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Editorial

CHEMOTHERAPY OF LEPROSY FOR CONTROL PROGRAMMES:* SCIENTIFIC BASIS AND PRACTICAL APPLICATION

When dapsone (DDS) was introduced as the first effective drug against leprosy in the 1940s, it was assumed that its mass administration to large numbers of leprosy patients would result not only in arrest or cure of the disease in individuals, but also in a steady decrease in the incidence of new cases. It was assumed that the latter would result from the reduction in the pool of infectious patients, so that the chain of transmission would be broken. Unfortunately, and not withstanding WHO's backing for the introduction of mass DDS control programmes, it was apparent by the mid-1960s that global leprosy had not been controlled by DDS monotherapy. In fact, DDS treatment had only been given to some quarter of those estimated to have leprosy, and of those treated less than half took dapsone regularly. Moreover, although by then the efficacy of DDS for the treatment of leprosy was amply confirmed, experience showed that for lepromatous patients arrest or cure required many years of regular treatment and this was difficult if not impossible to ever achieve in an unsupervised control programme.

Thus by the mid-1960s there was already an air of pessimism and frustration among those directly or indirectly concerned with the treatment and control of leprosy in the field. This was heightened by the increasing frequency of relapses among patients with lepromatous leprosy while under treatment with DDS or among those apparently successfully treated and released from control. In contrast with the frustration and deficiencies facing the field side, in this same period, research programmes based on the mouse footpad infection[1] were being exploited and applied successfully for the first time to the study of DDS and other antileprosy drugs. These studies revealed two serious and complicating phenomena arising in patients with lepromatous leprosy receiving standard DDS monotherapy. Both related to relapses in these patients. Thus resistance to DDS *per se* was first proved by the mouse footpad infection in 1964.[2] By 1976, based on

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detailed and longitudinal studies on the evolution of DDS resistance in Malaysia[3] and Ethiopia[4] and the monitoring of strains of *Mycobacterium leprae* from relapses among DDS-treated lepromatous patients from other countries, it was clear that DDS resistance was a serious and universal phenomenon and was on the increase. Moreover, because of the very long time (5–20 years or more)[3, 4] taken for the emergence of DDS resistance, this will inevitably result in more patients relapsing with DDS resistance from the ever increasing worldwide pool of lepromatous patients receiving DDS monotherapy. The other complication related to the phenomenon of 'bacterial persistence'. In 1974 it was reported that small numbers of viable and DDS-sensitive *M. leprae* may persist in the tissues of lepromatous patients (as revealed by footpad inoculation using T-cell deficient mice) treated with DDS for 10–12 years.[5] Thus the concurrent leprosy research programmes by defining the phenomena of DDS resistance and bacterial persistence provided for the first time a scientific explanation for the relapses reported in lepromatous patients receiving DDS monotherapy. In retrospect the emergence of drug resistance to monotherapy for leprosy exactly paralleled the inevitability observed many years earlier of drug resistance with monotherapy for tuberculosis, which could be prevented by giving two or more drugs together (combined therapy).

In 1976 the WHO Expert Committee on Leprosy, albeit somewhat belatedly, emphasized the need to prevent the serious and much feared development of DDS resistance, and, in view of this recommended that all active cases of multibacillary leprosy (LL, BL and BB), whether previously untreated or relapsed, should be treated with two effective drugs.[6] In 1977 ILEP (Heathrow Report) went much further in emphasizing the urgency of introducing multidrug regimens; without which the whole future of the treatment and control of leprosy by chemotherapy, including DDS, would be in jeopardy.[7] The Report recommended applicable regimens as well as outlining the operational requirements. Unfortunately, in spite of these clear warnings and recommendations, few countries subsequently introduced multidrug therapy in their leprosy control programmes. Therefore, by and large, DDS monotherapy continued to be standard treatment in control programmes, or where governments or donor agencies funded the purchase of rifampicin and/or clofazimine, these antileprosy drugs were used haphazardly in various multidrug regimens.

It was against this background that WHO determined to convene a Study Group in Geneva in 1981 to review the information since their 1976 Expert Committee Report on the problems related to chemotherapy of leprosy in the field, and above all to propose the most appropriate and universally applicable multidrug regimens to overcome these problems.[8] As was to be expected a further 5 years of DDS monotherapy had resulted in a spiralling increase in the prevalence of DDS resistance of 2–7% in surveys of lepromatous patients from China, Burundi, India, Israel and Mali, and with the isolation of DDS-resistant strains of *M. leprae* from such patients from more than 25 countries, it was

undoubtedly now a very serious world-wide problem.[8] Even more serious was the Study Group's report that since 1976, previously untreated lepromatous patients were presenting *ab initio* with DDS-resistant strains of *M. leprae*, indicating for the first time the spread of DDS-resistant leprosy (primary resistance) among the population at large. Already a devastatingly high incidence of 50% primary DDS resistance in untreated lepromatous patients had been reported from Ethiopia.[9] Similar patients with primary DDS resistance had been reported also from India, Malaysia, Mali, Philippines and USA.[8] Secondary resistance to rifampicin had also been reported.[9] The rapidly increasing prevalence throughout the world of multibacillary patients with mouse footpad proven secondary or primary DDS resistance convinced the Work Group that it was imperative to introduce as rapidly as possible multidrug regimens suitable for control programmes on a world-wide basis, for *both* multi- and paucibacillary patients. The reason for now having to use multidrug regimens for patients with paucibacillary leprosy (and therefore for all types of leprosy) is that primary DDS resistance is just as likely to occur in tuberculoid as in lepromatous patients. In fact, primary DDS resistance in new tuberculoid patients may well be occurring more commonly than in new lepromatous patients, because the incubation period is shorter for tuberculoid than for lepromatous leprosy.

In reviewing how best to deal with this crisis situation, the Study Group considered that the classical strategy of leprosy control based on early detection and effective chemotherapy (secondary prevention) was likely to remain unchanged for many years; since although ideally primary prevention (i.e. an antileprosy vaccine) might be more effective, no such vaccine was immediately available. Therefore the Study Group confined their review to the most efficacious and *immediately* available antileprosy drugs with proven activity against *M. leprae* in the mouse footpad infection, other than DDS, as potential candidates for multidrug regimens. Only three drugs met these criteria (rifampicin, clofazimine, ethionamide/prothionamide)[10] as well as their proven potency and acceptability in leprosy patients. Rifampicin was by far the most potent of the three drugs and from its very rapid bactericidal activity on *M. leprae*,[11] clinical trials have shown that once-monthly doses of 600 mg were as effective as daily, without resulting in any of the known serious toxic manifestations associated with rifampicin given once weekly. Clofazimine, although a bacteriostatic drug, because of its 'depot' property, was fully potent in man at a dose of 100 mg thrice weekly rather than daily, although its potency declined even with larger doses on a monthly basis. Although clofazimine has no toxicity in man over a wide range of doses, it unfortunately causes red-blue pigmentation of the skin/lesions at therapeutic doses to a degree that is unacceptable to most lighter-skinned patients. Ethionamide/prothionamide (both thioamides) are bactericidal, potent drugs against *M. leprae*, but because of their short half-lives and slower rate of killing *M. leprae* than rifampicin, they have to be administered daily. Moreover, both drugs (prothionamide less than ethionamide), at 500 mg daily, can cause

Table 1. WHO Study Group's recommended combined antileprosy regimens

For multibacillary leprosy		
(Duration, 2 years)*	Rifampicin	600 mg once-monthly, *supervised*
	Dapsone	100 mg daily, self-administered
	Clofazimine	300 mg once-monthly, *supervised*, and 50 mg daily, self-administered
	(Ethionamide/ prothionamide)‡	250–375 mg daily, self-administered
For paucibacillary leprosy		
(Duration, 6 months)†	Rifampicin	600 mg once-monthly, *supervised*
	Dapsone	100 mg daily, self-administered

* Minimum of 2 years; wherever possible, to smear negativity; then stop chemotherapy.

† Six months, then stop chemotherapy; if treatment is interrupted, re-start regimen to complete full 6 month course.

‡ Alternative drug when clofazimine is totally unacceptable.

unacceptable gastric symptoms in some patients. None of these three drugs develop cross-resistance with DDS or cross-resistance with themselves.

On the basis of all this currently available and carefully assessed experimental and clinical data on the only three potent antileprosy drugs for dealing effectively with the problems of DDS resistance, the Study Group recommended two multidrug regimens (Table 1). The great merit and applicability of these regimens for treatment in the field is that they will provide effective therapy for patients with pauci- or multibacillary leprosy irrespective of their past history of DDS (previously treated or untreated) or whether currently definite or potential cases of secondary or primary DDS resistance respectively. The need for two regimens, for pauci- or multibacillary patients respectively is essential as the regimen for the paucibacillary patients has only to cope with the possibility of primary DDS resistance with very small numbers of resistant organisms, whereas the regimen for multibacillary patients will have to cope with large potentially DDS-resistant bacterial populations, requiring two additional drugs to prevent the emergence of resistance to either one.

The absolutely vital component to both these regimens is dependent upon the potency of rifampicin and therefore to ensure its ingestion by the patient, every monthly dose *must be supervised*. Supervised administration of rifampicin entirely by the leprosy control staff, rather than by patient self-administration, will also help to prevent this expensive and highly sought-after drug getting into the black market. Daily self-administered DDS is included in both regimens. The regimen for multibacillary patients includes a third drug to prevent the emergence

of rifampicin resistance in those patients who may already be fully DDS resistant. In such patients the administration of rifampicin would equate to monotherapy. The choice for the third drug rests between clofazimine and prothionamide. From the data available, clofazimine is undoubtedly the drug of preference and to ensure maximum potency clofazimine is self-administered at a daily dose of 50 mg with a monthly supervised dose of 300 mg, at the same time the patient attends for the monthly supervised dose of rifampicin. Although there will undoubtedly be lighter-skinned patients who refuse to take clofazimine, every effort should be made to persuade the patient to continue in spite of the pigmentation. Since there is little experience on the degree of pigmentation resulting from the recommended WHO regimen for clofazimine it is important that this should be investigated as soon as possible. Prothionamide should only be included as the third drug for patients who from experience find clofazimine totally unacceptable. For although prothionamide is a bactericidal drug, it has to be administered daily because of its short half-life, thus relying entirely on the compliance of the patient for self-administration. Rifampicin alone would undoubtedly be fully effective for paucibacillary patients (based strictly on I, TT and BT cases), but the Study Group decided to include DDS to provide uniformity for the two regimens, as well as providing DDS as a second drug to help prevent the emergence of rifampicin resistance in more bacilliferous patients that might have been wrongly classified.

The objective of the Study Group was to come up with the most effective regimens for overcoming the very serious problem of DDS resistance that was threatening the whole future for the treatment and control of leprosy by chemotherapy. Therefore the regimens had also to be practical and applicable to control programmes. The recommended regimens admirably achieve these prerequisites, at the same time providing the most potent antileprosy therapy currently available. By taking advantage of the efficacy of pulsed rifampicin therapy, the administration of all doses of this valuable drug will be supervised. Another, and certainly the most appealing, feature of the recommendations to those responsible for maintaining efficient control programmes is the shortening of regimens to 6 months for paucibacillary patients and to a minimum of 2 years for multibacillary patients. Although these shorter courses may not be long enough for all patients, the inclusion of rifampicin will undoubtedly provide effective long-lasting therapy. Where the services can afford, it would certainly be preferable to continue the regimen for multibacillary patients to skin negativity and follow up these patients after stopping treatment. The great asset of both regimens is that they will stop the emergence of drug resistance and therefore any patients that relapse after stopping treatment will immediately respond on restarting with the same regimen.

Undoubtedly these regimens will be more costly (see Table 2), but will have to be accepted in the present 'crisis' situation which will only worsen if multidrug regimens are not introduced. Moreover, the additional cost of these drugs is only

Table 2. Cost per patient for combined antileprosy regimens recommended by WHO Study Group (January 1983 prices)

	Multibacillary case who accepts clofazimine (per year)		Multibacillary case who rejects clofazimine (per year)		Paucibacillary case (per 6 months)	
Drug	No.	Cost ($)	No.	Cost ($)	No.	Cost ($)
Rifampicin						
300 mg capsules	24	3·60	24	3·60	12	1·80
Clofazimine						
100 mg capsules	36	2·70	—	—	—	—
Clofazimine						
50 mg capsules	365	13·69	—	—	—	—
Dapsone						
100 mg tablets	365	0·95	365	0·95	182	0·47
Prothionamide						
250 mg tablets	—	—	365	20·08	—	—
Surface shipment		4·35		5·09		0·50
Total cost per patient		$25.29		$29.72		$2.77

Costs are based on the prices quoted by WHO Leprosy Division of Communicable Diseases, Geneva, when the drugs are bought in large quantities. The price for 50 mg capsules of clofazimine was not available and the estimate is based on half the 100 mg capsule price. The cost per patient includes a 20% allowance for the cost of surface shipment of the drugs to a project.

a small fraction of the additional costs to the control service who at present have increasing numbers of relapsed lepromatous patients who are maintained for many years on treatment. More importantly, the introduction of these new regimens will have to be preceded by extensive replanning of the treatment service and retraining of the treatment staff. The patients' cooperation will also be paramount and therefore time must be given for explaining the new treatment regimens, toxic drug symptoms to be reported and, above all, assurance that the shorter course of treatment is effective. This particularly applies to the paucibacillary patients, who may welcome not having to take tablets for several years but may still have one or more visible skin lesions when treatment is stopped after only 6 months.

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There will be two further editorials in 1983 on 'The Organisation and Management of Chemotherapy in the Field' and 'The Toxic Effects of Antileprosy Drugs in Common Use', both relating to the 1982 WHO Study Group Report on the Chemotherapy of Leprosy for Control Programmes.

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Editorial Note

Jane Neville, MBE, MPH joins the Editorial Board of *Leprosy Review*

It is with the greatest of pleasure that we welcome Jane Neville of The Leprosy Mission (International) as a member of the Editorial Board of this Journal. She has many years experience from Uganda and Ethiopia, ranging widely over occupational therapy, physiotherapy, social aspects of leprosy, teaching and training. Her great contribution to the selection, assessment and distribution of teaching and learning materials from TLMI is already well known, and much appreciated in many parts of the world. At a time when there is an outstanding and urgent need for the even further development of training in the broadest sense, including that concerned with chemotherapy, we shall no doubt benefit greatly from Jane Neville's experience and advice and we look forward to many years of fruitful cooperation in the production of this Journal.

EDITOR

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A study of case-holding in leprosy patients in Asia, based on duration of treatment, 1976–80

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Summary From 14 different centres treating leprosy patients in Asia, a study was made of the periods of time for which patients attended during the years 1976–80. They were divided broadly into 'local' and 'non-local', the former being essentially from allocated, nearby leprosy control areas (but also to a lesser extent from the vicinity of the base or hospital, if this was not in fact in the control area). The latter were from 'all other areas' and included visitors (rich and poor), vagrants and patients with no fixed address. Within the first year after starting treatment, 32·4% of 'local' and 62·9% of 'non-local patients were lost, and 2 years later they had not returned and no information had been received of their removal from the area, or death. Data are further presented on the percentage rate of loss for 5 years, and at the end of this period 66% of local and 88% of non-local patients had been lost. The possibility is discussed that in the case of 'non-local' patients these figures may be less disconcerting than they appear, since many may have reported back to some other leprosy control unit in their area of origin, or to another part of the country. The figures for loss of 'local' patients are, however, considered to be serious and possible reasons are discussed. The collection of these figures on case-holding and their presentation to the staff concerned had an almost immediately beneficial effect in raising standards of work. Possibly the most important factor in achieving this was an even greater attention to personal contact with each patient.

Introduction

It takes a long time to treat leprosy. Although the recent WHO recommendations on multiple drugs[1] considerably shorten the treatment periods for all types of leprosy, case-holding for adequate periods of time is still extremely important.

To find out whether we treat patients long enough to do any good, The Leprosy Mission (International) set up a study in 1976 to assess case-holding in 14 centres in Asia. The regrettably impersonal phrase 'case-holding' is used with reluctance for what is one of the most essentially personal aspects of leprosy work, including not only the duration of attendance, but also regularity and the

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quality of care given to patients by the staff. This study does not attempt to analyse regularity of attendance within any given period or to assess the quality of work; rather it concentrates on the periods of treatment (in months and years) for which patients attended after first registration.

Patients and methods

The centres chosen were regarded as having average or above average standards of work and good record keeping. All patients were treated with dapsone monotherapy. Details of patients and their attendances were recorded and analysed by computer, the present study being made on data collected up to October 1980. Since both commencement and attendance dates were recorded, analysis could be made on the basis of the length of time for which treatment was taken in the case of those patients who had discontinued it. Patients were classified as 'local' and 'non-local'. 'Local' patients were in nearby, allocated project areas but also included a few in the vicinity of the hospital or base clinic, in instances in which this was not actually in the project area. 'Non-local' patients were from 'all other areas' and included visitors both rich and poor, vagrants and those with no fixed address.

Of the data collected, only that which is complete and unaffected by distorting factors is used in the study. The count was of out-patients, including those who, during the study, became classified as 'Disease Arrested' or 'Lost by Non-attendance', but not those so classified before the study began. Patients known to have died, moved away or transferred to other centres were excluded. The scheme was set up in 1976, but as different centres commenced on different dates, 1977 was the first year when data collection was complete and consistent throughout. In 1979 there was a change in record-keeping practice, outside the control of the study. Most record-keepers in that year began to register new patients provisionally, only making the registration final after several attendances. Provisionally registered patients did not appear in the scheme. This would have distorted any figure for early losses based on that year. The years 1977 and 1978, however, contain undistorted data of new registrations and enough time has elapsed to study how patients who began treatment in those years have been held in their first year (and second, for those commencing in 1977). Data are held for patients who commenced treatment before 1976 provided they took treatment at some time after their centre entered the scheme. Complete figures for treatments commenced in the years before 1976 are not available. It is possible, however, to make valid comparisons between patient losses in the second, third, fourth and fifth years and figures of patients held up to the beginning of those years. In regard to Table 5, it should be noted that in making an attempt to ascertain if more or less frequent attendances made any difference to case-holding, the only readily available data were the number of weeks treatment (in tablets) given at each

patient's last visit. In the case of patients lost, this meant the visit after which they did not return. The term 'standard' refers to the normal period of treatment given to most out-patients in the centres studied, and this was 4 weeks. Other patients had longer or shorter periods of treatment for some special reason. Shorter periods might be given to those with a clinical problem or considered to be 'at risk', whilst longer periods would be given to those considered to be safe and reliable.

