprosy, however, the multiplication time of *M. leprae* is long and so the period till relapse is long. Thus, staphylococcal infections show streptomycin resistance within a few days, and streptomycin-resistant tuberculosis requires a few months to emerge. Streptomycin resistance in leprosy, however, requires several years to develop (Hastings *et al.*, 1969) and dapsone-resistant leprosy may emerge after 20 years or more of regular treatment (Pearson *et al.*, 1975).

2. *Clinical features*

The clinical features of acquired dapsone-resistant leprosy are characteristic. Patients are always suffering from lepromatous leprosy, and show a mixture of

old and new lesions. There is evidence (such as wrinkled ear lobes, and resolved nodules and plaques) of regressing leprosy. But there are also newly appeared, active nodules. These nodules often appear at unusual sites, such as the eye, abdomen, and antecubital and popliteal fossae. Skin smears taken from the active new lesions show high bacteriological and morphological indices (BI and MI). If, however, skin smears are taken from "routine" sites (such as the ear lobes) in these cases, both BI and MI are likely to be low. Biopsies from active lesions will show active leprosy; occasionally the clinical appearance and histological classification of the lesions in the very early stages are borderline rather than lepromatous.

3. *The demonstration of dapsone resistance under field conditions*

It is possible to define 3 stages which lead from suspicion to certainty of dapsone-resistant leprosy.

(a) The patient says he is taking treatment but that he is developing new lesions.

(b) On examination he has lesions that appear to be those of active lepromatous leprosy, and skin smears show a high BI and MI in these lesions, though they remain low elsewhere. The suspicion is enhanced if the lesions are in "unusual" sites.

(c) When the patient receives more closely supervised treatment with dapsone, he does not obtain lasting improvement. If it is certain that the patient's disease is failing to respond, and also certain that he is taking dapsone reasonably regularly, then the leprosy must be dapsone-resistant.

Proof of dapsone resistance depends therefore on confirmation (by means of a supervised clinical trial) of 2 points.

(a) *The patient's disease is progressing.* (In practice, this means distinguishing between active leprosy and reactions.)

For this, the most satisfactory method is the "old fashioned" clinical drawing, recording the leprosy lesions on body charts. These drawings have proved as accurate and useful as photographs, and are reasonably reliable even when sequential assessments are done by different workers. They are not hard to draw, as all that is needed is a record of the position, number and size of the lesions. Drawings are cheaper than photographs, and as reliable (except when first class colour pictures under identical conditions can be obtained over a period of months or years).

It is essential that the clinical assessment of progress or deterioration should be confirmed by good quality skin smears, well taken, well stained, and the BI and MI accurately determined. The smears should be taken from both ear lobes (representing "old" lesions) and from 4 other active skin lesions. It is not necessary for serial smears to be taken from the same sites; indeed, there are advantages in selecting the most active-looking lesions on each occasion.

This part of the diagnosis of dapsone resistance demands no more facilities than those which should be normally available in a leprosy control service.

(b) *The patient is taking dapsone regularly.* In practice, this means treatment that is as fully supervised as possible, ideally with dapsone given by injection (proof of intake) or monitoring dapsone excretion in the urine (proof of absorption of swallowed tablets). This aspect of the clinical trial is somewhat more demanding. Our priority in Ethiopia has been to encourage regular drug

taking (though we can also monitor the urine for the presence of dapsone). In addition to personal contact and encouragement, we have employed 2 methods of encouragement.

(1) For patients living close to clinics with facilities for injections, we have encouraged attendance for weekly injections of dapsone, each injection being recorded. The dosage (400 mg weekly) is adequate for a trial of this type.
(2) Patients who cannot attend clinics weekly are prescribed a dapsone tablet differing from the usual one in appearance. The one we use is a standard 100 mg tablet, sugar coated by a local manufacturer. This process is inexpensive.

Both methods have proved acceptable to patients. We have attempted to convey the impression that they are receiving new treatment, and this appears to have encouraged regularity of drug intake to an extent that would have been hard to achieve had the patient merely continued on treatment with a tablet with which he was already familiar and possibly dissatisfied.

The problems of such a trial in the context of a leprosy control programme are primarily administrative. A special group of patients must be recognized and receive special management. Additional documentation and medication may be needed, and measures should be taken to ensure that patients can be observed regularly over a long period. There is, however, one esential addition to training programmes. It must be taught that for the early diagnosis of dapsone resistance, smears should be taken from active lesions, not only from "standard sites". It is unusual for patients with dapsone resistance to show a gradual rise in BI at standard skin smear sites. Much more commonly there is a sudden jump from negative or almost negative to 4+ or 5+, when smears are taken from a small number of new active lesions. These lesions can only be seen if the patient is undressed and examined. Smears taken under any other conditions will give a false sense of security, and staff taking smears must be taught the need for care in selecting smear sites in potentially dapsone-resistant cases.

Urine tests for the presence of dapsone (Low and Pearson, 1974) are technically straightforward and inexpensive in materials. However, they require apparatus (a spectrophotometer) which is normally available only in central laboratories; they also require supervision and monitoring for quality control. The main problems of their use, however, are the obtaining in rural clinics of specimens from female patients, and the logistics of transportation of urine specimens from remote clinics to the central laboratory. If these problems can be solved, these tests can offer invaluable evidence of regularity of dapsone intake.

Two additional facilities can be of value in the proof of dapsone-resistant leprosy.

(a) Skin biopsies can be of value in assessing the progress and activity of the disease, and occasionally in the diagnosis of atypical reactions. But they are inconvenient for staff and patients, and require good quality processing and skilled interpretation, neither of which are always readily available.
(b) Mouse foot-pad tests can be used for independent confirmation of dapsone resistance. But they are not widely available, and give no more information than a well conducted clinical trial. If available, they should be reserved for occasional use to confirm the accuracy of the clinical trial technique, for

problem cases, and for possible cases of primary dapsone resistance. It is usually better for them to be initiated at the end of the clinical trial rather than the start.

GENERAL IMPLICATIONS OF DAPSONE-RESISTANT LEPROSY FOR LEPROSY CONTROL PROGRAMMES

For many years dapsone-resistant leprosy has hardly been considered as a problem for leprosy control, because of the small number of reported cases. There is now, however, good evidence that every year in the Addis Ababa area about 3% of lepromatous cases under treatment develop symptoms suggestive of dapsone resistance. There is also evidence, both documented and particularly anecdotal that this figure may not be atypical for other parts of the world. This high incidence must greatly influence the planning and execution of leprosy control programmes in the near future, though the final aim (reduction of the incidence of leprosy) and general methods (early detection and regular treatment of all cases for sufficiently long) will remain unchanged.

The low cost, low toxicity, and high "safety margin" of dapsone make it outstandingly the most suitable and widely used drug for the large scale treatment of leprosy by relatively unskilled personnel. Leprosy control in a situation where dapsone is ineffective is almost literally unthinkable. Leprosy control programmes must therefore have, as one of their aims, "the prevention of primary dapsone-resistant leprosy". This aim, in turn, may be divided into 2 components: "the prevention of acquired dapsone resistance" (affecting chiefly therapeutic policies and budgeting); and "the early diagnosis of dapsone-resistant leprosy" (affecting chiefly staff training, supervision and administration). In addition, once dapsone-resistant leprosy has been diagnosed it must be correctly treated. Supervision will be required, particularly for the organizational aspects of the diagnosis and treatment of dapsone-resistant leprosy. And finally, a high incidence of dapsone-resistant leprosy has implications for the integration of leprosy within general medical services.

1. *The prevention of acquired dapsone-resistant leprosy*

The principles of prevention of drug resistance are well known and have been proved in the chemotherapy of tuberculosis. If 2 drugs with different modes of action are employed together, the bacilli resistant to one will be killed by the other. In leprosy, however, the unusual "safety margin" of dapsone may make it necessary to employ multiple drug therapy only for an initial period of intensive treatment, monotherapy with dapsone sufficing thereafter.

The implications of multiple drug therapy are primarily financial; the "second line" drugs for leprosy (thiacetazone, streptomycin, clofazimine, rifampicin and ethionamide) are more expensive, generally by a factor of 100 or so, than dapsone. The necessity for their use will present a challenge to budgeting for leprosy control.

There are, however, other implications, for training and for organization.

(a) *Training.* Health workers and supervisors will need to be taught how to handle drugs with a much lower "safety margin" than dapsone. They must be aware of the symptoms of toxicity; and also aware that the drug combinations they use are novel and may have unpredictable toxic effects.

(b) *Organization.* Because little is known of the relative effectiveness or the

toxicity of any of the multiple drug regimens that must soon be introduced into leprosy chemotherapy, each programme must be regarded as experimental. This means that closer than average supervision will be required, to assess effectiveness, to determine cost-effectiveness, and to document toxicity (which may well vary in different parts of the world). Clinical documentation may require modification if these requirements are to be fulfilled, and the additional responsibilities will increase the burden of leprosy supervisors.

2. *The diagnosis and management of suspected dapsone-resistant leprosy*

Patients with acquired dapsone-resistant leprosy are all lepromatous, and therefore potentially infectious. There is little difficulty in the diagnosis of advanced cases; but early diagnosis is required to prevent the spread of dapsone-resistant bacilli. To achieve this is more a matter of training and organization than of money.

(a) The training syllabus of health workers must include the history and signs of dapsone-resistant leprosy, and how to differentiate it from reactions.
(b) There must be provision in leprosy clinics for regular (at least annual) examination (disrobed, in adequate light) of all patients under treatment for lepromatous leprosy. When patients show signs that are suspicious of dapsone resistance, careful clinical drawings must be performed, and good quality skin smears taken from active lesions. This might be the responsibility of health worker or supervisor, according to circumstances; it will probably require specific documentation.
(c) Alternative forms of dapsone for a period of trial treatment must be available. These should be reserved for patients with suspected dapsone resistance, and probably issued to field workers in accurate quantities for specific patients.
(d) There must be a registration system for these patients, to ensure that serial clinical assessments and skin smears are performed at least 6-monthly, and that special dapsone treatment is available for them in their clinics.
(e) If urine dapsone tests are available, arrangements for collection and transportation of specimens and recording of results are required.

3. *The treatment of proven dapsone-resistant leprosy*

The proof of dapsone resistance is failure to respond to supervised dapsone treatment. The trial period must be as short as possible, to prevent both damage to the patient and spread of dapsone-resistant *M. leprae.* Nevertheless the trial must be long enough to ensure that the diagnosis is accurate. Corect diagnosis is important for both the patient and the control programme. For the patient, because the second line drugs he must take are likely to be less effective and have more side effects than dapsone; and for the control programme, because the cost of drugs to treat this one patient will be comparable to that of dapsone to cure 1000 patients with tuberculoid leprosy.

The decision that a patient has dapsone-resistant leprosy is important clinically and administratively, and should therefore be the responsibility of a senior supervisor or doctor. Once the decision has been made, arrangements will be required for the patient to be supplied with the second line drugs he will need in his own clinic.

4. *Supervision of the programme*

The efficient performance of a programme for the management of dapsone-resistant leprosy is most likely to be achieved if it is the responsibility of a single person, either a doctor or senior supervisor. His areas of concern will include clinical work, teaching, supervision, and administration, though their proportions will vary greatly in different control programmes, and some responsibilities will be delegated.

(a) *Clinical work and teaching*

1. Teach leprosy staff and others concerned the history, clinical features, and differential diagnosis of dapsone-resistant leprosy.
2. Ensure that staff can take skin smears and perform clinical assessments of leprosy patients.
3. Teach staff the indications, dosage, and toxic effects of "second line" anti-leprosy drugs.
4. Teach staff how to conduct the clinical trial to confirm the diagnosis of dapsone-resistance in suspected cases.
5. Arrange for proven cases to be transferred to new treatment, and do so himself if authorized.
6. Undertake the activities he teaches, both on field trips and for patients referred to hospital.

(b) *Supervision and administration*

1. Maintain a register of suspected and proven cases of dapsone-resistant leprosy.
2. Ensure that registered patients are assessed regularly, that results of their assessments are recorded in the central registry, and that their medicines are available in their clinics.
3. Assess the accuracy of diagnosis by monitoring assessments and results of tests, and by field visits.
4. Ensure quality control of skin smears (their taking, staining, and counting) and of urine dapsone tests, if undertaken.
5. Organize for mouse foot-pad tests to be performed in sample patients and in problem cases.

It should be noted that these activities, conscientiously performed, are likely to upgrade the whole of a leprosy control programme. For instance, skin smears are usually inadequately performed, and few workers know how to assess the clinical progress of patients; these skills will be of value for other than dapsone-resistant cases. Also the general use of second line drugs in leprosy clinics is inevitable, and while it will increase the demands on leprosy workers, it may also increase their interest and job satisfaction, and so improve the general quality of patient care.

The training of such a supervisor should be sufficient to enable him to perform competently the tasks he must teach and supervise. For the clinical and technical aspects it will be necessary for him to work in a unit which is regularly involved in the management of patients with dapsone-resistant leprosy; a period of attachment of about a month will be needed even by an experienced supervisor. It will be important for his responsibilities to be precisely defined, particularly in administrative matters, where his programme should complement existing activities.

5. *Implications for integration*

The treatment of leprosy has never been merely the issue of dapsone tablets, and leprosy control involves far more than leprosy treatment. Nevertheless, in the past the simplicity and safety of treating uncomplicated leprosy provided a strong argument for the complete integration of leprosy programmes into general medical services. The benefit to patients of being able to obtain treatment at a non-specialized clinic, and so avoiding stigmatization, was also considerable in some parts of the world. The question, "Why, in the circumstances, did most leprosy control programmes remain specialized?" may best be answered by another question, "Why did so many integrated programmes fail to control leprosy?".

The demonstration that dapsone-resistant leprosy is now a significant problem for leprosy control greatly increases the responsibilities and problems of those treating leprosy. Incorrect large scale treatment (that is, monotherapy with dapsone) will certainly worsen the problem, possibly to the extent that dapsone could become almost valueless. Were this to happen, it is doubtful if leprosy control could ever be achieved by chemotherapy. On the other hand, what is "correct" therapy is still not known, and the problem can only be solved by large scale trials which can only be conducted by specialized programmes. For at least 5 or 10 years, till more answers are known to what are now chemotherapeutic problems, there appears to be a strong case for retaining and upgrading leprosy control as a specialized service. It is possible that such a service would be better able to undertake treatment of other diseases; but the ill-advised integration of leprosy services into general medical programmes now will seriously damage the prospects for leprosy control in the future.

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The Diagnosis and Management of Dapsone-resistant Leprosy

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Based on experience gained with some 120 proven dapsone-resistant patients, the clinical and bacteriological diagnosis of secondary sulphone resistance is described, and the differential diagnosis discussed. The various findings in the clinical trial and experimental proof of sulphone resistance are interpreted according to the pharmacokinetics of dapsone resistance in lepromatous (LL and BL) leprosy. The results of treatment of dapsone-resistant patients with clofazimine (for over 13 years) and with rifampicin (for up to 8.5 years) are compared and contrasted, and the scientific basis for future alternative regimens is briefly discussed.

Introduction

Although the sulphones were first introduced in 1941 (Faget *et al.*, 1943), *prima facie* evidence of sulphone resistance was not reported until 1953 by Wolcott and Ross, and the first clinical and experimental proof was obtained by Pettit and Rees in 1964. Twelve years ago, sulphone resistance was thought to be relatively rare (Pettit, Rees and Ridley, 1965); today, it is met with steadily increasing frequency. Experimentally-proven cases have been reported from the majority of laboratories which use the mouse foot-pad technique. Many other centres have also reported *prima facie* or clinically proven resistance, confirming that dapsone resistance has become a world-wide phenomenon.

Sulphone resistance is of the greatest importance; to the medical services because all alternative drugs are more costly and are usually more toxic than dapsone (DDS); to the patient, because relapse will result in a further period of ill health and perhaps in additional tissue damage; and to contacts, because primary sulphone resistance may only slowly be recognized during an initial period on dapsone therapy in which important clinical deterioration can occur. Therefore it is essential for the diagnosis to be suspected early, to be confirmed clinically and/or experimentally, and for correct alternative treatment to be instituted quickly. The following account of the diagnosis, differential diagnosis and treatment of dapsone-resistant leprosy is based on experience gained with some 120 proven cases seen at the National Leprosy Control Centre, Sungei Buloh between 1961 and 1977.

Diagnosis

Sulphone resistance should be suspected in every lepromatous or borderline-lepromatous (LL and BL on the Ridley-Jopling, 5-point spectrum) patient who

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relapses. Relapse here means the renewed multiplication of leprosy bacilli resulting in the appearance of new lesions, in a patient who had been responding normally to chemotherapy, and whose disease was becoming or had become quiescent or even arrested. Relapse may be due either to the emergence of drug-resistant *Myobacterium leprae,* or to the multiplication, when chemotherapy is stopped, of those small numbers of viable, drug-sensitive *M. leprae* which persist for many years despite adequate sulphone therapy (Waters *et al.,* 1974). The occurence of a relapse in a patient still receiving dapsone is *prima facie* evidence of drug resistance. On the other hand, relapse occurring in a patient who (either on the advice of his doctor or of his own accord) has ceased to take dapsone for at least several months, is usually due to the multiplication of "persisters", but is occasionally due to the emergence of dapsone-resistant mutants. Irregular treatment predisposes to sulphone resistance (Jacobson, 1973), as also does low-dose treatment (Meade *et al.,* 1973), and especially, initial very low dose followed by low-dose dapsone maintenance therapy (Pearson *et al.,* 1976). Patients treated in the past in this way require particularly careful long-term follow-up.