Results

Data on case-holding in the first year, losses after the first year, the 5-year loss rate, variations in case-holding by type of leprosy, frequency of treatment and variations between centres are shown in the accompanying Tables 1–5. Data was also collected on the age and sex distribution in relation to case-holding and absolutely no significant correlation was noted in this study.

Discussion

It is not part of this report to compare centres. It is sufficient to state that there were wide fluctuations between them. At the centre with the best results, the

Table 1. Case-holding in the first year. Of 15,980 patients registered in 1977 and 1978 the following were lost within a year from their treatment commencement date

	Local	(%)	Non-local	(%)	Total	(%)
After one visit only	864	10·9	1,981	24·7	2,845	17·8
After more than one visit but within 3 months	662	8·3	1,540	19·2	2,202	13·8
After 3 months but within 6 months	427	5·4	744	9·3	1,171	7·3
After 6 months but within 1 year	622	7·8	780	9·7	1,402	8·8
Total lost during the first year*	2,575	32·4	5,045	62·9	7,620	47·4
Out of	7,952		8,028		15,980	

* The patients lost had not returned by October 1980, nor had information been received of their removal or death.

Table 2. Losses after the first year. The figures from which rates of loss can be assessed

Losses	Local	Non-local
Second year		
Total studied (i.e. patients who had already been held for 1 year, based on commencements in 1975 or 1977)	5,142	2,918
Number of the above lost within the second year	676	776
Percentage loss in second year	13·1	26·6
If it is assumed that the first year loss rates had been the same as those calculated above, namely 'local' 32·4, 'non-local' 62·8, the second year losses can be expressed as a percentage of the original number		
This adjusted percentage is: 'local' 8·9, 'non-local' 9·9 and is referred to below as the 'accumulating loss'		
Third year		
Total studied (i.e. patients who had already been held for 2 years, based on commencements in 1974 or 1975)	3,996	2,416
Number of the above lost within the third year	413	591
Percentage loss in third year	10·3	24·5
Accumulating loss	6·1	6·7
Fourth year		
Total studied (i.e. patients who had already been held for 3 years, based on commencement in 1973, 1974 and 1975)	4,858	2,857
Number of the above lost within the fourth year	595	687
Percentage loss in fourth year	12·2	24·0
Accumulating loss	6·4	4·9
Fifth year		
Total studied (i.e. patients who had already been held for 4 years, based on commencement in 1972, 1973 and 1974)	3,967	2,860
Number of the above lost within the fifth year	526	642
Percentage loss in fifth year	13·3	22·4
Accumulating loss	6·2	3·5

percentages held for 5 years were: 'local' 62%, 'non-local' 26%. The worst results were 'local' 12%, 'non-local' 1%. In the latter category of patient, although the figures (for instance in Tables 1 and 3) are extremely disconcerting, it is considered that many may have returned to their region of origin, or to some other part of the country, and reregistered there. However, information on this is lacking. In the case of 'local' patients, although case-holding was better, the

Table 3. Combined table showing 5-year loss rate. This records the percentage rate of loss for 5 years, bearing in mind that the rates for each year are calculated on different groups of patients

	5-year table (%)					
	Local			Non-local		
	Lost	Cumulative	Held	Lost	Cumulative	Held
First attendance	10·9	10·9	89·1	24·7	24·7	75·3
3 months	8·3	19·2	80·8	19·2	43·9	56·1
6 months	5·4	24·6	75·4	9·3	53·2	46·8
1 year	7·8	32·4	67·6	9·7	62·9	37·1
2 years	8·9	41·3	58·7	9·9	72·8	27·2
3 years	6·1	47·4	52·6	6·7	79·5	20·5
4 years	6·4	53·8	46·2	4·9	84·4	15·6
5 years	6·1	59·9	40·1	3·5	87·9	12·1

Table 4. Variations in case-holding by type of leprosy*

Recorded classification (Madrid)	L	B	T	I
Patients in the study who were lost in the first year. Number (%)	2,463 (17)	2,123 (19)	4,551 (18)	686 (18)
Patients lost in the following 3 years	1,672 (12)	1,353 (12)	3,097 (12)	587 (16)
Patients held over 4 years	10,254 (71)	7,581 (69)	17,712 (70)	2,464 (66)
	14,389	11,057	25,360	3,737

* This analysis is of patients in the study from all commencement years, including those where only partial data are available. It is valid for studying *comparative* case-holding but gives no indication of actual case-holding as do Tables 1 and 2.

Table 5. Frequency of treatment

Losses (number %)	Standard	Shorter	Longer
First year	4,752 (21)	749 (17)	4,316 (16)
Second to fourth years	2,434 (11)	551 (12)	3,715 (14)
Held over four years	15,134 (68)	3,179 (71)	19,074 (70)
	22,320	4,479	27,105

analysis nevertheless revealed how poor case-holding may be, even in centres with devoted staff and many years of experience in the out-patient treatment of leprosy. The reasons for this failure were far from clear but it was apparent that they were numerous and complex. A sociological study would be needed to clarify the situation and this could probably be best carried out with the whole-hearted cooperation and enthusiasm of local (indigenous) staff behind it. On the whole, the centres with better results were better all round, that is to say, good first-year results usually went with good later-year results: good 'local' results with good 'non-local' results. The best results were also found at centres where, in the writer's subjective judgement, there was most enthusiasm among staff, especially junior staff. Although far from clear cut, there is a suggestion in Table 5 that case-holding is slightly better for special cases receiving shorter or longer treatment periods.

A subsequent visit to a centre whose holding was poor proved extremely encouraging; the problem, once revealed, had been taken very seriously, with a resultant improvement in the standard of work. It was noted that the previous training and organization of health workers had placed great emphasis on case-finding as a primary objective; even the routine reports and returns tended to favour information on case-finding, with little attention to case-holding. In fact, case-finding must be combined with meticulous attention to case-holding in order to ensure the regular administration of drugs such as those recently recommended by WHO,[1] for adequate periods of time. Case-holding should be taught as one of the first priorities in leprosy work generally and it should surely be recognized that any evaluation of a centre which does not take account of case-holding is misleading. Individual attention to patients and enthusiasm in the staff are vital factors if patients are to be cured before they are lost.

Acknowledgements

Gratitude is expressed to the 14 centres and their staff for cooperating in this study, and to the Leprosy Mission (International) for financing it.

Reference

[1] WHO Study Group. *Chemotherapy of Leprosy for Control Programmes.* Technical Report Series No. 675. WHO: Geneva, 1982.

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The immunopathology of erythema nodosum leprosum: the role of extravascular complexes

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Summary Skin biopsies of 20 patients with erythema nodosum leprosum were studied histologically, by acid-fast, silver and immunological methods for the demonstration of bacterial antigen, and by immuno-peroxidase for a variety of immunological factors. The results were compared with those in 10 non-reacting lepromatous patients.

At the centre of the ENL lesions there was always disintegration of macrophages and release of bacterial antigen, comprising cell walls and particulate or diffuse components of *Mycobacterium leprae*. These products were found to combine first with IgM, later with IgG, which together with complement components of the classical pathway were present at the same sites. These complexes were found both extracellularly and in neutrophils and macrophages, and were constant features of acute stage lesions. C-reactive protein and B-lipoprotein were present in varying amounts and were associated partly with connective tissue. It is thought that CRP, and the related SAP, may be factors in the disruption or repair of elastic and collagen, which are conspicuous in some ENL lesions. The results support the view that ENL is an immune complex phenomenon, possibly self-perpetuating, occurring at the site of breakdown of small lepromatous granulomas. The immune complexes are extravascular and in this respect ENL differs from the classical 'serum sickness' described by Arthus.

Introduction

Erythema nodosum leprosum (ENL) is a reactional episode of lepromatous leprosy where large amounts of mycobacterial antigen and of corresponding antibodies provide evidence for an immune complex aetiology. Support for this hypothesis comes from disease manifestations,[1] from the binding of C_1q of sera from patients with ENL,[2–5] and from the deposition of C_3 and immunoglobulins IgG and IgM in glomeruli.[6, 7] ENL has been regarded as a clinical manifestation of the Arthus reaction because of the demonstration of granular deposits of C_3 and immunoglobulin in the lesions of some patients.[8] The same group of workers in subsequent reports[9, 10] concluded that the reaction was due to the trapping of

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circulating immune complexes. No mycobacterial antigen was demonstrated in the lesion. A recent communication[11] casts doubt on the analogy that has been made between ENL reactions and serum sickness because ENL reactions are seen to centre round the granuloma.[12] Extravascular formation of immune complexes is a more likely suggestion[5, 11] but direct evidence is lacking.

Following our application of the immunoperoxidase technique to the study of the pathological response across the spectrum of leprosy,[13] and to the mechanism of granuloma development of the two polar groups[14] we decided to apply this technique to study the pathogenesis of ENL.

Material and methods

Twenty patients with ENL were included in the study. They comprised 10 cases seen at the Medical Research Council Unit at Sungei Buloh, Malaysia or at the Hospital for Tropical Diseases in London, and 10 seen in Papua New Guinea. The controls were biopsies from 10 patients from Malaysia and Ethiopia who had non-reacting lepromatous leprosy (6 untreated, active and 4 treated and in regression).

Biopsies were fixed in formol-mercuric chloride acetic acid fixative (FMA), used routinely for skin biopsies in leprosy over many years,[15] which is ideal for the immunoperoxidase technique.[16] They were processed for routine examination by haematoxylin eosin and a modified Fite–Faraco stain for acid-fast bacilli. Serial paraffin sections were cut at 4 μm, air dried and stored for use. Excessive heat was avoided in all stages of preparation of tissues. Other stains included Heidenhain's iron haematoxylin, PAS, Baker's acid haematin for phospholipids, MSB for fibrin, Gomori–Grocott methenamine silver, Gomori's reticulin, Verhoeff's elastic and Perl's reaction. Cryostat sections were used for demonstrating neutral fats and cholesterol.

The immunoperoxidase method of Sternberger[17] was used with modifications. Trypsin was not an advantage either for specificity or strength with the FMA fixative and was omitted. The method and optimal dilutions have been described previously.[13, 14]

Antisera were raised without the aid of Freund's complete adjuvant and were obtained from DAKO (Mercia Brocades, Watford). Their specificity has been described by numerous workers and reviewed recently.[18] They included immunoglobulins IgG, IgM, IgA, IgE, complement components C_3, C_4, C_1q, C_3d lysozyme, coagulation protein plasminogen, protease inhibitors α_1-antitrypsin, α_2-macroglobulin, and Mycobacterium BCG. (Antiserum to *Mycobacterium leprae* an

Antiserum to acute phase reactants C-reactive protein (CRP), serum amyloid P factor (SAP) and low density β-lipoprotein (LDL) were a gift from Dr M B Pepys, London, who also gave us pure CRP and SAP for controls.

One control section was stained for endogenous peroxidase by a mixture of diaminobenzidine hydrochloride and peroxide. Other controls included normal rabbit serum in place of specific antiserum and staining after absorption of the antibody by the antigen. This was possible with IgG, IgM, lysozyme, α_1-antitrypsin (Sigma) CRP and SAP (Dr M B Pepys) and with BCG (Glaxo, vaccine). The soluble antigens were diluted 1/10 in Tris buffer mixed and incubated for 20 min with an equal volume of antiserum before use. Five μg/ml BCG (vaccine) was added to the BCG antiserum incubated, centrifuged, filtered and used. Finally the use of these antisera to determine different immunological responses in the various groups of the leprosy spectrum [13] provided a control within the system.

Results

The reaction of ENL takes place in small well defined granulomas typical of regressing lepromas. They may be superficial or deep in the skin or in the subcutaneous fat. The early reaction shows scattered accumulations of foamy macrophages in an advanced state of decay and varying numbers of neutrophils in close association with them (Figure 1). In the acute phase mast cells and moderate numbers of plasma cells are present. The infiltrate appears massive in some areas, being situated centrally within the granuloma and irregularly scattered among the fat lobules of the subcutis. The fibrous septa between sweat ducts is often the seat of reaction and neutrophil infiltration. In some cases there is significant involvement of blood vessels, with fibrinoid change in the intima of small vessels, and in medium sized veins oedema and invasion of the vessel walls by inflammatory cells. The serous fibrinous exudate stains weakly with PAS indicating the presence of mucopolysaccharides. Fibrinoid connective tissue stains more darkly with PAS and is strongly positive for fibrin.

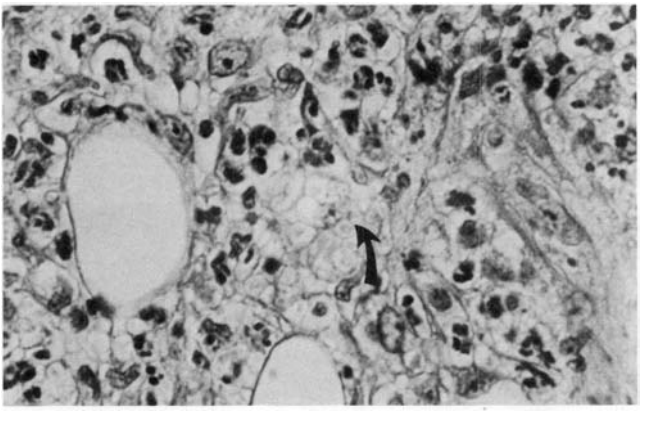

Figure 1. Polymorph neutrophil infiltration, centred on disintegrating macrophages (↑) containing bacterial debris in ENL lesion. H + E. × 525.

In the later stage of the reaction, after the neutrophil infiltration has receded, there are few remaining intact foam cells. Haemosiderin is often demonstrable. Residual accumulations of phagocytic vacuoles are invaded by B lymphocytes and plasma cells producing IgG and IgM, the numbers of which are increased.

THE GRANULOMA IN ENL

Macrophages

Macrophages involved in the acute reaction are large, foamy and degenerate. Iron haematoxylin shows cell membranes in variable states of preservation, those at the centre being most indistinct. Appropriate staining shows copious neutral fat, with irregular accumulations of phospholipid and glycoproteins present on the inner surface of the phagocytic vacuole. When ENL reactions take place in the superficial dermis, the macrophages often appear as single large rounded multinucleated cells, the cytoplasm of which is reduced to a single layer confluent with the cell membrane. The single large central vacuole within the cell is filled with a 'mat' of degenerating acid-fast debris. The macrophage cell membrane is often invaded by inflammatory cells indicating that it is unstable and degenerate, and it is these cells which participate most regularly in the reactions (Figure 2).

Lysozyme is present in all macrophages and in neutrophils; phagocytic vacuoles of degenerating foam cells can readily be identified by its presence. Similarly plasminogen and α_1-antitrypsin and α_2-macroglobulin are abundant, bound within cells containing bacillary debris. These inflammatory mediators are more marked in the reactive areas than in non-reacting areas of the lesion. Endogenous peroxidase is not demonstrated in macrophages.

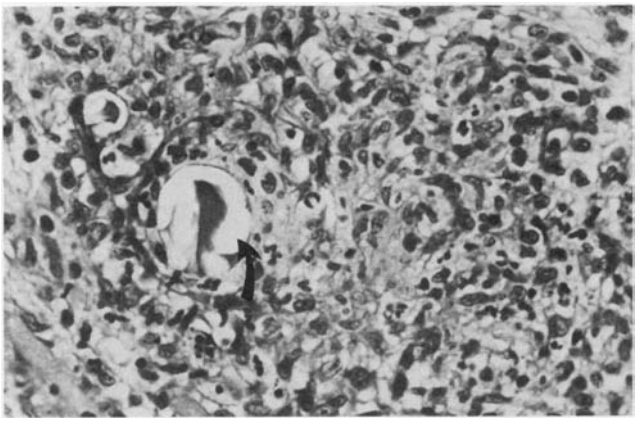

Figure 2. Disintegrating phagocytic vacuoles with mat of bacterial debris (↑) at the centre of a focus of neutrophil infiltration. H + E ×350.

Mycobacterium leprae *antigen*

In the acute reaction the most striking feature is the presence of bacillary products adherent to the plasma membrane of phagocytic vacuoles of degenerating foamy macrophages. With the disintegration of the cells and the rupture of the vacuole there is a release of bacterial debris into the intercellular space. Elsewhere this debris can be seen within the vacuoles as well as on the cell membrane. Throughout the reacting lesion it takes a variety of forms. It may be solid staining rods, or short fragments and granules, or it may be diffuse with no recognizable structure. Sometimes it appears in clumps. These various forms can be identified only by the use of special staining methods, as indicated in Table 1. In general the

Table 1. The appearance of bacterial forms and bacterial antigen in an ENL lesion by different staining methods

Stain	Solid	Fragmented or granular	Clumped debris	Diffuse 'soluble'
ZN	–	mø+	+	–
Rabbit anti-BCG	–	mø+	–	mø+
Methenamine silver	mø+++	–	mø+++	n+++

mø, macrophages; n, neutrophils; AFB, acid-fast bacilli.

largest amount of bacterial debris is demonstrated by impregnation with silver (Figure 3), moderate amounts with BCG antiserum and least of all with Ziehl–Neelsen. In the same preparation at the periphery of the granuloma the macrophages are better preserved, and contain fragmented and granular bacilli by acid-fast stains or solid rods by silver. This appearance is also seen elsewhere in non-reacting parts of the lesion. Neutrophils, particularly in the area of marked reaction, stain diffusely by silver and by anti-BCG antiserum (Figures 4 and 5). They contain no acid-fast material. Thus detectable acid-fast material is more persistent in macrophages than in neutrophils, probably on account of particle size. It appears that only a diffuse or 'soluble' but non-acid-fast bacterial product is present in neutrophils.

Acute phase reactants and M. leprae

In non-reacting areas CRP is closely bound to granular acid-fast bacilli. In reacting areas the macrophages contain clumps of CRP positive material. This material is not seen in neutrophils. SAP occurs as dark granular clumps or it is finely dispersed around the phagocytic vacuoles of macrophages. It is also seen in

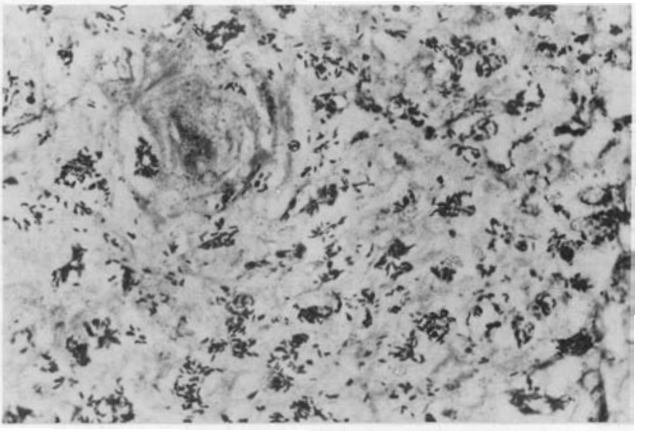

Figure 3. Bacterial cell walls in lepromatous granuloma of ENL lesion. (Acid-fast forms were scanty and mostly non-solid.) Methenamine silver. × 525.

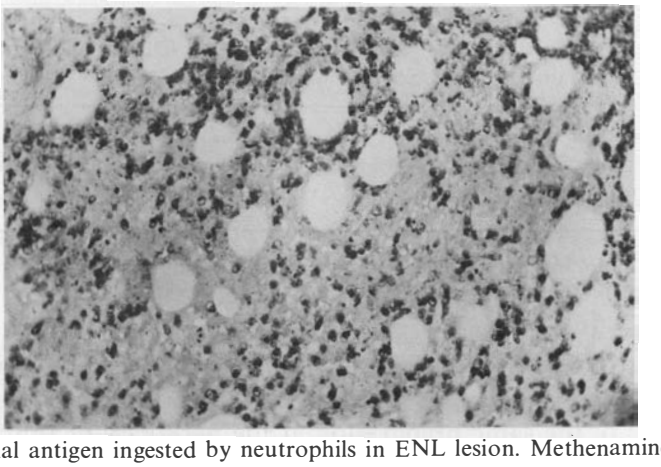

Figure 4. Bacterial antigen ingested by neutrophils in ENL lesion. Methenamine silver. × 175.

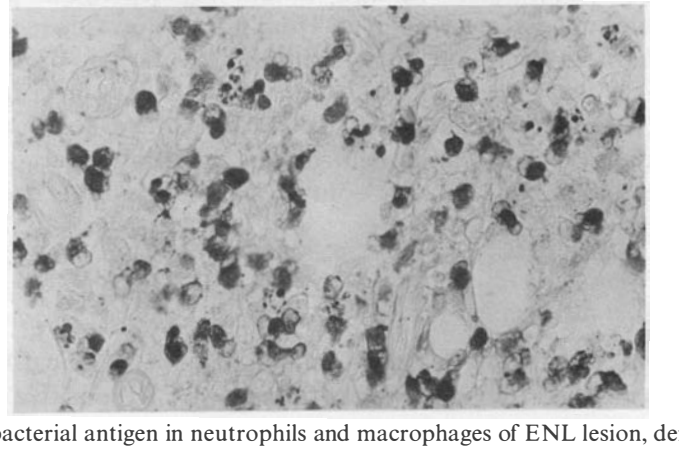

Figure 5. Mycobacterial antigen in neutrophils and macrophages of ENL lesion, demonstrated by mycobacterial BCG antigen. × 350.

neutrophils. β-lipoprotein appears to outline some bacillary rods, and occurs in the same area as CRP but is generally weaker.

Antibody

Most striking is the appearance of IgG and IgM in neutrophils and degenerating foamy macrophages which correspond to the cells containing *M. leprae* antigen. As a rule IgM appears first and is more prominent in macrophages containing fragmented bacilli. IgG is more marked in neutrophils and has the same granular or diffuse appearance as bacterial antigen demonstrated in these cells. In the later lesions, after the neutrophils have disappeared, there may be new macrophages containing IgG positive debris among the residual foam cells. Other foam cells containing bacterial debris remain intact with no intracellular antibody. Plasma cells and B lymphocytes are very numerous throughout the lesion and small capillaries are clearly outlined by several layers of these cells, indicating their haematogenous origin (Figure 6).

Complement

Complement, like antibody, is demonstrated in neutrophils. It is mainly C_3 with some C_1q and C_3d. In later lesions macrophages that have ingested IgG coated bacilli also show C_3, which is very marked also in the 'mat' of aggregated bacillary debris in the vacuoles of some superficial reactions.

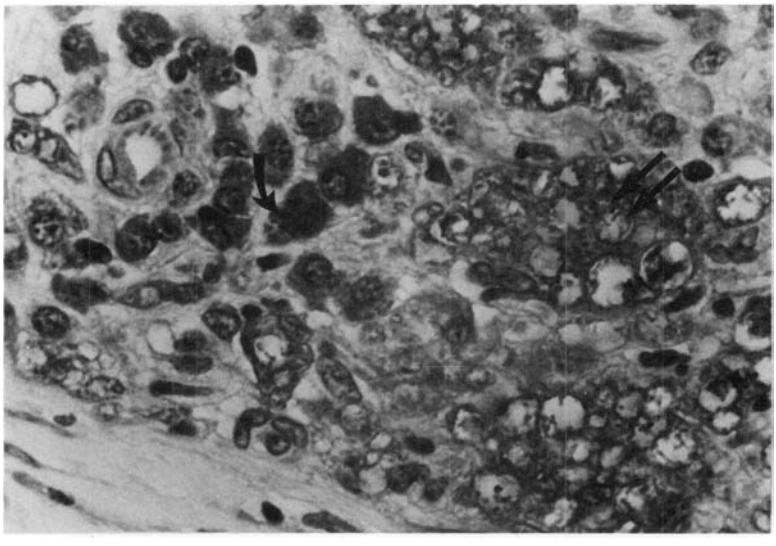

Figure 6. Plasma cells positive for IgG (↑). Residual macrophages have bacilli coated with IgG (↑↑). × 525.

THE CONNECTIVE TISSUE AND SKIN STRUCTURES IN ENL

A most notable feature is the marked serous fibrinous exudate, associated with fibrinoid degeneration of collagen and elastic fibres, in and around the reacting areas. The degree of severity is variable. The exudate contains a few neutrophils and other inflammatory cells. Mast cells are a prominent feature. The small, medium-sized and even large blood vessels may be markedly altered. This acute reaction resolves and is followed by regeneration of connective tissue. However, the elastosis persists and in no biopsy of the New Guinea group examined is there any detectable return to normal of the elastic fibres. Macrophages are commonly seen associated with degenerative elastic fibres between the newly formed collagen bundles. Fibrous septa in the subcutaneous reactive areas are slow to heal.

High levels of IgG and IgM, and variable amounts of complement C_3, C_4, C_1q and C_3d are seen in the exudate and in fibrinoid degenerate connective tissue. Lysozyme, plasminogen and acute phase reactants CRP and to a lesser extent β-lipoprotein can be demonstrated in the exudate and are deposited on connective tissue fibrils undergoing fibrinoid change. The amount of lysozyme and plasma proteins detected varies directly with the severity of the exudate. SAP is most marked in the extracellular space, and in macrophages and neutrophils of the early acute reaction. In later lesions it is conspicuous in macrophages between the collagen bundles (Figure 7), which also contain IgG. The protease inhibitors α_1-antitrypsin and α_2-macroglobulin are seen in the extracellular space in the acute stage. Endogenous peroxidase is found in some neutrophils and extracellularly.

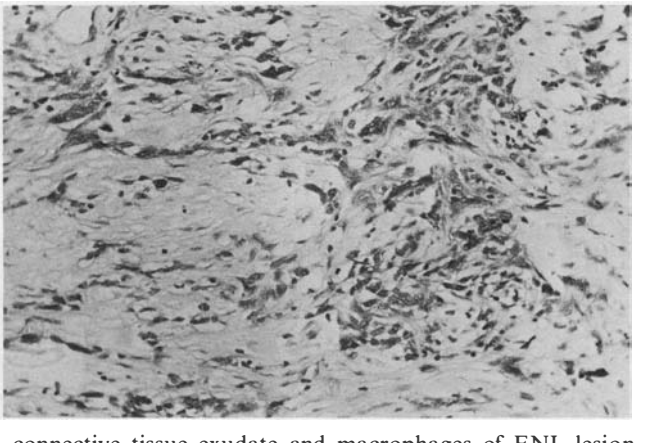

Figure 7. SAP in connective tissue exudate and macrophages of ENL lesion. Immunoperoxidase. ×175.

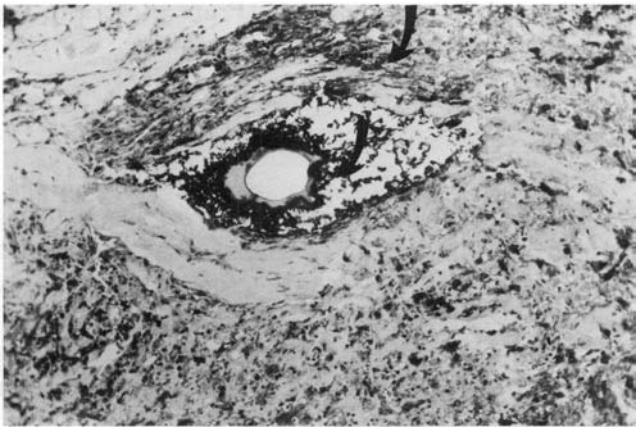

Figure 8. C_3 (↑) is marked around medium-sized blood vessels and in exudate after the early infiltration stage. Immunoperoxidase. × 120.

Blood vessels

No detectable immunological mediators or bacterial debris are detected in the vessels altered by the early inflammatory reaction. Later, with the appearance of serous exudate, small and medium-sized arteries are obliterated by swollen endothelium. At this time IgG, IgM and C_3, and diffuse bacterial debris stained by silver or anti-BCG serum, can be demonstrated in the endothelium, swollen muscle and adventitia of the vessel walls (Figure 8). Large vessels containing demonstrable acid-fast bacteria or debris become involved when the exudate is at its peak. IgG, IgM and C_3 are then present in very large amounts in association with the adventitia, or more particularly in the immediate neighbourhood of the vessel.

Nerve bundles

Nerve bundles are involved equally in the reacting and non-reacting areas. Granular bacilli and acid-fast debris appear to be coated with IgM and complement. Lysozyme is marked in the interaxonal spaces, as also is IgG, and CRP can be demonstrated.

NON-REACTING LESIONS

In control biopsies of lepromatous lesions at a comparable stage of activity or regression, CRP is bound to acid-fast bacilli or debris, which is nearly all intracellular. SAP is present in the phagocytic vacuole, and β-lipoprotein may produce a pale halo around the bacilli. There is no immunoglobulin bound to the

bacilli. All immunological factors except CRP are present in smaller amounts than in reacting lesions. Inflammatory cells are scanty.

Discussion

The weakness of the generally accepted immune complex aetiology of ENL has been that it has not so far been possible to confirm the previous demonstration of complexes at reaction sites using the rather insensitive fluorescent antibody technique,[8] and indeed it is not always possible to demonstrate mycobacterial antigen by acid-fast staining methods. It is known, however, that whether the reaction takes place in the skin,[12] synovia[19] or in nerves[20] residual lepromatous granulomata can be found at the reaction site.

In the present paper, we demonstrate that bacterial cell bodies, either intact or in fragments or diffuse debris, can invariably be demonstrated using the methenamine silver method, that this bacterial residue contains antigen which reacts with anti-BCG antiserum, and that the antigen is partly free as a result of the break-up of effete host-cell macrophages. This cellular disintegration and the attachment of ferritin-conjugated antibody to bacterial cytoplasm has already been demonstrated ultrastructurally.[21] We demonstrate also that bacterial antigen, IgG and IgM and complement components are all present at the same sites, both extracellularly in the neighbourhood of macrophages and intracellularly in the polymorphs, which are the hallmark of the acute stage of ENL reactions. The immunoperoxidase staining of these immunological factors, other than antigen, was stronger in the reacting lesions than in non-reacting lepromatous lesions at a comparable stage of regression. It can be inferred, therefore, that ENL is associated with immune complexes of which *Mycobacterium leprae* antigen is a component, that this is a constant finding, and that extracellular immune complexes are not a demonstrable feature of non-reacting lesions.

ENL, though centred around a granuloma, is known to involve the connective tissue of the dermis[22] causing fibrinoid change and disruption of the elastic tissue fibres which can be the main feature of the lesion.[23] In the present study the immunoperoxidase results produced a less clear cut distinction between these two variants of ENL than was apparent histologically. With the onset of oedema and fibrinoid change no bacterial antigen could be detected. This may be because it is degraded to an undetectable form, or because it is masked by the large amount of CRP, SAP and β-lipoprotein in the exudate. CRP is known to bind to microorganisms,[24] and to activate the complement system.[25] SAP binds to elastic,[24] and β-lipoprotein may be involved in complex formation.[26] However, CRP is present, bound to *M. leprae*, in equal amounts in reacting and non-reacting lepromatous lesions, and the antigen primarily involved in the connective tissue reaction is not established. The main role of CRP could be to

elicit the inflammation required for resolution and repair,[25] which would account for its association with collagen.

Vasculitis is sometimes conspicuous but only in about half of all ENL lesions.[27, 28] We suggest it is not the cause but is secondary to ENL, developing as a result of immune complexes and inflammatory mediators entering the circulation from the lesion, to which the vasculitis is localized. An association between ENL and glomulonephritis has not been established.[29] The response of ENL to thalidomide has been correlated with the presence in the lesions of immunoglobulin-containing cells.[30] The fact that thalidomide is not effective in the treatment of vasculitis or Arthus reaction[31] is further evidence against vasculitis playing a primary role in ENL.

There is much individual variation in the onset of ENL, from person to person and from one lesion to another. It is not possible to say precisely why one lesion reacts and another does not, but the events that culminate in a reaction may be as follows. The onset usually occurs after a period of therapy, or in a quiescent phase, and the onset is often preceded by a large diminution in the bacterial index.[32] Circulating immunoglobulins are variable but higher in ENL than in non-reacting patients.[33, 34] In young active lesions there will probably be an excess of antigen though it is not all accessible. As the infection goes into regression the antibody–antigen ratio will rise at the same time that more antigen becomes free. It is known that the antigen–antibody ratio is critical in determining the form of a granuloma in mycobacterial disease, and that necrosis with polymorph infiltration is associated with antigen and antibody at equivalence.[35] Our present results suggest that ENL may be precipitated slightly before equivalence is reached, i.e. at a small antigen excess, and that thereafter the antibody level continues to rise with an influx of lymphocytes in the late stage. The lesions which go into reaction, whether in skin or other tissues, are presumably those in which the amount of free antigen is appropriate to the antibody level at the site. The necrosis and oedema with which the reaction is associated could lead to the release and dispersal of further deposits of antigen, and in turn to more antibody production. Adjuvant would be provided by the release of lipid from disintegrating fat-filled macrophages, and by fat necrosis, if the reaction happened to be centred on a granuloma in the subcutis. CRP complexes may contribute to autostimulation.[36, 37] Thus there is probably a self-perpetuating element in the reaction.

The role of immune complexes in ENL and the histology of the reaction are analogous to the situation in an Arthus reaction, as many other workers have observed. The two reactions are, however, different in so far as Arthus[38] and von Pirquet[39] were dealing with circulating soluble immune complexes. Although ENL is unlikely to be a unique phenomenon it is difficult to think of any exact counterpart in other diseases. It is perhaps conditional on the slow degradation of large amounts of antigen of low immunogenicity.

Acknowledgements

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Timing of tendon-transfer surgery

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Summary Thirty-five leprosy patients who had tendon-transfer surgery recovered nerve function postoperatively. The tendon transfers were performed to correct paralytic deformities resulting from ulnar, median and common peroneal nerve damage. Nerve function recovery was found in 2·8% of the hands that had claw-finger correction for ulnar palsy; in 5·1% of the hands that had opponens replacement for median palsy and in 6–9% of the operated drop-feet.

Analysis of the records showed that none of the patients had been operated on within 6 months after the onset of nerve damage.

Postoperative deformity following nerve function recovery was rare in the hand, but occurred in 5 out of 18 of the feet that showed postoperative recovery.

Introduction

A surgeon engaged in tendon-transfer surgery in leprosy patients will usually only operate on a patient if the pattern of paralysis is 'stable'. The paralytic deformity is considered stable when no further nerve function changes, resulting in increasing paralysis or recovering muscle function, are expected. The general opinion is that tendon-transfer surgery should be postponed for 6 months after the onset of palsy, because it is believed that nerve function recovery is not very likely if a paralytic condition has persisted for 6 months.

Two[1, 2] textbooks on surgery in leprosy do not give any information on the timing of tendon-transfer surgery with regard to the duration of the palsy, but a third[3] states that the paralytic deformity to be corrected should have been present for 6 months.

When reviewing patients who had tendon transfers for their hands and feet at the All Africa Leprosy and Rehabilitation Training Centre (ALERT), we found a number of patients who had recovered nerve function postoperatively. By analysing the patients' files and surgical assessment forms we tried to answer the following questions:

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Had patients been operated on within 6 months from the time of nerve damage, or did nerve function recovery occur after the surgeon had waited for 6 months?

2 Does postoperative nerve function recovery result in deformity because of the apparent upsetting of muscle balance?

Method and material

Voluntary muscle testing (VMT) and sensory testing (ST) as described by Brandsma,[4] and in many instances motor conduction velocity (MCV) assessments were the techniques employed to assess and confirm nerve function recovery. Nerve function recovery was defined as an improvement of at least 2 points in muscle strength of a muscle or muscle group(s) innervated by that nerve using the MRC[5] 0–5 scale. Ulnar nerve function was assessed by testing abduction of the little and index finger. Median nerve function was assessed by testing abduction and opposition of the thumb and common peroneal nerve function was assessed by testing dorsiflexion and eversion of the foot. The two movements that were tested to determine ulnar and median nerve function recovery were totalled, thus giving a maximum score of 10 for full recovery per nerve.

Nerve function recovery was reviewed in 35 patients. The classification of these patients was 20 T/BT, 2B and 13 BL/LL.

We found 13 ulnar recoveries in 12 patients following tendon-transfer surgery for claw-finger correction. Seven patients recovered median nerve function only when operated for claw-fingers and loss of opposition. Three patients recovered ulnar and median function following claw-finger correction and opponens replacement.