Evidence of relapse due to sulphone resistance has been detected between 3 and 24 years after the start of dapsone treatment, with an average of 15.8 years in Malaysia (Pearson *et al.,* 1975), where dapsone was widely used in full dosage, and of 6-7 years in Ethiopia (Pearson *et al.,* 1976), where low-dose treatment was long in vogue. Sulphone resistance is thought to develop in a step-wise fashion.

The Malaysian patients found to be suffering from secondary dapsone resistance have either been LL or BL (87 and 13 respectively in the first 100 diagnosed); none has been BB. The great majority of patients have had a distinctive clinical appearance. On a background of old resolving lepromatous leprosy, were new active asymmetrical relapse papules and plaques. The ears were frequently lax and wrinkled, and smears from the lobes were either negative for acid-fast bacilli, or else had a low bacterial index (BI) with a morphological index (MI) of 0. On the other hand, the relapse papules were clinically active, some having the appearance of histoid lesions (histologically, 25 of 100 were graded histoid, expansile or hyperactive by Ridley). Such lesions had a high BI, usually 5+ on Ridley's logarithmic scale, with a raised MI. A few patients delayed reporting until their bodies and ears were covered by large numbers of relapse papules, and therefore their lesions appeared nearly symmetrical. But only one of the first 100 dapsone-resistant patients seen at Sungei Buloh was clinically indistinguishable from previously untreated lepromatous disease, with widespread symmetrical infiltration and a small number of near-symmetrical papules. Therefore the combination of history, clinical appearance and smear results gave the diagnosis in almost every case.

Differential Diagnosis

Although the clinical appearances of relapse are so distinctive, several dapsone-resistant patients have been referred to the Leprosy Research Unit as suffering from Erythema Nodosum Leprosum (ENL). ENL papules are usually tender, are purple in colour, may be associated with systemic upset and fever, and change in appearance within 48-72 h; smears taken from them have a variable BI, but the MI is almost always O. Any difficulty in distinguishing between relapse

papules and ENL can be resolved by watching the lesions over 2-3 days, as the former will remain unchanged whereas the latter will show typical progression in this time.

Proof of Resistance

Scientific proof is essential, for once a patient has developed sulphone resistance, it is never possible to revert to dapsone therapy. We have isolated *M. leprae* from 2 resistant patients 5 years and $7\frac{1}{2}$ years respectively after changing treatment to clofazimine. Both strains remained fully sensitive to clofazimine, and both were still dapsone resistant (Rees and Waters, unpublished data).

Proof is by drug-sensitivity testing in the mouse foot-pad infection, and by clinical trial of dapsone, preferably 400 mg twice weekly (in a full-sized adult) given by injection, or else 100 mg daily by mouth with frequent urine tests for dapsone to confirm that the drug is being ingested. These experimental and clinical methods have been well described in the past (Pettit and Rees, 1964; Pettit, Rees and Ridley, 1966) although a few points need stressing.

Excellent correlation has been obtained between the 2 methods of proof, in keeping with the known pharmacokinetics of drug resistance. The latter in general arises from the presence of a few specific resistant mutants in the microbial population. Although not yet studied for *M. leprae,* such mutants have been extensively studied in *M. tuberculosis* where the mutation rate is 10^{-6}-10^{-7} for low, and 10^{-8}-10^{-9} for high resistance. Therefore, out of every thousand million (10^9) tubercle bacilli, one would expect to find perhaps 500 naturally occurring, slightly resistant mutant bacilli, 50 moderately resistant bacilli and one highly resistant mutant against any drug which produces step-wise, as opposed to single-step, resistance. The situation is probably similar for *M. leprae* (Ellard, 1975; Pearson *et al.*, 1975). Untreated LL patients may be infected with 10^9-10^{11} viable *M. leprae.* Because of the exquisite sensitivity of *M. leprae* to dapsone, one would anticipate regular high dosage dapsone therapy to be reasonably successful. Only a proportion of patients might be assumed to possess small numbers of such highly resistant mutants as could survive the blood and tissue levels achieved with doses of the order of 100 mg dapsone daily (although the majority might possess low resistant mutants), and because of the prolonged generation time of *M. leprae* (12-13 days), clinical signs of resistance would take many years to develop. Such is the case. On the other hand, initial low dose therapy would help to "breed out" resistant mutants, and might allow low resistant mutants to multiply sufficiently to produce small numbers of highly resistant mutants even when the latter were initially not present. The situation would be even worse with irregular therapy, or very low dosage maintenance therapy.

Now consider the situation in a patient who has relapsed. Should the patient have been receiving—and taking—dapsone regularly, in full dosage, then the relapse will be due to highly resistant mutants. On the other hand, should the patient have been on low dosage dapsone, then the majority of viable *M. leprae* in his relapse lesions are likely to be only slightly or moderately resistant. But small numbers of highly resistant mutants may well also be present. These points have important applications in the proof of resistance.

EXPERIMENTAL PROOF

The fresh tissue source of the *M. leprae* for mouse foot-pad inoculation, should be obtained by skin biopsy of an active relapse lesion, with a high BI and raised MI. It is advisable to take the biopsy before commencing the full dosage regular dapsone treatment of the clinical test of resistance. This is because, if the patient has been on low dose and/or irregular treatment, the great majority of bacilli in the relapse lesions may be only low or moderately resistant mutants; most of these bacilli will die within about 3 months of starting full dosage dapsone, and at this stage the number of highly resistant mutants may as yet be too few (i.e. less than one in 10,000 living and dead bacilli) to be detected in the mouse foot-pad. The experiment would therefore be a failure, with no evidence of multiplication in either the control or the dapsone-fed mice.

It is customary to include groups of mice fed on 3 different concentrations of dapsone in their diet, namely 0.01%, 0.001% and 0.0001%. These produce serum levels of dapsone of the same order as those obtained in man with 100 mg, 10 mg and 1 mg dapsone daily, respectively. Until very recently, all strains of *M. leprae* obtained from previously untreated cases of leprosy were sensitive to 0.0001% dapsone (Ellard *et al.*, 1971; Levy and Peters, 1976). Patients infected with strains of *M. leprae* resistant to 0.0001% but sensitive to higher concentrations of dapsone, would be expected to respond to full dosage dapsone, taken regularly. However, such patients may also harbour small numbers of highly resistant mutants. Patients whose bacilli are found to be resistant to 0.001% are most likely also to harbour some mutants resistant to 0.01% dapsone in the mouse diet.

CLINICAL PROOF

Clinical proof is both important and practical. The majority of leprosy control schemes and leprosaria do not have access to the mouse foot-pad test, and must rely entirely on the clinical testing of resistance. However, it is desirable, wherever possible, for a proportion (say one in 10) of patients with *prima facie* evidence of dapsone resistance, to be subjected to experimental as well as clinical proof, to substantiate and support the clinical findings. A clinical trial is also of value in convincing a patient that dapsone is no longer of value in his case, and that he must change treatment.

It is essential that the clinical test of resistance should be carried out formally and scientifically, so that there can be no doubt subsequently of the validity of the result. It has been our practice to assess all patients referred with *prima facie* evidence of resistance by full clinical examination, by smears from both ear lobes and at least 4 other skin sites (usually taken from active, relapse lesions) for the BI and MI, and by skin histology, before commencing trial treatment. The latter has been dapsone 400 mg twice weekly by injection in full-sized adults, and 300 mg twice weekly in small adults, given either by the leprosarium or, by arrangement, by district hospitals or rural health centres. Very rarely, for example when a patient has been travelling in connection with his work, we have been forced to rely on the patient himself taking dapsone 100 mg daily by mouth. In such circumstances, it is essential to test the urine regularly to confirm the presence of sulphone.

Throughout the period of the trial, patients have been seen regularly. Smears have been taken at $1\frac{1}{2}$, 3, $4\frac{1}{2}$ and 6 months, and thereafter usually every 3 or 6 months. Clinical and histological assessments have been performed at 6 months,

1 year and thereafter annually (or earlier, should a patient be found to be relapsing).

The response to full dosage parenteral dapsone has varied from patient to patient. Some patients, especially those who were receiving full dosage dapsone regularly at the time of their relapse or referral, have shown no improvement. The lesions have remained active in appearance, sometimes new papules have continued to appear, and the MI has not fallen, so that proof of resistance has taken only 3-4½ months to complete. Such patients are assumed to harbour many highly resistant mutants. Other patients, especially those previously receiving lower dose dapsone, have shown an initial response to parenteral dapsone. The relapse papules have become less active for a time, and those which were ulcerated or scabbed have healed, and the smear MI has fallen towards or to zero, but within a few months the lesions have become active again, new lesions have once more started to appear, and the MI has started to climb. Such patients presumably had a mixed population of high and moderately resistant leprosy bacilli. Still other patients have shown a full response to treatment, with the MI falling to zero within 3-4½ months, and with the papules flattening at a rate comparable to that seen in previously untreated lepromatous leprosy. But after many months or years of clinical improvement with the MI remaining at zero throughout, further new lesions have begun to appear, with a high BI and MI. Such patients are considered to have had relatively few highly resistant mutants of *M. leprae* (at the 0.01% dapsone level) at the time of the first relapse, the majority of bacilli being resistant only at the 0.001 or 0.0001% level. The latter bacilli were killed by the high dosage dapsone therapy, resulting in the initial clinical improvement, but eventually the highly resistant mutants multiplied enough to cause the late relapse. This situation is similar to the "temporary sputum conversion" seen in some patients suffering from drug-resistant pulmonary tuberculosis.

In the Sungei Buloh series of 100 dapsone-resistant patients, of 74 patients whose leprosy bacilli were fully resistant to 0.01% dapsone in the mouse diet, the duration of the clinical trial before proof of resistance was obtained ranged from 3 months to 5 years and 4 months. Of 8 patients, whose bacilli were found to be resistant to 0.001%, but sensitive to 0.01% dapsone in the mouse diet, the clinical proof of resistance in 6 took from 7 months to 5 years, 10 months, to complete; one patient has not yet undergone further relapse (after initial improvement) after 4 years of trial, and the eighth who was previously grossly irregular, taking only 100-200 mg dapsone a month at the time of his relapse, has improved steadily since October, 1969, when he was started on dapsone, 300 mg twice weekly by injection. It is probable that this last patient had very few highly resistant mutants at the time of his initial relapse, but his long-term prognosis remains most uncertain.

In both groups of patients, in general the very prolonged clinical trials occurred among BL or BL/LI patients, who had been very irregular with their treatment up to the time of relapse, and whose relapse lesions were few in number.

Treatment

Drug-resistant patients pose a therapeutic problem, as they (together with lepromatous patients who develop sulphone allergy), require long-term, effective anti-leprosy treatment. However, the earlier "second-line" anti-leprosy drugs, thiacetazone, thiambutosine and streptomycin, were considered inadequate, as

drug resistance was known to develop over the course of a few years in the majority of cases.

From 1963-1968 our treatment of choice was clofazimine (B663, Lamprene). From 1968-1970 it was rifampicin (rifampin, Rifadin, Rimactane), and subsequently rifampicin in combination with thiambutosine, as the majority of our light-skinned patients refused clofazimine when there was a satisfactory alternative drug.

To date, 23 proven sulphone-resistant patients have received clofazimine as monotherapy, and 19 LL patients have completed $1\frac{1}{2}$-13 years' continuous treatment. Of the latter, 18 were Chinese, one Indian, and 18 were males. Initial dosage was not less than 100 mg clofazimine daily, 6 days a week, although many patients received 300 mg daily. Once a good clinical response had been achieved, dosage was slowly reduced, but never below 100 mg twice weekly; during episodes of ENL the dose was often temporarily raised again.

From 1968 to the end of 1976, a total of 88 proven sulphone-resistant patients commenced treatment with rifampicin, including 75 Chinese, 9 Malays, 3 Indians and one Gurkha; 72 were males and 16 were females. The first 4 patients received rifampicin 600 mg daily as monotherapy; subsequently all patients, except 5 suffering from coincidental thiambutosine resistance, received combined therapy with thiambutosine, either parenterally (1 g weekly) or by mouth (1 g b.d.). Our standard dose of rifampicin has remained 600 mg daily; only 3 patients have been given the drug weekly, either 900 mg (2 patients) or 600 mg (one patient); and about 10 others are receiving 600 mg daily on 2 consecutive days every 4 weeks in a double-blind trial of intermittent therapy organized by Dr A. B. G. Laing. Fifteen of the 88 patients received initial treatment for 4-12 weeks with lower dose daily rifampicin in a pharmacological study but we would not now recommend this practice as we consider initial full-dose intensive therapy of great importance.

All patients received regular clinical, histological and bacteriological (BI and MI) assessments. Independent clinical assessors and Leprosy Research Unit (LRU) staff made clinical assessments at 0, 6 and 12 months, then yearly to 5 years, and subsequently either yearly or every $2\frac{1}{2}$ years. At the same times, 2 skin biopsies were sent to the Hospital for Tropical Diseases, London, for independent histological assessment for the Logarithmic Biopsy Index (LIB). Smears from both ears and at least 4 initially active skin sites were taken frequently over the first 6 months, thereafter every 3 months to 2 years, and then every 6 months. The smears were coded and read blind by a single observer. Any toxic effects, or episodes of ENL were carefully recorded

An analysis of the clofazimine patients and of 52 LL rifampicin-treated patients (omitting those who received initial very low dosage) was presented in 1973 (Helmy *et al.*). Three years' further experience has confirmed the earlier findings.

The development of dapsone resistance did not alter the rate of response, as measured by the rate of fall in the MI, to either drug. All the patients treated with rifampicin showed the dramatic rapid fall in the MI which we have previously reported (Rees *et al.,* 1970), and which we consider indicative of rapid bactericidal activity. No late rise in the MI has been observed save in the one clofazimine-treated patient who relapsed at $7\frac{1}{2}$ years through failure to continue on therapy.

The rapid kill of leprosy bacilli by rifampicin was reflected in the clinical

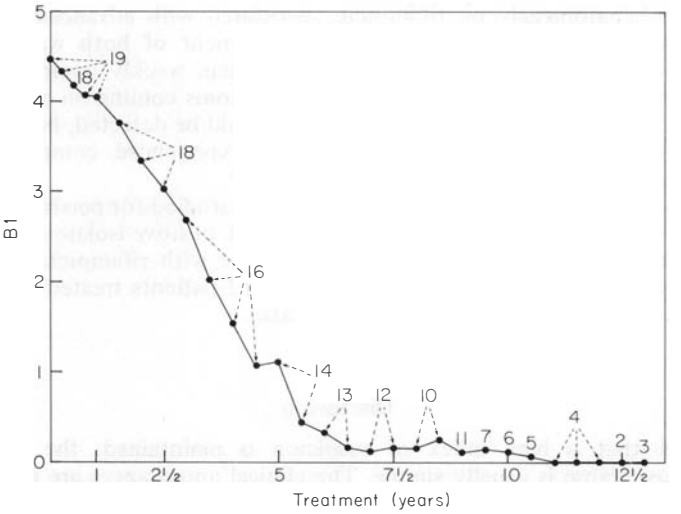

Fig. 1. Fall in bacteriological index (BI) in 19 dapsone resistant lepromatous patients treated with clofazimine. Number of patients given for each point.

assessment results. Over the first 4 months the inflammation and oedema of any very active relapse papules and plaques present tended to subside remarkably rapidly on rifampicin. Up to the end of the second year, higher scores for clinical improvement were given to these patients than to those receiving clofazimine. However, as clofazimine made clinical lesions easier to see, this could have biased the clinical assessor slightly against the latter drug.

Surprisingly, no difference could be detected in the rate of fall in the LIB in the 2 treatment groups. Mathematically, the major factor in the estimation of the LIB is the bacterial index. Figure 1 gives the rate of fall in BI in the clofazimine treated group of 19 LL patients. This shows no significant difference from that obtained with rifampicin (see Fig. 1, Rees *et al.,* 1976). We presume that neither drug affects the rate of removal of dead leprosy bacilli by the body.

An up-to-date analysis of ENL has not yet been carried out. However, in 1973 no very early and severe onset of ENL was detected in patients treated with rifampicin. At that time, 17 of the 28 patients (61%) on rifampicin included in the BI assessment (Fig. 1, Rees *et al.,* 1976) were suffering from ENL at 1 year, an incidence similar to that seen at Sungei Buloh in previously untreated patients receiving dapsone. This compares with only 7 of 21 patients (33%) in the clofazimine group, a figure reflecting the anti-inflammatory activity of clofazimine.