The following operations were performed for claw-finger correction: extensor–flexor–many-tailed 8 times, extensor–many-tailed 4 times and Bunnell sublimis transfer once. For opponens replacement the following muscles were employed: flexor digitorum superficialis 8 times, extensor pollicis longus once and extensor indicis once.

We found 18 common peroneal nerve recoveries in 16 patients. The following operations had been performed: tibialis posterior transfer 14 times, anterior transposition of tibialis posterior and peroneus brevis once and the 'Carayon' technique for drop-foot correction 3 times.

Results

Table 1 gives a break down of hands and feet in which we have noticed postoperative nerve function recovery. Unfortunately we were unable to determine exactly how many patients had been reviewed for drop-foot corrective surgery.

Table 1. Postoperative nerve function recovery

	Reviewed	Recovered
Ulnar	356	13 (3·8%)
Median	194	10 (5·1%)
Common per.	200–300	18 (6–9%)

We were able to determine the duration of the palsy in 27 patients. None of the patients had been operated within 6 months after the onset of paralysis except one patient who was operated while the nerve was recovering.

Table 2 gives the duration of the palsy as given by the patient (history) or as determined from the repeated preoperative nerve function assessments (record). The 5 recoveries of palsies that were reported to have been present for more than 12 months were all recoveries of the common peroneal nerve. Recovery of ulnar and median function was confirmed by MCV testing in all cases assessed by this technique, 9 ulnars and 7 medians, after recovery had previously been established by VMT.

The average improvement of the ulnar nerve by VMT was 6·2 points (3–10) and for the median nerve 8·1 (5–10).

Sensory recovery as tested with No. 5 bristle[6] was observed in 7 ulnar and 4 median nerves. Sensory loss remained in 5 ulnar and 2 median nerves. No records were available for the remaining cases.

Postoperative deformity was noticed in one ulnar correction which resulted in hyperextension of the proximal interphalangeal joints and in one median correction which resulted in luxation of the metacarpo phalangeal joint. There were 10 recoveries of the deep peroneal nerve, 7 of the deep and superficial

Table 2. Duration of palsy in months at time of surgery

Months	Record	History
6	1	1
7	4	3
8	2	3
9	2	0
10	3	1
11	0	1
12	1	0
More than a year	0	5

peroneal nerve and one of the superficial peroneal nerve. The peroneal muscles recovered 5 times from total paralysis and 3 times from partial paralysis.

In 4 feet, postoperative inverted foot deformity had developed, In 3 of these only the pretibial muscle group had recovered. An everted foot deformity was seen in one patient in which only the peroneal muscles had recovered.

Discussion

Considering the number of hands and feet reviewed in this study it seems to be relatively rare for nerve function to recover 6 months after the onset of a palsy. It seems advisable in the case of foot-drop corrective surgery to wait for 1 year as postoperative recovery may upset the balance of muscle forces in the ankle and subtalar joints. Patients should of course use a foot-drop strap or ankle orthoses when waiting for surgery.

No MCV assessments had been done for the common peroneal nerve to confirm recovery. Postoperative muscle grading of the pretibial muscles is difficult because the transferred muscle-tendon unit will contribute to the strength of dorsiflexion. Also the transferred tendon in many of our cases was attached to the toe extensors. Recovery of the pretibial muscle group was judged by palpation and measurement of circumference of the lower leg. These problems are not encountered in the testing of the peroneal muscles.

A contributing factor to the development of inverted foot deformity may have been a now abandoned technique. In this technique 2 slips were created out of the posterior tibial tendon after the tendon had been withdrawn in the lower leg. The slips were then tunnelled separately to the medial and laterial side of the foot. It is our observation that tension adjustment in this technique is difficult and that the medial tendon slip usually acts more strongly.

The 6-months' waiting time for corrective hand surgery seems justified. Postoperative deformity was only encountered once after claw-finger correction and once after opponens replacement. The dangers, however, for secondary deformities to develop in the hand when waiting for surgery are much greater than for the foot. Hands, therefore, should preferably be operated on as soon as conditions permit. A surgeon may decide to operate early for social reasons such as a patient in danger of losing his job.

Muscle grading of the abduction of the little finger and index finger is still possible postoperatively. The movements tested do not interfere much with the surgical technique employed for correction of the ulnar motor deficit and the muscle bellies can also be easily palpated. In median nerve recovery the transferred muscle-tendon unit will contribute to the testing. In these cases, however, the development of the thenar eminence will be indicative for recovery of nerve function. We found 8 median nerve recoveries in hands in which the

EFMT operation was performed for claw-finger correction. In these cases the median nerve had recovered with an extra tendon in the carpal tunnel.

Twelve of the 19 patients operated on for ulnar or combined ulnar and median palsy showed preoperative recovery of nerve function other than the one whose paralytic deformity was to be corrected.

This study also demonstrated that in all the cases reviewed median nerve damage was accompanied by ulnar nerve damage. Isolated median nerve damage, however, does occur in leprosy patients and we have reported on this in another communication.

Median nerve function recovery always preceded ulnar recovery when both nerves recovered. In the foot common peroneal nerve damage was in all but one case accompanied by posterior tibial nerve damage. Recovery of peroneal muscle preceded recovery of the pretibial muscle group if both the deep and superficial peroneal nerves were affected. This study also emphasizes the importance of regular nerve function testing and the importance of careful history-taking as we were often unable to determine from the patient's records the duration of the palsy.

An important finding from this study seems to be that patients should not be operated on when nerve functions are still changing. All the patients received antileprosy treatment and most patients had also received prednisolone suggesting that nerve function recovery was anticipated in the months preceding surgery. Nerve function recovery, however, without the use of prednisolone was observed 8 times in the hand and 10 times in the foot.

Conclusions

1 Nerve function recovery does occasionally happen 6 months after the onset of a palsy.
2 Patients should preferably not be operated on when nerve functions are still changing.
3 Six months' waiting time to allow for possible recovery of ulnar and median nerve function, after the onset of a palsy, seems reasonable.
4 In the case of foot-drop, corrective surgery usually should be postponed for 1 year after the onset of the palsy.
5 Postoperative deformity due to recovery of nerve function in the hand occurs rarely. However, the possibility should always be considered in foot-drop surgery.
6 Selection of surgical technique is important in those cases in which nerve function could be anticipated. For example, if a patient has to be operated on early for claw-finger correction and the fingers are fully mobile, the least powerful corrective tendon transfer should be selected.

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Grid system and body diagram for leprosy

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Summary Based to some extent on systems used for the charting of burns, multiple injuries and melanomas, a grid system and body diagram is described for the accurate charting of sites of skin smears in leprosy. It may, however, also be used for the recording of birthmarks, scars, 'doubtful' skin lesions and sites from which biopsies have been taken, either in drug trials or for routine purposes. It is suggested that the combined use of a body diagram and a written record of the relevant grid space, using figures 1–10 and letters A–L, will increase the accuracy with which such sites are recorded. It could also be of value if data are to be analysed by computer.

Introduction

Sites from which slit-skin smears of leprosy patients are taken may vary according to skin lesions, classification or personal preference. Reports on the smears are usually given in the form of an average bacterial index (BI) and morphological index (MI), combining the readings of all smears taken from the various sites of the patient at the same session. However, in the case of the smear of one of the sites having a BI and/or MI markedly higher than the average, as might occur in the case of patients who are not pure LL, in relapses of LL patients, or at sites of persistent positivity, it is of fundamental importance not only to record that one smear had a BI and/or MI markedly higher than the average, as already emphasized,[1] but also to record the smear site which produced this higher BI and/or MI. This is all the more important since a smear from this site must of course be included in the taking of subsequent smears.

To facilitate the accurate but simple recording of the site of a particular smear or of a skin lesion from which the smear was taken, and has to be taken in future, a search was carried out of the literature for grid systems and body diagrams which could be used for this purpose. The system appearing in *Leprosy in Theory and Practice*[2] and that used in Australia at the Sydney Hospital Melanoma Clinic

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have limited practical application in the present context, but the 'Simple grid system for charting burns and multiple injuries',[3] published specifically for the recording of sites from which specimens for bacteriological culture were taken in patients with extensive burns, is of considerable interest. With slight modifications, we in the northern part of Malawi have used such a grid system and body diagram for over a year, especially for the recording of 'unusual' sites of slit-skin smears, and found it of practical use both in the field and the laboratory.

Design and use of the grid system and body diagram

Sachs,[3] wherever possible, had the ordinates run through 'bony' landmarks, presumably in order not to get misled by sagging flesh. The front and back images (Figure 1) are consequently not in exactly ideal proportion, as they are restricted by the same ordinates—1/2: through eyebrows and upper part of the ears; 2/3: through the mouth; 3/4: through the suprasternal notch, and the claviculae; 4/5: through the xiphoid process, the inferior angle of the scapulae, and the middle of the humeri; 5/6: through the umbilicus, the iliac crests and the elbow joints; 6/7: through the pubis, the inferior margin of the buttocks and the wrist joints; 7/8: through the middle of the thighs; 8/9: through the knee joints; 9/10: through the malleoli.

In the grid system now described, A/B, D/E, F/G and K/L separate the arms from the trunk (and the ears from the head), C and H are front and back midline (adapted from Sydney Hospital Melanoma Clinic). Though Sachs had the letters A–J as ordinates and the figures 1–8 as abscissae, the present version has the letters as abscissae, and other letters are added for the front and back midlines (C and H), whilst leaving I and J out (since both may be confused with each other or with the figures), substituting them by K and L. The figures (1–10) are placed as ordinates, because map coordinates usually place the ordinate before the abscissa, and there will be less room for confusion in recording a BI of 5+ from a smear above the right breast as 4B5+, rather than as D25+ (as Sachs' system would have it).

The 10 abscissae and the 10 ordinates would make it practical to put data on the site of single-skin lesions into a computer. Lesions on the exact lateral side of the body or limbs can be indicated by a combination such as 4A/L (over the right deltoid muscle, as for BCG scars in Malawi), or 9/10B/K (for a lesion over the right lateral malleolus). When *smears* from both earlobes are taken *routinely*, these sites can be indicated as X (right earlobe) and Y (left earlobe), reserving 2A and 2E for *lesions* on the right and left ear, which are *not* on the earlobe. The grid as used in Malawi, has been designed with an outer border 12×12 cm, around a grid of 10×9 cm and it can easily be glued on the inside cover of the diaries used by our leprosy workers.

It is, however, possible to print this grid system and diagram on patients'

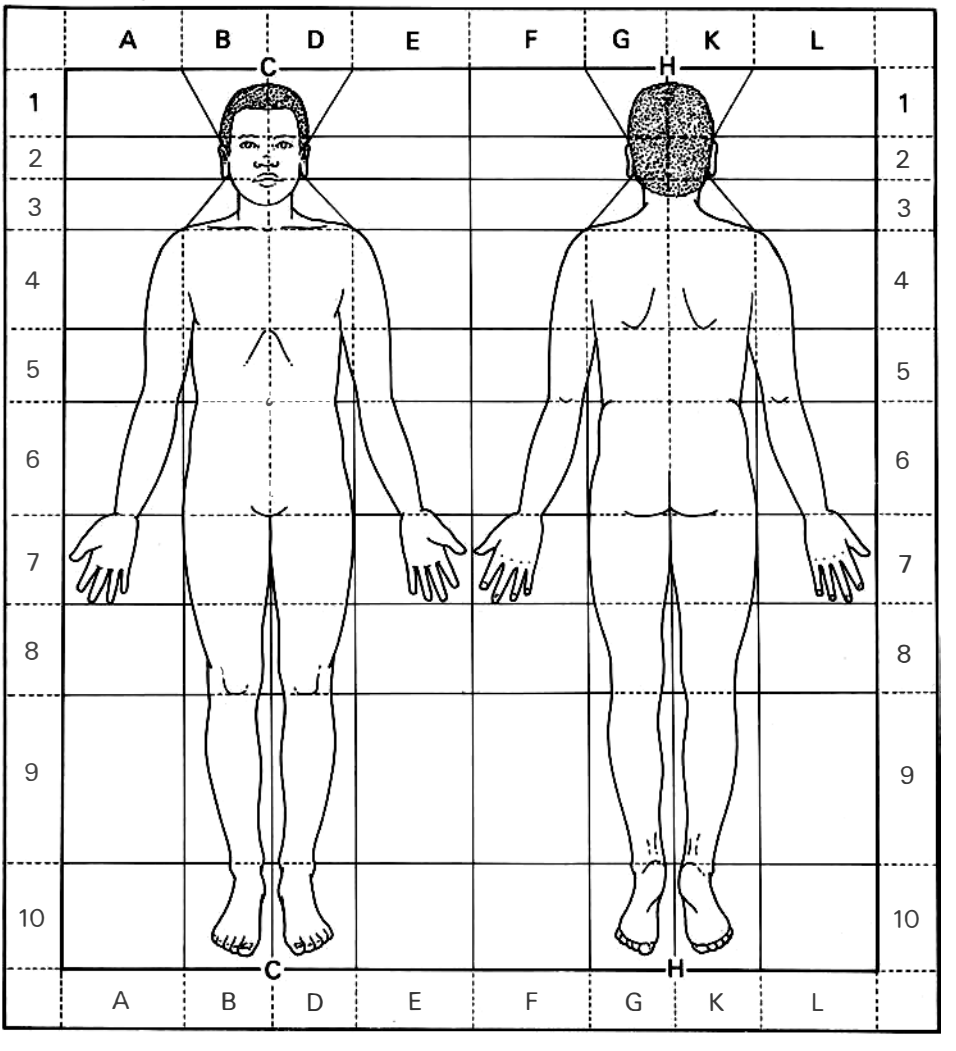

Figure 1

record cards, or to overprint the grid if such cards feature a diagram of the body already. This would almost certainly enhance the accuracy with which lesions are drawn in the diagram.

We have also started using this grid system to record the sites of presumed birthmarks, scars (for later identification) and doubtful leprosy skin lesions when examining contacts of leprosy patients. It also could be of value for the detailed recording of exact sites from which biopsies are taken in drug trials, or for routine purposes.

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The rate of loss of maxillary anterior alveolar bone height in patients with leprosy*†

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Summary Alveolar bone loss and periodontal status were measured radiographically and clinically in 22 patients with leprosy after a 4-year interval. The average reduction in alveolar bone height in the anterior maxilla ranged from 0·09 to 0·13 mm per year, being lowest in patients with lepromatous disease. These results are similar to previous measurements of attachment loss, a comparable parameter, in Norwegian patients without leprosy who exhibit good oral hygiene and much better than Sri Lankan patients with poor oral hygiene similar to that found in these patients with leprosy. These data suggest that previous observations of increased alveolar bone loss in patients with lepromatous disease are the result of bone lost before treatment and that reduced bone loss in the presence of abundant dental plaque and poor oral hygiene may be related to immune dysfunctions in patients with leprosy.

Introduction

Skeletal manifestations of leprosy in and around the oral cavity were first described as *facies leprosa*,[1, 2] a tripartite resorption of the maxillary bone involving the nasal surface of the hard palate, its anterior extension, the anterior nasal spine, and its oral projection, the alveolar bone supporting the maxillary incisor teeth. These discoveries made from examinations of the skeletal remains of a medieval population of Danes with leprosy have recently been documented in

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a monograph.[3] Clinical studies of contemporary populations of patients with leprosy have confirmed and extended these observations.[4–9] These studies have established that resorption of alveolar bone in the anterior maxilla is a characteristic manifestation of leprosy, being most pronounced in the lepromatous form of the disease.

The purpose of the present report is to extend observations made earlier[8] on a population of treated patients in Malaysia. Specifically, our aim was to perform radiographic and clinical examinations on as many former patients as possible in order to determine the rate of loss of maxillary alveolar bone over 4 years and to determine the incidence of local etiologic factors for the pathogenesis of periodontal disease in this population. We have found that the rate of alveolar bone loss over 4 years in these patients is extremely low, comparing favourably with measurements of attachment loss recorded in larger clinical studies of patients without leprosy, and that bone loss is less than that expected by the usual indicators of periodontal inflammation. These results suggest that the previously recorded differences between patients with lepromatous and other types of the disease could be due to accelerated bone loss in untreated lepromatous patients, and that treatment greatly reduces the risk of alveolar bone loss.

Materials and methods

All available patients (22) from a previous study[8] at the National Leprosy Control Centre, Sungei Buloh, Selangor, Malaysia were re-examined clinically and radiographically 4 years later. Twenty-five patients from our previous study had been sent back to their residence during this 4-year interval, in accordance with the national policy of decentralization of treatment, and were not available for follow-up. All patients were under continuous treatment for leprosy during this period and none exhibited any evidence of relapse. All procedures were explained in detail to each patient who gave written informed consent in advance.

Radiographic examination of alveolar bone in the anterior maxilla was performed in each patient using the paralleling long-cone technique as described previously.[8] Alveolar bone height was measured on these radiographs using a modification (Figure 1) of the Schei method.[10] Measurements of the distances between the apical foramen, the crest of alveolar bone and the cemento-enamel junction (Figure 1) were made on both sides of the maxillary central incisors using adjustable, fine-toothed calipers and a micrometer. Readings were made to the nearest 0·05 mm, and duplicate measurements differed less than 3%. Alveolar bone height on the four sides of the two maxillary central incisors was calculated (Figure 1) as: $AB/AC \times 100$ and then expressed as the mean of these four measurements. Percentage alveolar bone loss for each patient was determined as: 100 – alveolar bone height. This measurement taken in 1982 was then subtracted

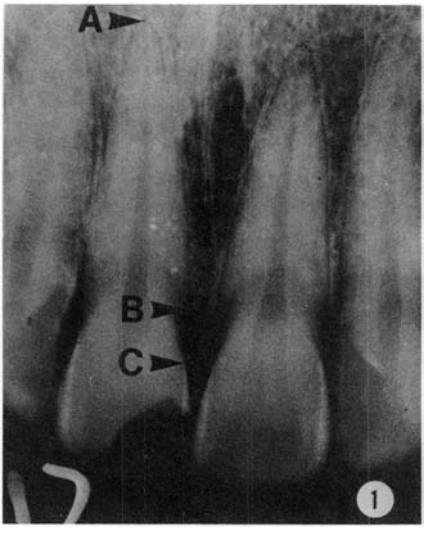

Figure 1. Periapical radiograph of the maxillary central incisors illustrating the radiographic landmarks used to measure alveolar bone loss. From above downward, these points (arrowheads) are the apical foramen (A), crest of the interproximal alveolar bone (B) and the cemento-enamel junction (C). Alveolar bone loss was expressed as the percentage reduction in alveolar bone height and calculated as follows: $100-(AB/AC \times 100)$. Alveolar bone loss in this patient was 14·8%. The patient identification number is in the lower left corner of the radiograph ($\times 2{\cdot}08$).

from the 1978 calculation performed under identical conditions to determine the change in alveolar bone height over 4 years.