Although 5 patients (4 of the 23 in the clofazimine and one of the 88 in the rifampicin series) have died from intercurrent disease, drug toxic effects have been rare. A few patients on clofazimine complained of mild abdominal pain and diarrhoea while receiving 300 mg daily, and one developed mild eczema; all the light-skinned patients developed the typical and unpopular discolouration. One patient on rifampicin developed mild jaundice associated with occult cirrhosis, and a second whose liver was palpable at the initial assessment developed

progressive hepatomegaly on rifampicin, associated with advanced fatty change and increase of portal fibrous tissue; the treatment of both was changed to clofazimine. The one patient on 600 mg rifampicin weekly complained after 3 years of treatment of fever and abdominal symptoms coming on about 2 h after each dose; no rifampicin dependent antibodies could be detected, but on changing her dosage to rifampicin 600 mg daily, she experienced complete relief of symptoms.

Patients from both treatment groups have been studied for persistence of viable *M. leprae.* As already reported (Rees *et al.,* 1976), positive isolates were obtained from 20 of 28 patients treated from 0.5-5 years with rifampicin. In addition, positive isolates have been obtained from 9 of 12 patients treated 2-6 years with clofazimine (Rees and Waters, unpublished data).

Discussion

Provided that a high index of suspicion is maintained, the diagnosis of lepromatous relapse is usually simple. The clinical appearances are nearly always diagnostic, and we have found that reliable smear results, especially of the MI, provided very helpful additional evidence.

The main differential diagnosis lies between those patients who have relapsed while receiving dapsone therapy, i.e. who have *prima facie* evidence of sulphone resistance, and those who have relapsed through failure to continue on treatment. In the latter circumstance, relapse is assumed to be due to the multiplication of the small numbers of viable dapsone-sensitive *M. leprae* which persisted despite adequate chemotherapy. In some countries and cultures patients will state with considerable accuracy whether or not they had ceased to take dapsone. But recent studies of self-medication treatment schemes have revealed a disturbingly high proportion of patients who fail to take dapsone, or who take it in much less than the prescribed dosage (Ellard *et al.,* 1974; Low and Pearson, 1974; Huikeshoven *et al.,* 1976), despite attending clinics regularly.

Proof of dapsone resistance is essential. Even though it takes 6-12 months to complete, drug sensitivity testing using the mouse foot-pad infection is very reliable and gives a helpful indication of the degree of dapsone resistance which has developed; moreover, if resistance to other drugs is suspected, they can be included in the test system using additional groups of mice. Provided that a satisfactory bacterial suspension has been obtained for foot-pad inoculation, the patient is able to change treatment immediately should this be indicated on medical and/or social grounds. However, the foot-pad test is available in only a small number of laboratories; the setting up of regional or national centres would appear highly desirable.

Clinical trial of dapsone resistance is also very reliable, provided that dapsone is given regularly by injection; if the drug is given by mouth, frequent urine testing for dapsone is essential. Clinical trial can be made available nearly everywhere, but it requires very regular supervision and medication of each patient for a period extending perhaps as long as 5 years, a discipline which may not always be acceptable. The trial is completed, and treatment changed, once there is evidence of either failure to respond to, or of further relapse after initial improvement on, full-dosage dapsone therapy.

The most satisfactory drug regimen(s), balancing efficacy, acceptability and

cost, for the treatment of dapsone-resistant leprosy remains uncertain, and further clinical studies are required. Although in the middle term we have found both clofazimine (over 13 years) and rifampicin (over $8\frac{1}{2}$ years) to be very satisfactory, it would appear from experience with dapsone that 20 years may be required for the full evaluation of an effective anti-leprosy drug. No case of secondary clofazimine resistance has so far been encountered, although Jacobson and Hastings (1976) have now reported the first patient suffering from rifampicin resistance. By analogy with the treatment of tuberculosis, we have strongly advocated (Pearson *et al.,* 1975; Waters, 1976) that patients suffering from dapsone resistance should be treated with combined therapy. This is because the risk of a naturally occurring mutant being present resistant to 2 as compared with only one drug is reduced from about 10^{-6} to 10^{-12} (from one in a million to one in a million million bacilli). Nevertheless, long-term treatment remains essential as it is still quite uncertain what effect, if any, combined therapy has on "persisters".

Once sulphone resistance has developed, there remain 3 proven bactericidal-type drugs (Committee on Experimental Chemotherapy, 1976) available, namely rifampicin, clofazimine and ethionamide. Of the "second-line drugs", thiambutosine and thiacetazone probably act by the same mechanism as, and give cross-resistance with, ethionamide (Colston and Hilson, personal communication), but their peak blood levels are but 3 and 4 times respectively the minimum inhibitory concentration, and they are only bacteriostatic (Colston and Hilson, 1976). Furthermore, thiambutosine is no longer being manufactured (Ciba-Geigy, personal communication). Streptomycin is bacteriostatic, has to be given by injection, and rapidly produces drug resistance in lepromatous leprosy (Hastings *et al.,* 1970).

It would appear, therefore, that dapsone-resistant patients should receive an initial intensive course of chemotherapy with at least 2 of the 3 drugs, rifampicin, clofazimine and ethionamide (or prothionamide). If the skin discolouration due to clofazimine is unacceptable, then rifampicin and ethionamide should be given; and Jacobson (personal communication) has used this combination on a long-term maintenance basis since 1973. If ethionamide cannot be afforded, then thiacetazone could be substituted provided that the limitations of this drug, and its high incidence of toxic effects in some races are appreciated. The use of thiacetazone as long-term maintenance monotherapy would appear inadvisable. Many patients will, however, accept clofazimine and we have recently started 7 patients (including 2 with coincidental thiambutosine resistance) on a combination of rifampicin 600 mg daily and clofazimine. The intention is to give at least 3 months of combined therapy, and then to continue with maintenance clofazimine, although we would not now advocate a minimum dosage below 100 mg 3 times a week.

The position of a lepromatous patient who develops sulphone resistance is uncertain. The most effective alternative drugs are all much more expensive and most are more toxic than dapsone. It is essential to prevent his developing further varieties of drug resistance. Formal long-term (open-ended) clinical trials of alternative regimens are essential. But such regimens must be selected on scientific merit as well as on the basis of cost and acceptability. For if leprosy is to be controlled throughout the world, it is essential for effective regimens to be selected and used now, even though it will take another 20 years for their efficacy to be proved.

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The Prevalence of Dapsone-resistant Leprosy in Israel*

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The prevalence of dapsone-resistance among patients with lepromatous leprosy treated in Israel for a minimum of 8 years was 3.7 per 100.

Introduction

For many years after the introduction of sulphone drugs in the treatment of leprosy in the 1940's, the belief was widely held that the risk of emergence of sulphone-resistant mutants of *Mycobacterium leprae* was negligible. However, beginning with the report of Pettit and Rees (1964) of the first patients from whom *M. leprae* resistant to dapsone (4,4′-diaminodiphenylsulphone, DDS) were isolated, it has become clear that relapse of lepromatous leprosy during sulphone monotherapy because of the emergence of sulphone-resistant organisms is by no means a rare occurrence. Efforts have been made recently to assess the risk in quantitative terms (Meade *et al.*, 1973; Peters *et al.*, 1976). In this paper, we report the results of such an effort among patients with lepromatous leprosy in Israel.

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Methods and Materials

After diagnosis, practically all leprosy patients in Israel are treated and observed as outpatients, under the supervision of the 14 subdistrict offices of the Ministry of Health. All of the inpatient records and abstracts of the outpatient records are filed at the Government Hospital for Hansen's Disease in Jerusalem, where approximately 25 patients are currently hospitalized. The outpatients who live in and near Jerusalem are seen regularly in the clinic located at the Hospital by one of us (J.S.), who also sees all of the other patients periodically in their home communities.

For the purpose of this study, the records of all 114 patients with leprosy classified as "lepromatous" who began treatment prior to 1966 were examined and abstracted. Of the 114 patients, 20 had been lost prior to the beginning of this study in 1974; 17 patients had died, 2 had emigrated, and one had simply been lost to follow-up. There was no evidence that any of these patients had died or emigrated because of their leprosy. Therefore, the value of the denominator to be used in calculating the prevalence of dapsone-resistant leprosy is 94.

Twenty patients who had kept their clinic appointments faithfully and who were believed to have taken their treatment regularly were observed to have suffered a relapse of their disease process, or to have failed to improve, on the basis of their clinical appearance and the continued appearance of acid-fast bacteria (AFB) in smears of skin scrapings, despite a minimum of 8 years of treatment. Skin biopsy specimens were obtained from active-appearing lesions of these patients by means of a 6 mm scalp punch, sealed in sterile tubes, placed together with wet ice in a vacuum flask, and shipped by air to San Francisco. The specimens were received in San Francisco within 72 h of biopsy, at which time ice remained in the flask. In San Francisco, the specimens were processed for mouse inoculation by published methods (Shepard, 1960; Shepard and McRae, 1968).

Twenty mice were inoculated with the organisms recovered from each specimen. Beginning 3 or 4 months after inoculation, one mouse from each group was killed for measurement of the "incubation period" (IP), the number of months elapsed between inoculation of the mice and the demonstration of AFB within 30-40 cells in histological sections of the inoculated foot-pad tissues. After evidence of multiplication of *M. leprae* was noted in a monthly section, a harvest was performed from the pooled tissues of 4 foot-pads. If no multiplication was apparent by the 12-month section, a harvest of *M. leprae* was performed from a pool of the inoculated foot-pad tissues of all surviving mice. From the number of AFB harvested and the number of days elapsed between inoculation of the mice and harvest, the "generation time" (G) was calculated as if all of the inoculated bacilli had multiplied at a constant rate between inoculation and harvest. Values for the IP $\leqslant 12$ months and for $G < 100$ days indicate that *M. leprae* had multiplied, and, therefore, that the inoculum had contained organisms infective for the mouse and presumably viable.

When *M. leprae* were found to have multiplied in mice, they were recovered by harvest and subsequently passaged to groups of 60 mice. Beginning on the day of passage, dapsone incorporated into the mouse diet in a concentration of 10^{-4}, 10^{-3}, or 10^{-2} g% was administered to 3 subgroups of 15 mice each, whereas the remaining subgroup received drug-free diet. Dapsone administration was continued until a harvest from the foot-pads of untreated control mice revealed that the *M. leprae* had multiplied to a level near 10^6 AFB per foot-pad. At this time,

M. leprae were harvested from pools of the tissues of 4 foot-pads of the treated mice of all 3 subgroups. Susceptible organisms were defined as those that failed to multiply in mice administered dapsone.

Results

Several characteristics of the entire group of patients, and of the 20 patients selected for further study, are summarized in Table 1. A little more than one-quarter of the patients had been born in Israel. About one-third of the patients were female. The 20 patients suspected of harbouring dapsone-resistant *M. leprae* did not differ from the larger group of 114 patients in terms of birthplace, sex, or year of birth.

TABLE 1

Characteristics of patient population

	Place of birth		Sex		Year of birth	
	Israel	Abroad	Female	Male	Before 1921	1921 or later
Total number	30*	84	37	77	56	58
Number lost	6	14	5	15	N.A.†	N.A.
Number at risk	24	70	32	62	N.A.	N.A.
Number studied	4	16	4	16	9	11

* All of these patients were born before 1948, the year the State of Israel was established.
† Not available.

The results of the study of the 20 skin biopsy specimens submitted for mouse inoculation are summarized in Table 2. No AFB were recovered from the specimens of 8 patients—nos 15, 46, 125, 131, 153, 199, 203 and 218; therefore, no mice were inoculated with *M. leprae* from these patients. In the case of 3 additional specimens—those from patients nos 171, 184 and 191, only one AFB was seen in the 60 oil-immersion fields examined on each counting slide. The numbers of AFB recovered were therefore very small, resulting in very small inocula. No evidence of multiplication of *M. leprae* was encountered in the mice inoculated with organisms recovered from any of these specimens. Nine specimens contained enough AFB to permit mice to be inoculated with 5000 organisms per foot-pad. The organisms from 3 of these specimens—those from patients nos 109, 193 and 202—did not prove infective for mice, and the organisms from a fourth specimen—that of patient no. 85—were only marginally infective, multiplying in the foot-pad of the mouse killed for histopathological examination after 10 months, but in none of the 8 mice sacrificed for harvest of *M. leprae* 398 days after inoculation. Five skin biopsy specimens—those of patients nos 42, 50, 58, 135 and 287—contained *M. leprae* infective for mice.

The results of testing these 5 strains of *M. leprae* for susceptibility to dapsone are presented in Table 3. Two of the strains—those isolated from the specimens of patients no. 42 and 287—were fully susceptible to dapsone, in that the organisms failed to multiply in mice fed any of the dapsone-containing diets. *M. leprae* of the 3 remaining patient-strains were partially resistant to dapsone, multiplying in mice fed 10^{-4} and 10^{-3} g% dapsone, although at a slower rate than in control

TABLE 2

Results of mouse inoculation

Patient no.	Inoculum		Harvest	
	No. AFB per specimen ($\times 10^5$)	No. AFB per foot-pad ($\times 10^3$)	Incubation period (months)	Generation time (days)
15	< 0.20	N.I.*		
42	409	5.0	8	43.0
46	< 0.20	N.I.		
50	29.8	7.08	9	39.3
58	1580	5.0	4	30.6
85	129	5.0	10	> 100
109	57.7	5.0	> 12	> 100
125	< 0.20	N.I.		
131	< 0.20	N.I.		
135	1430	5.0	8	40.8
153	< 0.20	N.I.		
171	0.32	0.12	> 12	> 100
184	0.30	0.33	> 12	> 100
191	0.20	0.20	> 12	> 100
193	536	5.0	> 12	> 100
199	< 0.20	N.I.		
202	697	5.0	> 12	N.H.†
203	< 0.20	N.I.		
218	< 0.20	N.I.		
287	199	5.0	8	39.4

* N.I., not inoculated.
† N.H., not harvested.

TABLE 3

Results of dapsone-susceptibility studies

Patient no.	Dapsone concentration (g%)			
	0	10^{-4}	10^{-3}	10^{-2}
	Generation time (days)			
42	23.7	> 100	> 100	> 100
50	14.9	33.6	32.1	> 100
58	22.3	31.2	52.3	> 100
135	22.8	32.7	41.8	> 100
287	25.4	> 100	> 100	> 100

mice, and failing to multiply in mice administered dapsone in the largest concentration.

In addition to these 20 patients whose *M. leprae* were suspected to be resistant to dapsone, examination of the medical records revealed 5 additional patients whose smears of skin scrapings contained AFB in 1973 or 1974. One of these patients died before a biopsy could be performed and the specimen shipped to San Francisco. No specimens were obtained from the 4 remaining patients, who

were thought to be demonstrating satisfactory progress without a change of treatment on clinical grounds.

Thus, there were 25 patients suspected of harbouring dapsone-resistant *M. leprae*; skin biopsy specimens were obtained from 20. Of these 20, 11 did not contain enough AFB to permit study of their susceptibility to dapsone. Of the remaining 9 specimens, the organisms recovered from 4 were not infective or only marginally infective for mice. The organisms recovered from the specimens of 2 patients were infective for mice but fully susceptible to dapsone, whereas the *M. leprae* of 3 patients were resistant to low concentrations but susceptible to a high concentration of dapsone in the mouse diet. If specimens had been obtained from the 5 patients not studied, it appears likely that 3 specimens would have contained insufficient organisms for inoculation of mice, one would have contained organisms not infective for mice, and one would have contained *M. leprae* capable of multiplying in mice, with a 50% likelihood of being resistant to dapsone. Thus, the numerator for the calculation of the prevalence of patients harbouring dapsone-resistant *M. leprae* is 3.5, and the prevalence is 3.5 per 94 patients, or 3.7 per 100.

Discussion

The purpose of this study was to estimate the frequency with which dapsone-resistant *M. leprae* emerge after years of treatment of lepromatous leprosy patients in Israel with sulphone monotherapy. Studies of this kind are ordinarily difficult to carry out. The patients who have relapsed with the emergence of resistant organisms, who form the numerator, are usually easily recognized, and are therefore well-known to leprosy treatment centres. The difficulty lies in calculating the denominator, the number of patients at risk; only in a few jurisdictions have good records been maintained and virtually complete patient follow-up practised.

Two such studies have already been reported. Meade and his coworkers (1973) reported a frequency of 2.5 per 1000 among patients beginning treatment in Malaysia with dapsone in full dosage, and 7.8 per 100 among patients who began treatment with solapsone. Peters *et al.* (1976) reported a frequency of 6.8 per 100 among Costa Rican patients treated for a minimum of 7 years. During the first years of sulphone therapy in Costa Rica, patients were treated with sulphoxone. The frequency of dapsone resistance in Israel—3.7 per 100, appears to represent an intermediate value. There is nothing to suggest a disproportionate number of relapses among the 20 patients lost to follow-up.

It has been pointed out (Pearson *et al.*, 1975, 1976) that consistent treatment with dapsone in full dosage results in the emergence of mutant strains of *M. leprae* that multiply in mice administered dapsone in a dosage of 10^{-2} g%, the largest dosage usually employed in measuring the susceptibility of strains of *M. leprae* to dapsone. On the other hand, treatment with dapsone in low dosage or with dapsone derivatives produces mutant *M. leprae* that multiply in mice administered dapsone in lower dosages (10^{-4} and 10^{-3} g%) but not in those mice administered the largest dosage. Such "low resistance" mutants were not encountered in Malaysia, where those patients beginning treatment with solapsone were all subsequently transferred to treatment with dapsone in full dosage (Pearson *et al.*, 1975). In the Costa Rican study, half of the 12 dapsone-resistant patient-strains of *M. leprae* isolated were found to be low-resistance mutants; this suggests that

the use of dapsone in full dosage, said to have been started in 1960, may not have been universal (Peters *et al.*, 1976).