Clinical examination of these patients in 1982 was more extensive than in 1978 and included complete charting of each patient's mouth. For each tooth we recorded the mean periodontal probing depth for 6 points and tooth mobility on a scale of 0–3.[11] The periodontal status of each patient was evaluated by the Gingival Index[12] and the Plaque Index.[13] These data were used to assess the general periodontal condition of each patient which was then correlated with the change in alveolar bone height.

Statistical evaluation of the results was performed using the Student's *t* test.[14]

Results

The reduction in alveolar bone height in the anterior maxilla for the 22 patients in this follow-up study is shown by disease type in Figure 2.

The rate of loss of alveolar bone height over 4 years in these three groups of patients is shown in Table 1. The data presented were obtained by subtracting the 1978 measurements of alveolar bone loss from those obtained for the same patient in 1982. The rate of alveolar bone loss in the patients with lepromatous

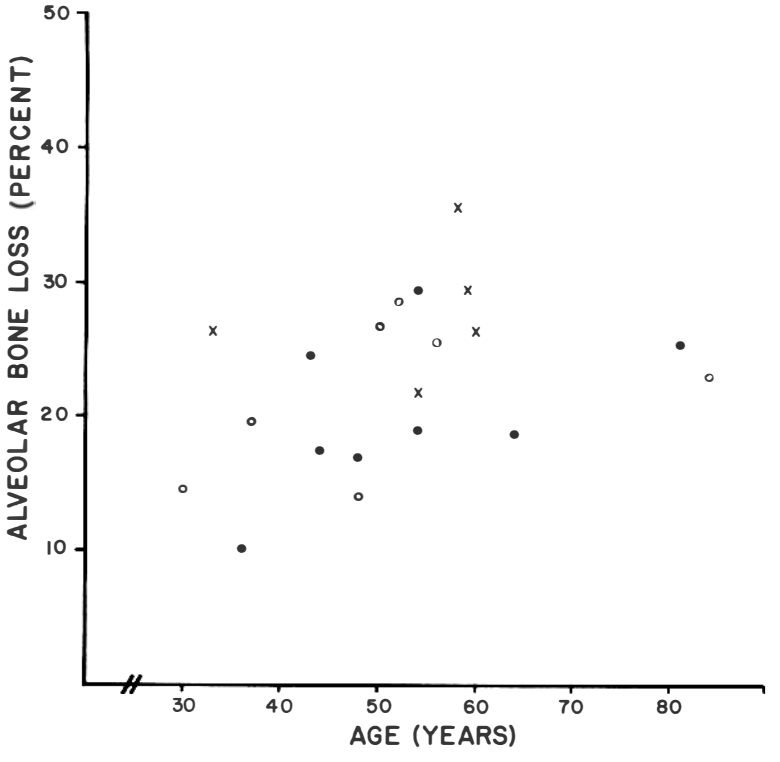

Figure 2. Graph depicting the reduction in alveolar bone height (percentage alveolar bone loss) by patient age and disease type in 1982. x, lepromatous; ●, borderline; ○, tuberculoid.

Table 1. The rate of loss of alveolar bone in the anterior maxilla by disease type

Type of leprosy	Number of patients	Range of ages	Mean loss of alveolar bone height in 4 years	
			(%)	(mm)
Lepromatous	6	33–60	2·1	0·34
Borderline	9	36–81	3·2	0·51
Tuberculoid	7	30–84	2·2	0·35

disease is not significantly different from the other patients. The original height of alveolar bone around the maxillary central incisor is closely approximated by the distance AC in Figure 1. This distance is actually the mean root length of this tooth (13·0 mm) plus 3·0 mm, the average curvature of the cervical line on the mesial and distal, a total of 16·0 mm.[15] Using this measurement, the actual loss of

alveolar bone height can be calculated (Table 1) to be between 0·34 and 0·54 mm over 4 years depending on disease type.

Notations of changes in bone height, patient age and various clinical parameters used to indicate periodontal status for each patient are shown in Table 2. The first two columns restate data from Figure 2. The mean age for lepromatous, borderline and tuberculoid patients is 52, 53 and 51 years respectively (Figure 2 and Table 2). The average alveolar bone loss for lepromatous patients (29·5%) is significantly greater ($P \leq 0{\cdot}05$) than that for tuberculoid patients (21·8%) but not significantly different from that for borderline patients (22·2%) (Table 2, Figure 2). The third column shows the change in alveolar bone height from 1978. The extremes ranged from a net gain of

Table 2. Rate of maxillary anterior alveolar bone loss and periodontal status of patients by age and disease type

Type of leprosy	Age of patient	Alveolar bone height		Plaque index (0–100%)	Gingival index (0–3·0)	Tooth mobility (>1)	Periodontal pocket		Deepest pocket in max. anterior (mm)
		1982 (% loss)	Change from 1978				(>3 mm)	(>4 mm)	
Lepromatous	33	26·5	−3·3	20	1·5	No	Yes	No	4
	49	36·7	0	100	2·0	Yes	Yes	Yes	2
	54	21·8	+2·2	10	1·0	No	No	—	1
	58	35·7	−3·6	65	1·3	No	Yes	No	3
	59	29·6	−4·2	100	2·0	Yes	Yes	Yes	5
	60	26·6	−3·8	15	0·4	No	Yes	Yes	2
Borderline	36	10·0	0	40	1·2	No	No	—	2
	43	24·9	−4·9	70	1·3	No	No	—	3
	44	17·3	−4·3	40	1·5	No	Yes	No	2
	48	17·0	0	75	1·3	No	Yes	Yes	3
	49	37·2	−4·3	70	1·0	Yes	Yes	Yes	3
	54	18·9	−2·0	35	0·6	No	No	—	2
	54	29·6	−5·5	100	1·8	No	Yes	Yes	5
	64	18·6	−3·8	80	1·0	No	No	—	2
	81	25·9	−3·8	100	1·1	Yes	Yes	Yes	3
Tuberculoid	30	14·8	−2·8	25	1·0	No	No	—	2
	37	19·5	−8·3	100	2·0	No	Yes	Yes	3
	48	13·7	+1·3	50	1·2	No	No	—	2
	50	27·0	−5·0	30	1·3	No	Yes	No	2
	52	28·9	0	50	1·0	No	Yes	No	1
	56	25·4	−2·5	60	1·2	Yes	Yes	Yes	4
	84	23·1	−1·9	40	1·2	Yes	Yes	Yes	4

2·2% (+2·2) for the third patient listed to a loss of 8·3% (−8·3) for the 37-year-old tuberculoid patient. Seven of the 22 patients had either a net gain in bone height or no loss during this 4-year period. Changes in alveolar bone height between lepromatous, borderline and tuberculoid patients were not statistically significant.

Several indices of periodontal status are shown in columns 4–9. The plaque index (column 4) is a calculation of the incidence of supragingival plaque on the surfaces of teeth. In our patients this ranged from 10 to 100%. The gingival index is a clinical estimate of inflammation in the gingiva and is scored from 0 (absence of inflammation) to 3 (colour changes and spontaneous bleeding). Only 2 patients had scores of less than 1·0 (mild inflammation but no bleeding on probing). Tooth mobility is scored on a scale of 0–3 (moderate movement in 2 directions and depressable). A reading of greater than 1·0 (column 6) indicates tooth mobility significantly greater than that present normally. The plaque index shows the extent of bacterial colonization (plaque) of the tooth surface, the gingival index the patient's local inflammatory response and ulceration (bleeding) of the pocket lining, and pocket depth (columns 7, 8) the progression of gingival enlargement and/or destruction of alveolar bone and periodontal ligament fibres holding the tooth to alveolar bone. Tooth mobility (column 6) then results from reduced tooth support and tends to be a later manifestation of periodontal disease. Data in columns 4–8 refer to the entire mouth, those in column 9 to the maxillary anterior region. Review of these data shows that plaque deposits are found around most teeth in most patients, all patients exhibit inflammatory changes in the gingiva, but that pocket depths vary. More than half the patients had no pockets greater than 4 mm (column 8), a measurement generally considered to be the limit of normal or indicative of minimal pathology. There is good correlation between these parameters and bone changes in the 2 patients at the extremes (+2·2 and −8·3). The most notable exception is the second patient listed where no bone loss is accompanied with a plaque index of 100%, a gingival index of 2·0, progressive mobility and pocketing (except in the maxillary anteriors).

Discussion

These data show that alveolar bone loss in the anterior maxilla is greater in patients with lepromatous leprosy compared to those with tuberculoid disease but that the rate of bone loss over 4 years is not different in patients with lepromatous, borderline or tuberculoid leprosy who have been under continuous treatment. Thus, treated patients with lepromatous disease are at no greater risk of alveolar bone loss than patients with other types of leprosy. These data suggest that the increased alveolar bone loss seen in patients with lepromatous disease may result from an unusual susceptibility of untreated lepromatous patients to maxillary alveolar bone loss. A study of the correlation of this bone loss and the

known duration of untreated disease in a large group of lepromatous patients could test this hypothesis.

The rate of alveolar bone loss (Table 1) in these patients compares favourably with that of larger populations of patients without leprosy. Over 1,000 patients were studied[16] in Norway and Sri Lanka for 6 years, during which time periodic measurements of plaque accumulation, gingival index and loss of attachment were made. Loss of attachment is a clinical measurement determined by probing and requires a prior loss of alveolar bone and periodontal ligament attaching tooth to bone. Thus, longitudinal measurements such as in their study correlate well with alveolar bone loss. They found the rate of attachment loss in Norwegians to be 0·08 mm/year and in Sri Lankans to be 0·29 mm/year. The main clinical difference in these two populations was that the Norwegians exhibited significantly less plaque and gingival inflammation and much better oral hygiene than the Sri Lankans.[17] Data from Table 1 converted to annual loss of alveolar bone show that our treated patients with leprosy lost 0·09–0·13 mm bone height per year. Thus, the patients in the present study lost alveolar bone (attachment) at a rate similar to the Norwegians. However, their oral hygiene was much worse than the Norwegians', being similar (Table 2) to that recorded for the tea plantation workers in Sri Lanka.[16, 17] This association of low bone loss and poor oral hygiene in patients with leprosy is puzzling, because numerous studies have confirmed a direct correlation between accumulation of plaque, alveolar bone loss and the severity of periodontal disease.[18, 19] The answer may lie in the complex host immune response in the periodontium where lymphocytes, macrophages and other components of the immune system responding to the microflora are believed to play key roles in the pathogenesis of periodontal disease.[20, 21] Recently evidence[22] has been provided for a selected suppression of lymphoproliferation by macrophages and T-lymphocytes in patients with leprosy. This inability of patients with leprosy to respond to certain antigens may also protect them from alveolar bone loss in the presence of numerous local factors that ordinarily increase bone loss. This clinical dilemma should be solved by a better understanding of the specific immune defects in leprosy and knowledge of the specific oral microflora[23] in patients with leprosy. The initial maxillary alveolar bone loss in patients with leprosy might be directly attributable to some local effect of *Mycobacterium leprae* on bone cells, the greater susceptibility of lepromatous patients being attributable to the bacillary concentrations in the nasal mucosa. Once treated, patients with leprosy may be protected from this influence on alveolar bone. In addition, the specific immune derangements that make patients susceptible to leprosy in the first place may also protect them from alveolar bone loss associated with periodontal disease. The fate of *M. leprae* and the patient's susceptibility to periodontal disease may well be decided by the immune response.

The observation that several patients exhibited either a gain or no loss of bone height over 4 years deserves comment. Some of these patients (Table 2) exhibited

good oral hygiene but this was not universal. The loss of alveolar bone is believed to be asynchronous. [24] Radiographic observations of increased bone height are not rare,[25] but are seen primarily after optimal oral hygiene and reduction of inflammation.[26–28] It is conceivable that the compromised immune response in patients with leprosy may not only protect them from bone loss proportional to the intensity of dental plaque but may also permit restoration of bone height. Answers to these questions will have to await more information. Clearly, the initial susceptibility of lepromatous patients to localized alveolar bone loss and the lack of correlation of bone loss and oral hygiene status in treated patients with leprosy deserve further study. What appears to be clear at this point is that early treatment of patients with lepromatous leprosy can reduce alveolar bone loss. This may be a fortunate clinical development because the well-known hand deformities of leprosy limit manual dexterity in patients with advanced disease and good oral hygiene in these patients may be impossible without assistance.

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A study of leprosy patients with deformities, and the implications for the treatment of all leprosy patients*†

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Summary The attendance of leprosy patients with grade 2 and 3 deformities for treatment and physiotherapy care at clinics run by the Bombay Leprosy Project (BLP) in the slums of the city was very poor. A survey was conducted to try and discover what factors might affect attendance. This showed that many patients had misconceptions about the disease and their deformity. The clearer their understanding, the more motivated they were to attend for treatment.

Appropriate education to improve knowledge about the disease may play a large part in motivating all patients, including those with deformities, to take treatment. To carry out this education effectively necessitates an understanding by leprosy workers of local attitudes and ideas about the disease.

The Bombay Leprosy Project (BLP) is an urban leprosy control group working in the slums of the city. In accordance with the Government-designated SET (survey–education–treatment) scheme they run clinics, conduct house-to-house surveys and do educational work. They also provide physiotherapy care and advice to those patients with deformities. This is available at both treatment and separate physiotherapy clinics. A few home visits are also made. Services offered include demonstration of massage and exercises, ulcer care, and provision of splints, aids and footwear. However, patient response to both physiotherapy and drug treatment was poor.

We carried out a survey of grade 2 and 3 patients registered with the project to investigate the factors that might influence their response to treatment with the aid of improving the care received. The areas of study included:

(a) Demographic and socio-economic data to provide background information about the group studied.

* This study was conducted under the auspices of Dr R Ganapati, Director, the Bombay Leprosy Project (BLP) and on a student sponsorship with LEPRA, the British Leprosy Relief Association.

† A full copy of the report (37 pages) is available on request. Please cover costs of photocopying.

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(b) Objective assessment and history of the disease and deformity.
(c) Patient's attitude to the disease, deformity and care offered: (i) Knowledge of and attitude towards leprosy and its treatment, to assess the clarity of the patient's concept of the disease. (ii) A comparable study of knowledge and attitude to the deformity and its care. (iii) The effect of the deformity upon the patient's life.

Method

(a) SAMPLE GROUP

Of 301 grade 2 and 3 patients registered with BLP, 259 were eligible for the study. (The remainder refused treatment or could not be traced in the slum areas.) A sample group of 91 was taken. Although no statistical sampling method was used, attempts were made to contact all patients; but due to the difficulties this entailed, the sample is biased towards those who attend clinics (Table 1).

(b) DATA

Baseline data was collected from project records. Primary data was collected by means of a questionnaire, compiled in English and directly translated into the native language of each respondent. This was necessary as there is no common

Table 1. Patient attendance for medical (drug) and physiotherapy care

	All registered patients		Sample group	
	No.	(%)	No.	(%)
Frequent* attendance for medical and physiotherapy care (seen in 6/12 or more)	43	14	39	42·9
Frequent attendance for medical care, infrequent attendance for physiotherapy	153	51·0	31	34·1
Infrequent attendance for medical care, frequent attendance for physiotherapy	3	1·0	1	1·1
Infrequent attendance for medical and physiotherapy care	102	34·0	19	20·9
Total	301	100·0	90†	99·0

* 'Frequent' indicates patients were seen in at least 6 months of the year.
† Plus 1 just registered = 91.

language amongst the patients who migrate to the Bombay slums from all over India.

Results

(a) DEMOGRAPHIC AND SOCIO-ECONOMIC DATA

The group consisted of 66 males and 25 females. Their ages covered a wide range: only a small number were children under 15 years (6) and old people (6). They had a very low socio-economic status, the majority living in slum-style accommodation and existing on or below the poverty line. Although 80% were of an age commensurate with regular employment, only about half had a permanent occupation and many of these earned a non-living wage.

The standard of general education was also low, just under half (39) having received no formal education of any type, approximately one-third (32) having studied for less than 5 years, and only 4 having completed more than 10 years' education.

(b) DISEASE

They were mainly long-term sufferers. Sixty-five per cent had known of their disease for more than 5 years, their deformities developing subsequently. Seventy-seven per cent attended fairly frequently for medical treatment but response to physiotherapy care was not as good, only 20% receiving regular advice and a further 20% being seen irregularly but in more than 6 months of the year (Table 1).

(c) KNOWLEDGE AND ATTITUDE TO DISEASE AND DEFORMITY

(i) *Cause*

We wanted to assess how aware the patients were of the true facts about leprosy. Their beliefs as to its cause could be classified into 5 major groups (Table 2). Even though most patients had been suffering from leprosy for a number of years very few had any correct notion as to its cause. However only a third had fixed, incorrect views (A, B, C) and a large proportion were undecided. Their general educational standard appears to be associated with their beliefs, a higher level eliminating the superstitious beliefs such as a curse of God, and leading to the idea of cause and effect, i.e. that specific actions, such as alcohol consumption, lead to leprosy. More informed notions such as germs were associated with higher levels again.

The respondents were also asked what they believed had caused their

Table 2. Patients' beliefs of cause of leprosy, and level of general education

	Belief	Education				Total	Percentage of patients
		Nil	1–5 Std	6–10 Std	SSC* pass		
A	'Superstitious' beliefs	12	5	—	—	17	18·7
B	Results of life-style	4	3	2	1	10	11·0
C	Hereditary	1	4	—	—	5	5·5
D(i)	Informed notions: (a) germs	3	3	5	2	13	14·3
D(ii)	(b) Contact with patients	5	7	1	—	13	14·3
E	Do not know	15	13	6	3	37	40·7
Total		40	35	14	6	95†	—

* SSC—School Certificate.