In Israel, a variety of treatment regimens has been used, so that it is difficult to characterize them in a few words. Prior to 1950, patients were treated with thiacetazone or sulphoxone. Dapsone, in daily doses of 25-100 mg, has been generally used since 1950. Until the introduction of thalidomide in 1964, however, the dosage of dapsone was frequently interrupted, or sulphoxone or solapsone was substituted when patients experienced severe lepra reactions. Also, solapsone was administered weekly by injection as a supplement to dapsone when patients were thought to be irregular in their self-administration of dapsone. Finally, solapsone was sometimes substituted for dapsone as a convenience to those patients required to work away from their homes. That the 3 dapsone-resistant mutants isolated from Israeli patients were of the low resistance variety appears consistent with these facts.

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Clinical Assessment and Management of Dapsone-resistant Leprosy for the Field Worker

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"Doctor, would you please look at this patient and advise me what to do. She has chronic Erythema Nodosum Leprosum (ENL) and does not respond to corticosteroids", asked the paramedical worker. The writer turned to see a young woman covered with hundreds of small to medium sized infiltrated lesions. Her history? She had first been diagnosed, as a teenager, some 10 years ago and started on dapsone. The treatment had been supervised by the paramedical worker most of the time without reference to a doctor. As the woman had had repeated bouts of ENL over the years her treatment had been rather irregular as the dapsone was usually stopped either by the paramedical worker or the patient whenever the ENL became severe. In the 1960s she had never received more than 100 mg twice weekly, and often had received much less, but her Bacillary Index (BI) had fallen until it was almost zero in 1970. At this time the dose of dapsone had been increased to 50 mg daily and maintained at that level. She had failed to attend clinic in 1975 and on careful questioning we extracted the information that there were already some new lesions appearing at her last attendance at clinic in October 1974. It was the persistence of these lesions and the increase in their number that had brought her back to clinic in March 1976. Because of the number of lesions, in a previously clear skin, the paramedical worker had assumed that she was having ENL and had given her corticosteroids and antihistamines. When she seemed to be getting worse rather than better he brought her to see the writer on my next visit, in June 1976. On careful examination it was obvious that these were new skin lesions and not ENL and her skin smear showed many bacilli, of which a fairly high proportion were solid in form. This then was a case of definite relapse, not of ENL, and the opportunity was taken of pointing out the difference in appearance. But the problem now was "Are the organisms still sensitive to dapsone or are they resistant?" As the lesions had appeared before she stopped dapsone it suggested resistance, especially with the history of low irregular dosage. But how to check her out with a poor laboratory cover?

The next patient had a similar problem. Bacillary resistance to dapsone is becoming a real problem in the field especially where much of the work has to be left to those who have been only partially trained and not recently updated. Many of them are not yet aware of the possibilities of dapsone resistance.

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As the writer travels through Asia she is repeatedly confronted with similar problems—patients who have been on treatment for some time and now are not doing as well as expected. Yes, a relatively high proportion of patients that I see are called specially because they are not responding adequately to their treatment, but even taking that into consideration, the numbers developing resistance, and their prognosis, if not adequately treated, is alarming. Let me first discuss the reasons why we are now having to combat so much resistance "on the field".

Dapsone was first used for the treatment of leprosy in the 1940s. Due to the inability to culture the organism the effective dosage had to be determined by trial and error. Initially patients received a high dosage which reportedly produced undesirable side effects, so that the dose was gradually reduced. In the 1950s the dose was usually between 400 and 800 mg weekly given in one or 2 doses, often by injection in institutions. In 1960, after 10-15 years of intensive usage there was no real evidence suggesting that resistance to dapsone occurred, so in the early 1960s workers were informed that there was no need to give dual therapy as was given in tuberculosis.

With the advent of the mouse foot-pad culture techniques the possibility of controlled drug trials became a reality and the treatment of leprosy came under more detailed and systematic investigation. Workers were informed that lower doses of dapsone were effective and produced less undesirable side effects. In the late 1960s doses as low as 1 mg per day were shown to be effective as an initial treatment, but at the same time they were not recommended, as warnings of the development of resistance to dapsone were also appearing.

Field workers were in a quandary. Many had reduced the dosage of dapsone in good faith so that patients were receiving doses of 10, 25, 50 or 100 mg twice weekly. On this they seemed to do well, the skin lesions healed and there seemed to be few adverse side effects. But, every now and again, one would find a patient who just did not seem to respond adequately to dapsone, either in large or small doses. Why was this?

The writer remembers 2 such cases. One was initially seen in 1966. He was a man of 60 years who had been treated with all the sulphones for 20 years. He had had dapsone, sulphetrone, diasone and promin, but they had been stopped and started as he frequently had ENL. When he was first seen in Hong Kong to which he had recently immigrated he appeared to be of the florid lepromatous type with a BI of 5.5 and a Morphological Index (MI) of 60% solid rods. Dapsone by injection in large doses for 6 months made little difference to the BI and MI and he had repeated ENL. After commencing Vadrine (which was the only drug available then that he had not already had) he did show some slow improvement. Eventually he did well on clofazimine when it became available in late 1967.

Another patient in Korea had received promin injections 3 times weekly for about 15 years. He presented with many new lesions—could this be resistance? He was adamant that he had not been irregular with his therapy. Yet at that time workers were being told "resistance to dapsone does not occur". All through the 1960s patients like this were being found. By 1970 the writer had some 15 or 20 under her care in Hong Kong alone. They were mostly patients who had been under treatment for a long time or who had been irregular with their treatment. Could one always blame the patient for irregularity?

Soon after dapsone became accepted as a standard treatment for leprosy it was observed that many patients under treatment developed severe ENL. It was assumed that the dapsone produced the ENL, though on careful observation one

realizes that patients get ENL without taking dapsone. Nevertheless the custom arose of stopping dapsone whenever reaction became severe, and patients learnt to stop it themselves. This meant that many patients in the LL, LI and LB groups were receiving irregular treatment because of recurrent ENL. But was this the only reason for their irregularity?

The usual instructions were to divide the weekly dose into 2 parts to be taken on 2 days. It is hard to regularly remember to do something twice a week, and one missed dose meant half the dose for that week was missed. Some workers realized that and daily dosage was instituted in some centres in the early 1960s. In some institutions the taking of dapsone was "supervised"—well the medicine was handed out and meant to be swallowed in front of the staff member. But, the number of "sucked" dapsone tablets available on the "black market" was mute evidence to the unreliability of this system.

Bearing this in mind dapsone was often given by injection, especially to relapsed patients, with very good initial effect. Was it a problem of malabsorption? Sometimes dapsone tablets are stored for long periods and may become very hard. Sometimes in the manufacture they are compressed so hard that they can pass through the gut unaltered. It is easy to test solubility by dropping one into a glass of water but that does not of necessity say anything about the absorption of the drug.

So through the 1960s more clinical evidence was collecting to be confirmed by laboratory studies with the mouse foot-pad. Why shouldn't the bacilli become resistant to dapsone? Other bacilli become resistant to drugs, and in a much shorter time that *M. leprae* had needed to show resistance to dapsone. Yes now it is accepted, the bacilli were much smarter than we thought they were, not only can they become resistant to dapsone but to other antileprosy drugs also. They have also revealed themselves as being able to remain alive and viable, for years, in the presence of a concentration of drug that should be enough to eliminate the infection. These bacilli are called persisters and may complicate the diagnosis of dapsone resistance, as they resume multiplication when the dapsone level falls and produce relapse that is fully sensitive to dapsone.

So workers cannot assume that every relapsed patient has dapsone resistant leprosy. As most centres do not have the facilities for mouse foot-pad tests a clinical test for resistance is essential. The writer started using that in the late 1960s in Hong Kong and on a few occasions was able to check results with mouse foot-pad inoculation. In each patient so tested dapsone resistance was confirmed in the mouse, and usually these patients showed resistance to thiambutasone as well as it had often been used for patients who did not show adequate progress on dapsone.

This then is the problem that we now face. Let us look at it more systematically.

Who to Suspect

Workers must learn to think of dapsone resistance as a possibility in any leprosy patient who had been multibacilliferous and has received dapsone for a fairly long period of time and is now showing signs of relapse. The possibilities of resistance increase with:

1. The nearness to the lepromatous end of the immunological spectrum (resistance has so far only been proved in patients who were initially LL, LI or LB in type).

2. The longer the period of dapsone medication.
3. The smaller the dose of dapsone that has been used.
4. The irregularity of the dapsone medication.
5. The consistent use of monotherapy.

The typical patient is an LL type patient who has been on treatment for 10–15 years with dapsone alone in relatively low doses that have been interrupted because of reaction (or other causes) or lack of co-operation. However resistance has been proved in patients under treatment for only 4–5 years and in those who have received high doses of dapsone regularly for 20 years.

What Does It Look Like?

The lesions of dapsone-resistant leprosy do not really differ in appearance from the lesions of ordinary dapsone-sensitive relapsed leprosy. It may be possible to see the old healed lesions behind the new ones which are usually reddish (in the lighter skins, bronzed in darker skins) papules or macules. They may become heavily infiltrated rather more rapidly than normally expected. There may be plaques of infiltration, or with time nodules may develop which may become very gross. It has been stated that one can recognize dapsone resistance by an umbilication of the papules and nodules, but the writer has not found this so. Sometimes the new lesions appear to be just a flat, non-irritant, persistent rash on the forearms that can be mistaken for a drug eruption. The patient does not feel ill, he has no fever or general symptoms such as one may get in lepra reaction—though of course he may have lepra reaction as well as relapse. On skin smear (or biopsy) in relapsed leprosy the lesions will be found to be teeming with acidfast bacilli (AFB). The most productive site will be a small fleshy papule that has newly developed. If resistance is suspected and the first smear is negative or less than suspected it should be repeated each 2 weeks until the lesions subside or the diagnosis is determined.

Relapsed leprosy covers any situation in which new active lesions appear in a patient already responded to treatment. The relapse may be due to dapsone resistance, failure to take dapsone (or other antileprotic drug) in adequate dosage, or to persister organisms. It is important that the cause of the relapse be determined before there is any change in specific drug therapy.

Differential Diagnosis

The lesions of relapsed leprosy are often mistaken for ENL especially by paramedical workers who have been taught to watch for ENL and not to suspect resistance. Why shouldn't they think they are ENL? ENL is common; teaching may have neglected resistance; both show new reddish lesions in a patient who is under treatment. But it should not be difficult to distinguish ENL from the lesions of relapse. Table 1 should help paramedical and other field workers who are not yet familiar with the difference.

If the patient has ever had ENL before he will usually realize that the lesions of relapse are not the same. It may be helpful to count the lesions on a defined area (such as an arm) and observe if they fluctuate over a period of weeks. With ENL the number will fluctuate from day to day but in relapse they will increase in number and the lesions may get larger.

TABLE 1

Differentiation between ENL and relapsed leprosy

ENL	Relapse
Crops of lesions that come and go	Lesions that persist
Lesions may be tender	Lesions are not tender
Lesions may ulcerate	Lesions usually do not ulcerate
On pressure with a glass slide the lesions will disappear, but sometimes there may remain a dark spot in the centre if thrombosis has occurred	There is true infiltration and associated erythema which do not completely disappear on pressure
Lesions are not really infiltrated	True infiltration may go on to papules, nodules and plaques
Systemic symptoms of pain, fever and malaise may dominate the picture	There may be no systemic symptoms
Urine may show RBC, and albumin	No specific urinary changes
May be acute anaemia in some races	No haemoglobin changes
Lesions usually subside with corticosteroids	Lesions get worse if corticosteroids are given without antileprotics

Investigation

(a) Check the history as carefully as possible.

(b) Is the patient reliable—did he really take his dapsone as he says he did. Is there anyone who can verify his story?

(c) Take skin smears and check BI and MI at 6 sites and also take nasal swabs. It is essential that good laboratory coverage be available whenever dapsone resistance is being investigated.

(d) Tests for resistance.

(i) *Laboratory.* If possible take a biopsy from a site with a high BI and MI for mouse foot-pad investigation before giving any new specific medication.

(ii) *Clinical testing in the absence of mouse foot-pad testing.* This will be the only method of testing for most of the field workers.

Methodology of Clinical Testing

Carefully list the actual sites from which the skin smears were taken, and the individual results of BI and MI readings. Results from different sites can vary very much in the same patient and it is best to be able to follow the progress in a specific site.

Give 100 mg dapsone daily—preferably under proper supervision (check that it is swallowed) or give by injection.

Repeat the smears from the same sites every 2 weeks.

If the MI falls consistently we can assume that the bacilli are still sensitive to dapsone. It may take 6–9 months for the MI to reach 0% solids in a badly relapsed patient who is still dapsone sensitive, and the BI may not fall significantly until the MI is 0% (observed in Chinese patients receiving intramuscular dapsone). So we do need to observe closely for a prolonged period of time. Smears should be done each 2 weeks for 4–6 times and then every 2–3 months for several years in any person who has been suspected of being dapsone

resistant but shows clinical response to higher dapsone dosage. After an initial period of improvement in both BI and MI the smears may appear to remain stationary for months or even years and then there may be a sudden rise in the bacterial counts, which is usually accompanied by new lesions again. This would suggest that there has been a partial resistance to dapsone which has now become a complete resistance.

It is important, when no mouse foot-pads are available to make a definite decision regarding dapsone resistance as this decision may influence the whole of the patient's future life. It may be difficult but at some stage the decision must be made and the patient's chart endorsed accordingly and his treatment adjusted. If the MI has not fallen by 50% in the first 6 weeks on full dapsone dosage it is best to assume that the bacilli are dapsone resistant and commence alternative therapy as soon as possible.

Management of Dapsone-resistant Leprosy

First: endorse the patient's chart so that it cannot easily be missed.

Second: explain to the patient something of what has happened and of the severity of the situation and of the necessity of his being regular with therapy in the future if he is to get well and to stay well.

The patient who is dapsone resistant should never be given dapsone as the sole drug for treating his leprosy again. Theoretically it may still be of help in the patient who is partially resistant to dapsone, or in the prevention of a second infection with a dapsone-sensitive organism, but in both of these situations the organisms should be dealt with by the alternate drug given which is usually clofazimine. With our present drugs clofazimine is the only drug available for long term treatment of the patient with dapsone-resistant leprosy. As clofazimine pigments the skin it is essential that the patient realises the situation and is prepared to accept this pigmentation for life. If he is not convinced that clofazimine is essential he may stop it himself as soon as he looks better and resume dapsone with the result that he relapses again.

When it is possible to inoculate mouse foot-pads it is practical to give clofazimine as soon as the biopsy material is taken. If Rifampycin can be given also the patient will become non-infectious within 2 weeks and this is of obvious advantage when we are seeking to stop the spread of dapsone-resistant organisms. Once foot-pad inoculation is set up we can eventually determine the possibility of giving dapsone again later, though the patient may not readily accept the verdict that he is dapsone resistant, once he looks and feels better. On the other hand is the time taken to convince one patient that he is dapsone resistant, providing an unnecessarily long period during which dapsone-resistant organisms can be disseminated?

There are many different regimes for treating dapsone-resistant leprosy but it would appear that the use of Rifampycin 600 mg daily with clofazimine 100 mg daily for 2 weeks followed by clofazimine 100 mg daily for the first 6 months has much to recommend it. At the end of 6 months the clofazimine can be reduced to alternate days for life. Unfortunately this means that the patient, after the initial 2 weeks is once again on monotherapy. For this reason workers are trying combinations of second line drugs in an attempt to reduce the incidence of further resistance but results of these trials will not be available for many years.

What Should Be Our Response to This Problem?

Now that we know that dapsone resistance is a definite entity and that it also means that there is resistance to all the related sulphones and sulphonamides it is important that we modify our thinking in relation to those persons who are infected with *M. leprae.* How should we do this?

(1) Higher dosage of dapsone should be given as soon as possible, especially in patients with low resistance forms of leprosy (LL, LI & LB types). At least 1 mg/kg/day should be given within 6 months of the commencement of therapy and maintained for as long as dapsone is given. Daily therapy is preferable to twice weekly but second daily medication is probably acceptable. The writer is one who cannot agree that every patient should commence with 100 mg daily. She has seen too many tragedies that have seemed to result from this form of therapy, but she does agree that very small doses should not be given even for short periods, unless a second drug is being used at the same time. This may happen when a patient needs to be desensitized to dapsone allergy and is receiving clofazimine during the desensitization. The use of smaller than maximal doses of dapsone may also be justified when it is being given as part of dual therapy in a patient who does not seem to tolerate a full dose of any antileprotic drug.

Regular therapy in adequate dosage is the key to the prevention of dapsone resistance. While we do all in our power to encourage the newly diagnosed patient to take his treatment regularly there comes a time when a different attitude may be wise. If a patient after many years' treatment is skin smear negative and becomes irregular in taking his dapsone it may be better to stop giving him dapsone. Of course the situation should be explained to him and he should be told that there is a chance of relapse, and that if new lesions appear he should return quickly for more treatment. If he has been irregular the chance of dapsone resistance is much greater, but if he has not been taking dapsone for some years he is more likely to be dapsone sensitive at relapse, and to take treatment regularly again, at least for some time. If we give dapsone irregularly not only are we encouraging resistance to occur but he may come to feel the treatment is no good and delay unduly when new lesions do occur.

(2) Wherever possible dual therapy should be given, at least for a short initial period to all patients with multibacilliferous leprosy. Rifampycin or clofazimine are the drugs usually preferred for giving in combination with dapsone for this purpose, but in theory any drug with antileprotic action that does not belong to the sulphone-sulphonamide group should help to reduce the chance of dapsone resistance.

(3) A good laboratory backing is an essential part of every leprosy treatment programme. Even if full laboratory facilities are not available it is important that good quality skin smear taking and staining and reading must be developed and maintained, especially if resistance is to be realistically tackled. As the writer has travelled in Asia she has seen many centres where the laboratory results cannot be relied upon. Poor results are worse than useless. They produce false negatives more often than false positives and do not give consistent results. It is very easy to take a smear that is too small, to understain or over-decolourize so that when it is examined under the microscope it is impossible to see any acid-fast material. It is also common to find dirty equipment that eliminates the possibility of making good clean slides. It is not difficult to teach a technician how to make a good

clear well-stained slide, but the doctor or senior paramedical worker needs to be on the alert to keep the standard up. The technician must also have enough time to examine adequately the slide, especially when Morphological Index is required or the acid-fast material is becoming scanty. A well motivated technician does not need to be trained in all aspects of laboratory work to "do" good skin smears. The clinical diagnosis of testing for dapsone resistance depends on good laboratory support. A good leprosy programme cannot exist without a reliable laboratory backing. It is essential that every doctor in leprosy acquaints himself with the laboratory side of the work and takes time to train good technicians (if he cannot get them trained) and to check on the quality of their work from time to time.

(4) Antileprotic therapy should not be stopped for intercurrent diseases or ENL or lepra reaction, which can usually be controlled by use of supportive drugs. If for some reason it is not possible to give an adequate dose of dapsone it is better to use some secondline antileprotic, if available, such as thiosemicarbasone which will not be needed for long term treatment so that if resistance to that drug does develop it will not be such a problem. Although it is generally accepted that dapsone of itself does not cause ENL the writer is one who feels that dapsone in high dosage may, in some patients, increase the severity of the ENL which at low dose is only of nuisance value and becomes disabling on high dosage. Ideally these patients with severe or chronic ENL should receive clofazimine but there are still many countries where this is not freely available and in these situations it may be possible to treat these patients, as we did for many years in Hong Kong before clofazimine became available, with 2 antileprotics in smaller than usual dosage. In theory the use of the 2 drugs together should eliminate the predisposition to emergence of dapsone-resistant organisms.

(5) The maintenance of adequate records is essential. These must include an adequate description of the lesions when first seen, and of any new lesions as they present. It is not enough to just state "Borderline" leprosy as fashions in classification have changed many times over the years. If the lesions are properly described then the next person can tell if there has been any real change in the lesions. It is easiest to have some sort of chart to fill in but do not assume that a space left blank means "normality"—it may not have been examined. If a careful description is given it is possible for someone many years later to classify and compare the present situation with what it was initially. In some centres there are patients who have relapsed and even developed dapsone resistance because initially they were incorrectly classified on the front cover and over the years they have been treated according to that classification. On review after relapse it is possible from the incomplete notes available to see that some were classified as BT who were really BL. Tragedy could have been prevented by a little more care. Please make good examinations and record the findings. Please record all distributions of dapsone, regularity is important and the chart is the place to keep note of it, not in the head of some worker who may not be available when the information is needed. Please record all skin smear results with the examination records. Yes, a book in the laboratory is helpful to the technician but the real place for results is with the other details about the patient, so anyone reading his notes has access to all the relevant information at once.

(6) Educate the patients to understand more about their disease and the necessity of regular prolonged treatment.

(7) Educate the public so that patients will come earlier when therapy is easier and before severe ENL or deformity have occurred.

(8) Be thorough with the follow-up of patients who have been under treatment for years. They need regular skin and nasal examination (smears) and the whole skin must be examined in a good light. It is no good asking "have you any new skin lesions?" There are many patients under treatment who have never had a complete examination by a doctor or a paramedical worker. How can a patient tell if he has new lesions on his own buttocks?

Dapsone resistance has crept up on us—we blissfully went on believing that it could not happen until we now have a real problem on our hands. In fact it has been said that the problem of getting leprosy under control now is greater than it was 15 years ago, as we now have dapsone resistance. The widespread scattering of dapsone that is taken irregularly is never going to control this disease, especially as now there are patients who will not respond at all to dapsone. We must be more methodical and we must remember that clofazimine is the only drug that we have at present that can be given for long-term treatment of the dapsone-resistant patient. Theoretically resistance to clofazimine could also occur though it has not yet been proven, but we must remember this in the use of clofazimine. The search for new and more effective drugs continues but until and even when another drug becomes available we must remember the lessons of dapsone resistance and use clofazimine as best we know how in the hope that clinical resistance to clofazimine does not occur also.

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Sulphone Resistance and Its Implications

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The most important factors in the emergence of sulphone resistance are low dose therapy and irregular treatment with dapsone. Measures are discussed how to increase treatment in depth and effectiveness.

Introduction

Around 1961 the first cases of sulphone-resistant leprosy were detected at Carville, U.S.A., and Sungei Buloh, Malaysia. At first leprosy workers were slow to appreciate the serious implications of these findings. During the 9th International Leprosy Congress in London (1968) only 2 papers (Rees, 1968; Pearson *et al.*, 1968) out of 236 were devoted to sulphone resistance in leprosy and the 10th Congress in Bergen (1973), with 7 papers out of 378 paying full attention to the subject, did hardly any better. Since then detailed reports from all over the world have made it clear that sulphone resistance is rapidly on the increase, in some countries at the rate of 2–3% per annum in lepromatous patients. Although by now most leprosy workers are aware of the existence of sulphone resistance there seems to be a curious reluctance to accept this unpleasant truth and act upon it. In many places policies of control programmes and treatment of individual patients continue in much the same way as before, perhaps in the hope that one day the problem of resistance, simply by ignoring it, will have disappeared of its own account.

Low Dose Therapy

The main reasons for the emergence of sulphone resistance appear to be low dose therapy and irregular treatment with DDS. Low dose therapy was inspired by the conception that there is a direct connection between the dosage of dapsone and the occurrence of reactions. Hence treatment is usually started with a small dose of DDS, e.g. $2\frac{1}{2}$–5 mg daily, and this is slowly increased over a number of months to 50–100 mg daily. But as soon as reactions occur the dosage is reduced or treatment stopped, with the result that many lepromatous patients continue for months or even years on a dosage of DDS insufficient to prevent the occurrence of sulphone resistance. Nowadays a growing number of leprologists are of the opinion that reactions are not due to treatment with DDS and that as a consequence the dosage need not be reduced during episodes of reaction.

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However this may be, while weighing against each other the risks of sulphone resistance and of reactions it is evident that the former is the graver and should be tackled first. This means that all patients should be started *ab initio* on full dose DDS ($1\frac{1}{2}$–2 mg/kg bodyweight/day) and should continue on the same regardless whether reactions occur.

An important implication of this policy is that para-medical workers should be better equipped to cope with reactions. They should be trained in the use of steroids and they should have clofazimine (Lamprene) freely at their disposal as an alternative to dapsone.

Irregular Treatment

Irregular treatment may be due to several factors, the most important being the leprosy worker himself who is often not aware of the fact that once he has started treating a lepromatous patient with DDS, he has taken a heavy personal responsibility upon himself: to see that that patient will receive uninterrupted full dose therapy throughout the duration of his illness. Conversely, every leprosy worker should realise that inadequate treatment of lepromatous patients during the first years may lead much later to sulphone resistance which cannot be undone by subsequently resorting to uninterrupted full dose therapy.

In the treatment of leprosy with its psychological and social overtones the relationship between patient and doctor or paramedical worker plays a crucial part. On the side of the patient confidence is a key factor in sustaining regular treatment. On the side of the leprosy worker this presumes professional skill, e.g. in coping with reactions, ulcers and deformities, personal interest in the patient which means willingness to spend time with him, perseverance and imagination, e.g. in setting up a postal DDS service for patients who are unable to collect their medicines at the appointed time.

Another important reason for irregular treatment viz. discontinuation of DDS during episodes of reaction has already been discussed.

Finally treatment may be interrupted because drugs like clofazimine or even dapsone are not readily available on account of production problems or import restrictions. The leprosy worker must be given his tools and nothing is more undermining to his morale than the absence of essential drugs. It is a tragedy when economical factors are responsible for the emergence of sulphone resistance with all its consequences to the patient and the community. Surely it ought to be possible to find a solution for such situations on a national or international level.

Research

While regular full dose therapy with DDS will reduce the risk of sulphone resistance in lepromatous patients, it will not completely exclude it, because *M. leprae* throws off drug-resistant mutants. There is also the possibility of a primary infection with DDS-resistant strains of *M. leprae*. For these reasons monotherapy with dapsone of lepromatous patients can no longer be considered to be adequate and studies of drug combinations in the treatment of leprosy deserve high priority.

Another subject which urgently needs to be investigated is the prevalence of sulphone resistance in various countries. Central registration of suspected cases may give valuable information regarding the risk of sulphone resistance in relation

to dosage and duration of treatment with DDS. This means that all leprosy workers should be constantly on the watch for such cases and have a good knowledge of the clinical signs of resistance, e.g. they should be aware that lepromatous nodules on the sclera, when seen in a patient on treatment with DDS almost always indicate resistance (Ross, 1976). They also should have a good knowledge of the interpretation of bacteriological findings (BI, MI). To assess accuracy of reported cases facilities may have to be arranged for mouse foot-pad inoculation of sample biopsies.

Conclusion

Sulphone resistance has emerged because of inadequate treatment of lepromatous patients. Therefore, it might be argued that unless one is certain that a lepromatous patient can be properly treated throughout the whole period of his disease, it would be wiser not to accept him for treatment at all! For once a patient has developed sulphone resistance he has become not only a therapeutic problem but a public health problem as well. Incidental treatment of lepromatous patients in hospitals or by private practitioners, and leprosy control programmes with a high rate of defaulters are likely to do more harm than good. Initially they may seem to be fairly successful but this is only because *M. leprae* is such a slow growing organism. Sooner or later, after a period of 5–20 years, sulphone resistance will catch up with us and we may find ourselves facing a greater problem than at the onset. Experience with tuberculosis and malaria makes it clear that in leprosy control programmes there is no room for light-hearted optimism. The implication for large scale treatment schemes is that the emphasis has to shift from quantity to quality. The population for whom a paramedical worker is responsible may have to be reduced and it may even become necessary to leave certain areas temporarily untouched in order to cover strategic areas properly. Only as individual and mass treatment increase in depth and effectiveness will hope be restored that leprosy can be controlled and eventually eradicated.

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Management of Sulphone-resistant Lepromatous Leprosy

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The first thing to be said on the subject of dapsone resistance in leprosy is that we know very little about it apart from the fact that resistant strains of *Mycobacterium leprae* arise by spontaneous mutation, that resistance appears to be on the increase, and that up to the present time it has been reported only in lepromatous leprosy. I have never encountered it in tuberculoid or borderline leprosy, and I have not heard of anyone who has, although I accept that one day it may be reported as a rare occurrence in Mitsuda-negative borderline leprosy (i.e. BL and BB).

When relapse occurs after a period of initial response to chemotherapy, and the patient has been taking small doses of dapsone, the clinician is tempted to assume that a dapsone-resistant strain of *M. leprae* has arisen because of small dosage, and when relapse occurs in a patient who has been on large doses, and it is known that the patient (like the majority of lepromatous patients) in unreliable on treatment, the clinician is tempted to blame irregular treatment, but, to the best of my knowledge, both these hypotheses are still without scientific proof. It should be noted that when a strain of pathogenic bacteria develops resistance to a given drug, the infection can sometimes be controlled by giving greatly increased dosage of that particular drug, and this probably accounts for the fact that a patient harbouring dapsone-resistant *and* dapsone-sensitive strains of *M. leprae* is less likely to relapse on large, rather than small, doses of dapsone, and *vice versa.* Therefore a case can be made for giving adult lepromatous patients 100 mg dapsone daily even though much smaller doses are effective against dapsone-sensitive strains. Readers will be familiar with the reports of Russell and colleagues from Papua New Guinea showing that intramuscular injections of acedapsone (DADDS; Hansolar) every $2\frac{1}{2}$ months, liberating only 2.4 mg dapsone daily, gave results comparable with those obtained from standard oral dapsone dosage of 100 mg daily.

The therapeutic policy which I would advise in order to reduce the likelihood of relapse in lepromatous leprosy while under treatment is the one outlined by Waters and Helmy (1974), namely, to give adults 100 mg dapsone daily from the outset, using steroid or thalidomide (without reduction of dapsone dosage) should serious Type 2 lepra reaction (ENL reaction) occur. It is my policy, if relapse does occur, to add clofazimine (Lamprene; B663) to treatment in a dosage of 100 mg twice a week, and results have been consistently satisfactory; pigmentary changes,

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even in light-skinned patients, have been absent. It is important that dapsone should be continued, together with clofazimine, so that it can continue to inhibit the dapsone-sensitive strains, thus leaving clofazimine to inhibit the dapsone-resistant strains. I am opposed to the policy (which is widely being proposed) of giving combined treatment routinely and *de novo* in lepromatous leprosy before the problem of overcoming the high defaulter rate among outpatients has been tackled, for patients who default on 1 drug are more likely to default on 2, and combined treatment will then have the disadvantage of being expensive as well as wasteful. I would prefer to see dapsone given alone, combined with an all-out effort to overcome defaulting, with the proviso that skin smears are taken routinely every 6 months in order to get early intimation of relapse (long before clinical relapse can be observed); 2 smears should include the dorsa of fingers (Ridley *et al.*, 1976), preferably over the first phalanges. Only if there is an increase in solid-staining bacilli need action be taken, and this consists in assessing bacteriological response to regular dosage of dapsone by *intramuscular injection* over a period of 3 months; testing in the mouse foot-pad calls for a specialized laboratory and, in any case, takes more than twice as long to prove. I would like to sound a note of warning against assuming that a patient who relapses is harbouring dapsone-resistant bacilli, for it is equally possible that he has not been taking the drug, and therefore, dapsone resistance must be proved before being accepted.

The above remarks apply to the management of lepromatous leprosy, as it is in this type that the problem of dapsone resistance is important, therefore observations on the treatment of borderline leprosy are irrelevant at this stage, but I would like to stress that large doses of dapsone in this type of the disease are both unnecessary and dangerous (Jopling, 1977).

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Primary Dapsone-resistant Leprosy

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Persons living in areas where acquired dapsone resistance is common may be infected and develop leprosy with dapsone-resistant strains of *Mycobacterium leprae*. Mouse foot-pad tests on bacilli from 8 such patients, with active and previously untreated lepromatous leprosy, have shown that strains from 5 were dapsone resistant. These findings demonstrate for the first time the presence of patients with primary dapsone resistant leprosy in the community at large. The preliminary findings are presented because of the high proportion of primary dapsone resistance in the first 8 patients in a survey of some 50 patients in Ethiopia. The implications of these preliminary findings are discussed.

Introduction

As the number of lepromatous patients with acquired dapsone-resistant leprosy increases, the likelihood that they will become the source of new cases showing primary dapsone resistance, also increases. However, primary dapsone-resistant leprosy can only be diagnosed by dapsone-sensitivity testing using the mouse foot-pad infection, unless the degree of resistance is so high that patients fail to show any response to dapsone therapy. We report here the results of mouse foot-pad sensitivity tests performed in 8 patients with previously untreated lepromatous leprosy.

Patients and Methods

Patients were selected from those attending the Addis Ababa Leprosy Hospital. All had active lepromatous leprosy and denied previous treatment. All had lived for at least 5 years in areas where anti-leprosy treatment with mainly dapsone had been available for 10 years or more. A biopsy was taken from an active skin lesion from each patient and transported by air on wet ice to England. The dapsone-sensitivity testing, using the mouse foot-pad infection, was performed at the National Institute for Medical Research, London, not more than 5 days after the biopsy of skin was taken in Ethiopia. The skin was homogenized for the

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preparation of suspensions of *M. leprae* for the inoculation of both hind foot-pads of mice by the standard procedures previously described (Rees, 1964). For assessment of the dapsone sensitivity of the strains of *M. leprae* the inoculated mice were divided into groups of 6 animals. One group acted as a control and the other group or groups received dapsone incorporated in different concentrations in their diet. Strains of *M. leprae* from the first 4 patients were screened against only a concentration of 0.0001% dapsone in the diet whereas the later 4 strains were screened against 0.001, 0.0001 and 0.00003% dapsone in the diet, see Table 1 (Rees, 1967; Pearson, Rees and Waters, 1975).