† The total is greater than in the sample group as 4 patients gave more than one response.

deformity (Table 3). About 40% accepted that their deformity was due to leprosy, but a high proportion attributed it to other factors. Reasons given included burns, wearing a tight ring, and 2 young girls attributed it to decorating their hands with henna. Thus many patients felt that they were suffering from two unconnected complaints: leprosy, and their physical handicap.

Table 3. Patients' beliefs about the cause of their deformity

Belief	No. of respondents
Leprosy	37
Negligence	6
Physical damage/accident	22
Burns	9
Automatically	14
Do not know	2
Other	5
Total	95*

* Four patients gave more than one cause for their deformity.

(ii) *Cure*

Almost all respondents (80/91) said that leprosy was curable, 6 were uncertain and 5 did not believe a cure was possible.

We asked patients about the curability of their deformity and ways in which this could be achieved to discover whether they were a group who felt that their disability was permanent or whether they would react positively towards treatment in the belief that it would be of some benefit to them. Their feelings about the permanence of their handicap would also affect their psychological reactions towards it.

About 90% (81) expressed the view that their deformity was curable. Twenty-six per cent felt that tablets on their own would effect a cure, 24% believed a combination of tablets and physiotherapy as necessary and 37% had faith in physiotherapy alone. In total, more than 60% expressed a belief in the benefit of physiotherapy. A small number felt that the deformity would disappear of its own accord or that some other remedy such as native leaf juices would help. Only 8 said that their deformity was not curable, and 2 had no definite view.

We compared patients' beliefs about the nature of cure with their concepts about the cause of their deformity. Those who accepted that it was due to leprosy had a greater confidence in physiotherapy (with or without tablets). Those who attributed it to other causes had equal confidence in tablets and physiotherapy.

(iii) *Advice*

Patients were questioned about the advice they had been given and whether they had experienced any improvement in their condition with physiotherapy (Table 4). They remembered most clearly that advice which could be demonstrated and

Table 4. Care/advice that patients remembered

Care remembered	No. of patients
Health education	44
Massage	84
Exercises	72
Ulcer care	30
Operation	3
Aids/footwear	29
Total	*

* Patients recorded all types of care given: total is greater than 91.

which they could practise in clinic in the presence of a worker, i.e. massage and exercises. Health education and information about the dangers associated with their deformity would have been given to all registered patients, but their recollection of spoken advice and acceptance of new ideas was not good. (This is supported by the small number who held informed ideas about the disease and deformity.)

Seventy per cent said there had been some improvement in their deformity with physiotherapy care. Fewer had previously expressed a belief that physiotherapy would cure their deformity (60%) and an even smaller number said they followed advice regularly. A greater proportion of this latter group attributed their deformity to leprosy rather than to other causes. This suggests that they may have had a clearer concept of their illness and so were better motivated to follow advice.

(iv) *Emotional reactions*

In view of the great stigma attached to leprosy we felt that the patients' emotional reaction might be of importance in their motivation to take advice. In addition, although it is often assumed that a handicap will cause some physical difficulty, less attention is paid to the possible psychological effects on the individual. Over 70% felt either worry, shame, embarrassment or a combination, whilst just under 30% did not admit to any problem. (Only 53% said that they experienced physical difficulties.) They gave various reasons for their concern (Table 5).

Although a large number of respondents experienced psychological problems connected with their deformity, only about half of them were disturbed because of the association between their handicap and leprosy and fear of the attached stigma. Many did not connect the two and suffered mentally purely because of their physical imperfection. It is well known that the physically handicapped may

Table 5. Reasons for patients' concern about their deformity

Reason	No. of patients
Shame/embarrassment of physical imperfection	11
Fear that people would ask about the deformity	11
Fear that people would know of disease by seeing deformity	15
Problems with work	10
Concern about the future	7
Other/unable to explain	11
Unconcerned	26
Total	91

find it difficult to readjust and alter their body image to come to terms with their physical imperfection and it is important to remember in dealing with deformity cases that this will be a problem experienced by all of them, whilst a much smaller number will actually have fears connecting their deformity and the stigma of leprosy.

We also looked at the extent and degree of their deformity to see whether this affected their reactions. Minor degrees of handicap caused few problems, but as they became more noticeable the patients experienced greater fears. They reacted more strongly to hand deformities which were less easy to disguise, and for which it was more difficult to find plausible excuses, than to feet deformities which could be hidden by footwear or explained away in terms of physical trauma. However, when their deformities became very extensive and impossible to disguise some patients became resigned to them. They knew that people would be able to identify them as sufferers from leprosy and the uncertainty and fear which afflicted the less severely handicapped had been removed. They had been able to readjust and accept a new body image, realizing their deformity was permanent, in contrast to others who had hopes of a cure and so were not able to establish a clear and constant image of themselves.

Conclusion

It appears from these results that reactions to handicap are determined by the concepts patients hold about the disease and that these affect motivation and response to treatment.

Those patients who admit that their deformity is due to leprosy are more likely to: (a) believe physiotherapy will help cure it; (b) say that they are regular in following physiotherapy advice; and (c) attend a physiotherapy clinic frequently, believing it will cure the deformity. They are also more likely to attend regularly for medical treatment. The incidence of psychological problems is the same amongst these as other patients but a larger proportion are concerned or fearful due to reasons linked with leprosy. This group appears to have a fairly clear understanding of their disease. They accept that regular drug treatment is necessary to cure leprosy but realize the additional benefits of physiotherapy. A large number, being better informed about the disease and more conscious of its possible social implications, are also frightened and worried about it. They fear the stigma that may be attached to them if others come to know of their disease. Others have overcome this fear and with their clearer knowledge are willing to admit openly to others that they are suffering.

A large group of cases appear to be confused in their understanding. They do not believe leprosy caused their deformity, giving a variety of other reasons for it, and they are not clear as to the ways in which drug treatment and physiotherapy can help them.

Finally there is a small pool of sufferers who are totally unconcerned about their disease and physical problems, or who have no faith in treatment. They usually constitute those with the severer grade of deformity for whom it is much more difficult to give constructive advice. They have become resigned to their handicap, believing that nothing will restore the function of their hands and feet, and so do not accept or follow physiotherapy advice. They are also irregular for medical treatment feeling that there is little point in taking drugs to cure a disease which has already affected them so severely and irreversibly.

This study was carried out amongst a normal slum population in Bombay. However, around the city there is also a large number of leprosy sufferers with deformities who survive by begging. They tend to live in pavement slum dwellings or in leprosy colonies, and are often unwilling to take treatment or advice, as their deformities represent their source of livelihood.

That response to treatment appears to be linked with patients' concepts of the disease and their total health awareness holds implications for the treatment of all leprosy sufferers not just those with deformities. The fact that such a large proportion of patients who have suffered and been treated for many years do not have even a basic knowledge of the cause of the disease indicates that the dissemination of information is very poor. This could be due to an inadequate approach to education by the various organizations who provide care. It is also possible that there is only a core of individuals who have been able to adjust to and accommodate new ideas, the remainder being unmoved from their pre-existing patterns of thought and belief.

It would be interesting to compare these findings with studies of patients' response to other 'chronic' diseases for which people must take long-term treatment, that have gradually progressive physical effects which often do not appear to be related to the actual complaint, e.g. diabetes, or cardiac failure in hypertensive people. The physical signs of leprosy are much more distinctive and stigmatizing than in all other diseases, but the problem of long-term treatment for what may appear to be an 'asymptomatic' illness, and associated care for seemingly unconnected physical problems is not a unique one.

Great emphasis needs to be laid upon education, and the way in which facts are presented is of great importance. The physiotherapy advice that patients remembered was that which was demonstrable, i.e. massage and exercises—and this had the greatest impact. A greater use of visual aids in presenting facts about the disease may be of value in helping them to grasp new concepts and to clarify their views. Greater attempts should be made to present the material in a way that is culturally acceptable to the people, taking into account their existing beliefs, rather than working from the basis of a scientific background which they may not accept. Leprosy workers should be aware of local attitudes and ideas about the disease. Although educating patients in the early stages of treatment when they first come into contact with the care organization may be time-consuming and staff-intensive, this survey suggests that the benefits to patients in terms of clearer

understanding of the disease, better compliance with treatment and hence, ultimate cure, may be invaluable.

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Further reading

Background data and parts of questionnaire from: R K Mutatkar, *Society and Leprosy* (Shubhada-Saraswat, Pune).

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SPECIAL ARTICLE

The immunopharmacology of antileprosy agents

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Introduction

Unlike other acute and chronic bacterial infections, the antimicrobial chemotherapy of leprosy is complex due to the occurrence of adverse immunological reactions. The role played by antimicrobial agents in precipitating or exacerbating these reactions is controversial. Whilst conceding that various mechanisms of induction of adverse immunological reactions exist in this disease, the purpose of this review is to suggest immunopharmacological mechanisms by which chemotherapeutic agents may enhance immune reactivity in individuals with leprosy. To understand these mechanisms by which antimicrobial chemotherapy may contribute to immunologically mediated conditions it is necessary to consider the immunological status of untreated individuals with the lepromatous (LL) form of the disease.

Immunological status of untreated individuals with LL

Acquired specific immunological unresponsiveness (tolerance, anergy) to *Mycobacterium leprae* antigens is found in individuals with LL and may be total or partial according to the state of advancement of the disease and bacillary load. This specific anergy develops as a consequence of the extremely high antigen load which occurs in LL. Apparently, the high antigen concentrations *in vivo* reach a threshold at which the host immune system detects that sustained immune reactivity against *M. leprae* is to the continued detriment of the host. In this situation the immune response is ineffective in eradicating the antigen, but continues to inflict damage on bystander tissues in the vicinity of the antigen. Immunologically mediated tissue damage occurs by the release of toxic oxygen radicals and proteolytic enzymes, such as elastase and collagenase, from phagocytic cells (Figure 1) which have been mobilized and activated by pro-inflammatory lymphokines released from antigen-activated T-lymphocytes.

Predisposition to the development of this chronic, ineffective inflammatory response which leads to LL may be genetically determined or acquired (e.g. in nutritional deficiency states). There is no conclusive evidence to indicate the existence of genetic susceptibility to the disease. Induction of

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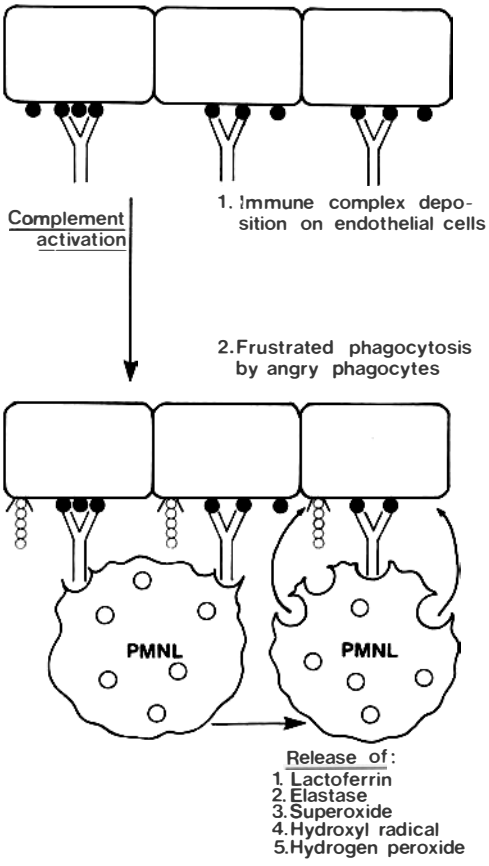

Figure 1. This is a diagrammatic representation of a possible mechanism of ENL assuming an immune complex pathology. *M. leprae* antigens (●) bind with antibody (γ) to form localized or circulating immune complexes which are deposited in the skin, joints, kidney or endothelial cells of blood vessels. Resultant complement activation releases factors (C3a and C5a) which activate and attract phagocytes, especially PMNL and the cell membrane attack unit C5b, 6, 7, 8, 9 (ooooo). These cells bind to the immune complexes but are unable to ingest them (since the complexes are tissue bound). The phagocytes therefore become 'frustrated' and 'angry' with consequent degranulation and release of toxic agents such as lactoferrin, elastase, the toxic oxidizing radicals superoxide and hydroxyl radical and hydrogen peroxide which probably cause the tissue damage in ENL. The mechanisms by which these agents mediate inflammation and tissue damage have been recently reviewed.[19]

tolerance is mediated by recruitment of antigen-specific suppressor T-lymphocytes[1] which suppress specific cell-mediated immunity (CMI) to *M. leprae*. Other mechanisms which decrease CMI responses to *M. leprae* are also operative such as generalized anergy and humoral factors with immunosuppressive activity. Paradoxically, the induction of suppression of specific CMI is probably beneficial by reducing the degree of immunologically mediated tissue damage. However, damage to tissues is an on-going process due to non-specific and antibody mediated immune mechanisms and immunologically uncontrolled growth of *M. leprae*.

The situation in individuals with LL prior to the commencement of antimicrobial chemotherapy is that they have: (a) an extremely high antigen load; and (b) specific immunological tolerance to *M. leprae*.

Activation of immune reactivity in LL following antimicrobial chemotherapy

Antimicrobial agents may contribute to the development of adverse immunological reactions by either or both of two possible mechanisms:

(a) As a consequence of the antibacterial activity of the drugs with activation of latent or hitherto suppressed immunological reactions. Antimicrobial agents cause disintegration of the bacterial cells with release of antigens which form circulating or localized immune complexes. These complexes cause regional or generalized complement activation with mobilization of granulocytes which migrate to sites of immune complex deposition. Binding of granulocytes to the immune complexes with subsequent phagocytosis or exocytosis causes release of toxic oxygen radicals and proteolytic enzymes which damage surrounding tissues. It is likely that granulocyte activation by the interaction of immune complexes and complement is responsible for the development of erythema nodosum leprosum (ENL) and its complications in individuals with a high bacillary load (BL–LL).

Antigen-elimination during antimicrobial chemotherapy causes a decrease in the antigen load with a consequent reduction in the extent of antigen-induced immunosuppression and recovery of specific CMI to *M. leprae*. Reactivation of CMI leads to the development of an adverse immunological reaction (reversal immunity reaction) caused by the induction of production of pro-inflammatory lymphokines which mobilize, attract and activate granulocytes, macrophages and T-lymphocytes. These highly reactive cells release toxic oxidants and proteases which, although important in the intracellular destruction of microorganisms, are also released extracellularly and may mediate the tissue damage which accompanies reversal immunity reactions. These reactions may occur anywhere in the leprosy spectrum except the polar groups.

It must be emphasized that these proposed mechanisms are speculative. However, should they exist all agents used in the antimicrobial chemotherapy of leprosy have the potential to cause ENL and/or reversal immunity reactions in susceptible individuals.

(b) The second mechanism by which antimicrobial agents may contribute to the development of adverse immunological reactions is by possession of intrinsic immunostimulatory activity, i.e. direct drug-mediated enhancement of cellular immune responsiveness independent of antimicrobial activity. Such a mechanism is probably less important than antigen release mechanisms related to antimicrobial activity. However, a drug such as dapsone which has been reported to increase granulocyte motility and lymphocyte proliferation[2] could be expected to potentiate ENL and reversal immunity reactions in susceptible individuals.

Effects of antileprosy drugs on cellular-immune reactivity

The three widely used antimycobacterial agents rifampicin, dapsone, and clofazimine may regulate cellular immune functions by antigen-elimination mechanisms as described above. However, in this section their effects *per se* on immune reactivity are considered.

RIFAMPICIN

The immunomodulating effects of rifampicin have recently been reviewed.[3] This antimicrobial agent is an inhibitor of lymphocyte responses to mitogens and antigens and of PMNL migration *in*

vitro. Animal studies have also shown that rifampicin is immunosuppressive *in vivo* causing inhibition of both antibody and cell-mediated immune responses. However, studies[4] have shown that rifampicin at concentrations of 0·01–100 μg/ml had no effects on human monocyte migration *in vitro*.[4] The effects of rifampicin on humoral and cellular immunity have been investigated[5] in a double blind comparison in which 33 patients with pulmonary tuberculosis were treated with streptomycin, isoniazid and rifampicin or with streptomycin, isoniazid and pyrazinamide and 41 healthy controls were treated with rifampicin or a placebo. Treatment was for 6 months with a 1 year follow-up. No effects of rifampicin could be demonstrated on parameters of humoral or cellular immunity. In two separate studies we observed no inhibitory effects of rifampicin intake on polymorphonuclear leucocyte (PMNL) migration[6, 7] over a 1-month period in individuals with LL and actually observed improved lymphocyte responsiveness to mitogens. The effects of rifampicin on humoral and cell-mediated immune responses appear to be variable according to the response studied and the *in vivo* model used. However, the presently available evidence suggests that ingestion of the antibiotic by individuals with LL and normal adults has no striking immunosuppressive effects. There is no evidence to show that rifampicin *per se* stimulates any cellular immune function although improved lymphocyte proliferation in patients with LL may be associated with the antimicrobial activity of the antibiotic.[7]

DAPSONE

It has been reported from this laboratory that dapsone *per se* causes stimulation of PMNL motility in normal adults and individuals with LL *in vitro*.[2] Furthermore ingestion of the drug over short periods was associated with increased PMNL migration and lymphocyte responsiveness to mitogens in the control and LL groups.[2, 6, 7] These effects of dapsone were related to the anti-oxidant activity of the drug and not to its antimicrobial properties. Anti-oxidants sustain and enhance cellular immune reactivity by preventing the auto-oxidative loss of migratory responsiveness of PMNL and mitogen and antigen-induced lymphocyte proliferation.[8] A second possible mechanism of dapsone-mediated immunostimulation, also related to an anti-oxidant mechanism, may be inhibition of the synthesis of immunosuppressive prostaglandins (PGs). Recent reports have indicated that PGs released by monocytes induce suppressor cell activity which may be the cause of the impaired CMI observed in diseases such as Hodgkin's disease.[9] It has been reported[10] that this PG-dependent suppression is operative in individuals with the BT and TT forms of the disease but not in the BL and LL forms. However, it is possible that during antimicrobial chemotherapy associated recovery of CMI in BL–LL cases that T-lymphocytes may become more responsive to PG-mediated suppression. Inhibition by dapsone of this mechanism may therefore possibly contribute to enhanced CMI and development of reversal immunity reactions. It must be stressed, however, that there is no available data to substantiate the existence of this mechanism.