Results

Of the 8 patients only 3 had strains of *M. leprae* that were fully sensitive to dapsone, in that their growth was completely inhibited in mice receiving 0.0001% dapsone in the diet. The levels of dapsone resistance of the strains from the remaining 5 patients are summarized in Table 1. Of the 3 resistant strains more

TABLE 1

Multiplication of 8 strains of Mycobacterium leprae *in mice receiving different concentrations of dapsone in the diet*

Patient	Bacillary multiplication				Dapsone sensitivity
	% Dapsone in diet				
	0	0.00003	0.0001	0.001	
1	+	–	+	–	Resistant
2	+	–	0	–	Sensitive
3	+	–	+	–	Resistant
4	+	–	0	–	Sensitive
5	+	+	0	0	Sensitive
6	+	+	+	+	Resistant
7	+	+	+	+	Resistant
8	+	+	+	0	Resistant

broadly screened, 2 showed a higher degree of resistance (i.e. to 0.001% dapsone in the diet), the third was resistant to only 0.0001% dapsone in the diet, as were the 2 other dapsone resistant strains tested only at this concentration.

Discussion

Resistance to dapsone may be either acquired or primary, as is the case with any other drug or micro-organism. Acquired dapsone resistance occurs as a result of the selective multiplication of spontaneous drug-resistant mutant bacilli during the course of dapsone therapy. It is likely to occur more commonly when dapsone dosage is sub-optimal (Pearson *et al.,* 1975), but has been recorded in patients who have been prescribed dapsone in full dosage and taken treatment regularly (Pearson *et al.,* 1975). Primary resistance, on the other hand, implies that the bacilli which infected the patient were dapsone resistant from the beginning.

Acquired dapsone resistance is now commonly seen, and is becoming a major problem for many leprosy control services. In Addis Ababa, for example, the incidence of suspected acquired dapsone resistance is about 3% per annum among patients already under treatment for lepromatous leprosy (Pearson, Ross and Rees, 1976). However, this study is the first reported systematic attempt to look for primary dapsone-resistant leprosy, and the fact that bacilli from 5 out of the first 8 newly-diagnosed patients with lepromatous leprosy tested showed dapsone resistance indicates that primary resistance in their home areas may now be the norm rather than an occasional exception.

All the patients tested were suffering from lepromatous leprosy. Dapsone resistance in non-lepromatous ("paucibacillary") cases has not yet been reported, and will only be diagnosable on clinical grounds (though occasionally biopsies might contain enough bacilli for mouse foot-pad tests to be undertaken). However, all leprosy patients are likely to derive their infections from the same index cases. It is therefore probable that, in areas where primary dapsone-resistant lepromatous leprosy is found, non-lepromatous cases will also often be dapsone resistant.

In this survey of primary dapsone resistance we have defined a resistant strain of *M. leprae* as being one capable of multiplying in the foot-pads of mice receiving dapsone at a concentration of 0.0001%. This is based on our own extensive data, and that of others (Levy and Peters, 1976), that all strains of *M. leprae* from apparently previously untreated patients, from many different parts of the world, were sensitive to this or lower concentrations of dapsone. Therefore when we started the survey strains of *M. leprae* from the first 4 patients were tested only in mice receiving 0.0001% dapsone, although all subsequent patients, including patients 5 to 8 in this paper, were in addition tested at 0.00003% and 0.001% dapsone. The extended assay was introduced, in part, to check the dapsone *sensitivity* of strains of *M. leprae* from new lepromatous patients currently arising in Ethiopia but also, and importantly, to determine the degree of *resistance* in patients showing primary dapsone resistance. Since only one of the 3 dapsone resistant strains that were checked showed low grade resistance (to 0.0001% dapsone), the 2 resistant strains not checked above 0.0001% dapsone might, unfortunately, also have a higher grade resistance. Low grade resistance determined in the mouse is equivalent to failure to respond to dapsone 1 mg daily in man (Shepard, 1973). Most such patients have responded only for a few years when treated with dapsone in maximal dosage, though occasionally more prolonged remissions occur. It is likely therefore that most patients with lepromatous leprosy who show even low grade primary dapsone resistance will not be cured by monotherapy with dapsone, even in maximal dosage. It is possible that supplementation with a second drug would be curative; but it is not unlikely that triple therapy will be needed for these cases, at least during an initial period of intensive therapy. It is our experience that patients with higher grade resistance (to 0.001% dapsone) respond only for a year or perhaps two when treated with dapsone in maximal dosage.

In areas where cases of primary dapsone resistant lepromatous leprosy are common, it must be assumed that the non-lepromatous cases are also resistant. Because of their lower bacterial load, it is more likely that such patients would be cured with dapsone alone, and probable that dual therapy will suffice. Certainly it would be advisable as a minimum measure, to use dual therapy for all leprosy cases in such areas.

The finding of primary dapsone resistance on a significant scale in Ethiopia has several important implications:

(1) Experimental chemotherapy is needed to determine optimal drug regimens for the treatment as well as the prevention of drug resistant leprosy. Such trials will probably require armadillos infected with sensitive or resistant strains of *M. leprae.*

(2) Surveys using mouse foot-pad tests of patients in other parts of the world with previously untreated lepromatous leprosy should be planned. It is unlikely that primary dapsone resistance is confined to Ethiopia, and the extent of the problem must be determined.

(3) Multiple drug therapy must become routine practice in leprosy control programmes: this presents a challenge for budgeting and staff training. Furthermore, large scale controlled drug trials will be required if the cost effectiveness of different drug regimens is to be accurately determined.

(4) It is likely that treatment regimens for leprosy should vary according to the risk of dapsone resistance in any particular area. This could be an argument for retaining leprosy as a specialized service, at least until more is known of the problems of chemotherapy, which are only now coming to light for leprosy. Correct anti-leprosy treatment is no longer either simple or cheap, and ill-advised integration could turn a problem into a disaster for the future of leprosy control.

Acknowledgements

We are grateful to the staff of the Addis Ababa Leprosy Hospital and the All Africa Leprosy and Rehabilitation Training Centre (ALERT) for referral of patients and provision of facilities for investigation and treatment. We are indebted to Mrs Susan Cate and Miss Gillian Cooper for technical assistance in the studies carried out at the National Institute for Medical Research, London.

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Leprosy and the Community

INTERNATIONAL FEDERATION OF ANTI-LEPROSY ASSOCIATIONS

The great importance, scope and potential of the International Federation of Anti-Leprosy Associations (ILEP) is well brought out in a recent report which includes the following:

"ILEP, the International Federation of Anti-Leprosy Associations, is a co-ordinating body whose Member-Organizations are partners in a working community. The basic principle that determines all the working relations within as well as outside this community is an absolute respect for the individuality and freedom of each partner.

Presently ILEP brings together 24 voluntary agencies concerned with helping leprosy sufferers. They represent 16 countries of the West. Their global expenditure for leprosy work in the 5-year period of 1970-1975 amounted to US $ 57.5 million. Detailed information is not yet available for the year 1976, but the provisional budget amounted to US $ 23.8 million.

The actual 1975 expenditure reached US $ 15.3 million, of which US $ 12.5 million were granted to 467 field projects in 60 countries for the benefit of 1,225,000 leprosy patients, amongst whom more than 900,000 patients received treatment in 156 leprosy control programmes with a total expenditure of US $ 7.4 million.

As a matter of fact, ILEP Member-Organizations are participating with an expenditure of US $ 3.5 million in the national leprosy control programme of 27 countries (20 in Africa, 4 in Asia and 3 in the Americas).

Research is a high priority which a total expenditure of US $ 1.5 million for the support of 7 training projects amongst which 3 international institutions along with US $ 0.2 million for scholarships.

In 1975 ILEP has given support to some special programmes including US $ 0.5 million to 9 urban programmes, mostly in India, and US $ 0.2 million to 3 Tuberculosis and Leprosy combined programmes (2 in Africa and 1 in Asia).

ILEP has a long experience in rehabilitation of leprosy sufferers, more than US $ 1 million were devoted in 1975 to rehabilitation activities including physical, vocational, economic and social rehabilitation, especially in 24 technical co-operation programmes. As a matter of fact, ILEP is still caring for 55,000 permanent in-patients in some 300 institutions. Furthermore special ad hoc working groups are studying psycho-social factors in leprosy."

It is most encouraging that the recent great developments in the World Health Association concern for leprosy on its research side are matched by an international organization on this scale for applying treatment and care to patients.

LEPROSY IN BRAZIL: NATIONAL CONFERENCE TO ASSESS THE POLICY OF CONTROL OF HANSENIASIS

> "Brazil officially admits the failure of conventional policies to control hanseniasis and adopts new measures based on removal of the cultural barriers of leprosy".

Under this quotation we have received a copy of a report on a national conference, held in March 1976 and attended by leading Brazilian leprologists, to reconsider the approach to leprosy control now current in that country. In his opening address, Professor Paulo de Almeida Machado, Minister of Health, stated that 140,000 patients with leprosy are registered in Brazil, 126,000 of them over 15 years of age. 8500 new cases are registered each year. Those registered are estimated to represent an economic loss to the country of US $ 46 million a year, but their numbers are believed to be greatly exceeded by those who fail to register, largely on account of the persistent fear and prejudice associated with "leprosy".

The conference agenda was broadly based, and 7 groups considered the following aspects of the problem: cultural barriers; hospitals, colonies, asylums and preventoria; legislation; prophylaxis; social re-integration; prevention of deformities and rehabilitation; training of personnel.

Recommendations of the conference cover the following:

1. The introduction at national level of a new terminology as the first step to change present stigmatizing concepts and overcome cultural barriers.
2. The formation of broadly based groups to plan more appropriate strategies.
3. The discouragement of organizations whose concerns are exclusively with hanseniasis patients and/or their children.
4. The hampering of activities which although well intended do aggravate stigma, sensationalism and prejudice.
5. The integration of leprosy institutions into wider medical and social concerns.
6. Hospitalization should be restricted to a few special cases.
7. Family planning should be instituted on account of the teratogenicity of some anti-hansenic drugs.
8. Patients should be assured of the right to work. Except for incurable physical disability, patients should not be granted the right to retire or be forced to retire. No special salaries should be given to workers in this disease. No credit or fiscal favours should be granted to organizations taking care exclusively of problems of this disease.
9. Basic teaching on this disease should be included in health courses at all levels, and ample time be given to it in medical education.
10. Government social welfare agencies should accept responsibility for the economic problems of patients.
11. Children should not be separated from their parents.
12. Treatment by private practitioners should be encouraged and drugs provided to them.
13. Tuberculosis and hanseniasis programmes should be integrated, and control policy and procedures should become uniform.

14. Re-integration of patients should be planned as soon as the diagnosis is made, at whatever stage of the disease.
15. "Vocational agencies" with representatives of the Ministries of Health, Social Welfare, State public health services, community and patients, should be established in each State.
16. Totally disabled patients should receive permanent economic aid.
17. Techniques for the prevention and treatment of deformities and disabilities should become routine.

WORKSHOPS IN LEPROSY AT BOMBAY

The Acworth Leprosy Hospital Society for Research, Rehabilitation and Education in Leprosy is now organizing periodic "Workshops on Leprosy" in order to encourage leprosy research in Bombay. The reports on the first and second workshops include the following, selected as of general interest.

1. *Regularity of dapsone intake by leprosy patients attending urban treatment centres,* by S. S. Naik

The daily attendance of outpatients at the Acworth Leprosy Hospital is from 250 to 300. In order to investigate how far the self-administration of dapsone is reliable in these patients, randomized urine samples were tested for dapsone and the dapsone creatinine ratio. Analysis of the records had shown that 60% of patients drop out from regular treatment within 1 year. The study was therefore conducted on those patients who were attending regularly, and who were presumed to be receiving and swallowing dapsone by self-administration. The results suggest that only about 24% of registered cases are taking regular treatment in the long term.

Dr A. D. Somson mentioned his experience in rural areas where there is a drop-out rate of 30%.

Dr N. H. Antia emphasized that a reduction in the drop-out rate could only be achieved by attending to the psychological, social, economic and educational needs of patients, for which more medical social workers will be required than doctors.

2. *"H" reflex in leprosy,* by Dr (Mrs) S. S. Pandya

The "H" reflex is the electrophysiological equivalent of the ankle jerk. A small study was undertaken to test the validity of the oft-repeated statement that the reflexes are never compromised in leprosy. The "H" reflex was studied in 15 normal people and 12 patients with lepromatous leprosy. Latency was normal in 10 patients and absent in 2 patients. This suggests that degeneration of the calf muscles does occur in some patients with lepromatous leprosy.

3. *The study of hydnocarpus oil as an antileprotic agent in the mouse foot-pad,* by A. C. Desia and Dr M. B. Bhide.

Hydnocarpus oil alone when fed to mice infected with *Mycobacterium leprae* resistant to dapsone, induced inhibition of the growth of bacilli in the mouse foot-pad. When combined with dapsone this drug also showed an additive effect on DDS-sensitive bacilli.

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News and Notes

RIFAMPIN-RESISTANT LEPROSY

Letter to *The Lancet*, 11 December, 1976*

The rifamycin antibiotics have been used in the treatment of leprosy since 1963 (Opromolla, de Souza Lima and Caprara, 1965). The orally active rifamycin, rifampicin, or rifampin has been utilized more recently (Rees, Pearson and Waters, 1970; Shepard, Levy and Fasal; Opromolla and Tonello, 1975). Rifampin exerts a rapid bactericidal effect on *Myobacterium leprae* in man (Shepard *et al.*, 1972; Levy, Shepard and Fasal, 1972), but concern has been expressed regarding the possible development of rifampin-resistant *M. leprae* (Shepard *et al.*, 1972; Opromolla and Tonello, 1975; Ellard, 1975; Rees, Waters and Pearson, 1976).

We have seen a patient with sulphone-resistant lepromatous leprosy who experienced clinical and bacteriological relapse while on rifampin monotherapy. The patient is a 49-year-old male of Scandinavian extraction who has had lepromatous leprosy since the age of 18. He was treated with sulphones, glucosulphones ("Promine"), and, later, sulfoxone ("Diasone") both of which he took irregularly from 1946 until 1968. In 1968 he developed clinical relapse despite sulfoxone therapy and mouse foot-pad studies by Dr Charles Shepard in

TABLE 1

Drug sensitivities in mouse foot-pads

Treatment	% w/w in diet	No. of pads positive for acid/fast bacilli/total	Acid-fast bacilli/foot-pad
Controls		6/6	$1.750\ (\pm 0.810) \times 10^5$
Dapsone	0.0001	6/6	$1.033\ (\pm 1.013) \times 10^5$
	0.001	6/6	$4.502\ (\pm 3.406) \times 10^4$†
	0.01	0/6	$<7.298 \times 10^3$‡
Clofazimine	0.0001	0/6	$<7.298 \times 10^3$‡
	0.001	0/6	$<7.298 \times 10^3$‡
	0.01	0/6	$<7.298 \times 10^3$‡
Rifampin	0.001	6/6	$3.773\ (\pm 0.857) \times 10^4$†
	0.01	6/6	$8.757\ (\pm 8.648) \times 10^4$
	0.03	6/6	$5.718\ (\pm 2.669) \times 10^4$†
	0.06	0/6	$<7.298 \times 10^3$‡
Ethionamide	0.01	0/6	$<7.298 \times 10^3$‡

† $0.01 > P > 0.001$, Student's *t*-test, compared with controls.

‡ $0.01 > P > 0.001$, χ^2_1, test with Yates' correction, compared with controls and compared with any group with 6 of 6 positive harvests.

Values are means (S.D.) of acid-fast bacilli harvested from individual animals $6\frac{1}{2}$ months after inoculation with 5×10^3 *M. Leprae*.

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We are grateful to the Editor of *The Lancet* and the authors for permission to reprint this letter.

Atlanta, Georgia showed intermediate levels of sulphone resistance (multiplication in mice fed 0.0001% and 0.001% w/w dapsone in the diets but no growth in animals fed 0.01% dietary dapsone). The patient was put on high doses of dapsone (up to 200 mg daily) from 1968 to 1970, and, because his disease continued to progress, he was then treated with streptomycin from 1970 to 1972. His disease responded to streptomycin, but in July 1972, it became progressive once again despite continued therapy, and treatment was changed to rifampin 600 mg daily. The patient took 93.5% of his prescribed doses of rifampin from July 14, 1972 to July 10, 1976. In February, 1976, after 43 months of rifampin therapy, a new nodular skin lesion developed on his left lower chest. Biopsy was done and mouse foot-pad drug-sensitivity studies were started. The patient had slow progression of his lepromatous leprosy despite rifampin until July, 1976, at which time he was placed on clofazimine ("Lamprene") 100 mg daily. The results of drug-sensitivity tests are given in the table.

To our knowledge this is the first case of rifampin-resistant leprosy confirmed by mouse foot-pad studies. The pattern of rifampin resistance in *M. leprae* appears to be of a streptomycin type or single-step mutant. This contrasts to our experience with 75 dapsone-resistant strains in which the pattern of growth in mice fed dapsone indicates a penicillin or multiplestep type mutation. The spectre of multiple drug-resistant leprosy bacilli suggests that consideration be given to routine multiple drug therapy of lepromatous leprosy, particularly in regimens including rifampin.