These observations suggest that dapsone is pro-inflammatory and may contribute to ENL and reversal immunity reactions by stimulating PMNL motility and lymphocyte responsiveness to antigens respectively. However, the drug has well-documented anti-inflammatory activity in a variety of dermatological conditions[11] which is probably related to its ability to inhibit phagocyte degranulation.[12] It has also been suggested[13] that dapsone may confer a measure of protection against the development of reversal immunity reactions in individuals with BL. This may seem difficult to reconcile with the proposed pro-inflammatory activity of the drug in LL. However, in individuals with LL and a high antigen load it is possible that the immunostimulatory, pro-inflammatory activities of the drug are dominant since the anti-inflammatory effect on degranulation may be negated as a result of increased leucocyte infiltration and high concentrations of immune complexes.

CLOFAZIMINE

Clofazimine, known alternatively as lamprene (R) or B663, is also a widely used antileprosy drug. However, clofazimine has no documented immunostimulatory properties and on the contrary has been reported to be useful in controlling both ENL[14, 15] and reversal immunity reactions[15, 16] whilst conferring antimicrobial chemotherapy. Recent investigations in this laboratory have shown that clofazimine inhibits the motility of PMNL and mitogen-induced transformation of lymphocytes from normal adults and individuals with LL *in vitro*; similar effects were observed following ingestion of the drug.[17, 18] These observations suggest that the most probable mechanisms of clofazimine-mediated anti-inflammatory activity are inhibition of PMNL migration and T-lymphocyte responsiveness to antigens which may control ENL and reversal immunity reactions respectively. Although the drug is therapeutically useful as a combined anti-inflammatory and antimicrobial agent its ability to precipitate adverse immunological reactions in susceptible individuals by antigen release mechanisms should, however, not be underestimated.

Conclusions

Inadvertent immunological manipulation occurs during antimicrobial therapy of individuals with leprosy with possible development of adverse immunological reactions in some cases. This is due to the formation of immune complexes and loss of antigen-induced immunosuppression and occurs as a consequence of the antimicrobial activity of the drugs. Rifampicin, dapsone and clofazimine may precipitate ENL and reveral immunity reactions by this mechanism. Dapsone-associated reactions may be intensified by the ability of the drug *per se* to potentiate PMNL migration and T-lymphocyte proliferation. Clofazimine, however, is immunosuppressive and may be useful in the control and prevention of such reactions whilst continuing to provide antimicrobial chemotherapy.

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Domiciliary and Field Work

Teaching Guide for Para-medical Workers in Leprosy, Volumes I and II

Writing with all the benefit of his experience in the leprosy treatment and health education programme in Calcutta, Dr Chaudhury (Editor) has produced a comprehensive guide in two volumes. Volume I (78 pp.) deals with virtually all aspects of leprosy and its control; Volume II with communicable diseases, public health, anatomy, physiology, the microscope and an exercise in health education in leprosy. Some of the recommendations and recorded usage of drugs for the bacillary infection in leprosy (Vol. I, pp. 32–4) will not meet with universal acceptance, but it must be acknowledged that they have proved valuable in the circumstances for which these excellent books have been written. To some extent they have, however, also been overtaken by recent WHO advice on multiple drug regimens, but this can probably be adjusted in future editions. We congratulate Dr Chaudhury and his colleagues on the production of this guide and wish it every success. The above two volumes are published by the Greater Calcutta Leprosy Treatment and Health Education Scheme (May 1982). Price 10 rupees (U.S. $2).

Tuberculosis: WHO and IUAT. 'Defeat TB now and forever'

Press release WHO/4 of 5 February 1982 begins as follows:

> One hundred years after Robert Koch discovered the tuberculosis bacillus, the number of TB cases in the world is actually still increasing; yet the means exist to eliminate this disease as a major health problem by the year 2000. Writing in the current issue of *World Health*, the illustrated magazine of WHO, Dr Halfdan Mahler, Director-General of the Organization, says: 'For more than 30 years, highly effective drugs and vaccine have been available, making TB a preventable and curable disease. Technologically sound strategies to prevent, detect and cure TB were gradually perfected. But progress has been agonizingly slow. In the majority of developing countries, there has been little or no improvement in the epidemiological situation. Between four and five million highly infectious cases emerge each year, and TB brings death to at least three million persons annually.'
>
> Dr Mahler suggests that the Centenary of Koch's discovery should be dedicated to appraising the strategies for TB control. 'We should courageously admit the many mistakes of the past and make a new commitment to eliminate TB as a major health problem, at the latest by the year 2000. This goal is fully attainable, but to attain it requires a better understanding of the true causes of the genesis and spread of the disease.'

The International Union Against Tuberculosis (3 Rue Georges Ville, 75116, Paris) has produced a number of supportive documents and posters for this theme. The issue of *World Health* referred to above (January 1982) contains material and photographs of exceptional interest, including a review of the early work of Robert Koch.

0305-7518/83/054145+03 $01.00

Teaching techniques in leprosy

The October 1981 issue of the *Monthly News Bulletin of the Hind Kusht Nivaran Sangh* (Indian Leprosy Association, 1 Red Cross Road, New Delhi 110001, India) carries a section on teaching techniques in leprosy. This was developed from a WHO workshop held in the Central Jalma Institute for Leprosy in Agra, and the following were the main headings: (1) Integration of leprosy with the general health service. (2) Curriculum of general medical subjects. (3) Methods of case detection. (4) Surgical problems in the field. (5) Methods of health education.

ATH Newsletter, WHO

In view of recent publications in this journal on Primary Health Care, Number 10 of the Appropriate Technology for Health Newsletter is of interest; it is over 20 pages long and is devoted entirely to the subject of health education methods and materials in PHC. The Newsletter is well worth reading regularly by those in domiciliary and field work and is obtainable free from Appropriate Technology for Health, Division of Strengthening of Health Services, WHO, 1211 Geneva, 27 Switzerland.

Least Developed Countries: listing by United Nations

In the *WHO Chronicle*, Volume 35, 1981, appears the following list of countries designated by the United Nations as least developed.

In *Africa*: Benin, Botswana, Burundi, Cape Verde, Central African Republic, Chad, Comoros, Ethiopia, Gambia, Guinea, Guinea-Bissau, Lesotho, Malawi, Mali, Niger, Rwanda, Somalia, Sudan, Uganda, United Republic of Tanzania, and Upper Volta. In *Asia and Oceania*: Afghanistan, Bangladesh, Bhutan, Democratic Yemen, Lao People's Democratic Republic, Maldives, Nepal, Samoa, and Yemen. In the *Americas*: Haiti.

The article also includes a table of health and related socio-economic conditions for 'least developed', other 'developing' countries and 'developed' countries.

INSA in India: Rural Health and Development Trainers' Programme

Mrs Sujatha de Magry, Programme Director of INSA (International Nursing Services Association) has written to inform us that the first course for this programme started in June 1982; of the 15 participants, 4 were from institutions treating leprosy. The background to this initiative is as follows:

> The International Nursing Services Association is a registered organisation in Atlanta, U.S.A. with affiliation to the Georgia State University. From 1973 it has offered intensive three-month inservice education programmes at Atlanta for nurses from the developing countries. In 1980 INSA Faculty members visited India to follow up some of the INSA graduates and to conduct a series of workshops, discussions and visits. During this time nurses, heads of institutions and government personnel expressed the need for training programmes that would prepare nurses for implementing and developing comprehensive community health programmes. This resulted in setting up a training programme for 'Rural Health and Development Trainers' Programme' in Bangalore, India.
>
> The purpose of this programme is to prepare indigenous registered nurses, auxiliary nurses, and other para-medical personnel to be trainers of village health workers and managers of local health and development projects in India.

(Although on a limited scale, and of necessity somewhat slow in development, the success of a similar approach by Mrs Sujatha de Magry in various South India projects supported by OXFAM in recent years, suggests that these courses by INSA/INDIA should be worthy of considerable attention. There is already some evidence to support the idea that this approach, rather than that of the conventionally planned health service, may produce results of great practical value, at relatively low cost.) Address: INSA/INDIA, Rural Health and Development Trainers' Programme, 2 Benson Road, Benson Town, Bangalore, 560-046, India.

Korean Leprosy Association: Technical Handbook for Leprosy Service, 1982

This little handbook, 10 × 15 cm, has recently been issued by the Korean Leprosy Assocation and is available on application to Dr Do-Il Kim, Director, Institute for Leprosy Research, Korean Leprosy Association, Anyang, PO Box 27, Kyeonggi-do, Korea. There are 40 pages, with virtually no 'text' in the usual sense, but many tables and diagrams. They cover all those aspects of leprosy which are essentially practical and related to field work, including an up-to-date account of the recent (1982) WHO recommendations on multiple chemotherapy. This is a remarkable (and unique) effort; it is a 'pocket' book of potentially great value. The small print is presumably unavoidable in view of its dimensions and the amount of subject matter covered, but—for the purpose intended—there can be few other points of criticism. Dr Do-Il Kim and the Association are to be congratulated on the production of this handbook, which may well prove useful in other countries.

Carville, USA: Audio-visual Loan Programme

The August 1982 issue of *International Health News*, published by the National Council for International Health, Suite 303, 212 Virginia Avenue, NW Washington DC 20037, U.S.A., carries the following piece of information:

> A primary function of the National Hansen's Disease Center is to promote an increased awareness of Hansen's disease within the health and medical communities. Accordingly, the Center has instituted an audiovisual loan program by which instructional materials produced for inhouse use—including slide series with tapescripts, videocassettes, and audiotapes—may be loaned to other medical and educational institutions for teaching purposes. Materials are loaned at no cost for a period of two weeks.
>
> For a listing of materials available, contact Dr R J O'Connor, Director of Education and Training, National Hansen's Disease Center, Carville, LA70721, or call (504) 642-7771.
>
> [*Ed. Note:* Dr O'Connor is interested in hearing from anyone with experience in the successful use of video in medical education programs overseas, especially in developing countries. The National Hansen's Disease Center makes use of it at Carville in teaching medical personnel about leprosy, and it is expected that others have had comparable success. Readers are encouraged to contact Dr O'Connor regarding video usage at the above address. He is also currently involved in a project attempting to interface a microcomputer with a videocassette player. He indicates that this combination of computer and video technologies, now possible because of advances in microelectronics, opens up an entirely new type of educational methodology—one which is ideally suited to continuing medical education.]

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Reports, News and Notes

XII International Leprosy Congress, New Delhi, India, 20–25 February 1984

An information brochure has already been widely circulated giving details of the Workshops, Sessions of Congress, fees and instructions to authors. Abstracts should reach Dr S G Browne, Secretary General, International Leprosy Association, 16 Bridgefield Road, Sutton, Surrey SM1 2DG, England, not later than 30 June 1983.

XI International Congress for Tropical Medicine and Malaria, Canada

This will be held in Calgary, 16–22 September 1984 and the programme will include plenary sessions, symposia, workshops and free communication (oral and poster) sessions. The subject matter will include the following:

1 Malaria and other parasitic and infectious diseases of the tropics.
2 Nutrition and health in the tropics.
3 Health care services for tropical communities.
4 Population dynamics: maternal and child health protection.
5 Environmental health protection: water, liquid and solid wastes, disease vectors.
6 Impact and management of tropical disease problems in the temperate zone.
7 The development process: impact on health in the tropics.

The objectives are to provide a review of current knowledge of the major disease problems of the tropics; an assessment of the state-of-the-art for prevention, control and treatment of these diseases.

The Committee requests that participants give special consideration to progress being achieved and problems still unsolved in addressing curative and preventive measures. New and significant findings and concepts will be particularly welcome.

Apply: Secretariat, Conference Office, University of Calgary, Calgary, Alberta, Canada T2N 1N4.

British Council Tuberculosis Course, September 1983

This will be directed by Professor Wallace Fox of the Medical Research Council Tuberculosis and Chest Diseases Unit, Brompton Hospital, London, and Professor D A Mitchison, Honorary Director at the Medical Research Council Unit for Laboratory Studies of Tuberculosis, Royal Postgraduate Medical School, London. The first week will be at the Royal Postgraduate Medical School and the second week at the Cardiothoracic Institute. There will be a 3-day review of leprosy at the National Institute for Medical Research, Mill Hill, organized by Dr M J Colston.

Apply to British Council representatives in any country.

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Second European Course in Tropical Epidemiology, Royal Tropical Institute, Amsterdam, August–September 1983

The course is open to physicians and other persons with a professional interest in the field of tropical medicine and hygiene. It will provide participants with additional skills in the epidemiological ascertainment of local health problems and service priorities, especially in the planning of local field studies. Emphasis will be on the adaptation of standard epidemiological methods in the particular conditions of most developing countries, on the interpretation of data obtainable in such countries, and on the reporting of field studies. The number of participants will be limited.

The 1983 course will be organized at the Royal Tropical Institute, Amsterdam. The following institutes and schools collaborate in the development and conduct of the course: Royal Tropical Institute, Amsterdam; Institute for Tropical Medicine, Antwerp; Institute of Tropical Hygiene, Heidelberg; Liverpool School of Tropical Hygiene; London School of Hygiene and Tropical Medicine.

Further information can be obtained from: H J Nordbeck, Epidemiology and Statistics Section, Department of Tropical Hygiene, Royal Tropical Institute, Mauritskade 63, 1092 AD Amsterdam, The Netherlands.

ILEP Catalogue on Training, 1983

A catalogue of training centres has been produced by ILEP, London. The nine centres listed are as follows:

ALERT, All Africa Leprosy and Rehabilitation Training Centre, Addis Ababa, Ethiopia
Bamako, Institut Marchoux, Bamako, Mali.
Carville, National Hansen's Disease Center, Carville, U.S.A.
Dakar, Institut de Léprologie Appliquée, Fann, Dakar, Senegal.
Fontilles, Sanatorio de Fontilles, Alicante, Spain.
Karigiri, Schieffelin Leprosy Research and Training Centre, Karigiri, India.
Ujung Pandang, National Leprosy Training Centre, Indonesia.
Wau, National Leprosy Training and Demonstration Centre, Wau, Sudan.
Yaounde, Centre d'Enseignement de l'OCEAC, Yaounde, Cameroon.

Details have also been supplied of courses run by Dr Jacinto Convit in the Pan-American Centre for Research and Training in Leprosy and Tropical Diseases, Instituto Nacional de Dermatologia, Caracas, Apartado 4043, Correo de Carmelitas, Caracas 1010, Venezuela. His courses for 1984 have not yet been finalized, but are likely to be on similar lines. Full addresses are in the ILEP catalogue and full details of 1983 and subsequent courses may be obtained on application to the centre concerned. It should be noted that in most cases bookings have to be made far in advance.

AIGA publications: ***Some important questions about Hansen's disease, and some plain answers***

We are indebted to Fay Diers Lindsay, Editor, AIGA Publications, 744 Frances Harriet Drive, Baton Rouge, Louisiana, 70815, U.S.A. for a copy of this 9-page booklet. It uses question and answer format to raise some basic questions about leprosy, and to answer them in simple easily understood terms. It is unusual in having a translation into Hausa (one of the Nigerian languages) and the organization seems to be interested in the translation of similar material into languages such as Arabic, Spanish, Hawaiian pidgin, Vietnamese and Tagalog.

CHROMACOPY: photocopies in colour

Not altogether surprisingly, in view of the astonishing progress in black-and-white photostat technology, it is now possible to make copies in colour from colour originals. Copies can also be made from three-dimensional objects provided they are not more than 4 inches (10 cm) deep. Apply for further details to either Chromocopy Franchise, DPM Design Consultants Ltd, DPM House, 63 Poland Street, London W1V 3DF or Chromocopy Overseas Office, 227 East 56th Street, New York, New York 10022, U.S.A. The charges are far from high and the quality is good.

***Excerpta Medica* Abstract Journals. Leprosy and related subjects (Section 51)**

In addition to the clinical, experimental, legal, political, psychological and public-health related aspects of leprosy and the leprosy bacillus per se, this relatively specific section includes material on tuberculosis and other mycobacterial diseases and related pathology, particularly to the extent that their management, prevention or epidemiology may be relevant to the leprosy problem.

All this information which is currently found not only in specific leprosy journals but scattered over primary journals in many different disciplines is concentrated in a single convenient source, and is published with the aid of the Netherland Leprosy Relief Association. The subscription price (10 issues per year) is Dfl 190.00 and for America and Canada US$65.00 (including postage). Back volumes are available. Apply to: Excerpta Medica, PO Box 1126, 1000 BC Amsterdam, The Netherlands or PO Box 3085, Princeton, New Jersey, 0840, USA.

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Letters to the Editor

USE OF COLCHICINE IN THE MANAGEMENT OF ERYTHEMA NODOSUM LEPROSUM (ENL)

Sir,

Erythema nodosum leprosum (ENL) has classically been thought of as a clinical manifestation of the Arthus phenomenon.[1] Recently, however, this concept has been challenged[2, 3] and many immunological differences have been noted in patients with ENL compared to those without ENL.[4–7] The understanding of the pathogenesis of this complication will, it is hoped, allow the formulation of a rational management of ENL.

Since 1965, the superiority of thalidomide in the treatment of ENL has been well documented.[8–11] Due to teratogenicity, however, this drug is not easily available. Clofazimine (lamprene) has also been shown to be useful, especially in patients with chronic or recurrent ENL attacks.[12–14] Other drugs, including steroids, have also been used with varying efficacy in the management of ENL. The exact mechanisms by which these drugs produce their effects are not known.

Recently it has been shown that colchicine is able to suppress the Arthus reaction in rabbits despite deposition of immune complexes.[15] This effect was thought to be due to suppression of polymorphonuclear leukocyte directional chemotaxis by colchicine. This drug is expected, therefore, to have a beneficial effect in diseases thought to have a pathogenetic mechanism similar to the Arthus phenomenon. Indeed colchicine has been used successfully in the treatment of Behçet's syndrome[16–18] and cutaneous lesions of necrotizing vasculitis.[19] If ENL really is a clinical manifestation of the Arthus phenomenon, then colchicine could be expected to have a beneficial effect. Immunoregulatory disturbances occurring during ENL have been documented[4–7] and one of the outstanding features is a decrease in thymus-dependent lymphocytes (T-cells) carrying a suppressor/cytotoxic phenotype:[4–6] this has been shown to revert to pre-ENL levels after clinical improvement of ENL.[6] It is interesting to note that patients with familial Mediterranean fever (FMF) can develop skin eruptions accompanied by fever, and this has been shown to be associated with a decrease of suppressor T-cells:[20–2] colchicine has been used in this disease to prevent amyloidosis[23–5] as well as the recurrent skin eruptions. Interestingly, colchicine has been shown to be able to restore the T-cell balance[26] and may thus have immunoregulatory effects. If ENL is precipitated by an imbalance of immunoregulatory T-cells,[3–5] colchicine would be expected, therefore, to be of value in its management.

Based on these observations we have treated 10 male adult patients with recurrent or chronic ENL with colchicine, 1·5–2·0 mg daily given in divided doses. All drugs known to affect ENL namely, thalidomide, clofazimine, steroids, chloroquine and analgesics were withdrawn prior to the administration of colchicine. Patients were thus receiving dapsone and colchicine alone during the entire period of the pilot study. All patients were taken into the study when they had clear evidence of ENL and were observed for 3 months. After clinical improvement had been achieved, patients were given a maintenance dose of of 1 mg colchicine daily. Two of the patients have had several attacks of ENL in the past despite concurrent use of clofazimine, steroids and thalidomide.

0305-7518/83/054151+06 $01.00

Twenty-four hours after initiation of colchicine the fever had gone down in all patients, and in 8 hours ENL lesions had begun to resolve. During this time too, the leukocytosis and raised ESR had been considerably reduced. By the end of the second day most of the lesions had disappeared and no new nodular eruptions had occurred. During the whole follow-up period none of these patients have developed new ENL attacks while using a maintenance dose of colchicine. In one patient colchicine was withdrawn after the patient had improved from the ENL attack. Two days after withdrawal of colchicine, the patient developed fever and a substantial number of ENL nodules on the forearms and thighs. Colchicine was then reinstituted and within 24 hours the lesions had started to disappear and the fever had gone down. We have thus noted a dramatic effect of colchicine in the management of acute ENL attacks. Furthermore, a maintenance dose of 1 mg daily seemed to prevent recurrent ENL attacks. The fact that these lesions started to resolve within 24 hours, and that in one patient withdrawal of colchicine led to eruption of new nodules which were subsequently controlled by colchicine, would indicate that colchicine has a direct beneficial effect in the management of ENL. Colchicine can be used for prolonged periods without major side effects as has been shown in FMF.[23–5, 27] Furthermore, the risks incurred seem to be less than those of using steroids or thalidomide for a prolonged time.

Since this was not a controlled double blind study we cannot draw any hard conclusions. However, we feel that a controlled double blind study to evaluate the use of colchicine in the management of ENL is now warranted.

Acknowledgements

We wish to thank the Directors of All Africa Leprosy Rehabilitation and Training Centre (ALERT) and Armauer Hansen Research Institute (AHRI) for allowing us to carry out this study. We are extremely grateful both to our patients and the nursing staff for their excellent cooperation. W/ro Shitaye Wolde Kidan kindly typed this manuscript. Armauer Hansen Research Institute is supported by the Norwegian and Swedish Save the Children funds.

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FAILURE OF LEVAMISOLE TO RESTORE *IN VITRO* LYMPHOCYTE RESPONSIVENESS IN LEPROMATOUS LEPROSY PATIENTS

Sir,

Leprosy exists in two polar forms: high-resistance tuberculoid (TT) and low-resistance lepromatous leprosy (LL). Borderline forms exist between the two extremes. In LL, cell-mediated immune responses to *Mycobacterium leprae* are depressed,[1, 3] although the nature of the defect has not been established.

Levamisole, an antihelminthic drug, restores defective *in vitro* T-lymphocyte responses,[6–8] though it does not restore cutaneous delayed hypersensitivity to lepromins in leprosy patients.[5] We report the effect of levamisole on the depressed *in vitro* responses to *M. leprae* antigens and tuberculin PPD in lepromatous leprosy patients.

Fourteen Ethiopian patients (6 females and 8 males, mean age 23, range 12–36 years) were studied. Eleven of the patients had either borderline lepromatous (BL) or LL and 3 had borderline tuberculoid (BT) leprosy. The patients were untreated except for 5 patients in the lepromatous group who had been treated with dapsone for periods from 2 weeks to 20 years prior to the study.

Peripheral blood lymphocytes from these patients were stimulated in the lymphocyte stimulation test (LST) with either sonicated *M. leprae*, 10^6 bacilli/ml, of human origin or tuberculin PPD, 1 μg/ml. Freshly diluted levamisole (kindly provided by Janssen Pharmaceutica, Belgium, through Dr J Symoens) was added at the start of the cultures at concentrations varying from 0·1 μg/ml to 100 μg/ml.

We found that levamisole did not significantly enhance the depressed *in vitro* lymphoproliferative responses to *M. leprae* in LL patients, and in BT patients the drug did not alter the response to *M. leprae*. Levamisole added to cultures of lymphocytes from the same patients did not influence the *in vitro* response to PPD either.

Levamisole possesses immunostimulating properties and has been reported to restore defective cutaneous delayed hypersensitivity in cancer patients,[2, 10] to influence the clinical course of malignancies[11] and it has been suggested that levamisole may be of therapeutic value in conditions associated with excessive suppressor T-cell functions.[4] We found that levamisole did not enhance the depressed *in vitro* T-cell responsiveness to *M. leprae* antigens in LL patients. This is in agreement with previous reports that levamisole did not alter the lepromin reaction or lead to clinical improvement in leprosy patients, especially LL,[5, 9] and suggests that the nature of the defect in lepromatous leprosy is different from cases where levamisole is reported to have immunostimulating properties.

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LEPROSY AND PRIMARY HEALTH CARE WORKERS

Sir,

In *Leprosy Review*, **53,** No. 3, dedicated to Leprosy and Primary Health Care, many thoughts have been expressed by a variety of authors. Although posts for the primary, village or community health worker (PHW) have been established in only a few countries to date, one gathers most authors agree that where PHWs have been shown to function efficiently it would be worth trying to involve them in leprosy work as well.

However, one wonders whether the PHWs could manage the many tasks various people would like to put on their shoulders. Certainly all authors agreed that support and supervision of the PHWs would be essential. I suggest that unless this condition is indeed fulfilled, the integration of leprosy work with the general work of the PHW should not be attempted, since it might well prove to be counterproductive—a case of throwing the bathtub away with the baby to save water.

If one agrees that the PHW's role in leprosy control should remain basic, one could suggest as tasks:

1 To refer anyone with a suggestion of clinical leprosy to the nearest health centre for examination, diagnosis, classification, registration and prescription for treatment.
2 To record and issue drugs according to prescription, regularly, to registered leprosy patients; to encourage and supervise drug compliance.
3 To recognize and refer to the nearest health centre complications, reactions and suspected drug allergies/toxicities.
4 To trace defaulters and encourage them to return to the fold.
5 To educate the community and leprosy patients on leprosy.

Staff at the nearest health centre should be able, prepared and willing not only to deal with most of the patients referred by the PHW, but also to visit the PHW from time to time to see which cases have not been referred. The question arises as to which staff should visit the PHW in order to monitor their work with respect to leprosy.

It is possible the medical assistant or nurse/midwife of the nearest health centre (dispensary?) could undertake this if they have the time, transport, energy and inclination. However, even though leprosy may feature on the training curriculum of medical assistants and nurses and might be included on refresher courses, it is my experience that general health personnel show little aptitude in the careful examination of patients suspected to have clinical leprosy, or in the diagnosis or classification of the disease.

I think most of your readers will agree that the diagnosis of leprosy is easy except when it is not easy, and then it is very difficult indeed. This poses a dilemma: one should only register and treat a patient as having leprosy when the diagnosis is virtually certain, but not miss the diagnosis of early leprosy either. To handle this dilemma in an acceptable manner one requires time, skill and

experience in leprosy to a degree rarely available to general peripheral health personnel. For the diagnosis and classification of leprosy and the initiation of treatment, one needs a person skilled and experienced in leprosy who can afford to concentrate on that one job at that moment. If one thinks of adopting the multi-drug regimens as recommended by the WHO Study Group (Geneva, October 1981), the classification should be very accurate.

A person with the capability to supervise PHWs with respect to leprosy might be the district tuberculosis/leprosy coordinator (DTLC) as exemplified in the Tanzanian National Tuberculosis/Leprosy Programme. It will be of great interest to learn how successful the DTLCs are in the leprosy aspect of their work. In Malaŵi it is possible that leprosy control assistants who have a minimum of 2 years training in leprosy could be groomed into DTLCs. However, except in cases of outstanding excellence their relatively junior position in the medical hierarchy may be a problem. For this reason the former Malaŵi Government Dermatologist/Leprologist (Dr V Gooskens) suggested the creation of district dermatology/tuberculosis/leprosy clinical officers, but unfortunately no clinical officers can for the moment be made available for training in this specialized task.

In conclusion it would appear unwise to consider incorporating leprosy control work into a primary health care system until PHC has become well established in a country or a part of a country.

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Lepr Rev (1983) **54**, 157–159

Abstracts

The following are reproduced with our grateful acknowledgement to the Bureau of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT.

SACHDEV K N, MATHUR D R, CHAWLA S N (1980) **Status of circulating 'T' lymphocyte population in leprosy.** *Leprosy in India* 1980; 52(3): 383–9

'"T" lymphocyte population was estimated in 40 cases of various types of leprosy by E-rosette formation. The mean percentage value of T-lymphocyte was significantly low in the lepromatous group as compared to tuberculoid and borderline leprosy. The mean percentage population of "T" lymphocyte was also compared with 24 normal healthy control cases and significantly low levels were observed in all types of leprosy. The population of "T" lymphocytes was also co-related with tuberculin tests in leprosy patients and healthy control cases. Lowest count of "T" lymphocyte population and smallest diameter of erythema was observed in lepromatous leprosy, suggesting impaired cell mediated immunity in this group.'

MELSOM R, DUNCAN M E, HARBOE M, BJUNE G **Antibodies against *Mycobacterium leprae* antigen 7 from birth to 18 months of age: an indicator of intra-uterine infection in leprosy.** *Clinical and Experimental Immunology* 1980; 42(1): 107–13

'All babies of three non-leprosy mothers and ten tuberculoid leprosy mothers and four of five babies of mothers with inactive lepromatous leprosy showed a decline in serum concentration of antibodies against *M. leprae* antigen 7 during the first 4 months of life, as expected from catabolism of maternal IgG. By contrast, ten of twenty babies of mothers with active lepromatous leprosy showed a decline in concentration of anti-*M. leprae* 7 antibodies considerably less than expected. This indicates that these babies have been stimulated by *M. leprae* antigen 7, either as free antigen or by viable *M. leprae* before birth, and thus that leprosy may occur as a congenital infection. Studies of anti-*M. leprae* antibodies in repeated serum samples obtained during the first 18 months of life indicated that children of mothers with bacilliferous leprosy are frequently exposed to *M. leprae* to a sufficient extent to stimulate the immune system of the baby to production of anti-*M. leprae* antibodies during this period. The consequences of this exposure to *M. leprae* should be ascertained by careful clinical studies.'

HUSSER J -A, ARNOLD J, MARCHAND J -P Corrélation entre clinique et histologie dans la lèpre. **[Correlation between clinical and histological classification in leprosy]** *Dakar Médical* 1980; 25(2): 137–42 English summary

'The histo-clinical correlations have been studied in newly detected cases of leprous patients during consultations in the Dakar Department of Endemic Diseases.

'These stress the difficulty of a pure clinical diagnosis in unstable forms of leprosy and indicate the importance of a histological examination in their classification and in the study of their therapeutic evolution.'

0305–7518/83/054157 + 03 $01.00

KOYA G, NARITA N, ARAKAWA I **[Histopathological findings of serial preparation including the total length of nerve of extremitas thoracica in leprosy]** *Japanese Journal of Leprosy* 1980; 49(1): 1–9 [In Japanese]

'Most reports on the histological changes in the peripheral nerves in leprosy have been made from the study of biopsy specimens. A study of bigger nerves, in their entire length, including the spinal cord, has been made occasionally as this is possible only at autopsy. We have undertaken a detailed study of the peripheral nerves in lepromatous leprosy by which made an addition to modified embedding method of their entire length. In addition, a detailed histological examination of the spinal cord was also undertaken. Histological examination of peripheral nerves of the upper extremities including the plexus and the roots of origin from the spinal cord dissected from three autopsy cases showed a greater degree of destruction of the axis cylinders and myelin sheaths in a spindle-like form and moderate destruction of them in proximal parts. Lepra bacilli, besides being present all along the peripheral nerves were found to be concentrated in a spindle-like form part.

'The examination of the spinal cords in three cases of lepromatous leprosy both histopathologically as well as by the staining method for the bacilli by Harada, failed to reveal acid fast organisms.

'It is concluded, therefore, that the lepra bacilli travel along the peripheral nerves to the roots, but fail to enter the spinal cord and it degenerates only secondarily.'

HAN S -H, TSAI L -C, HU S C, LOO S -T **Conversion of reactions to leprolin and lepromin in patients with lepromatous leprosy by the transfer factor.** *Chinese Journal of Microbiology and Immunology* 1980; 13(1): 1–8

'Conversion of leprolin and early lepromin reactions was achieved by two injections of transfer factor made of lymphocytes from lepromin-positive tuberculoid leprosy patients. However, the late reaction to lepromin remained unchanged. The importance of the degree of sensitivity of the cell donor was demonstrated, and a booster dose was also found to be useful. The feasibility of using transfer factor in treatment of lepromatous leprosy is briefly discussed.'

NATH I, VON ROOD J J, MEHRA N K, VAIDYA M C **Natural suppressor cells in human leprosy: the role of HLA-D-identical peripheral lymphocytes and macrophages in the *in vitro* modulation of lymphoproliferative responses.** *Clinical and Experimental Immunology* 1980; 42(2): 203–10

'Six families with HLA-D identical siblings suffering from leprosy were studied. Lymphocytes and macrophages isolated from the peripheral blood were co-cultered with allogeneic, HLA-D-identical cells and stimulated with *M. leprae* antigens and concanavalin A. Tuberculoid patients had circulating lymphocytes which showed marked functional suppression of lymphoproliferative responses to antigen and mitogen. In contrast, lepromatous patients showed weak lymphocyte suppressor activity. Macrophages derived from responder individuals augmented, while those derived from lepromatous patients inhibited, *M. leprae*-induced proliferation of lymphocytes.'

NATH I, SINGH R **The suppressive effect of *M. leprae* on the *in vitro* proliferative responses of lymphocytes from patients with leprosy.** *Clinical and Experimental Immunology* 1980; 41(3): 406–14

'Peripheral blood lymphocytes from sixty leprosy patients and eight healthy contacts known to be responsive to *M. leprae*, were stimulated *in vitro* with concanavalin A (Con A) or PPD alone or in combination with autoclaved, whole *M. leprae*. Time kinetics and the percentage of inhibition induced by *M. leprae* differed in the two

disease groups and contacts. Antigen-generated suppression of Con A-stimulated lymphocyte transformation was observed on day 4 in seventeen of twenty-one (80%) tuberculoid patients and six of seventeen (35.3%) untreated lepromatous patients. Healthy contacts and 53% lepromatous individuals showed enhanced Con A responses in the presence of antigen. On prolongation of antigen presence to 6 days, a marginal effect was noted in the tuberculoid group. In contrast, all healthy individuals and some lepromatous patients showed increased inhibition of Con A responses. *M. leprae* antigens showed uniform inhibition of PPD-induced ^{3}H-thymidine incorporation in leprosy patients and healthy contacts.'

ABE M, MINAGAWA F, YOSHINO Y, OZAWA T, SAIKAWA K, SAITO T **Fluorescent leprosy antibody absorption (FLA-ABS) test for detecting subclinical infection with *Mycobacterium leprae*.** *International Journal of Leprosy* 1980; 48(2): 109–19

The FLA-ABS test is an indirect fluorescent antibody test using *Mycobacterium leprae* as antigen, test sera having been previously absorbed with suspensions of BCG and *Myco. vaccae*. Under these modified conditions it was found to be positive in nearly 100% of patients with bacteriologically positive leprosy, in 80% of those with tuberculoid leprosy, but negative in pulmonary tuberculosis and in healthy non-contacts. There were 2 false positives in 138 hospital patients, due to cross-reactions with *Myco. smegmatis*.

The test was positive in 92% of household contacts of leprosy patients, among whom 7 out of 39 showed dubious Mitsuda reactions attributed to infection with *Myco. leprae* with an inadequate immune response. The test was positive in 109 of 173 schoolchildren with signs suggestive of leprosy. A comparison of results with the FLA-ABS test using different mycobacterial antigens was used to assess the incidence of subclinical leprosy infection in schoolchildren which, it is thought from the results, may be nearly 200 times higher than the incidence of leprosy in this area (Okinawa).

D S Ridley

KAWAGUCHI Y, MATSUOKA M, SUSHIDA K, TANEMURA M **[Susceptibility to murine leprosy bacilli of C3H/He mice]** *Japanese Journal of Leprosy* 1980; 49(1): 14–19 [In Japanese]

'C3H/He strain mice, approximately 5 weeks of age, were subcutaneously inoculated at the thorax with 0.25 ml of a 1:1000 saline suspension prepared from a malignant leproma in a C3H mouse infected with murine leprosy bacilli, strain Hawaiian, about 25 weeks earlier. The susceptibility of these mice to the bacilli was evaluated by the development of leproma at the infection site and also by the involvement of visceral organs.

'In only 2 out of 10 male mice tested, typically malignant leproma was observed at the infection site throughout the observation period. In almost all the other mice, subcutaneous leproma showed benign-like features at the early stage of infection. The leproma increased in size gradually, but did not show typically malignant features even at 40 to 50 weeks. However, visceral lesions in all the mice seemed to be severe with time, since autopsy revealed extensive involvement of the viscera. The visceral lesions and mean survival time of C3H/He mice were similar to those obtained in C3H mice. There were no pronounced differences in the susceptibility between male and female groups.

'The susceptibility of C3H and C57BL/6 strain mice was also examined by the same manner above mentioned, as controls. Mice of C3H and C57BL/6 strains showed typically malignant and benign features, respectively.

From the observations of this and of our earlier experiments, it is clear that the disease course in C3H/He mice was intermediate to that observed in C3H and CF 1 mice.'

CONTENTS

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