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11th INTERNATIONAL LEPROSY CONGRESS MEXICO CITY, 13-18 NOVEMBER, 1978

The special Advisory Committee, nominated by the President of the International Leprosy Association, Dr J. Convit, to advise him on the content and form of the Scientific Sessions and general arrangements for the 11th Congress, met in Mexico City on 7 and 8 January, 1977.

The Committee waited on Dr Emilio Martinez Manautou, the newly appointed Secretary for Health. Like his predecessor in office, he expressed warm interest in the Congress and assured the delegation of his Government's support.

The Committee met with the active participation of Drs Latapi, Saúl and Rodriguez, local President, Vice-President and Secretary respectively, and also had a session with the full local Organizing Committee.

The President's Advisory Committee considered the numerous suggestions that have come since the Bergen Congress from members of the International Leprosy Association and others. While many of these suggestions cancelled each other out,

and others were quite impracticable for various reasons, the Committee arrived at a series of compromises which, it is hoped, will augment the value of the Congress to the majority of the participants without impairing its scientific purpose and content.

An innovation that will commend itself to many will be the designation of named workers to present papers on a given theme, of a didactic or review nature. Unfortunately, this will mean that fewer proffered papers will be read.

Another innovation will be the introduction of "poster sessions" at which designated authors of abstracts will speak of their material, prepared in the form of posters (photographs, charts, graphs, letterpress, etc.) suitable for hanging in the Exhibition area.

The deadline for the receipt of abstracts is 28 February, 1978 (to Dr S. G. Browne, 57a Wimpole Street, London W1M 7DF). Full details of all matters concerned with the Congress will appear in the preliminary announcement, now in course of active preparation.

Pre-Congress Workshops will be held. Members suggested by the President's Advisory Committee, and those nominated by the respective Chairmen, will be notified personally by letter.

The new format of the Scientific Sessions will permit of more time for open discussion.

Since it is not possible (for various reasons) for the afternoon sessions to begin before 1500 h, it is suggested that groups with a common interest may wish to meet in suitable rooms at the Congress Centre, between the hours of 1400 and 1500.

While the President's Advisory Committee dares not hope to have reconciled the irreconcilable, it has tried in its suggestions for the Scientific Sessions at the forthcoming Congress to please most of the people most of the time.

Correspondence regarding the Congress should be addressed to: Dr Amado Saúl, Dermatologo, Insurgente Sur 363–303. Mexico 11, DF, Mexico.

WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES

At a meeting at WHO Headquarters, Geneva, on 7-8 December, 1976, representatives of health ministries, bilateral and multilateral aid agencies, missions and private foundations reviewed developments during the past year in the WHO Special Programme for Research and Training in Tropical Diseases. The 35 delegations were unanimous in expressing support for the Special Programme, and US $7.5 millions was pledged for 1977 by, The UN Development Programme; ILEP; The Sasakawa Memorial Health Foundation; The Japan Shipbuilding Industry Foundation; and Governments or Aid Missions of Austria, Belgium, Denmark, Finland, Nigeria, Norway, Switzerland and the United Kingdom. This is good news for all concerned with leprosy, for it indicates that the financial backing for the IMMLEP and THELEP programmes is secure.

SECOND REGIONAL CONFERENCE OF DERMATOLOGY
Bangkok, 17-21 January, 1977

This Conference, organized by the Dermatological Society of Thailand at the instigation of the International Society of Tropical Dermatology proved to be a

resounding success. It attracted more than 300 participants from 15 countries, mainly from Asia and Australasia, but also from Europe and the United States of America. The joint sponsors were the Thailand Ministry of Public Health and SEAMEO Tropical Medicine, whose indefatigable co-ordinator is Professor Chamlong Harinasuta.

In addition to discussions on matters of general interest to dermatologists working in the area, leprosy came in for a very fair share of attention. One of the concurrent scientific sessions was entirely devoted to leprosy, under the chairmanship of Dr John Pettit (of Kuala Lumpur) and Dr V. R. Mehta (of Bombay).

The 2 guest speakers at the closing plenary Session were Dr Stanley Browne, who spoke on "Recent advances in leprosy of general and dermatological interest" and Dr William Jopling, whose subject, illustrated by an abundance of coloured transparencies, was "The differential diagnosis of leprosy in the tropics".

It is planned to hold the Third Regional Conference in Indonesia towards the end of 1978.

C.I.O.M.S.

As a Founder-Member of the Council for International Organizations of Medical Sciences, the International Leprosy Association was represented at the recent (November 9–11, 1976) Tenth General Assembly of the Council in Geneva by its Secretary Treasurer, Dr S. G. Browne. Under the dynamic presidency of Dr Alfred Gellhorn and its newly-appointed Executive Secretary, Dr Z. Bankowski, the Council is actively pursuing its role of ethical watchdog on the progress of medical sciences throughout the world.

During the Geneva meeting, the ethical and moral repercussions of drug trials were discussed, and the meaning in practice of "informed consent". Delegates were encouraged to discover if the principles of the Declaration of Helsinki and other internationally recognized pronouncements were being observed in medical publications in which they had an interest or which were published in their countries.

The Council was empowered by its General Assembly to develop a programme on the role and functions of ethical review committees for research involving human subjects. It will work closely in this programme with the WHO and UNESCO. Initially, information will be collected from certain countries where ethical review committees have already been established, such as Ireland, Sweden, the United Kingdom and the Unites States of America. Reference was made at the meeting to the valuable pioneering work in this field of the Medical Research Council of Great Britain.

Any relevant experiences of members engaged in drug trials, which might be of value in the compilation of the report, would be welcomed by Dr S. G. Browne.

Future activities of the Council will include further debates on medical education and on various aspects of biochemical ethics, and an investigation (on the invitation of the WHO) of the views of medical scientists and other health workers on the protection of prisoners and detainees against torture and other cruel, inhuman or degrading treatment or punishment.

The Secretary-Treasurer of the International Leprosy Association, who was elected Vice-President of the CIOMS at its General Assembly will welcome any comments from members (under confidential cover if thought advisable) to

enable him to represent their views. The reactions of all CIOMS Member-Organizations, now numbering 90—including 68 international organizations and 22 national bodies representing national academics of science and research councils—will be sought and studied.

TRAINING OF LEPROSY WORKERS IN ASIA

The First International Workshop on Training of Leprosy Workers in Asia was held in Thailand from 25 to 28 November, 1976, under the auspices of the Ministry of Public Health of Thailand and the Sasakawa Memorial Health Foundation. A total of 36 delegates and observers from 10 Asian countries and 8 international anti-leprosy organizations, as well as representatives from the Leprosy Division of Thailand Department of Communicable Disease Control, spent a very full 4 days in Bangkok and Pattaya, discussing and debating in a very practical fashion the problems posed by the training of leprosy workers in countries where the disease is a major health hazard With the exception of Japan, Taiwan and Singapore the countries represented at the workshop might be described as poor and developing, and they all had to cope with other diseases that numerically took precedence over leprosy.

After the inaugural ceremony, at which Mr Kyoichi Sasakawa himself spoke, Dr Stanley Browne gave the opening paper entitled "The Training of Health Workers in Leprosy—ILEP's approach", after which Dr J. Walter from the WHO Headquarters in Geneva read a paper on "Manpower formation for leprosy control".

In addition to very able presentations from delegates from Thailand and other countries of South-East Asia, and some excellent sessions on "How to teach" by Thai medical education experts, Dr Ernest Fritschi (Karigiri), Dr J. Cap (ALERT, Addis Ababa), and Dr Felton Ross (now Medical Adviser to the American Leprosy Missions, Inc.) contributed not only in papers they read but also in the discussions that occupied a commendable part of each session.

After the Workshop, the delegates were taken by coach to the Provincial capital of Khonkaen, where they saw the Nonsumboon Leprosarium, the Miramon Medical and Social Centre, and the Provincial Training School and Health Department Headquarters. A concluding visit was paid to the Pharpradeung Leprosarium and Training Centre just outside Bangkok.

This valuable seminar will have considerable influence upon the standards of training of health workers in leprosy for years to come in the countries of South-East Asia.

CHEMOTHERAPY OF LEPROSY IN ASIA

The first International Workshop on the Chemotherapy of Leprosy in Asia was held in Manila (Philippines) from 26 January to 2 February, 1977 under the joint sponsorship of the Department of Health of the Republic of the Philippines and the Sasakawa Memorial Health Foundation, Japan. Governments of countries in South-East Asia had been invited to send delegates to the Workshop, and in addition there were guest lecturers from England, Belgium, the United States of America and the Philippines, as well as a number of local observers.

With an appreciation of the size of the leprosy problem in the countries represented, and conscious of the threat of the emergence of sulphone-resistant

bacilli on a wide scale, the Workshop reviewed the very practical problems of the treatment of huge numbers of patients within the context of meagre financial resources and, in most of the countries, of incomplete medical coverage.

The Workshop stressed the importance of regular treatment, and was gratified to be assured that monotherapy with dapsone was still considered to be adequate for patients suffering from paucibacillary forms of leprosy. The menace of sulphone-resistance called for a comprehensive prevalence study of the condition, since in many areas where it should be occurring its existence was not yet suspected. This study would presuppose accurate records of treatment given before the appearance of relapse due to resistant organisms.

Rifampicin or clofazimine should be given in addition to dapsone at the beginning of treatment to all patients suffering from multibacillary forms of leprosy. The financial implications of this recommendation to the poorer countries of Asia faced with a considerable leprosy problem, would be brought to the attention of governments and voluntary agencies.

As in previous workshop sponsored by the Sasakawa Memorial Health Foundation, the importance of adequate training of health workers was stressed, as well as the necessity to treat adequately all cases of reaction arising when optimally large doses of dapsone were given daily to patients in danger of developing reversal reaction.

THE CLASSIFICATION OF LEPROSY

A very useful series of 35 mm transparencies on the classification of leprosy has been produced by the Institute of Child Health, 30 Guilford Street, London WC1N 1EH, U.K. That these have been prepared by Dr Jopling and Dr Ridley is sufficient testimony to their authority. Microscopic photographs illustrating the various type of leprosy are matched by clinical photographs, and there are 2 accompanying scripts, one by Drs Jopling and Ridley the other by Dr C. McDougall which includes a questionnaire. The set is available from Foundation for Teaching Aids at low cost, c/o The Institute of Child Health at the above address, for a small charge.

RESEARCH IN LEPROSY CONTROL

A vacancy exists at Schieffelin Leprosy Research and Training Centre, Karigiri, Tamil Nadu S. India, for an Epidemiologist to work in the Leprosy Control Project. The Control Project, established in 1962, is one of the best documented projects in the world. A very high level of co-operation between local population leprosy patients and the staff of SLR and TC has been achieved. The project offers unrivalled opportunities for use as a field laboratory. The basic control procedures are undertaken by 20 trained paramedical workers, most of whom have been with the project since its inception, supervised by 3 supervisors and 2 doctors. 8600 patients are registered in a population of 426,000. The appointment will be for 3-5 years.

Successful applicants should have an M.P.H. or equivalent in addition to medical qualifications. Field experience in endemic disease control in the tropics will be an advantage. Further information about this appointment may be obtained from Mr A. D. Waudby, The Leprosy Mission, 50 Portland Place, London W1N 3DG, England, to whom application should also be addressed.

Lepr. Rev. (1977) **48**, 143–147

Letters to the Editor

Are There Regional Differences Regarding Secondary Amyloidosis in Leprosy?

If we consider patients with Hansen's disease from different environments, we may be concerned with similar populations from the statistical point of view, but this is not necessarily the case. The relative prevalence of the different clinical forms of leprosy varies between one country and another. In comparative studies of this subject, mistakes may be avoided if properly randomized samples are taken from each country, but if such care is not taken, conclusions can be applied with safety only to the samples on which work was performed.

For some time emphasis has been laid on the fact that the incidence of amyloidosis in leprosy in oriental countries differs from that registered in occidental countries (Satyanarayama, 1972; Editorial, 1975; Krisnamurthy, 1966; Mittal, 1972).

In the United States, Shuttleworth and Ross (1956), in a necropsy study, found that 10 out of 18 patients who had been treated at Carville (Louisiana) had amyloidosis (55%). Bernard (1956), in the Argentine Republic, found that 28 out of 40 patients who underwent autopsy at the Sommer Sanatorium had amyloidosis (70%). Williams *et al.* (1965) at Carville, found that 31% of patients had amyloidosis. Williams' work is a most important contribution in favour of the existence of intergroup differences non-attributable to the clinical forms. In work published in 1965 and conducted among reactional lepromatous patients studied with the Bennhold's test, we found a 15% incidence of amyloidosis.

These high indices are opposed by the data cited by certain authors from eastern countries and Mexico. Williams *et al.* found a percentage of amyloidosis of 3.3 among farmers in Mexico suffering from hanseniasis. In India, Satyanarayama *et al.* (1972) mention a percentage of 7.5%. Krishnamurthy, at Vellore, India, found 8% among 25 patients. Finally, Mittal *et al.* (1972) at New Delhi, did not find any case of amyloidosis in 30 kidney biopsies.

From the above data, apparently, there exists a marked difference in incidence of amyloidosis between orientals and occidentals.

Williams *et al.* (1965), interested in the reasons for the differences between the Carville patients and the Mexican farmers (31% and 3.3% respectively on the basis of gingival biopsies), studied the diets and work habits of both groups, to determine differences in their alimentary habits and way of life. They suspected that these might be the cause of the different behaviour of the 2 populations. We tried (1972) to test Williams' hypothesis in the patients at the Sommer Leprosarium in the Argentine Republic, and on that occasion we were not able to confirm their findings. In our group the amyloidosis incidence was similar to that registered at Carville, while the diet was more like the Mexican one.

Before discussing our position, we wish to point out some observations that we believe are important in order to attempt the elucidation of the problem in question.

(a) Amyloidosis incidence varies according to the clinical forms and complications of the disease. Comparing the incidence of amyloidosis among 3 groups of patients (1962) we found 15% in reactional lepromatous leprosy, 4% in non-reacting lepromatous leprosy, and 5% in the relatively benign forms (tuberculoid, borderline, uncharacteristic, etc.). In other work (1963) we found that patients suffering from reactional lepromatous leprosy and/or infections were the most affected by amyloidosis.

(b) In a study conducted with Jonquieres (1968) we found among 200 urine samples from hanseniasis outpatients at a preventorium specializing in leprosy only 3 urines with proteinuria, which at best would represent 1.5% or renal amyloidosis and, taking into account that the kidney is usually affected in about 80% of cases, nearly 2% or amyloidosis in general.

We believe that the above data are sufficient to affirm that the incidence of amyloidosis in leprosy varies remarkably according to the clinical forms, the complications (reactions, infections, etc.) and the place where the patients are seen (external consulting offices, sanatoria).

The importance of this last item does not lie in the kind of food patients receive or the environment where they live, but in the fact that to a great extent it determines the type of patients that are included in the studies. Inpatients from sanatoria are generally affected by the most severe and complicated forms of leprosy while outpatients include a very high percentage of milder forms without complications.

In the same country (Argentina) amyloidosis incidence varied according to the patients that were considered; 2.0% in patients seen in external consulting offices, 4% in non-complicated lepromatous, 5% in benign forms (tuberculoid, borderline, etc. (generally complicated with chronic infections), 15 to 22% in reactional lepromatous or lepromatous with chronic infections, and 70% in necropsied patients.

The data outlined above lead us to think that the comparisons which suggest a different behaviour in different countries are possibly erroneous; in fact we believe that groups that are not really comparable are being compared. In our opinion the group of inpatients cannot be compared with outpatients.

Finally, we would like to make one more comment about the heterogeneous character of some of the groups that have been compared and the mistakes made when analysing them. Krishnamurthy *et al.* (1966) report only 8% of amyloidosis among 25 autopsies of leprosy patients. If the data are further analysed, one can see that only 17 of the cases were lepromatous and in this group the percentage would go up to 11%. Unfortunately, as the authors do not present any more information on the patients (existence or not of reactions and infections) one cannot go deeper into the data. Mittal *et al.* (1972) did not find any case of amyloidosis among 30 leprosy patients who underwent kidney biopsy. This affirmation, apparently lapidary, loses much of its force if the following is taken into account. Twelve out of the 30 patients were not lepromatous and only 8 out of the 18 lepromatous patients were reactional. The sample is very small and therefore it may happen that by chance no case of renal amyloidosis appears. After what has been said, and despite the interesting study of Williams *et al.*, our doubts have not vanished. Really, are there any regional differences based on race, life habits, etc., or in fact, have "eggs" been compared to "oranges"?

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Comparison of *o*-Diphenoloxidase of *Mycobacterium leprae* from Armadillo Tissues and from Human Sources: A Few General Observations

ENZYME LEVELS

Preparations of *Mycobacterium leprae* obtained from infected armadillo tissues show great variations in the level of phenoloxidase activity. Some preparations contain high enzyme levels while others have very low activities. In preparations with high activity, the enzyme has the same properties as those of *M. leprae* separated from infected human tissues. They oxidize D-dopa rapidly, giving rise to indole-5,6-quinone with a peak at 540 nm in the spectrum. (Mammalian tyrosinase does not oxidize D-dopa.) In preparations with low activity, the reaction is rather slow, and the spectrum of the supernatant fraction shows only general absorbance with no well-defined peak. However, these bacilli also oxidize D-dopa producing melanin pigment. *M. leprae* from human sources do not show such wide variations in the enzyme levels.

TISSUE INHIBITORS

Bacterial preparations from the liver tissue of certain armadillos (especially those infected with *M. leprae* intravenously) sometimes show a greenish tinge, indicating the presence of bile pigments. Such preparations contain little dopa oxidase activity. However, bacilli separated from the spleen of the same animals do oxidize D-dopa. Obviously, some inhibitor(s) interfere with the oxidation of the substrate by the liver organisms. *M. leprae* obtained from most liver tissues does not show this type of inhibition.

BINDING OF DOPA AS AN IDENTIFICATION TEST

It may be interesting to note that in the preparations described above, only the oxidative mechanism is inhibited, while the binding of dopa is not. This is readily

demonstrated by incubating the bacilli with [^{14}C]-dopa and measuring the radioactivity of the organisms due to the bound substrate. Since other mycobacteria have been found not to take up dopa, binding of the substrate could serve as a reliable indentification test for *M. leprae* (in laboratories where the necessary facilities exist).

A SIMPLER PROCEDURE FOR IDENTIFYING *M. LEPRAE*

We have demonstrated oxidation of dopa by *M. leprae* spectrophotometrically (by measuring the quinone formed), polarographically and manometrically (by measuring the amount of oxygen consumed), and radiographically (by determining the amount of labelled water formed when tritiated dopa is used as substrate). When quantitative readings are not needed, a simpler method may be adopted for identification of the bacilli. The purified bacterial preparations (10^9-10^{10} organisms or more) are incubated with dopa at 37° C (pH 6.8) for 30 min or 60 min, depending on the level of enzyme activity in the bacilli. (The colour development in the incubation mixture can be visually assessed.) When the reaction mixtures are centrifuged, the sediment of *M. leprae* incubated with dopa would be black. Other mycobacteria do not show any change in colour. Controls should be run with bacilli alone, and with heat-inactivated *M. leprae* to which dopa is added. The bacterial suspensions are heated at 100° C for 30 min and then cooled. Heated *M. leprae* with dopa might show a light brown colour or no colour change at all.

SPECIFICITY OF THE REACTION AND PRECAUTIONS

We tested mycobacteria separated from the skin and liver tissues of 3 different mammalian species, as well as several cultivable mycobacteria. Some of the mycobacterial cultures were claimed to be *M. leprae,* and 2 strains were claimed to oxidize D-dopa. These mycobacteria (both from infected tissues and from cultures) showed no reaction with dopa. Cultivable mycobacteria have to be thoroughly washed free of the growth medium; otherwise, false positive results may be obtained. Components of certain culture media (especially metal ions) might stimulate auto-oxidation of dopa; however, heated samples also would stimulate the auto-oxidation of the substrate, indicating that this is not an enzymatic reaction. The enzyme activity in *M. leprae* is abolished on heating. After separating *M. leprae* from infected organs, host-tissue materials are inactivated or removed by treating the bacilli with 0.1 N NaOH, trypsin, or acetone and ether. Since tissue enzymes do not act on D-dopa, these treatments may not always be necessary in routine tests. If the *M. leprae* preparations have little activity to start with (due to presence of inhibitors or inactivation of the enzyme as a result of prolonged storage), both the heated and the unheated samples would show no colour development or might give only a light brown colour (caused by any residual enzyme activity).

LABILITY OF *o*-DIPHENOLOXIDASE IN ARMADILLO BACTERIA

A significant feature of the phenoloxidase of the armadillo bacteria is that it is more labile than the enzyme in *M. leprae* obtained from human tissues. We have stored lepromatous human spleen and skin nodules for a year or more at −20° or −80° C. In the bacilli separated from the stored human tissues, the enzyme remains active, although at a slightly diminished rate. We have obtained *M. leprae* preparations from armadillo tissues which readily convert D-dopa to indole-

5,6-quinone. However after storage for about a year, the bacilli separated from these organs were found to have completely lost their ability either to oxidize or to bind dopa, indicating that the enzyme had been inactivated. These tissues had been thawed and refrozen previously to remove material for other experiments. Very little activity was lost by *M. leprae* from human tissues treated similarly. We have reported before that the *o*-diphenoloxidase of *M. leprae* is associated with a decarboxylase. The phenoloxidase oxidizes dopa to dopachrome (with a peak at 480 nm in the spectrum); it is the decarboxylase that converts dopachrome to indole-5,6-quinone (with a peak at 540 nm in the spectrum). During storage of the infected tissues or the separated bacteria, the decarboxylase activity is lost sooner than the phenoloxidase. In such instances, the immediate reaction product would be dopachrome and not indole-5,6-quinone.

HYPOTHESIS

At present we can only speculate on why the phenoloxidase of *M. leprae* from armadillo tissues is relatively more labile. In most armadillos, at the time they are killed, the bacilli apparently are continuing to multiply in the tissues; i.e. the bacilli are in the growth phase. In rapidly multiplying organisms, as many enzyme molecules may not accumulate, as in organisms in the stationary phase. Moreover, the structure of the cell membrane of the armadillo bacteria could be of a more "leaky" nature, as compared to the cell membrane of *M. leprae* from human tissues. These phenomena might explain the lower level of phenoloxidase activity (per unit number of bacilli) and the earlier inactivation of the enzyme in the armadillo bacteria than in *M. leprae* from human sources. Other explanations are possible. However, without experimental evidence, they remain as hypotheses.

CONCLUSION

The armadillo bacteria contain *o*-diphenoloxidase as *M. leprae* from human tissues. The activity has been demonstrated in organisms separated from the spleen, liver, lymph nodes and skin nodules of armadillos, from the spleen, testis and skin nodules of lepromatous patients, and from the mouse foot-pads. The enzyme has been solubilized from the bacterial particles by detergent-treatment and shown to be a copper-containing protein. *o*-Diphenoloxidase is the only specific metabolic activity detected in *M. leprae* so far.

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Lepr. Rev. (1977) **48**, 149

Book Review

Design for Medical Buildings. A manual for the planning and building of health care facilities under conditions of limited resources, published by the Housing Research and Development Unit, University of Nairobi.

In pioneering situations it still sometimes falls to the lot of the leprosy medical officer to become involved in the planning and maybe erection of buildings needed for clinics, primary health care units and suchlike. Here is a book which poses just about all the questions that need to be considered, and offers expert answers to them which are clear, practical, and suitable for many rural situations in developing countries. There are numerous plans and diagrams and the manual can strongly be recommended within the terms of reference to which it is addressed. No price is given, but the address of the publishers is, Housing Research & Development Unit, University of Nairobi, Director Jon Skokke M. A. A., P. O. Box 30197, Nairobi, Kenya.

T. F. DAVEY

Abstracts

60. ALMEIDA, J. O. & KWAPINSKI, J. B. Reatividade de antigenos de actinomicetos com soros de lepra, avaliada por immunofluorescência em suporte de acetato de celulose. **[The reactivity of antigens from actinomycetes against leprosy sera, measured by the immunofluorescent test utilizing cellulose acetate.]** *Publções Cent. Estud. Leprol.,* 1974, v. 14, No. 2, 73-90. English summary.

The description is given of an immunofluorescence reaction between leprosy sera on the one hand and antigen from lepromata or from cultures of Actinomycetales (9 species) on the other. Either the sera or the antigens were absorbed in discs of cellulose acetate and, when the reaction was completed, the fluorescence of the disc was measured in a Turner fluorometer. The text should be consulted for full details. Two hundred and seventy-six sera from tuberculin-negative persons were negative (i.e. Turner fluorometer reading was less than 50). In 24 sera from tuberculoid leprosy 18 were negative and 6 showed fluorescence less than 100. In 420 sera from lepromatous leprosy, 310 gave a reaction greater than 100, 68 gave reactions between 51 and 100, and 42 gave reactions of 50 or less. The reproducibility of the reaction was verified by repeating the test with 30 discs against the same negative serum; 3 tests showed readings greater than 100 and 23 gave readings of 50 or less. A further 30 discs were tested against a known positive leprosy serum; 24 fluoresced between 300 and 500, 2 and 200, and 4 at more than 500. Antigens which inhibited the Rubino reaction [see *Trop. Dis. Bull.,* 1931, v. 28, 960] provided greater fluorescence that those which did not. Sera from lepromatous leprosy reacting with antigens from Actinomycetales produced more fluorescence than those from tuberculoid leprosy. There was no constant relationship between the capacity of antigens to inhibit the Rubino reaction and their precipitation in gel by anti-leprosy sera.

F. Hawkins

61. PATTYN, S. R., ROLLIER, M. T., ROLLIER, R. & VERDOOLAEGHE-VAN LOO, G. Sensibilité envers la dapsone, la sulfamethoxypyridazine et l'éthionamide, de *Mycobacterium leprae* provenant de malades traités par ces substances. **[Sensitivity to dapsone, sulfamethoxypyridazine and ethionamide of *Mycobacterium leprae* strains obtained from patients treated with these drugs.]** *Int. J. Lepr.,* 1975, v. 43, No. 4, 356-363. English summary.

Patients suffering from multibacillary forms of leprosy, and having clinically suspicious signs of relapse accompanied by the reappearance (in most cases) of morphologically normal *Mycobacterium leprae,* are the subject of this paper. Interest centres on the emergence of drug-resistant strains in patients who, after an initial period as inpatients under investigation, were entrusted with a 6-months' supply of medicine and asked to report at regular intervals.

The incidence of drug-resistant strains discovered is not indicated, except in the case of ethionamide, where it was of the order of 4%.

Two strains (out of the 4 tested by the standard mouse foot-pad inoculation technique) proved to be dapsone-resistant, after 13 and 14 years' treatment respectively.

The 5 patients suspected of harbouring organisms resistant to sulfamethoxypyridazine proved to be suffering from clinical relapse associated with drug-sensitive *Mycobacterium leprae.* The point is made that, in view of the small difference in serum concentrations of the

drug between the levels achieved in practice and the minimal inhibitory concentrations, absolute regularity of treatment is necessary if clinical relapse is to be avoided. The authors therefore suggest that sulphonamides have no place in the treatment of patients suffering from multibacillary forms of leprosy.

Ethionamide is considered to have a fairly rapid bactericidal action, but demonstrable decrease in morphologically normal bacilli follows only after a certain delay. In 2 patients out of the 4 harbouring ethionamide-resistant bacilli, among 104 patients taking the drug, the resistant forms appeared after 6 years of treatment.

S. G. Browne

62. MEHRA, N. K., DASGUPTA, A. & VAIDYA, M. C. **An evaluation of the immune state in leprosy**. *Lepr. India,* 1976, v. 48, No. 3, 231-237.

"An evaluation of the immune state in leprosy was done by the application of a system of graft-versus-host reaction. Peripheral blood lymphocytes obtained from patients with different forms of leprosy and from normal healthy individuals were injected intravenously into the irradiated mice. The rate of blast transformation of the donor cells was measured by the radio-active thymidine uptake. The number of cells labelled with tritiated-thymidine was much higher in the normal individuals and patients with tuberculoid leprosy than in patients with lepromatous leprosy with the borderline group placed in between the two. However, following successful treatment with DDS, an increased responsiveness and active DNA synthesis could be observed in the previously less responsive lepromatous lymphocytes."

63. FABER, W. R., LEIKER, D. L. & CORMANE, R. H. **Immunoglobulin-bearing cells in leprosy**. *Acta Derm.-Vener.,* 1976, v. 56, No. 5, 319-326.

"Peripheral blood lymphocytes of 28 untreated and 17 treated patients with different types of leprosy were investigated for the occurrence of immunoglobulin (Ig) bearing cells by means of a smear method. Seven healthy Africans served as controls. In a later stage a complementary study was performed on 6 tuberculoid and 6 lepromatous leprosy patients by means of a suspension method. The immunofluorescence technique was used for the detection of Ig-bearing cells. In tuberculoid leprosy an increase of Ig-bearing cells seems to occur during treatment, predominantly expressed by an increase in IgD-bearing cells. In lepromatous leprosy no increased percentages of Ig-bearing cells were observed."

64. ELLIS, B. P. B. & THOMAS, J. E. P. **First lesion sites in leprosy**. *Cent. Afr. J. Med.,* 1976, v. 22, No. 5, 96-97.

This short article tabulates the sites of first lesions in 1523 patients with leprosy at Harare Central Hospital, Salisbury, Rhodesia. In 35.3% of patients the first lesions would normally be hidden by clothing. 31.1% of patients described as first symptoms abnormalities other than skin lesions, i.e. paraesthesiae, blisters, anaesthesia or ulcers. The figures were obtained by questioning the patients and this may explain the low scoring values of sites where patients could not see themselves—e.g. the back, buttocks and back of thighs.

T. F. Davey

65. ALMEIDA NETO, E. Viragem lepromínica em crianças de 4 a 26 meses. [**Changes in lepromin reaction in children aged 4-26 months.**] *Anais Bras. Derm.,* 1975, v. 50, No. 2, 111-134.

The English summary appended to the paper is as follows:

"This is a trial of repeated BCG vaccination by the oral route in children previously lepromin and tuberculin (PPD) negative, in a social institution for children whose patients live in a

leprosy hospital. Twenty-two of them were followed-up through 2 years and 7 successive BCG doses, the Mitsuda test being performed after each. A control group of 17 children from other origins was also tested and followed in the same way. At the end of the study 2 children remained Mitsuda negative (5.2%), 6 had doubtful reactions (15.4%) and 31 had turned positive (79.4%). The effect of successive doses is analysed in detail and genetic factors which might affect the reaction are discussed. Results are also compared with those of other trials of BCG vaccination against leprosy, techniques for the reading of the Mitsuda test being discussed."

66. TURK, J. L. **Leprosy as a model of subacute and chronic immunologic diseases.** *J. Invest. Derm.,* 1976, v. 67, No. 3, 457-463.

"A review has been made of the immunologic bases for the various clinical appearances that may be found during infection with *M. leprae.* This infection may serve as a model for the understanding of the mechanisms behind the same clinical appearances when they occur in situations in which the primary etiologic agent has not yet been discovered. . . ."

[This paper was one of many contributions to a symposium on immune mechanisms in cutaneous disorders, published in this special issue of the journal. There are 33 references.]

67. OLITSKI, A. L. **The effect of dioxyphenylalanine (DOPA), amides and some potential sources of energy on the multiplication of** *Mycobacterium leprae. Bull. Ist Sieroter. Milan.,* 1976, v. 55, No. 2, 110-119.

The multiplication of 2 out of 3 strains of *Mycobacterium leprae* on a medium containing substances from digested non-acid fast micro-organisms, or even free of them, was promoted by D-3-4-dihydroxyphenylalanine (DOPA). Growth-promoting effects on several strains were also found with a variety of organic substances but the effects were variable. An oxidation-reduction reaction was also observed when media containing DOPA and malachite green were inoculated with at least 0.12×10^6 *M. leprae* and it is suggested that this may be a means of identifying *M. leprae.*

T. F. Davey

68. KRONVALL, G., STANFORD, J. L. & WALSH, G. P. **Studies of myco-bacterial antigens, with special reference to** *Mycobacterium leprae. Infection & Immunity,* 1976, v. 13, No. 4, 1132-1138.

Antigenic preparations were made from a number of mycobacterial species and from *Mycobacterium leprae.* The latter had been grown in armadillos. With the use of crossed immunoeletrophoresis and tandem crossed immunoelectrophoresis with the antigens and pooled sera from lepromatous subjects it was shown that 4 precipitin lines (numbered 1, 21, 40 and 41) were common to *M. leprae, M. avium-intracellulare* and *M. smegmatis.* Antigen 1 gave a reaction of complete identity in a number of mycobacterial species including *M. leprae.* Sephadex gel filtration showed this antigen to have a molecular weight of approximately 285,000. Antigen 40 was also common to a variety of mycobacterial species, again including *M. leprae.*

There was a reaction of complete identity between antigen 21 of *M. avium-intracellulare* and the corresponding antigen in 3 other slow-growing mycobacteria and 8 fast growers. This antigen shared a partial reaction of identity with antigen 21 from *M. leprae.* This was indicated by the formation of a spur by antigen 21 from *M. leprae* over the precipitin arcs formed by antigen 21 from the other mycobacterial species. This indicates the presence of at least 2 antigenic determinants, one shared by all mycobacteria and the other only in *M. leprae.*

Using a rabbit antiserum to *M. smegmatis,* it was shown that antigen 21 of *M. avium-intracellulare* and *M. lactis* gave reactions of complete identity with the corresponding antigen

from 3 slow growers and 6 fast growers. Again, however, antigen 21 from *M. leprae* formed a spur in these tests indicating the presence of yet another antigenic determinant.

There are thus 3 antigenic determinants associated with antigen 21. One is common to all mycobacteria, one is specific for *M. leprae* and one is present in slow- and fast-growing mycobacteria but not in *M. leprae*. The implications of this for the taxonomic position of *M. leprae* are discussed together with the possible role of these specific antigens in leprosy.

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